Clinical trial results:
A randomized, investigator-blinded, multicenter, parallel group study to compare efficacy, safety and tolerability of Coartem® dispersible tablet formulation vs. Coartem® 6-dose crushed tablet in the treatment of acute uncomplicated Plasmodium falciparum malaria in infants and children

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2012-001333-14
Trial protocol	Outside EU/EEA
Global end of trial date	02 March 2007
Results information	
Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification	
Sponsor protocol code	CCOA566B2303
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00386763
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)	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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 March 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 March 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of the Coartem pediatric formulation in infants and children with a body weight of ≥5 kg and <35 kg suffering from P. falciparum malaria by testing the hypothesis that Coartem 6-dose regimen pediatric formulation is non-inferior to the presently used Coartem 6-dose regimen of crushed conventional tablet formulation on the 28-day Polymerase Chain Reaction (PCR)-corrected parasitological cure rate.

Protection of trial subjects:

Rescue treatment involved therapy with an effective antimalarial available locally. Administration may have been orally or parenterally depending on the child's clinical condition. In line with the treatment policy for that area, the best possible treatment option was provided, e.g. an effective 1st or 2nd-line antimalarial available in the country.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 August 2006
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	Mali: 225
Country: Number of subjects enrolled	Kenya: 193
Country: Number of subjects enrolled	Tanzania, United Republic of: 269
Country: Number of subjects enrolled	Mozambique: 102
Country: Number of subjects enrolled	Benin: 110
Worldwide total number of subjects	899
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)	1
Infants and toddlers (28 days-23 months)	219
Children (2-11 years)	669
Adolescents (12-17 years)	10
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:

Patients taking daily cotrimoxazole and those who received any anti-malarial drug known to influence cardiac
function within 4 weeks prior to the screening visit and those taking drugs that are known to influence cardiac function and to prolong the QTc interval were excluded.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	Dispersible tablet

Arm description:

Coartem® was provided as dispersible tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) and supplied in 3 blisters of 8 tablets.

Arm type	Experimental
Investigational medicinal product name	Coartem®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Eighteen dispersible tablets were for regular treatment according to body weight and six replacement dispersible tablets in case of vomiting. Tablets given should have been followed whenever possible by food/drink.

Arm title	Crushed tablet

Arm description:

Coartem® was provided as standard tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) and supplied in 3 blisters of 8 tablets.

Arm type	Reference therapy
Investigational medicinal product name	Coartem®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Eighteen tablets were for regular treatment according to body weight and six replacement tablets in case of vomiting. Tablets given should have been followed whenever possible by food/drink. Tablets were to be crushed and dissolved before being taken.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: For a double-blind trial, a double-dummy technique would need to be applied, whereby each patient would receive active drug plus placebo at each dosing point. This would require the patients to take an unnecessary large number of tablets. In addition, placebo tablets have not been developed for Coartem® dispersible or crushed tablets. Therefore in this study, in order to keep the safety

assessment as objective as possible, the investigator remained blinded.

Number of subjects in period 1	Dispersible tablet	Crushed tablet
Started	447	452
Treated (at least one full dose)	444	446
Completed treatment period	431	435
Completed	394	388
Not completed	53	64
Adverse event, serious fatal	2	1
Consent withdrawn by subject	6	11
Adverse event, non-fatal	30	40
Lost to follow-up	15	12

Baseline characteristics

Reporting groups	
Reporting group title	Dispersible tablet
Reporting group description:	
Coartem® was provided as dispersible tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) and supplied in 3 blisters of 8 tablets.	
Reporting group title	Crushed tablet
Reporting group description:	
Coartem® was provided as standard tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) and supplied in 3 blisters of 8 tablets.	

Reporting group values	Dispersible tablet	Crushed tablet	Total
Number of subjects	447	452	899
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	1	0	1
Infants and toddlers (28 days-23 months)	110	109	219
Children (2-11 years)	331	338	669
Adolescents (12-17 years)	5	5	10
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	3.6	3.7	
standard deviation	± 2.69	± 2.84	-
Gender categorical Units: Subjects			
Female	215	205	420
Male	232	247	479

End points

End points reporting groups

Reporting group title	Dispersible tablet
Reporting group description:	
Coartem® was provided as dispersible tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) and supplied in 3 blisters of 8 tablets.	
Reporting group title	Crushed tablet
Reporting group description:	
Coartem® was provided as standard tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) and supplied in 3 blisters of 8 tablets.	

Primary: Polymerase chain reaction (PCR)-corrected 28-day cure rate, by treatment

End point title	Polymerase chain reaction (PCR)-corrected 28-day cure rate, by treatment
End point description:	
The proportion of patients who were clinically free of parasitemia at 28 days as measured by a 28-day PCR-corrected parasitological cure rate. PCR was used to determine whether reappearance of parasites was due to recrudescence or new infection. Populkations evaluated were: Primary Analysis (PA) – all ITT patients that completed 28 days with a valid PCR evaluation (if parasitemia present at Day 28) OR all ITT patients that would be classified as treatment failures prior to Day 28. Per Protocol (PP) – all PA patients that took at least 80% of scheduled study drug; had parasite counts between 2000 and 200,000 /µL at baseline and had a body weight of ≥5 kg and <35 kg Intent-to-treat (ITT) – all randomized patients with acute, uncomplicated P. falciparum malaria at baseline, had at least one relevant post-baseline efficacy assessment, and who had at least one dose of study drug.	
End point type	Primary
End point timeframe:	
Day 28	

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	447[1]	452[2]		
Units: percent				
number (confidence interval 95%)				
PA (primary) population	97.8 (96.3 to 99.2)	98.5 (97.4 to 99.7)		
PP population	98.2 (96.9 to 99.5)	98.5 (97.3 to 99.7)		
ITT population	95 (92.9 to 97.1)	96.2 (94.4 to 98)		

Notes:

[1] - n = 403, 398, 418

[2] - n = 409, 406, 423

Statistical analyses

Statistical analysis title	PA - Dispersible minus crushed tablet group
Comparison groups	Crushed tablet v Dispersible tablet
Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [3]
Method	Hauck-Anderson correction
Parameter estimate	Treatment group difference, (%)
Point estimate	-0.8
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-2.7

Notes:

[3] - For testing the null hypothesis of inferiority of proportions versus the alternative hypothesis of non-inferiority of proportions.

Statistical analysis title	PP - Dispersible minus crushed tablet group
Comparison groups	Dispersible tablet v Crushed tablet
Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [4]
Method	Hauck-Anderson correction
Parameter estimate	Treatment group difference, (%)
Point estimate	-1.2
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-2.2

Notes:

[4] - For testing the null hypothesis of inferiority of proportions versus the alternative hypothesis of non-inferiority of proportions.

Statistical analysis title	ITT - Dispersible minus crushed tablet group
Comparison groups	Dispersible tablet v Crushed tablet
Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0039 [5]
Method	Hauck-Anderson correction
Parameter estimate	Treatment group difference, (%)
Point estimate	-1.2
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-4

Notes:

[5] - For testing the null hypothesis of inferiority of proportions versus the alternative hypothesis of noninferiority
of proportions.

Primary: PCR-corrected 28-day cure rate, by treatment and body weight group

End point title	PCR-corrected 28-day cure rate, by treatment and body weight group[6]

End point description:

PCR = polymerase chain reaction, used to determine whether reappearance of parasites was due to recrudescence or new infection.

End point type	Primary

End point timeframe:

Day 28

Notes:

[6] - 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 analyses have been reported for this primary end point.

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	447[7]	452[8]		
Units: percent cured				
number (confidence interval 95%)				
5 ≤ 15 kg	97.5 (95.4 to 99.5)	99.2 (98 to 100)		
15 ≤ 25 kg	98.6 (96.6 to 100)	97.1 (94.3 to 99.9)		
25 ≤ 35 kg	96.4 (89.6 to 100)	100 (100 to 100)		

Notes:

[7] - PA population; n = 236, 139, 28

[8] - n = 241, 138, 30

Statistical analyses

No statistical analyses for this end point

Secondary: PCR-corrected 14- and 42-day cure rates

End point title	PCR-corrected 14- and 42-day cure rates

End point description:

End point type	Secondary

End point timeframe:

Day 14 and day 42

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	447[9]	452[10]		
Units: percent cured				
number (confidence interval 95%)				
ITT 14 days	97.2 (95.6 to 98.8)	97.9 (96.6 to 99.3)		
ITT 42 days	91 (88.1 to 93.9)	93.3 (90.7 to 95.8)		

PA 14 days	99.5 (98.8 to 100)	99.8 (99.3 to 100)		
PA 42 days	96 (94 to 98.1)	96.9 (95.1 to 98.7)		
PP 14 days	100 (100 to 100)	99.8 (99.3 to 100)		
PP 42 days	96.6 (94.6 to 98.5)	96.9 (95.1 to 98.7)		

Notes:

[9] - PA, ITT and PP population: n = 429, 377, 403, 354, 398, 349

[10] - n = 433, 372, 409, 355, 406, 352

Statistical analyses

No statistical analyses for this end point

Secondary: Time to parasite clearance and time to fever clearance in hours

End point title	Time to parasite clearance and time to fever clearance in hours

End point description:

End point type	Secondary

End point timeframe:

Up to 48 hours

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	447[11]	452[12]		
Units: hour				
median (confidence interval 95%)				
Time to parasite clearance	34.3 (24.6 to 35.5)	34.9 (25.2 to 35.6)		
Time to fever clearance	7.9 (7.8 to 8)	7.8 (7.8 to 7.9)		

Notes:

[11] - ITT population: n = 442, 441

[12] - n = 444, 443

Statistical analyses

No statistical analyses for this end point

Secondary: Number (%) of patients with patients with parasite clearance by hours

End point title	Number (%) of patients with patients with parasite clearance by hours

End point description:

End point type	Secondary

End point timeframe:

Up to 72 hours

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442[13]	444		
Units: percent				
number (not applicable)				
>0 - 24 hours	38.5	37.4		
>24 - 48 hours	50	52		
>48-72 hours	7.5	7.4		
>72 hours	0.7	0.7		
Parasite clearance not achieved	3.4	2.5		

Notes:

[13] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Number (%) of patients with gametocytes by time in the trial

End point title	Number (%) of patients with gametocytes by time in the trial

End point description:

End point type	Secondary

End point timeframe:

After Day 8; after start of treatment

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442[14]	444		
Units: percent				
number (not applicable)				
Baseline	4.5	4.7		
>0-72 hours	9.7	10.6		
>72 hours to Day 8	1.4	1.2		
After Day 8	0.5	1.2		

Notes:

[14] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Descriptive statistics of artemether and DHA plasma maximum concentrations (Cmax) per bodyweight group in pediatric patients treated with 6-

dose regimen Coartem crushed or dispersible tablets

End point title	Descriptive statistics of artemether and DHA plasma maximum concentrations (Cmax) per bodyweight group in pediatric patients treated with 6-dose regimen Coartem crushed or dispersible tablets

End point description:

End point type	Secondary

End point timeframe:

Up to 2 hours after the first dose

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91[15]	93[16]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cmax artemether (group 5-<15 kg)	196 (± 204)	223 (± 309)		
Cmax artemether (group 15-<25 kg)	150 (± 106)	198 (± 179)		
Cmax artemether (group 25-<35 kg)	134 (± 56.7)	174 (± 145)		
Cmax DHA (group 5-<15 kg)	67.8 (± 74.7)	54.7 (± 58.9)		
Cmax DHA (group 15-<25 kg)	66.5 (± 49)	79.8 (± 80.5)		
Cmax DHA (group 25-<35 kg)	73.9 (± 48.7)	65.3 (± 23.6)		

Notes:

[15] - body weight groups; n = 52, 30, 9

[16] - n = 55, 29, 8

Statistical analyses

No statistical analyses for this end point

Secondary: Lumefantrine Cmax per body weight group in PK population treated with 6-dose regimen Coartem crushed or dispersible tablets

End point title	Lumefantrine Cmax per body weight group in PK population treated with 6-dose regimen Coartem crushed or dispersible tablets

End point description:

End point type	Secondary

End point timeframe:

6 hours after dose 3, 6 hours after dose 5, Day 3, Day 7 and Day 14

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310[17]	315[18]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Cmax (5-<15 kg group)	5.16 (± 3.41)	6.13 (± 5.62)		
Cmax (15-<25 kg group)	8.03 (± 4.78)	9.37 (± 4.26)		
Cmax (25-<35 kg group)	12.3 (± 10.3)	21.9 (± 999.9)		

Notes:

[17] - PK subset; n = 14, 48, 3

[18] - n = 101, 53, 1
999.9 = represents only one value/patient sampled at this timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: Lumefantrine AUC0-last per body weight group in PK population treated with 6-dose regimen Coartem crushed or dispersible tablets

End point title	Lumefantrine AUC0-last per body weight group in PK population treated with 6-dose regimen Coartem crushed or dispersible tablets

End point description:

End point type	Secondary

End point timeframe:

6 hours after dose 3, 6 hours after dose 5, Day 3, Day 7 and Day 14

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310[19]	315[20]		
Units: µg·h/mL				
number (not applicable)				
AUC0-last (5-<15 kg group)	441	577		
AUC0-last (15-<25 kg group)	704	699		
AUC0-last (25-<35 kg group)	1260	1150		

Notes:

[19] - PK subset; n = 14, 48, 3

[20] - n = 101, 53, 1

Statistical analyses

No statistical analyses for this end point

Secondary: Lumefantrine exposure and cure rates in patients treated with 6-dose regimen Coartem crushed or dispersible tablets

End point title	Lumefantrine exposure and cure rates in patients treated with 6-dose regimen Coartem crushed or dispersible tablets

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310[21]	315[22]		
Units: percent				
number (not applicable)				
28-day cure rate (5-<15 kg group)	97.5	99.2		
28-day cure rate (15-<25 kg group)	98.6	97.1		
28-day cure rate (25-<35 kg group)	96.4	100		

Notes:

[21] - PK subset; n = 14, 48, 3

[22] - n = 101, 53, 1

Statistical analyses

No statistical analyses for this end point

Secondary: Lumefantrine exposure and cure rates in patients treated with 6-dose regimen Coartem crushed or dispersible tablets

End point title	Lumefantrine exposure and cure rates in patients treated with 6-dose regimen Coartem crushed or dispersible tablets

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Dispersible tablet	Crushed tablet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310[23]	315[24]		
Units: mg/kg				
arithmetic mean (standard deviation)				
Lumefantrine dose (5-<15 kg group)	68.6 (± 16.9)	66.7 (± 15.3)		
Lumefantrine dose (15-<25 kg group)	80.6 (± 11.5)	82.9 (± 11)		
Lumefantrine dose (25-<35 kg group)	77.8 (± 8.57)	75.9 (± 7.21)		

Notes:

[23] - PK subset; n= 191, 102, 17

[24] - n = 194, 102, 19

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	10.0

Reporting groups

Reporting group title	Crushed tablet

Reporting group description:

Crushed tablet

Reporting group title	Dispersible tablet

Reporting group description:

Dispersible tablet

Serious adverse events	Crushed tablet	Dispersible tablet	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 452 (1.33%)	7 / 447 (1.57%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 452 (0.00%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	0 / 452 (0.00%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Convulsion			

subjects affected / exposed	1 / 452 (0.22%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 452 (0.22%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 452 (0.00%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	1 / 452 (0.22%)	0 / 447 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 452 (0.22%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 452 (0.00%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 452 (0.00%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			

subjects affected / exposed	0 / 452 (0.00%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laryngotracheo bronchitis			
subjects affected / exposed	1 / 452 (0.22%)	0 / 447 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 452 (0.00%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmodium falciparum infection			
subjects affected / exposed	4 / 452 (0.88%)	2 / 447 (0.45%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 452 (0.22%)	0 / 447 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 452 (0.00%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral intake reduced			
subjects affected / exposed	0 / 452 (0.00%)	1 / 447 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Crushed tablet	Dispersible tablet	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	282 / 452 (62.39%)	283 / 447 (63.31%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	20 / 452 (4.42%)	27 / 447 (6.04%)	
occurrences (all)	22	30	
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 452 (7.30%)	33 / 447 (7.38%)	
occurrences (all)	39	36	
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	30 / 452 (6.64%)	30 / 447 (6.71%)	
occurrences (all)	32	32	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	165 / 452 (36.50%)	166 / 447 (37.14%)	
occurrences (all)	249	258	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	31 / 452 (6.86%)	37 / 447 (8.28%)	
occurrences (all)	35	47	
Diarrhoea			
subjects affected / exposed	26 / 452 (5.75%)	35 / 447 (7.83%)	
occurrences (all)	31	37	
Vomiting			
subjects affected / exposed	76 / 452 (16.81%)	74 / 447 (16.55%)	
occurrences (all)	81	79	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	113 / 452 (25.00%)	105 / 447 (23.49%)	
occurrences (all)	132	128	
Infections and infestations			
Plasmodium falciparum infection			
subjects affected / exposed	97 / 452 (21.46%)	86 / 447 (19.24%)	
occurrences (all)	99	86	

Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	 30 / 452 (6.64%) 36	 28 / 447 (6.26%) 32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2007	Changes included: • incorporate all changes resulting from Amendments 1 and 2 that were applicable to a limited number of sites and/or countries. • revise the definition of the PA and ITT populations and the method to construct the confidence interval for the cure rate difference. • improve protocol clarity by correcting inconsistencies, typographical errors and omissions.

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: