



Clinical trial results:

An open-label, single-arm study to evaluate the efficacy, safety and PK of artemether-lumefantrine dispersible tablet in the treatment of acute uncomplicated Plasmodium falciparum malaria in infants <5 kg body weight

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-005852-33 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 08 July 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 15 July 2016 |
| First version publication date | 15 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CCOA566B2306 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01619878 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000777-PIP01-09 |
| 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 | 08 July 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 08 July 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of a 3-day regimen of artemether-lumefantrine dispersible tablet (1 tablet twice daily) in infants <5 kg of BW with acute uncomplicated *P. falciparum* malaria using the polymerase chain reaction (PCR)-corrected 28-day parasitological cure rate.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 08 October 2012 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Benin: 4 |
| Country: Number of subjects enrolled | Burkina Faso: 16 |
| Worldwide total number of subjects | 20 |
| 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) | 20 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |

| | |
|----------------------|---|
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The participant that did not complete in the "6 week follow-up phase" was also included in "Follow-up at 12 Months of Age" and was lost to follow-up

Period 1

| | |
|------------------------------|--|
| Period 1 title | Cohort 1- 6 week / 12 month follow-up (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|----------|
| Arm title | Cohort 1 |
|-----------|----------|

Arm description:

One Artemether-lumefantrine (COA566) dispersible tablet taken orally twice a day during 3 days. Infants age >28 days.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Artemether-lumefantrine |
| Investigational medicinal product code | COA566 |
| Other name | |
| Pharmaceutical forms | Dispersible tablet |
| Routes of administration | Oral use |

Dosage and administration details:

20 mg artemether/ 120 mg dispersible tablet was given twice daily for 3 consecutive days. Each tablet was dispersed in water (approximately 10 mL) and given orally.

| Number of subjects in period 1 | Cohort 1 |
|---------------------------------------|------------------|
| Started | 20 |
| completed 6-week follow-up phase | 19 |
| DC'D prior to completion of 6 wk f/up | 1 ^[1] |
| Completed | 17 |
| Not completed | 3 |
| Adverse event, serious fatal | 2 |
| Lost to follow-up | 1 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The participant that did not complete in the "6 week follow-up phase" was also included in "Follow-up at 12 Months of Age" and was lost to follow-up

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Cohort 1 |
|-----------------------|----------|

Reporting group description:

One Artemether-lumefantrine (COA566) dispersible tablet taken orally twice a day during 3 days.
 Infants age >28 days.

| Reporting group values | Cohort 1 | Total | |
|---|----------|-------|--|
| Number of subjects | 20 | 20 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 20 | 20 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age Continuous | | | |
| Units: days | | | |
| arithmetic mean | 99.1 | | |
| standard deviation | ± 51.75 | - | |
| Gender, Male/Female | | | |
| Units: participants | | | |
| Male | 10 | 10 | |
| Female | 10 | 10 | |

End points

End points reporting groups

| | |
|--|----------|
| Reporting group title | Cohort 1 |
| Reporting group description: One Artemether-lumefantrine (COA566) dispersible tablet taken orally twice a day during 3 days. Infants age >28 days. | |

Primary: Polymerase Chain Reaction (PCR) corrected 28 day parasitological cure rate

| | |
|-----------------|---|
| End point title | Polymerase Chain Reaction (PCR) corrected 28 day parasitological cure rate ^[1] |
|-----------------|---|

End point description:

Number of participants with clearance of asexual parasites by day 7 after initiating study treatment without recrudescence at day 28, corrected for re-infection by Polymerase Chain Reaction (PCR) assay.
"No statistical analysis was planned for this primary outcome."

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

28 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome.

| | | | | |
|-------------------------------|-----------------|--|--|--|
| End point values | Cohort 1 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: number of participants | 16 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Polymerase Chain Reaction (PCR) corrected parasitological cure rate at day 14 and 42

| | |
|-----------------|--|
| End point title | Polymerase Chain Reaction (PCR) corrected parasitological cure rate at day 14 and 42 |
|-----------------|--|

End point description:

Number of participants with clearance of asexual parasites by day 7 after initiating study treatment without recrudescence at day 14 and day 42, corrected for re-infection by Polymerase Chain Reaction (PCR) assay.

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

End point timeframe:

Day 14 and 42

| End point values | Cohort 1 | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: Number of participants | | | | |
| Day 14 | 16 | | | |
| Day 42 | 16 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with parasitological uncorrected cure rate at day 3, 7, 14, 28 and 42

| | |
|---|--|
| End point title | Number of participants with parasitological uncorrected cure rate at day 3, 7, 14, 28 and 42 |
| End point description: Number of patients with clearance of asexual parasites at day 3, 7, 14, 28 and 42 after initiating study treatment. | |
| End point type | Secondary |
| End point timeframe: Day 3, 7, 14, 28 and 42 | |

| End point values | Cohort 1 | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: participants | | | | |
| Day 3 | 20 | | | |
| Day 7 | 16 | | | |
| Day 14 | 16 | | | |
| Day 28 | 10 | | | |
| Day 42 | 7 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change of parasite count from baseline at 24 hours

| | |
|--|--|
| End point title | Percent Change of parasite count from baseline at 24 hours |
| End point description: Percent change of parasite count from baseline at 24 hours | |
| End point type | Secondary |
| End point timeframe: baseline, 24 hours | |

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Cohort 1 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | -99.4 (± 1.19) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with parasitaemia at 48 hours after treatment initiation greater than at baseline

| | |
|------------------------|--|
| End point title | Number of participants with parasitaemia at 48 hours after treatment initiation greater than at baseline |
| End point description: | Number of participants with parasite density at 48 hours after treatment initiation greater than parasite density at baseline. |
| End point type | Secondary |
| End point timeframe: | 48 hours |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Cohort 1 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: participants | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with parasitaemia at 72 hours after treatment initiation greater than or equal to 25 percent of count at baseline

| | |
|------------------------|--|
| End point title | Number of participants with parasitaemia at 72 hours after treatment initiation greater than or equal to 25 percent of count at baseline |
| End point description: | Number of participants with parasite density at 72 hours after treatment initiation greater than or equal to 25 percent of parasite density at baseline. |
| End point type | Secondary |
| End point timeframe: | 72 hours |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Cohort 1 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: participants | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to parasite clearance (PCT)

| | |
|---|----------------------------------|
| End point title | Time to parasite clearance (PCT) |
| End point description: Time from first dose until first total and continued disappearance of asexual parasite forms which remains at least a further 48 hours. | |
| End point type | Secondary |
| End point timeframe: Up to 7 days | |

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Cohort 1 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 29.1 (± 9.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to fever clearance (FCT)

| | |
|--|-------------------------------|
| End point title | Time to fever clearance (FCT) |
| End point description: Time from first dose to the first time the axillary body temperature decreased below and remained below 37.5° C for at least 48 hours. | |
| End point type | Secondary |
| End point timeframe: Up to 7 days | |

| End point values | Cohort 1 | | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 4.02 (\pm 6.433) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to gametocyte clearance (GCT)

| | |
|--|------------------------------------|
| End point title | Time to gametocyte clearance (GCT) |
| End point description: Time from first dose until first total and continued disappearance of gametocytes which remains at least a further 48 hours. | |
| End point type | Secondary |
| End point timeframe: Up to 7 days | |

| End point values | Cohort 1 | | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 36.32 (\pm 77.294) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 16.1 |

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Cohort 1 |
|-----------------------|----------|

Reporting group description:

Cohort 1

| Serious adverse events | Cohort 1 | | |
|--|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Infections and infestations | | | |
| Cerebral malaria | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Meningitis | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | Cohort 1 | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 20 (80.00%) | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 20 (30.00%) | | |
| occurrences (all) | 6 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 20 (25.00%) | | |
| occurrences (all) | 5 | | |
| Gastrointestinal disorders | | | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 20 (20.00%) | | |
| occurrences (all) | 4 | | |
| Infections and infestations | | | |

| | | | |
|-----------------------------|------------------|--|--|
| Bronchitis | | | |
| subjects affected / exposed | 6 / 20 (30.00%) | | |
| occurrences (all) | 9 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | | |
| occurrences (all) | 2 | | |
| Malaria | | | |
| subjects affected / exposed | 11 / 20 (55.00%) | | |
| occurrences (all) | 11 | | |
| Rash pustular | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| occurrences (all) | 1 | | |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 27 May 2013 | Amendment 1: issued 33 weeks after study start of patients, introduced the following changes: Bioanalytics laboratory and corresponding shipping address for pharmacokinetic samples were changed from WuXi AppTec Co., China to Swiss BioQuant AG, Switzerland; Corresponding adjustments were made in the timings for delivery of shipment of pharmacokinetic samples. This amendment was not considered to have affected the interpretation of study results as these changes were minor and mainly administrative |

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.

interim review after Cohort 1 6-week follow-up period the joint DMC recommended not to continue with the initiation of Cohort 2. The study therefore concluded when Cohort 1 patients completed their follow-up visit at 12 months of age.

Notes: