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)	EMEA-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 (± 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 (± 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: