Clinical trial results:
An open-label, randomized, single-center, parallel group study of the effects of artemether-lumefantrine (Coartem®) atovaquone-proguanil (Malarone®) and artesunate-mefloquine on auditory function following the treatment of acute uncomplicated Plasmodium falciparum malaria in patients 12 years of age or older

Summary

EudraCT number	2016-004321-16
Trial protocol	Outside EU/EEA
Global end of trial date	22 November 2008

Results information

Result version number	v1 (current)
This version publication date	16 November 2017
First version publication date	16 November 2017

Trial information

Trial identification

Sponsor protocol code	CCOA566A2417

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00444106
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)	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	22 November 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 November 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the auditory safety of artemetherlumefantrine after 3 days of treatment in patients with acute, uncomplicated falciparum malaria by testing the null hypothesis that the rate of auditory brainstem pathway abnormalities as assessed by ABR at Day 7) is ≥ 15% in such patients. An "auditory brainstem pathway abnormality" was defined as a greater than 0.30 msec change in Wave III latency from baseline to Day 7

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	02 May 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Colombia: 265
Worldwide total number of subjects	265
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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	90
Adults (18-64 years)	175
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were randomized in a 3:1:1 ratio to artemether-lumefantrine, atovaquone-proguanil (Malarone®,GlaxoSmithkline) or artesunate-mefloquine (Plasmotrim® + Mephaquin®, Mepha).

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	Artemether-lumefantrine (Coartem)

Arm description:

Artemether-lumefantrine (Coartem) tablets containing 20 mg artemether and 120 mg lumefantrine twice a day for 3 days dosage dependent on body weight.

Arm type	Experimental
Investigational medicinal product name	Artemether-lumefantrine (Coartem)
Investigational medicinal product code	COA566
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Artemether-lumefantrine (Coartem) tablets containing 20 mg artemether and 120 mg lumefantrine twice a day for 3 days, dosage dependent on body weight.

Arm title	Atovaquone-proguanil (Malarone)

Arm description:

Atovaquone-proguanil (Malarone) tablets containing 250 mg atovaquone and 100 mg proguanil hydrochloride once daily for 3 days dosage dependent on body weight.

Arm type	Active comparator
Investigational medicinal product name	Atovaquone-proguanil (Malarone)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Atovaquone-proguanil (Malarone) tablets containing 250 mg atovaquone and 100 mg proguanil hydrochloride once daily for 3 days, dosage dependent on body weight.

Arm title	Artesunate-mefloquine

Arm description:

Artesunate (Plasmotrim) 50 mg tablet; based on body weight for a dosage of 4 mg/kg/day for 3 days-mefloquine (Mephaquin) 250 mg tablets; based on body weight for a total dosage of 25 mg/kg once daily on days 2 and 3.

Arm type	Active comparator

Investigational medicinal product name	Artesunate-mefloquine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Artesunate-mefloquine tablets containing 50 mg artesunate (Plasmotrim) and 250 mg mefloquine (Mephaquin). Artesunate 4 mg/kg/day (for 3 days) and mefloquine 25 mg/kg/day (days 2 and 3) total dose was given once daily dependent upon body weight.

Number of subjects in period 1	Artemether-lumefantrine (Coartem)	Atovaquone-proguanil (Malarone)	Artesunate-mefloquine
Started	159	53	53
Completed Treatment Period	159	53	53
Completed	157	52	52
Not completed	2	1	1
Abnormal Test Procedure Results	-	-	1
Lost to follow-up	2	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Artemether-lumefantrine (Coartem)
Reporting group description:	
Artemether-lumefantrine (Coartem) tablets containing 20 mg artemether and 120 mg lumefantrine twice a day for 3 days dosage dependent on body weight.	
Reporting group title	Atovaquone-proguanil (Malarone)
Reporting group description:	
Atovaquone-proguanil (Malarone) tablets containing 250 mg atovaquone and 100 mg proguanil hydrochloride once daily for 3 days dosage dependent on body weight.	
Reporting group title	Artesunate-mefloquine
Reporting group description:	
Artesunate (Plasmotrim) 50 mg tablet; based on body weight for a dosage of 4 mg/kg/day for 3 days-mefloquine (Mephaquin) 250 mg tablets; based on body weight for a total dosage of 25 mg/kg once daily on days 2 and 3.	

Reporting group values	Artemether-lumefantrine (Coartem)	Atovaquone-proguanil (Malarone)	Artesunate-mefloquine
Number of subjects	159	53	53
Age categorical Units: Subjects			
in Utero	0	0	0
Preterm newborns infants	0	0	0
0 - <28 d	0	0	0
28 d-<2 y	0	0	0
2 y -<12 y	0	0	0
12 y - <18 y	51	21	18
18 y - <65 y	108	32	35
65 y - <85 y	0	0	0
>85 y	0	0	0
Age Continuous Units: years			
arithmetic mean	25.6	25.1	25.2
standard deviation	± 11.6	± 11.16	± 11.26
Gender, Male/Female Units: Subjects			
Female	63	19	22
Male	96	34	31

Reporting group values	Total		
Number of subjects	265		
Age categorical Units: Subjects			
in Utero	0		
Preterm newborns infants	0		
0 - <28 d	0		
28 d-<2 y	0		
2 y -<12 y	0		
12 y - <18 y	90		

18 y - <65 y	175		
65 y - <85 y	0		
>85 y	0		
Age Continuous Units: years arithmetic mean standard deviation	- -		
Gender, Male/Female Units: Subjects			
Female	104		
Male	161		

End points

End points reporting groups

Reporting group title	Artemether-lumefantrine (Coartem)

Reporting group description:

Artemether-lumefantrine (Coartem) tablets containing 20 mg artemether and 120 mg lumefantrine twice a day for 3 days dosage dependent on body weight.

Reporting group title	Atovaquone-proguanil (Malarone)

Reporting group description:

Atovaquone-proguanil (Malarone) tablets containing 250 mg atovaquone and 100 mg proguanil hydrochloride once daily for 3 days dosage dependent on body weight.

Reporting group title	Artesunate-mefloquine

Reporting group description:

Artesunate (Plasmotrim) 50 mg tablet; based on body weight for a dosage of 4 mg/kg/day for 3 days-mefloquine (Mephaquin) 250 mg tablets; based on body weight for a total dosage of 25 mg/kg once daily on days 2 and 3.

Subject analysis set title	Artemether-lumefantrine
Subject analysis set type	Per protocol

Subject analysis set description:

Artemether-lumefantrine (Coartem) tablets containing 20 mg artemether and 120 mg lumefantrine twice a day for 3 days dosage dependent on body weight.

Primary: Percentage of participants with Auditory abnormalities at Day 7 assessed by Auditory Brainstem Response (ABR) Wave III latency changes on Day 7(a type of hearing test)

End point title	Percentage of participants with Auditory abnormalities at Day 7 assessed by Auditory Brainstem Response (ABR) Wave III latency changes on Day 7(a type of hearing test)[1][2]

End point description:

To demonstrate the safety of artemether-lumefantrine after 3 days of treatment in patients with acute, uncomplicated falciparum malaria by testing the null hypothesis that the rate of auditory abnormalities is ≥ 15% in the population treated with artemether-lumefantrine as assessed by ABR at Day 7 following initiation of treatment compared with their baseline values. An "auditory nerve abnormality" is here defined as a greater than 0.30 ms change in Wave III latency from baseline to Day 7. Exact Pearson-Clopper two-sided 95% confidence limits were constructed for all three treatment groups.

End point type	Primary

End point timeframe:

7 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: Stat analysis was conducted for one arm artemether-lumefantrine but system does not allow us to report statistical analysis for a single arm. The P Value was <0.0001.
[2] - 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: The primary objective of the study was to evaluate the effects of artemether-lumefantrine on the auditory system based on ABR and pure-tone threshold findings after treatment in adults and adolescents suffering from acute uncomplicated malaria. Hence, the other two arms are not compared.

End point values	Artemether-lumefantrine (Coartem)			
Subject group type	Reporting group			
Number of subjects analysed	151			
Units: Percentage of Participants				
number (confidence interval 95%)	2.6 (0.7 to 6.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Auditory changes following 3 days of treatment at Days 3, 7, 28, and 42 days as assessed by pure tone thresholds assessments (a type of hearing test)

End point title	Auditory changes following 3 days of treatment at Days 3, 7, 28, and 42 days as assessed by pure tone thresholds assessments (a type of hearing test)

End point description:

Audiometric measurements such as pure-tone threshold (air conduction tested at 250 to 8000 HZ) day 3, 7, 28 and 42 following initiation of treatment, including changes from baseline. Pure-tone average (PTA) calculated for each ear by averaging the pure-tone threshold values at 500, 1000, 2000 and 3000 HZ.

End point type	Secondary

End point timeframe:

Baseline (Day 1), 3, 7, 28 and Day 42

End point values	Artemether-lumefantrine (Coartem)	Atovaquone-proguanil (Malarone)	Artesunate-mefloquine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	51	47	
Units: dB				
arithmetic mean (confidence interval 95%)				
Baseline Right Ear	12.2 (11.4 to 13.0)	12.0 (10.5 to 13.6)	12.7 (11.2 to 14.2)	
Change from baseline to Day 3 Right Ear	-2.5 (-3.1 to -1.9)	-2.4 (-3.6 to -1.2)	-1.9 (-3.0 to -0.7)	
Change from baseline to Day 7 Right Ear	-2.2 (-2.9 to -1.5)	-2.6 (-4.0 to -1.1)	-2.6 (-3.9 to -1.3)	
Change from baseline to Day 28 Right Ear	-2.7 (-3.5 to -1.9)	-2.6 (-4.2 to -1.0)	-3.6 (-4.8 to -2.3)	
Change from baseline to Day 42 Right Ear	-3.0 (-3.8 to -2.2)	-3.3 (-4.9 to -1.7)	-3.1 (-4.2 to -1.9)	
Baseline Left Ear	11.4 (10.5 to 12.3)	11.3 (9.9 to 12.7)	12.5 (10.8 to 14.3)	
Change from baseline to Day 3 Left Ear	-1.2 (-1.8 to -0.5)	-1.5 (-2.6 to -0.3)	-1.2 (-2.2 to -0.1)	
Change from baseline to Day 7 Left Ear	-1.7 (-2.4 to -0.9)	-1.3 (-2.8 to 0.2)	-1.4 (-2.8 to -0.1)	
Change from baseline to Day 28 Left Ear	-2.0 (-2.8 to -1.1)	-1.8 (-3.0 to -0.5)	-2.5 (-4.3 to -0.7)	
Change from baseline to Day 42 Left Ear	-1.5 (-2.7 to -0.4)	-2.1 (-3.5 to -0.6)	-3.0 (-4.7 to -1.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship between changes in auditory function and treatment groups

End point title	Relationship between changes in auditory function and treatment groups

End point description:

ABR Wave III latency (ms) changes from baseline to Day 7 in the three drug exposure groups.

End point type	Secondary

End point timeframe:

From Baseline to Day 7

End point values	Artemether-lumefantrine (Coartem)	Atovaquone-proguanil (Malarone)	Artesunate-mefloquine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	151	50	45	
Units: ms				
arithmetic mean (confidence interval 95%)				
Baseline Right Ear	3.86 (3.83 to 3.90)	3.89 (3.84 to 3.94)	3.86 (3.8 to 3.93)	
Change from baseline to Day 7 Right Ear	0.01 (-0.01 to 0.03)	-0.01 (-0.04 to 0.02)	-0.04 (-0.08 to 0.01)	
Baseline Left Ear	3.85 (3.82 to 3.88)	3.88 (3.84 to 3.93)	3.82 (3.77 to 3.88)	
Change from baseline to Day 7 Left Ear	0.01 (-0.01 to 0.03)	-0.01 (-0.04 to 0.02)	-0.03 (-0.07 to 0.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Polymerase Chain Reaction (PCR) adjusted malaria cure rates of the three treatment regimens at Days 14, 28 and 42

End point title	Efficacy of Polymerase Chain Reaction (PCR) adjusted malaria cure rates of the three treatment regimens at Days 14, 28 and 42

End point description:

Percentage of patients with clearance of asexual parasitemia (observed by optical microscopy) within 7 days of initiation of trial treatment without recrudescence within 14, 28 and 42 days respectively after initiation of treatment. Patients with recurrent parasitemia and paired PCR results were classified as

either a new infection (different paired genotypes) or a recrudescence (matching paired genotypes). Patients without paired PCR results or ambiguous results were classified as treatment failures.

End point type	Secondary

End point timeframe:

Days 14, 28 and 42

End point values	Artemether-lumefantrine (Coartem)	Atovaquone-proguanil (Malarone)	Artesunate-mefloquine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	151	53	53	
Units: Percentage of Participants				
number (confidence interval 95%)				
Day 14	99.4 (96.5 to 100.0)	100.0 (93.3 to 100.0)	98.1 (89.9 to 100.0)	
Day 28	98.7 (95.5 to 99.8)	98.1 (89.9 to 100.0)	98.1 (89.9 to 100.0)	
Day 42	97.5 (93.7 to 99.3)	98.1 (89.7 to 100.0)	98.1 (89.9 to 100.00)	

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.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	Artemether lumefantrine
Reporting group description:	
Artemether lumefantrine	
Reporting group title	Artesunate mefloquine
Reporting group description:	
Artesunate mefloquine	
Reporting group title	Atovaquone proguanil
Reporting group description:	
Atovaquone proguanil	

Serious adverse events	Artemether lumefantrine	Artesunate mefloquine	Atovaquone proguanil
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 159 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 159 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Artemether lumefantrine	Artesunate mefloquine	Atovaquone proguanil
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 159 (14.47%)	30 / 53 (56.60%)	17 / 53 (32.08%)
Nervous system disorders			

Dizziness			
subjects affected / exposed	9 / 159 (5.66%)	14 / 53 (26.42%)	5 / 53 (9.43%)
occurrences (all)	10	15	5
Headache			
subjects affected / exposed	5 / 159 (3.14%)	7 / 53 (13.21%)	7 / 53 (13.21%)
occurrences (all)	5	7	7
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 159 (3.77%)	2 / 53 (3.77%)	4 / 53 (7.55%)
occurrences (all)	6	2	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 159 (1.89%)	4 / 53 (7.55%)	2 / 53 (3.77%)
occurrences (all)	3	4	2
Diarrhoea			
subjects affected / exposed	3 / 159 (1.89%)	7 / 53 (13.21%)	2 / 53 (3.77%)
occurrences (all)	3	7	2
Vomiting			
subjects affected / exposed	2 / 159 (1.26%)	15 / 53 (28.30%)	9 / 53 (16.98%)
occurrences (all)	2	15	9
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 159 (0.00%)	4 / 53 (7.55%)	0 / 53 (0.00%)
occurrences (all)	0	4	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2008	The main purpose of this amendment was to clarify the use of primaquine as concomitant medication in this study. The Ministry of Health policy in Colombia stipulates that primaquine is administered to patients with uncomplicated P. falciparum malaria. Primaquine is primarily active against the sexual stages (gametocytes) of P. falciparum with only a weak effect on its asexual blood stages that cause the disease in humans. Despite the absence of documented interaction between Coartem and primaquine which would impact efficacy or the auditory brainstem pathway response, it was deemed necessary to define the conditions of its use in order to preclude any confounding effects that may affect the study outcome. As per the present amendment, it is now recommended to administer primaquine only at Day 7, once the study primary endpoint has been assessed. Audiometric testing specific exclusion criteria were ambiguously worded in the study synopsis and have been corrected. Pharmacokinetic sampling was reduced by one blood sample that was incorrectly included in the visit schedule.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported