



Clinical trial results:

A cluster randomized, single-centre, controlled, parallel, 12-month prospective study and additional 12-month follow-up in Africa of malaria incidence in a community setting following systematic treatment of *P. Falciparum* asymptomatic carriers with artemether-lumefantrine (Coartem® / Coartem® Dispersible)

Summary

EudraCT number	2015-004461-85
Trial protocol	Outside EU/EEA
Global end of trial date	26 July 2012

Results information

Result version number	v1 (current)
This version publication date	27 December 2016
First version publication date	27 December 2016

Trial information

Trial identification

Sponsor protocol code	CCOA566B2401/E1
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceuticals AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 July 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 July 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To evaluate at the community level whether treatment of AC of *P. falciparum* is associated with a lower number of symptomatic malaria episodes RDT confirmed (SMRCs) per person-year over a 12 month follow-up in the infant and children population (i.e. <5 years of age) in the intervention clusters (villages) compared with the control clusters.
 - To evaluate whether treatment of AC of *P. falciparum* is associated with an improvement in hemoglobin levels after 28 days by comparing the change in hemoglobin levels from Day 1- of CSC 1 to Day 28 of CSC 1 for microscopy confirmed AC > 6 months of age in the intervention versus the control arms.
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Protection of trial subjects:

Development of danger signs or symptoms of severe malaria in the presence of parasitemia on Days 1, 2 or 3 or a clinical requirement for parenteral treatment warranted discontinuation of investigational treatment and the implementation of rescue medication.

Rescue treatment involved therapy with an effective antimalarial available locally as per national treatment guidelines. Administration could be oral or parenteral depending on the subject's clinical condition. Rescue treatment was not considered study medication.

The MT is a mobile team of healthcare professionals from the central investigational site who will travel to each cluster as required to ensure that the same standard of care is provided in both study arms in order to decrease possible bias.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2010
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	Burkina Faso: 14075
Worldwide total number of subjects	14075
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)	198

Infants and toddlers (28 days-23 months)	1126
Children (2-11 years)	4427
Adolescents (12-17 years)	2062
Adults (18-64 years)	5528
From 65 to 84 years	669
85 years and over	65

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were identified in a series of four community screening campaigns (CSCs).

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

treatment is artemether-lumefantrine (tablets or dispersible tablets).

Arm type	Experimental
Investigational medicinal product name	artemether-lumefantrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet or dispersible tablet contains 20 mg artemether and 120 mg lumefantrine and the treatment is given twice a day for 3 consecutive days.

Arm title	Control
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Arm description:

no study treatment was given except for the treatment of Symptomatic malaria episode, RDT-confirmed (SMRCs)

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Intervention	Control
Started	6817	7258
Completed	5897	6510
Not completed	920	748
Adverse event, serious fatal	48	44
Consent withdrawn by subject	35	43
Lost to follow-up	837	661

Period 2

Period 2 title	Period 2 (follow-up)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Intervention
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Arm description:

treatment is artemether-lumefantrine (tablets or dispersible tablets).

Arm type	Experimental
Investigational medicinal product name	artemether-lumefantrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet or dispersible tablet contains 20 mg artemether and 120 mg lumefantrine and the treatment is given twice a day for 3 consecutive days.

Arm title	Control
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Arm description:

no study treatment was given except for the treatment of Symptomatic malaria episode, RDT-confirmed (SMRCs)

Arm type	No intervention
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No investigational medicinal product assigned in this arm

Number of subjects in period 2^[1]	Intervention	Control
Started	5854	6372
Completed	0	0
Not completed	5854	6372
Adverse event, serious fatal	6	8
Study terminated by sponsor	5777	6287
Lost to follow-up	71	77

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A subject who emigrated was discontinued from the study, however, if later on during the study this subject immigrates to the cluster he/she was treated as an immigrant and was counted twice, once as a resident subject and once as an immigrant during the study.

Baseline characteristics

Reporting groups

Reporting group title	Intervention
Reporting group description: treatment is artemether-lumefantrine (tablets or dispersible tablets).	
Reporting group title	Control
Reporting group description: no study treatment was given except for the treatment of Symptomatic malaria episode, RDT-confirmed (SMRCs)	

Reporting group values	Intervention	Control	Total
Number of subjects	6817	7258	14075
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	123	75	198
Infants and toddlers (28 days-23 months)	558	568	1126
Children (2-11 years)	2096	2331	4427
Adolescents (12-17 years)	1017	1045	2062
Adults (18-64 years)	2644	2884	5528
From 65-84 years	348	321	669
85 years and over	31	34	65
Age continuous Units: years			
arithmetic mean	23.41	23.42	
standard deviation	± 21.026	± 20.371	-
Gender categorical Units: Subjects			
Female	3656	3816	7472
Male	3161	3442	6603

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description: treatment is artemether-lumefantrine (tablets or dispersible tablets).	
Reporting group title	Control
Reporting group description: no study treatment was given except for the treatment of Symptomatic malaria episode, RDT-confirmed (SMRCs)	
Reporting group title	Intervention
Reporting group description: treatment is artemether-lumefantrine (tablets or dispersible tablets).	
Reporting group title	Control
Reporting group description: no study treatment was given except for the treatment of Symptomatic malaria episode, RDT-confirmed (SMRCs)	
Subject analysis set title	Intervention
Subject analysis set type	Sub-group analysis
Subject analysis set description: Cluster level data, Eligible clusters set	
Subject analysis set title	Control
Subject analysis set type	Sub-group analysis
Subject analysis set description: Cluster level data, Eligible clusters set	

Primary: Number of SMRC5000s per person-year in infants and children (<5 years) in post CSC follow-up at month 12

End point title	Number of SMRC5000s per person-year in infants and children (<5 years) in post CSC follow-up at month 12
End point description:	
End point type	Primary
End point timeframe: Month 12	

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Number of SMRC5000s				
arithmetic mean (standard deviation)	1.69 (± 0.436)	1.6 (± 0.526)		

Statistical analyses

Statistical analysis title	Number of SMRC5000s per person
Comparison groups	Intervention v Control

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3482
Method	t-test, 1-sided

Primary: Change in hemoglobin level (g/dL) in asymptomatic carriers >6 months of age from CSC1/Day 1 to CSC1/Day 28 by study arm (Asymptomatic carriers at CSC1 analysis set)

End point title	Change in hemoglobin level (g/dL) in asymptomatic carriers >6 months of age from CSC1/Day 1 to CSC1/Day 28 by study arm (Asymptomatic carriers at CSC1 analysis set)
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End point description:

End point type	Primary
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End point timeframe:

Day 1 to Day 28

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9 ^[1]		
Units: g/dL				
arithmetic mean (standard deviation)				
CSC1/Day 1	11.81 (± 0.329)	12.06 (± 0.345)		
CSC1/Day 28	12.33 (± 0.318)	11.86 (± 0.373)		
Change	0.53 (± 0.256)	-0.21 (± 0.266)		

Notes:

[1] - Applicable for about 40% randomly selected subjects of the control clusters.

Statistical analyses

Statistical analysis title	Change in hemoglobin level in asymptomatic carrier
Comparison groups	Intervention v Control
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	t-test, 1-sided

Secondary: Microscopy confirmed gametocyte carriers CSC4 by study arm (Eligible clusters set)

End point title	Microscopy confirmed gametocyte carriers CSC4 by study arm
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End point description:

End point type Secondary

End point timeframe:

Day 1

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9 ^[2]		
Units: prevalence of GCs				
least squares mean (confidence interval 90%)	4.9 (4.16 to 5.58)	5.1 (4.37 to 5.79)		

Notes:

[2] - Measured in about 40% randomly selected subjects of the control clusters.

Statistical analyses

No statistical analyses for this end point

Secondary: Microscopy confirmed asymptomatic carriers of *P. falciparum* at CSC4 by study arm (Eligible clusters set)

End point title Microscopy confirmed asymptomatic carriers of *P. falciparum* at CSC4 by study arm (Eligible clusters set)

End point description:

End point type Secondary

End point timeframe:

Day 1

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9 ^[3]		
Units: prevalence of ACs				
least squares mean (confidence interval 90%)	34.6 (31.36 to 37.9)	37.6 (34.29 to 40.82)		

Notes:

[3] - Measured in about 40% randomly selected subjects of the control clusters.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hemoglobin level (g/dL) from CSC1/Day 1 to CSC4/Day 1 in infants and children (>6 months and <5 years) by study arm (Eligible clusters set Overall-C)

End point title	Change in hemoglobin level (g/dL) from CSC1/Day 1 to CSC4/Day 1 in infants and children (>6 months and <5 years) by study arm (Eligible clusters set Overall-C)
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9 ^[4]		
Units: g/dL				
arithmetic mean (standard deviation)				
CSC1/Day 1 - Overall-C	10.24 (± 0.371)	10.04 (± 0.476)		
CSC4/Day 1 - Overall-C	10.99 (± 0.267)	11.13 (± 0.36)		
Change - Overall-C	0.76 (± 0.389)	1.08 (± 0.487)		

Notes:

[4] - Applicable for about 40% randomly selected subjects of the control clusters.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hemoglobin level (g/dL) from CSC1/Day 1 to CSC4/Day 1 in infants and children (>6 months and <5 years) by study arm (Eligible clusters set Overall-I)

End point title	Change in hemoglobin level (g/dL) from CSC1/Day 1 to CSC4/Day 1 in infants and children (>6 months and <5 years) by study arm (Eligible clusters set Overall-I)
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6817 ^[5]	7258 ^[6]		
Units: g/dL				
arithmetic mean (standard deviation)				
CSC1/Day 1	10.2 (± 1.777)	10.09 (± 1.762)		
CSC4/Day 1	10.98 (± 1.55)	11.17 (± 1.586)		
Change	0.74 (± 1.791)	1.03 (± 1.794)		

Notes:

[5] - n = 819, 827, 745

[6] - n = 348, 321, 308 Applicable for about 40% randomly selected subjects of the control clusters.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of SMRC5000s per person-year in post CSC follow-up by study arm (Eligible clusters set)

End point title	Number of SMRC5000s per person-year in post CSC follow-up by study arm (Eligible clusters set)
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End point description:

End point type	Secondary
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End point timeframe:

365.25 days

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6817	7258		
Units: days				
number (not applicable)				
Number of SMRC5000	2217	2091		
Person-year observed	4945.7	5405.2		
Number of SMRC5000 per person-year	0.45	0.39		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with SAEs including death, severe malaria, hospitalizations post CSC follow-up period (Eligible clusters set)

End point title	Number of participants with SAEs including death, severe malaria, hospitalizations post CSC follow-up period (Eligible clusters set)
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End point description:

End point type	Secondary
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End point timeframe:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV)

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Number of participants				
arithmetic mean (standard deviation)				
Death	0.4 (± 0.19)	0.4 (± 0.19)		
Severe malaria	0.1 (± 0.11)	0.1 (± 0.19)		
Hospitalizations	1.1 (± 0.46)	0.9 (± 0.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with SAEs including death, severe malaria, hospitalizations post CSC follow-up period (Eligible clusters set)

End point title	Number of participants with SAEs including death, severe malaria, hospitalizations post CSC follow-up period (Eligible clusters set)
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End point description:

End point type	Secondary
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End point timeframe:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV)

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6817	7258		
Units: Percentage of participants				
number (not applicable)				
Death	0.5	0.4		
Severe malaria	0.1	0.1		
Hospitalizations	1	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects in post CSC follow-up period with SAEs including death, severe malaria and hospitalizations in infants and children (> 6 months and < 5 years) Eligible clusters set

End point title	Number of subjects in post CSC follow-up period with SAEs including death, severe malaria and hospitalizations in infants and children (> 6 months and < 5 years) Eligible clusters set
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End point description:

End point type	Secondary
End point timeframe:	
Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV)	

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Number of participants				
arithmetic mean (standard deviation)				
Death	0.2 (± 0.39)	0.2 (± 0.44)		
Severe malaria	0.4 (± 0.52)	0.5 (± 0.71)		
Hospitalizations	2.2 (± 1.59)	2.1 (± 1.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects in post CSC follow-up period with SAEs including death, severe malaria and hospitalizations in infants and children (> 6 months and < 5 years) Eligible clusters set

End point title	Number of subjects in post CSC follow-up period with SAEs including death, severe malaria and hospitalizations in infants and children (> 6 months and < 5 years) Eligible clusters set
End point description:	

End point type	Secondary
End point timeframe:	
Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV)	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1023	1040		
Units: Percentage of participants				
number (not applicable)				
Death	0.2	0.2		
Severe malaria	0.04	0.5		
Hospitalizations	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean of microscopy-confirmed asymptomatic carriers at day 1 of CSC1, CSC2, CSC3 and CSC4(Eligible clusters set

End point title	Mean of microscopy-confirmed asymptomatic carriers at day 1 of CSC1, CSC2, CSC3 and CSC4(Eligible clusters set
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6817 ^[7]	7258 ^[8]		
Units: percentages of cluster frequencies				
number (not applicable)				
CSC1/Day 1	43.6	46.6		
CSC2/Day 1	4.2	35.4		
CSC3/Day 1	2.8	30.6		
CSC4/Day 1	34.8	36.2		

Notes:

[7] - n = 5575, 5680, 6114, 5820

[8] - n=2472, 2355, 2424, 2449 Applicable for about 40% randomly selected subjects of the control clusters

Statistical analyses

No statistical analyses for this end point

Secondary: Prevalence of microscopy-confirmed gametocyte carriers over time by study arm (Eligible clusters set)

End point title	Prevalence of microscopy-confirmed gametocyte carriers over time by study arm (Eligible clusters set)
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9 ^[9]		
Units: cluster frequencies				
arithmetic mean (standard deviation)				
CSC1/Day 1	9.5 (± 2.95)	10.2 (± 4.54)		
CSC2/Day 1	0.6 (± 0.38)	5.5 (± 2.54)		
CSC3/Day 1	0.4 (± 0.4)	5.8 (± 1.77)		

CSC4/Day 1	4.8 (\pm 1.34)	5.1 (\pm 1.38)		
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Notes:

[9] - Applicable for about 40% randomly selected subjects of the control clusters.

Statistical analyses

No statistical analyses for this end point

Secondary: Prevalence of microscopy-confirmed gametocyte carriers over time by study arm (Eligible clusters set)

End point title	Prevalence of microscopy-confirmed gametocyte carriers over time by study arm (Eligible clusters set)
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End point description:

End point type	Secondary
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End point timeframe:

Day 1

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6817 ^[10]	7258 ^[11]		
Units: percent				
number (not applicable)				
CSC1/Day1	9.7	10		
CSC2/Day1	0.6	5.5		
CSC3/Day1	0.4	5.9		
CSC4/Day1	4.8	5		

Notes:

[10] - n = 5575, 5680, 6114, 5820

[11] - n=2472, 2355, 2424, 2249 Applicable for about 40% randomly selected subjects of the control clusters

Statistical analyses

No statistical analyses for this end point

Secondary: Prevalence of microscopy- and qRT-PCR-confirmed gametocyte carriers at CSC4/Day 1 by study arm (Eligible clusters set)

End point title	Prevalence of microscopy- and qRT-PCR-confirmed gametocyte carriers at CSC4/Day 1 by study arm (Eligible clusters set)
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End point description:

End point type	Secondary
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End point timeframe:

Day 1

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1023	976 ^[12]		
Units: percent				
number (not applicable)				
Negative - Microscopy	92.8	93.8		
Negative - qRT-PCR	50.2	52.4		
Positive - Microscopy	6	5.4		
Positive - qRT-PCR	49.7	47.3		
Not evaluable - Microscopy	1.3	0.8		
Not evaluable - qRT-PCR	0.1	0.3		

Notes:

[12] - Applicable for about 40% randomly selected subjects of the control clusters.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall summary and change in hemoglobin level from CSC1/Day 1 to CSC1/Day 28 in infants and children (>6 months and <5 years) by study arm (Asymptomatic carriers at CSC1 analysis set)

End point title	Overall summary and change in hemoglobin level from CSC1/Day 1 to CSC1/Day 28 in infants and children (>6 months and <5 years) by study arm (Asymptomatic carriers at CSC1 analysis set)
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 to Day 28

End point values	Intervention	Control	Intervention	Control
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6817 ^[13]	7258 ^[14]	9	9
Units: (g/dL				
arithmetic mean (standard deviation)				
CSC1/Day 1	9.83 (± 0.411)	9.68 (± 0.409)	9.78 (± 1.763)	9.67 (± 1.707)
CSC1/Day 28	11.03 (± 0.321)	10.16 (± 0.394)	10.95 (± 1.543)	10.17 (± 1.748)
Change	1.19 (± 0.282)	0.48 (± 0.356)	1.19 (± 1.52)	0.51 (± 1.308)

Notes:

[13] - n = 432, 406, 404

[14] - n = 179, 174, 173

Statistical analyses

No statistical analyses for this end point

Secondary: Anemia status based on CSC1/Day 1 and CSC4/Day 1 in infants and children (>6 months and <5 years) by study arm (Eligible clusters set)

End point title	Anemia status based on CSC1/Day 1 and CSC4/Day 1 in infants and children (>6 months and <5 years) by study arm (Eligible clusters set)
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End point description:

End point type	Secondary
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End point timeframe:

Day 1

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: percentage of participants				
number (not applicable)				
CSC1/Day 1 - Severe	0.4	0.1		
CSC1/Day 1 - Moderate	9.8	3.5		
CSC1/Day 1 - Mild	55.9	42.2		
CSC1/Day 1 - No	33.9	54.2		
CSC1/Day 1 - Total	100	100		
CSC4/Day 1 - Severe	0.3	0.3		
CSC4/Day 1 - Moderate	10.3	2.8		
CSC4/Day 1 - Mild	56	36.4		
CSC4/Day 1 - No	33.3	60.4		
CSC4/Day 1 - Total	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin level in CSC1/Day1 and CSC4/Day1 by study arm and age group (Eligible clusters set)

End point title	Hemoglobin level in CSC1/Day1 and CSC4/Day1 by study arm and age group (Eligible clusters set)
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End point description:

End point type	Secondary
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End point timeframe:

Day 1

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9 ^[15]		
Units: g/dL				
arithmetic mean (standard deviation)				
5 - 9 years CSC1/Day1	11.63 (± 0.223)	11.59 (± 0.239)		
5 - 9 years CSC4/Day1	11.97 (± 0.224)	12.13 (± 0.324)		
10 - 14 years CSC1/Day1	12.32 (± 0.227)	12.71 (± 0.301)		
10 - 14 years CSC4/Day1	12.58 (± 0.161)	12.72 (± 0.487)		
>= 15 years CSC1/Day1	13.13 (± 0.304)	13.49 (± 0.355)		
>= 15 years CSC4/Day1	13.25 (± 0.167)	13.42 (± 0.266)		

Notes:

[15] - Applicable for about 40% randomly selected subjects of the control clusters.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of COA566-treated microscopy-confirmed asymptomatic carriers (AC) at any CSCs (1, 2 and 3) with parasitological cure rate at day 7

End point title	Percentage of COA566-treated microscopy-confirmed asymptomatic carriers (AC) at any CSCs (1, 2 and 3) with parasitological cure rate at day 7 ^[16]
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End point description:

For AC any occasion: Subjects are counted multiple times if diagnosed and treated for AC more than once during the study.

End point type	Secondary
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End point timeframe:

Day 7

Notes:

[16] - 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 end point is reporting statistics for all the arms analysed in the baseline period.

End point values	Intervention			
Subject group type	Reporting group			
Number of subjects analysed	6817 ^[17]			
Units: Percentage of participants				
number (not applicable)				
CSC1 - Any	99.5			
CSC1 - Tablet	99.6			
CSC1 - Dispersible Tablet	99.5			
CSC2 - Any	100			
CSC2 - Tablet	100			
CSC2 - Dispersible Tablet	100			
CSC3 - Any	96.7			
CSC3 - Tablet	96.4			

CSC3 - Dispersible Tablet	97			
AC any occasion - Any	99.4			
AC any occasion - Tablet	99.5			
AC any occasion - Dispersible Tablet	99.4			

Notes:

[17] - CSC1 n=2161 CSC2 n=182 CSC3 n=121 AC any occasion n=2464

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of microscopy-confirmed gametocyte carriers treated with COA566 for asymptomatic carriers (Safety analyzable asymptomatic carriers set)

End point title	Percentage of microscopy-confirmed gametocyte carriers treated with COA566 for asymptomatic carriers (Safety analyzable asymptomatic carriers set) ^[18]
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End point description:

End point type	Secondary
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End point timeframe:

Day 1, Day 7 and Day 28 (Applicable to subjects with a positive RDT at Day 1 of the corresponding CSC)

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: The end point is reporting statistics for all the arms analysed in the baseline period.

End point values	Intervention			
Subject group type	Reporting group			
Number of subjects analysed	6817 ^[19]			
Units: Percentage of carriers				
number (not applicable)				
CSC1 Day1: Any	15.7			
CSC1 Day1: Tablet	11.5			
CSC1 Day1: Dispersible Tablet	20.9			
CSC1 Day7: Any	1.4			
CSC1 Day7: Tablet	0.5			
CSC1 Day7: Dispersible Tablet	2.6			
CSC1 Day28: Any	0.1			
CSC1 Day28: Tablet	0.1			
CSC1 Day28: Dispersible Tablet	0.2			
CSC2 Day1: Any	2.6			
CSC2 Day1: Tablet	2.3			
CSC2 Day1: Dispersible Tablet	2.9			
CSC2 Day7: Any	0.1			
CSC2 Day7: Tablet	0			
CSC2 Day7: Dispersible Tablet	0.2			
CSC3 Day1: Any	4.7			
CSC3 Day1: Tablet	2.1			
CSC3 Day1: Dispersible Tablet	9.2			
CSC3 Day7: Any	0			
CSC3 Day7: Tablet	0			

CSC3 Day7: Dispersible Tablet	0			
Immigrants after CSC3 Day1: Any	4			
Immigrants after CSC3 Day1: Tablet	2.1			
Immigrants after CSC3 Day1: Dispersible Tablet	7.1			
Immigrants after CSC3 Day7: Any	0			
Immigrants after CSC3 Day7: Tablet	0			
Immigrants after CSC3 Day7: Dispersible Tablet	0			

Notes:

[19] - CSC1 = 3045; CSC2 = 850; CSC3 = 363; Immigrants after CSC3 = 75

Statistical analyses

No statistical analyses for this end point

Secondary: Number of asymptomatic carriers with increase in hemoglobin levels by at least 0.5 g/dL from Day 1 to Day 28 of CSC1 in infants and children (>6 months and <5 years) by study arm (Asymptomatic carriers at CSC1 analysis set)

End point title	Number of asymptomatic carriers with increase in hemoglobin levels by at least 0.5 g/dL from Day 1 to Day 28 of CSC1 in infants and children (>6 months and <5 years) by study arm (Asymptomatic carriers at CSC1 analysis set)
End point description:	
End point type	Secondary
End point timeframe:	
Day 1 to Day 28	

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9 ^[20]		
Units: Percentages of cluster frequencies				
arithmetic mean (standard deviation)	66.1 (± 9.17)	43.2 (± 12.45)		

Notes:

[20] - Applicable for about 40% randomly selected subjects of the control clusters.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of asymptomatic carriers with increase in hemoglobin levels by at least 0.5 g/dL from Day 1 to Day 28 of CSC1 in infants and children (>6 months and <5 years) by study arm (Asymptomatic carriers at CSC1 analysis set)

End point title	Percentage of asymptomatic carriers with increase in hemoglobin levels by at least 0.5 g/dL from Day 1 to Day 28 of CSC1 in infants and children (>6 months and <5 years) by study arm (Asymptomatic carriers at CSC1 analysis set)
End point description:	

End point type	Secondary
End point timeframe:	
Day 1 to Day 28	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	434	180 ^[21]		
Units: percent				
number (not applicable)	66.4	43.9		

Notes:

[21] - Applicable for about 40% randomly selected subjects of the control clusters.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of SMRC5000 in asymptomatic carriers at any time of diagnosis

End point title	Number of SMRC5000 in asymptomatic carriers at any time of diagnosis
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End point description:

End point type	Secondary
End point timeframe:	
Day 1 to Day 28	

End point values	Intervention	Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: Percentages of cluster frequencies				
arithmetic mean (standard deviation)				
1 SMRC5000	15.25 (± 3.531)	9.49 (± 3.123)		
2 SMRC5000	3.56 (± 1.258)	2.78 (± 1.759)		
3 SMRC5000	1.28 (± 0.693)	97 (± 0.934)		
>3 SMRC5000	0.67 (± 0.664)	0.31 (± 0.417)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of SMRC5000 in asymptomatic carriers at any time of diagnosis

End point title	Number of SMRC5000 in asymptomatic carriers at any time of diagnosis
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 to Day 28

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2740	1381		
Units: percent				
number (not applicable)				
1 SMRC5000	15.1	9.8		
2 SMRC5000	3.5	2.8		
3 SMRC5000	1.2	0.9		
>3 SMRC5000	0.6	0.4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Intervention core
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Reporting group description:

Intervention core

Reporting group title	Control core
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Reporting group description:

Control core

Reporting group title	Intervention Follow-up
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Reporting group description:

Intervention Follow-up

Reporting group title	Control Follow-up
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Reporting group description:

Control Follow-up

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: AEs were collected within 7 days of initiation of treatment in subjects treated with artemether-lumefantrine for all SMRC episodes. All of them SAEs and included 14 deaths) were reported during the study.

Serious adverse events	Intervention core	Control core	Intervention Follow-up
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 4826 (1.91%)	67 / 2275 (2.95%)	7 / 467 (1.50%)
number of deaths (all causes)	6	2	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	0 / 467 (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
ABORTION THREATENED			

subjects affected / exposed	1 / 4826 (0.02%)	1 / 2275 (0.04%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMPLICATION OF DELIVERY			
subjects affected / exposed	2 / 4826 (0.04%)	1 / 2275 (0.04%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FOETAL DISTRESS SYNDROME			
subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	0 / 467 (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
STILLBIRTH			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE CERVICAL LACERATION DURING LABOUR			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DEATH			
subjects affected / exposed	4 / 4826 (0.08%)	2 / 2275 (0.09%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
PYREXIA			
subjects affected / exposed	4 / 4826 (0.08%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
TESTICULAR TORSION			

subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ASTHMATIC CRISIS			
subjects affected / exposed	1 / 4826 (0.02%)	1 / 2275 (0.04%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
CHEMICAL POISONING			
subjects affected / exposed	0 / 4826 (0.00%)	2 / 2275 (0.09%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER LIMB FRACTURE			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC FRACTURE			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
SNAKE BITE			
subjects affected / exposed	2 / 4826 (0.04%)	0 / 2275 (0.00%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	0 / 467 (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
WOUND			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Congenital, familial and genetic disorders SICKLE CELL ANAEMIA	subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	0 / 467 (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
Cardiac disorders CARDIAC FAILURE	subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	0 / 467 (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
Nervous system disorders DIZZINESS	subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE	subjects affected / exposed	2 / 4826 (0.04%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
	occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SOMNOLENCE	subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	0 / 467 (0.00%)
	occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders EYELID OEDEMA	subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	0 / 467 (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
Gastrointestinal disorders ABDOMINAL PAIN	subjects affected / exposed	2 / 4826 (0.04%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
	occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA				

subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FOOD POISONING			
subjects affected / exposed	2 / 4826 (0.04%)	1 / 2275 (0.04%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INGUINAL HERNIA STRANGULATED			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIP OEDEMA			
subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	0 / 467 (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
NAUSEA			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PEPTIC ULCER			
subjects affected / exposed	0 / 4826 (0.00%)	0 / 2275 (0.00%)	0 / 467 (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
VOMITING			
subjects affected / exposed	14 / 4826 (0.29%)	16 / 2275 (0.70%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	3 / 14	9 / 17	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
NEPHROTIC SYNDROME			

subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	0 / 467 (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
RENAL COLIC			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			
subjects affected / exposed	1 / 4826 (0.02%)	1 / 2275 (0.04%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACTERIAL INFECTION			
subjects affected / exposed	2 / 4826 (0.04%)	1 / 2275 (0.04%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	3 / 4826 (0.06%)	1 / 2275 (0.04%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	6 / 4826 (0.12%)	4 / 2275 (0.18%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
HEPATIC AMOEBIASIS			
subjects affected / exposed	0 / 4826 (0.00%)	0 / 2275 (0.00%)	0 / 467 (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
INFECTION			

subjects affected / exposed	0 / 4826 (0.00%)	0 / 2275 (0.00%)	0 / 467 (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
MALARIA			
subjects affected / exposed	34 / 4826 (0.70%)	27 / 2275 (1.19%)	5 / 467 (1.07%)
occurrences causally related to treatment / all	0 / 35	0 / 27	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS			
subjects affected / exposed	0 / 4826 (0.00%)	2 / 2275 (0.09%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORCHITIS			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARASITIC GASTROENTERITIS			
subjects affected / exposed	1 / 4826 (0.02%)	1 / 2275 (0.04%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	14 / 4826 (0.29%)	12 / 2275 (0.53%)	1 / 467 (0.21%)
occurrences causally related to treatment / all	0 / 14	0 / 12	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 4826 (0.04%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 4826 (0.00%)	1 / 2275 (0.04%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
TYPHOID FEVER			

subjects affected / exposed	2 / 4826 (0.04%)	4 / 2275 (0.18%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
MALNUTRITION			
subjects affected / exposed	1 / 4826 (0.02%)	0 / 2275 (0.00%)	0 / 467 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Control	Follow-up		
Total subjects affected by serious adverse events				
subjects affected / exposed	10 / 386 (2.59%)			
number of deaths (all causes)	0			
number of deaths resulting from adverse events	0			
Pregnancy, puerperium and perinatal conditions				
ABORTION SPONTANEOUS				
subjects affected / exposed	0 / 386 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ABORTION THREATENED				
subjects affected / exposed	0 / 386 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COMPLICATION OF DELIVERY				
subjects affected / exposed	1 / 386 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FOETAL DISTRESS SYNDROME				
subjects affected / exposed	0 / 386 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
STILLBIRTH				

subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
UTERINE CERVICAL LACERATION DURING LABOUR			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
DEATH			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PYREXIA			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
TESTICULAR TORSION			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
ASTHMATIC CRISIS			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
CHEMICAL POISONING			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LOWER LIMB FRACTURE			

subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PELVIC FRACTURE			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SNAKE BITE			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
WOUND			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
SICKLE CELL ANAEMIA			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
CARDIAC FAILURE			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

HEADACHE			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SOMNOLENCE			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
EYELID OEDEMA			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DIARRHOEA			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
FOOD POISONING			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INGUINAL HERNIA STRANGULATED			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

LIP OEDEMA			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
NAUSEA			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PEPTIC ULCER			
subjects affected / exposed	1 / 386 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VOMITING			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
NEPHROTIC SYNDROME			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RENAL COLIC			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RENAL FAILURE			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

BACTERIAL INFECTION				
subjects affected / exposed	0 / 386 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
BRONCHITIS				
subjects affected / exposed	1 / 386 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTROENTERITIS				
subjects affected / exposed	0 / 386 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
HEPATIC AMOEBIASIS				
subjects affected / exposed	1 / 386 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INFECTION				
subjects affected / exposed	1 / 386 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MALARIA				
subjects affected / exposed	5 / 386 (1.30%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
MENINGITIS				
subjects affected / exposed	0 / 386 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ORCHITIS				
subjects affected / exposed	0 / 386 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PARASITIC GASTROENTERITIS				

subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	2 / 386 (0.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SEPSIS			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
TYPHOID FEVER			
subjects affected / exposed	0 / 386 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
MALNUTRITION			
subjects affected / exposed	0 / 386 (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	Intervention core	Control core	Intervention Follow-up
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 4826 (0.00%)	0 / 2275 (0.00%)	0 / 467 (0.00%)

Non-serious adverse events	Control Follow-up		
Total subjects affected by non-serious			

adverse events			
subjects affected / exposed	0 / 386 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2010	<ul style="list-style-type: none">• To update the human sample collection description based on new information in the respective analysis technique validation process.• To clarify that, for the primary analyses and the analysis of similar secondary objectives assessed at community level, only the time period after completion of the series of community screenings 1 to 3 is considered. This period should cover the full transmission season. Even though only a negligible number of SMRCs is expected to occur during the dry season between CSC1 and CSC3, it is felt worthwhile to clarify that this period of time is excluded from the primary analysis variable and related analysis variables to prevent any potential bias introduced into this open-label trial.• To include in the protocol the information that a ± 1 day window will be accepted for the study to account for public holidays at the local healthcare facilities or subject's absence due to private/business reasons. This was previously not mentioned in the original protocol. Also, to clarify that the visits should be scheduled in full 24h periods days after Visit day 1. For example: visit Day 7 should occur 7 full days after visit Day 1, i.e. often on the 8th day. This was not mentioned before in the original protocol by error.• To clarify that an emigrant who returns permanently to a study cluster (after being away for > 3 months) will be treated as an immigrant (following the protocol guidance for immigrants). Therefore, a new ICF will be obtained if the subject would like to enter the study again. As subjects will keep the same DSS (demographic surveillance system) identifier, the CRF will be able to capture that the same subject has re-entered the study, despite being assigned a distinct subject number.• Correction of the study code in Appendix 1 Section: PK sample handling, labeling and shipment instructions as per ethics committee request.
18 October 2011	<ul style="list-style-type: none">• Refining of the definition of symptomatic malaria used for the primary analysis to include a parasite density cut-off of 5000/μL (microscopy-measured) to help elicit true malaria episodes. Malarial episode now defined by RDT-confirmed plus signs and symptoms [fever, either measured ($\geq 37.5^{\circ}\text{C}$) or by history], and a parasite density >5000/μL• Describing more accurately the total body weight categories (Coartem/Coartem dispersible treatment dosing recommendation).• Clarifying a discrepancy between protocol and ICF regarding the process for random selection of the qRT-PCR sub-group.• Adding a term, SMRC5000 in Glossary of Terms: In addition to "Symptomatic malaria episodes, RDT confirmed (SMRC)", SMRC5000 will describe the primary analysis viz "Malaria episode defined by signs and symptoms [fever, either measured ($\geq 37.5^{\circ}\text{C}$) or by history], RDT-confirmed and associated with a parasite density >5000/μL
16 January 2012	<ul style="list-style-type: none">• Extending the follow-up of the population of the current study by 1 year• Treating and following up all symptomatic malaria episodes in the current population over the additional 1 year period• Implementing an additional screening campaign (CSC 5) after the 1-year extension, to assess the prevalence of asymptomatic carriers

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 May 2012	The 1-year extension was stopped as the outcome of the original study was unfavorable. The investigator was informed of additional procedures to be followed and he was to inform IECs of the early termination of the trial.	-

Notes:

Limitations and caveats

None reported