Clinical trial results:
A phase II, open-label, multicentre, pharmacokinetic, pharmacodynamics and safety study of a new paediatric eurartesim dispersible formulation and crushed film coated eurartesim tablet, in infant patients with Plasmodium falciparum malaria

Summary

EudraCT number	2013-002255-15
Trial protocol	Outside EU/EEA
Global end of trial date	02 June 2015

Results information

Result version number	v1 (current)
This version publication date	19 July 2020
First version publication date	19 July 2020

Trial information

Trial identification

Sponsor protocol code	ST3073-ST3074-DM-12-002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.
Sponsor organisation address	V. le Shakespeare 47, Roma, Italy,
Public contact	Giovanni Valentini, Alfasigma S.p.A., 0039 0691393916,
Scientific contact	Giovanni Valentini, Alfasigma S.p.A., 0039 0691393916,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000153-PIP01-07
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	27 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2015
Global end of trial reached?	Yes
Global end of trial date	02 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the PK of the eurartesim (PQP/DHA) new water dispersible formulation, film coated tablet and crushed film coated tablet in venous blood samples during and after a therapeutic course of Eurartesim in paediatric population

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (1964) and its subsequent amendments and in accordance with the "ICH Topic E6, Guideline for Good Clinical Practices".

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Congo: 33
Country: Number of subjects enrolled	Mozambique: 143
Country: Number of subjects enrolled	Tanzania, United Republic of: 6
Country: Number of subjects enrolled	Burkina Faso: 104
Country: Number of subjects enrolled	Gambia: 14
Worldwide total number of subjects	300
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)	300
Children (2-11 years)	0
Adolescents (12-17 years)	0

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Number of screened subjects=443
Number of randomised subjects= 300

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

As the primary objective of this study was to determine the pharmacokinetic profile of DHA and PQ of both formulations in a small children population, blinding procedures were considered not mandatory. Therefore, the study used an open label design since the impossibility of establishing a double-blind dosing schedule involving dispersible and crushed tablets.

Arms

Are arms mutually exclusive?	Yes
Arm title	DHA/PQP Dispersible Tablets

Arm description:

Eurartesim dispersible tablet arm

Arm type	Experimental
Investigational medicinal product name	Eurartesim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Each child received a specific amount of drug according to body weight once a day for 3 consecutive days. Dispersible tablets were completely dispersed in 5 to 10 mL of water. After ingestion, other 5 mL of water were added to the container and consumed by the patient. The 1st dose was administered as soon as the patient was randomized in the study and possibly no food was given in the following 3 hours. For the 2nd and the 3rd doses, the child had to be fed 3 hours before the scheduled drug intake and, possibly, food was not given in the following 3 hours. If children required food during the restricted periods, it consisted of a small amount of porridge with water. Infants who still required breast-feeding only received maternal milk. Patients were observed for 1 h after dosing. If the dose was: a) vomited within 30 min., a further full dose was given; b) vomited between 31 and 60 min., a further half dose was given.

Arm title	DHA/PQP Crushed Tablets

Arm description:

Eurartesim crushed tablet arm

Arm type	Active comparator
Investigational medicinal product name	Eurartesim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Each child received a specific amount of drug according to body weight once a day for 3 consecutive days. Tablets were crushed to form a powder. The mortar was cleaned with 5-10 mL of water, that was then used to disperse powder. After administration, 5 mL of water were used to rinse the mortar and the

container and then administered. The 1st dose was administered as soon as the patient was randomized in the study and possibly no food was given in the following 3 hours. For the 2nd and the 3rd doses, the child had to be fed 3 hours before the scheduled drug intake and, possibly, food was not given in the following 3 hours. If children required food during the restricted periods, it consisted of a small amount of porridge with water. Infants who still required breast-feeding only received maternal milk. Patients were observed for 1 h after dosing. If the dose was: a) vomited within 30 min., a further full dose was given; b) vomited between 31 and 60 min., a further half dose was given.

Number of subjects in period 1	DHA/PQP Dispersible Tablets	DHA/PQP Crushed Tablets
Started	201	99
Completed	135	61
Not completed	66	38
Adverse event, serious fatal	-	1
Consent withdrawn by subject	4	8
Treatment failure	42	22
Repeated study drug vomiting	10	2
Negative Parasitaemia at baseline	1	-
Mother And Child Have Left The Hospital	-	1
Lost to follow-up	8	4
Move Out Of Study Area	1	-

Baseline characteristics

Reporting groups	
Reporting group title	DHA/PQP Dispersible Tablets
Reporting group description: Eurartesim dispersible tablet arm	
Reporting group title	DHA/PQP Crushed Tablets
Reporting group description: Eurartesim crushed tablet arm	

Reporting group values	DHA/PQP Dispersible Tablets	DHA/PQP Crushed Tablets	Total
Number of subjects	201	99	300
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	201	99	300
Age continuous			
Note: Two randomized patients assigned to the dispersible treatment group were excluded from all the study populations since one of them did not have parasites at Day 0 (treated with two doses by mistake and then withdrawn) and the other one withdrawn the informed consent before the first study drug intake. Consequently, they have not been included in the baseline characteristics description and therefore the age continuous values reported for the Reporting group 1 correspond to those of the ITT/Safety population dispersible tablets analyses set.			
Units: months			
arithmetic mean	9.1	9.2	
standard deviation	± 1.8	± 2.0	-
Gender categorical Units: Subjects			
Female	111	52	163
Male	90	47	137

Subject analysis sets	
Subject analysis set title	ITT/Safety Population Dispersible Tablets
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-Treat (ITT) population included all patients taking at least one dose of the study drug. This population has been used for the Efficacy and Safety analysis. As for the Safety data presentation, it has been referenced as Safety Population.
Note: Two randomized patients assigned to the dispersible treatment group were excluded from all the study populations since one of them did not have parasites at Day 0 (treated with two doses by mistake and then withdrawn) and the other one withdrawn the informed consent before the first study drug intake.

Subject analysis set title	PP Population Dispersible Tablets
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population included all patients who took the complete treatment and who did not meet any major protocol violations.
Note: two randomized patients assigned to the dispersible treatment group were excluded from all the study populations since one of them did not have parasites at Day 0 (treated with two doses by mistake and then withdrawn) and the other one withdrawn the informed consent before the first study drug intake.

Subject analysis set title	ITT/Safety Population Crushed Tablets

Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-Treat (ITT) population included all patients taking at least one dose of the study drug. This population has been used for the Efficacy and Safety analysis. As for the Safety data presentation, it has been referenced as Safety Population.

Subject analysis set title	PP Population Crushed Tablets
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population included all patients who took the complete treatment and who did not meet any major protocol violations.

Subject analysis set title	DHA PK Population Dispersible Tablets
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic analysis population included all the data from samplings taken under regular treatment course with no major PK specific protocol violations (e.g. use of not permitted concomitant medication, violation of major inclusion/exclusion criteria). The PK population has been used for the PK analysis.

Subject analysis set title	PQ PK Population Dispersible Tablets
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic analysis population included all the data from samplings taken under regular treatment course with no major PK specific protocol violations (e.g. use of not permitted concomitant medication, violation of major inclusion/exclusion criteria). The PK population has been used for the PK analysis.

Subject analysis set title	DHA PK Population Crushed Tablets
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic analysis population included all the data from samplings taken under regular treatment course with no major PK specific protocol violations (e.g. use of not permitted concomitant medication, violation of major inclusion/exclusion criteria). The PK population has been used for the PK analysis.

Subject analysis set title	PQ PK Population Crushed Tablets
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic analysis population included all the data from samplings taken under regular treatment course with no major PK specific protocol violations (e.g. use of not permitted concomitant medication, violation of major inclusion/exclusion criteria). The PK population has been used for the PK analysis.

Reporting group values	ITT/Safety Population Dispersible Tablets	PP Population Dispersible Tablets	ITT/Safety Population Crushed Tablets
Number of subjects	199	173	99
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	199	173	99
Age continuous			
Note: Two randomized patients assigned to the dispersible treatment group were excluded from all the study populations since one of them did not have parasites at Day 0 (treated with two doses by mistake and then withdrawn) and the other one withdrawn the informed consent before the first study drug intake. Consequently, they have not been included in the baseline characteristics description and therefore the age continuous values reported for the Reporting group 1 correspond to those of the ITT/Safety population dispersible tablets analyses set.			
Units: months			
arithmetic mean	9.1	9.2	9.2
standard deviation	± 1.8	± 1.8	± 2.0

Gender categorical Units: Subjects			
Female	110	96	52
Male	89	77	47

Reporting group values	PP Population Crushed Tablets	DHA PK Population Dispersible Tablets	PQ PK Population Dispersible Tablets
Number of subjects	84	119	174
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	84		
Age continuous			
Note: Two randomized patients assigned to the dispersible treatment group were excluded from all the study populations since one of them did not have parasites at Day 0 (treated with two doses by mistake and then withdrawn) and the other one withdrawn the informed consent before the first study drug intake. Consequently, they have not been included in the baseline characteristics description and therefore the age continuous values reported for the Reporting group 1 correspond to those of the ITT/Safety population dispersible tablets analyses set.			
Units: months			
arithmetic mean	9.1		
standard deviation	± 2.0	±	±
Gender categorical Units: Subjects			
Female	45		
Male	39		

Reporting group values	DHA PK Population Crushed Tablets	PQ PK Population Crushed Tablets	
Number of subjects	56	85	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)			
Age continuous			
Note: Two randomized patients assigned to the dispersible treatment group were excluded from all the study populations since one of them did not have parasites at Day 0 (treated with two doses by mistake and then withdrawn) and the other one withdrawn the informed consent before the first study drug intake. Consequently, they have not been included in the baseline characteristics description and therefore the age continuous values reported for the Reporting group 1 correspond to those of the ITT/Safety population dispersible tablets analyses set.			
Units: months			
arithmetic mean			
standard deviation	±	±	
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	DHA/PQP Dispersible Tablets
Reporting group description: Eurartesim dispersible tablet arm	
Reporting group title	DHA/PQP Crushed Tablets
Reporting group description: Eurartesim crushed tablet arm	
Subject analysis set title	ITT/Safety Population Dispersible Tablets
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intention-to-Treat (ITT) population included all patients taking at least one dose of the study drug. This population has been used for the Efficacy and Safety analysis. As for the Safety data presentation, it has been referenced as Safety Population. Note: Two randomized patients assigned to the dispersible treatment group were excluded from all the study populations since one of them did not have parasites at Day 0 (treated with two doses by mistake and then withdrawn) and the other one withdrawn the informed consent before the first study drug intake.	
Subject analysis set title	PP Population Dispersible Tablets
Subject analysis set type	Per protocol
Subject analysis set description: The Per Protocol (PP) population included all patients who took the complete treatment and who did not meet any major protocol violations. Note: two randomized patients assigned to the dispersible treatment group were excluded from all the study populations since one of them did not have parasites at Day 0 (treated with two doses by mistake and then withdrawn) and the other one withdrawn the informed consent before the first study drug intake.	
Subject analysis set title	ITT/Safety Population Crushed Tablets
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intention-to-Treat (ITT) population included all patients taking at least one dose of the study drug. This population has been used for the Efficacy and Safety analysis. As for the Safety data presentation, it has been referenced as Safety Population.	
Subject analysis set title	PP Population Crushed Tablets
Subject analysis set type	Per protocol
Subject analysis set description: The Per Protocol (PP) population included all patients who took the complete treatment and who did not meet any major protocol violations.	
Subject analysis set title	DHA PK Population Dispersible Tablets
Subject analysis set type	Sub-group analysis
Subject analysis set description: The pharmacokinetic analysis population included all the data from samplings taken under regular treatment course with no major PK specific protocol violations (e.g. use of not permitted concomitant medication, violation of major inclusion/exclusion criteria). The PK population has been used for the PK analysis.	
Subject analysis set title	PQ PK Population Dispersible Tablets
Subject analysis set type	Sub-group analysis
Subject analysis set description: The pharmacokinetic analysis population included all the data from samplings taken under regular treatment course with no major PK specific protocol violations (e.g. use of not permitted concomitant medication, violation of major inclusion/exclusion criteria). The PK population has been used for the PK analysis.	
Subject analysis set title	DHA PK Population Crushed Tablets
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic analysis population included all the data from samplings taken under regular treatment course with no major PK specific protocol violations (e.g. use of not permitted concomitant medication, violation of major inclusion/exclusion criteria). The PK population has been used for the PK analysis.

Subject analysis set title	PQ PK Population Crushed Tablets
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic analysis population included all the data from samplings taken under regular treatment course with no major PK specific protocol violations (e.g. use of not permitted concomitant medication, violation of major inclusion/exclusion criteria). The PK population has been used for the PK analysis.

Primary: DHA Cmax (ng/ml) GMR Dispersible/Crushed

End point title	DHA Cmax (ng/ml) GMR Dispersible/Crushed

End point description:

The primary endpoint was to estimate the population and individual PK parameters and variability of PQ and DHA in paediatric populations administered with Eurartesim. DHA and PQ were modelled separately in order to determine the sampling schedule for a study to be performed in infants with malaria. In the learn phase, the population PK analysis was performed using plasma data for DHA and PQ from 5 previous studies. Plasma concentrations of DHA and PQ data obtained from the present study were subsequently pooled with the data from the previous studies for the confirmatory aspects of the study. Actual dosing (and dose per kg) and actual blood sampling times were used for the compartmental modelling of DHA and PQ.
The DHA Cmax (ng/ml) Geometric Mean Ratio (GMR) of dispersible vs crushed tablets is here reported. In order to complete and validate all mandatory fields, the same GMR value has been reported for both the relevant analyses sets.

End point type	Primary

End point timeframe:

Overall study

End point values	DHA PK Population Dispersible Tablets	DHA PK Population Crushed Tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	119	56		
Units: Geometric Mean Ratio (%)				
number (confidence interval 90%)	71.6 (64.9 to 79.0)	71.6 (64.9 to 79.0)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio

Statistical analysis description:

The geometric mean ratios (GMR), lower and upper 90%CI for bioequivalence assessment for Cmax and AUCinf obtained from the simulation of the two formulations in paediatric male and female patients are presented. The point estimate for the bioequivalence ratios of the new dispersible formulation over the old crushed formulation were within the 80-125% acceptance range for PQ but not for DHA.

Comparison groups	DHA PK Population Dispersible Tablets v DHA PK Population Crushed Tablets

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Geometric Mean Ratio
Point estimate	71.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	64.9
upper limit	79

Notes:

[1] - Bioequivalence

Primary: PQ Cmax (ng/ml) GMR Dispersible/Crushed

End point title	PQ Cmax (ng/ml) GMR Dispersible/Crushed

End point description:

The primary endpoint was to estimate the population and individual PK parameters and variability of PQ and DHA in paediatric populations administered with Eurartesim. DHA and PQ were modelled separately in order to determine the sampling schedule for a study to be performed in infants with malaria. In the learn phase, the population PK analysis was performed using plasma data for DHA and PQ from 5 previous studies. Plasma concentrations of DHA and PQ data obtained from the present study were subsequently pooled with the data from the previous studies for the confirmatory aspects of the study. Actual dosing (and dose per kg) and actual blood sampling times were used for the compartmental modelling of DHA and PQ.
The PQ Cmax (ng/ml) Geometric Mean Ratio (GMR) of dispersible vs crushed tablets is here reported. In order to complete and validate all mandatory fields, the same GMR value has been reported for both the relevant analyses sets.

End point type	Primary

End point timeframe:

Overall study

End point values	PQ PK Population Dispersible Tablets	PQ PK Population Crushed Tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	174	85		
Units: Geometric Mean Ratio (%)				
number (confidence interval 90%)	93.7 (84.7 to 103.8)	93.7 (84.7 to 103.8)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio

Statistical analysis description:

The geometric mean ratios (GMR), lower and upper 90%CI for bioequivalence assessment for Cmax and AUCinf obtained from the simulation of the two formulations in paediatric male and female patients are presented. The point estimate for the bioequivalence ratios of the new dispersible formulation over the old crushed formulation were within the 80-125% acceptance range for PQ but not for DHA.

Comparison groups	PQ PK Population Crushed Tablets v PQ PK Population

	Dispersible Tablets
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Geometric Mean Ratio
Point estimate	93.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	84.7
upper limit	103.8

Notes:

[2] - Bioequivalence

Primary: DHA AUCinf (ng/ml*h) GMR Dispersible/Crushed

End point title	DHA AUCinf (ng/ml*h) GMR Dispersible/Crushed

End point description:

The primary endpoint was to estimate the population and individual PK parameters and variability of PQ and DHA in paediatric populations administered with Eurartesim. DHA and PQ were modelled separately in order to determine the sampling schedule for a study to be performed in infants with malaria. In the learn phase, the population PK analysis was performed using plasma data for DHA and PQ from 5 previous studies. Plasma concentrations of DHA and PQ data obtained from the present study were subsequently pooled with the data from the previous studies for the confirmatory aspects of the study. Actual dosing (and dose per kg) and actual blood sampling times were used for the compartmental modelling of DHA and PQ.
The DHA AUCinf (ng/ml*h) Geometric Mean Ratio (GMR) of dispersible vs crushed tablets is here reported. In order to complete and validate all mandatory fields, the same GMR value has been reported for both the relevant analyses sets.

End point type	Primary

End point timeframe:

Overall study

End point values	DHA PK Population Dispersible Tablets	DHA PK Population Crushed Tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	119	56		
Units: Geometric Mean Ratio (%)				
number (confidence interval 90%)	69.9 (63.3 to 77.2)	69.9 (63.3 to 77.2)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio

Statistical analysis description:

The geometric mean ratios (GMR), lower and upper 90%CI for bioequivalence assessment for Cmax and AUCinf obtained from the simulation of the two formulations in paediatric male and female patients are presented. The point estimate for the bioequivalence ratios of the new dispersible formulation over the old crushed formulation were within the 80-125% acceptance range for PQ but not for DHA.

Comparison groups	DHA PK Population Dispersible Tablets v DHA PK Population Crushed Tablets
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Geometric Mean Ratio
Point estimate	69.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	63.3
upper limit	77.2

Notes:

[3] - Bioequivalence

Primary: PQ AUCinf (ng/ml*h) GMR Dispersible/Crushed

End point title	PQ AUCinf (ng/ml*h) GMR Dispersible/Crushed

End point description:

The primary endpoint was to estimate the population and individual PK parameters and variability of PQ and DHA in paediatric populations administered with Eurartesim. DHA and PQ were modelled separately in order to determine the sampling schedule for a study to be performed in infants with malaria. In the learn phase, the population PK analysis was performed using plasma data for DHA and PQ from 5 previous studies. Plasma concentrations of DHA and PQ data obtained from the present study were subsequently pooled with the data from the previous studies for the confirmatory aspects of the study. Actual dosing (and dose per kg) and actual blood sampling times were used for the compartmental modelling of DHA and PQ.
PQ AUCinf (ng/ml*h) Geometric Mean Ratio (GMR) of dispersible vs crushed tablets is here reported. In order to complete and validate all mandatory fields, the same GMR value has been reported for both the relevant analyses sets.

End point type	Primary

End point timeframe:

Overall study

End point values	PQ PK Population Dispersible Tablets	PQ PK Population Crushed Tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	174	85		
Units: Geometric Mean Ratio (%)				
number (confidence interval 90%)	93.5 (83.3 to 104.9)	93.5 (83.3 to 104.9)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio

Statistical analysis description:

The geometric mean ratios (GMR), lower and upper 90%CI for bioequivalence assessment for Cmax and AUCinf obtained from the simulation of the two formulations in paediatric male and female patients are presented. The point estimate for the bioequivalence ratios of the new dispersible formulation over the

old crushed formulation were within the 80-125% acceptance range for PQ but not for DHA.

Comparison groups	PQ PK Population Dispersible Tablets v PQ PK Population Crushed Tablets
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Geometric Mean Ratio
Point estimate	93.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	83.3
upper limit	104.9

Notes:

[4] - Bioequivalence

Secondary: PCR-Corrected Adequate Clinical and Parasitological Cure Rate

End point title	PCR-Corrected Adequate Clinical and Parasitological Cure Rate

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	ITT/Safety Population Dispersible Tablets	PP Population Dispersible Tablets	ITT/Safety Population Crushed Tablets	PP Population Crushed Tablets
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	199	173	99	84
Units: Subjects	173	170	84	84

Statistical analyses

No statistical analyses for this end point

Secondary: PCR-Uncorrected Adequate Clinical and Parasitological Cure Rate

End point title	PCR-Uncorrected Adequate Clinical and Parasitological Cure Rate

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	ITT/Safety Population Dispersible Tablets	PP Population Dispersible Tablets	ITT/Safety Population Crushed Tablets	PP Population Crushed Tablets
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	199	173	99	84
Units: Subjects	161	158	80	80

Statistical analyses

No statistical analyses for this end point

Secondary: PCR-Corrected Adequate Clinical and Parasitological Cure Rate

End point title	PCR-Corrected Adequate Clinical and Parasitological Cure Rate

End point description:

End point type	Secondary

End point timeframe:

Day 42

End point values	ITT/Safety Population Dispersible Tablets	PP Population Dispersible Tablets	ITT/Safety Population Crushed Tablets	PP Population Crushed Tablets
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	199	173	99	84
Units: Subjects	171	167	82	81

Statistical analyses

No statistical analyses for this end point

Secondary: PCR-Uncorrected Adequate Clinical and Parasitological Cure Rate

End point title	PCR-Uncorrected Adequate Clinical and Parasitological Cure Rate

End point description:

End point type	Secondary

End point timeframe:

Day 42

End point values	ITT/Safety Population Dispersible Tablets	PP Population Dispersible Tablets	ITT/Safety Population Crushed Tablets	PP Population Crushed Tablets
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	199	173	99	84
Units: Subjects	135	132	61	61

Statistical analyses

No statistical analyses for this end point

Secondary: Early and Late Treatment Failures (ETF and LTF)

End point title	Early and Late Treatment Failures (ETF and LTF)

End point description:

ETF was defined as:
1. Development of danger signs or severe malaria on Days 0, 1, 2 or 3, in the presence of parasitaemia.
2. Parasite density on Day 2 > Day 0 count, irrespective of axillary temperature.
3. Presence of parasitaemia on Day 3 with fever (axillary temperature ≥37.5°C).
4. Parasitaemia on Day 3 ≥ 25% of count on Day 0.

LTF at Day 42 was divided into LCF and LPF.
-Late Clinical Failure (LCF) was defined as:
1. Development of danger signs or severe malaria from Day 4 to Day 42 in the presence of parasitaemia.
2. Presence of parasitaemia and fever on any day from Day 4 to Day 42, without previously meeting the criteria of ETF.
-Late Parasitological Failure (LPF) at Day 42 was defined as reappearance of parasitaemia between Day 4 and Day 42 (identified as recrudescent infection by PCR analysis) in the absence of fever (axillary temperature <37.5°C) without previously meeting the criteria of ETF or LCF.

End point type	Secondary

End point timeframe:

Day 42

End point values	ITT/Safety Population Dispersible Tablets	ITT/Safety Population Crushed Tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	99		
Units: Subjects	42	22		

Statistical analyses

No statistical analyses for this end point

Secondary: True Treatment Failures

End point title	True Treatment Failures

End point description:

True Treatment Failures were both the ETF and malaria recrudescences

End point type	Secondary

End point timeframe:

Day 42

End point values	ITT/Safety Population Dispersible Tablets	ITT/Safety Population Crushed Tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	99		
Units: Subjects	5	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Parasitemic Patients

End point title	Proportion of Parasitemic Patients

End point description:

End point type	Secondary

End point timeframe:

Day 7

End point values	ITT/Safety Population Dispersible Tablets	PP Population Dispersible Tablets	ITT/Safety Population Crushed Tablets	PP Population Crushed Tablets
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	199	173	99	84
Units: Subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Afebrile Patients

End point title	Proportion of Afebrile Patients

End point description:

End point type	Secondary

End point timeframe:

Day 3

End point values	ITT/Safety Population Dispersible Tablets	PP Population Dispersible Tablets	ITT/Safety Population Crushed Tablets	PP Population Crushed Tablets
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	199	173	99	84
Units: Subjects	183	167	94	84

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients Presenting Gametocytes

End point title	Proportion of Patients Presenting Gametocytes

End point description:

End point type	Secondary

End point timeframe:

Day 42

End point values	ITT/Safety Population Dispersible Tablets	ITT/Safety Population Crushed Tablets		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	99		
Units: Subjects	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of New P. Falciparum Infections

End point title	Incidence of New P. Falciparum Infections

End point description:

End point type	Secondary

End point timeframe:

Day 42

End point values	ITT/Safety Population Dispersible Tablets	PP Population Dispersible Tablets	ITT/Safety Population Crushed Tablets	PP Population Crushed Tablets
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	163	138	78	64
Units: Subjects	36	35	21	20

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Recrudescences of P. Falciparum Infections

End point title	Incidence of Recrudescences of P. Falciparum Infections

End point description:

End point type	Secondary

End point timeframe:

Day 42

End point values	ITT/Safety Population Dispersible Tablets	PP Population Dispersible Tablets	ITT/Safety Population Crushed Tablets	PP Population Crushed Tablets
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	194	169	98	84
Units: Subjects	5	4	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Recurrences of P. Falciparum Infections

End point title	Incidence of Recurrences of P. Falciparum Infections

End point description:

End point type	Secondary

End point timeframe:
Day 42

End point values	ITT/Safety Population Dispersible Tablets	PP Population Dispersible Tablets	ITT/Safety Population Crushed Tablets	PP Population Crushed Tablets
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	158	134	77	64
Units: Subjects	41	39	22	20

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0
Reporting groups	
Reporting group title	ITT/Safety Population
Reporting group description:	
The Intention-to-Treat (ITT) population included all patients taking at least one dose of the study drug. This population has been used for the Efficacy and Safety analysis. As for the Safety data presentation, it has been referenced as Safety Population	

Serious adverse events	ITT/Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 298 (0.34%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Infections and infestations			
Malaria			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	ITT/Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	244 / 298 (81.88%)		
Investigations			
Aspartate aminotransferase increased aminotransferase increased			
subjects affected / exposed	7 / 298 (2.35%)		
occurrences (all)	7		
Blood bilirubin increased			

subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	38 / 298 (12.75%)		
occurrences (all)	38		
Haematocrit decreased			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	3 / 298 (1.01%)		
occurrences (all)	3		
White blood cell count abnormal			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 298 (0.67%)		
occurrences (all)	2		
Injury			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	34 / 298 (11.41%)		
occurrences (all)	34		
Thrombocytosis			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	19 / 298 (6.38%)		
occurrences (all)	19		
Eye disorders			

Eyelid oedema subjects affected / exposed occurrences (all)	1 / 298 (0.34%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 298 (0.34%) 1		
Abdominal tenderness subjects affected / exposed occurrences (all)	1 / 298 (0.34%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 298 (0.34%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	22 / 298 (7.38%) 26		
Enteritis subjects affected / exposed occurrences (all)	3 / 298 (1.01%) 3		
Mucous stools subjects affected / exposed occurrences (all)	1 / 298 (0.34%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 298 (0.34%) 1		
Salivary hypersecretion subjects affected / exposed occurrences (all)	4 / 298 (1.34%) 7		
Vomiting subjects affected / exposed occurrences (all)	82 / 298 (27.52%) 83		
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	2 / 298 (0.67%) 2		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	14 / 298 (4.70%)		
occurrences (all)	14		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Dermatosis			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Rash papulosquamous			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Bronchiolitis			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	31 / 298 (10.40%)		
occurrences (all)	33		
Bronchopneumonia			
subjects affected / exposed	7 / 298 (2.35%)		
occurrences (all)	7		
Burn infection			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	3 / 298 (1.01%)		
occurrences (all)	3		
Ear infection			
subjects affected / exposed	3 / 298 (1.01%)		
occurrences (all)	3		
Fungal infection			

subjects affected / exposed	2 / 298 (0.67%)			
occurrences (all)	2			
Furuncle				
subjects affected / exposed	4 / 298 (1.34%)			
occurrences (all)	4			
Gastroenteritis				
subjects affected / exposed	11 / 298 (3.69%)			
occurrences (all)	12			
Gastrointestinal fungal infection				
subjects affected / exposed	1 / 298 (0.34%)			
occurrences (all)	1			
Herpes simplex				
subjects affected / exposed	1 / 298 (0.34%)			
occurrences (all)	1			
Infection				
subjects affected / exposed	2 / 298 (0.67%)			
occurrences (all)	2			
Influenza				
subjects affected / exposed	8 / 298 (2.68%)			
occurrences (all)	9			
Joint abscess				
subjects affected / exposed	1 / 298 (0.34%)			
occurrences (all)	1			
Laryngitis				
subjects affected / exposed	3 / 298 (1.01%)			
occurrences (all)	3			
Lower respiratory tract infection				
subjects affected / exposed	8 / 298 (2.68%)			
occurrences (all)	8			
Lung infection				
subjects affected / exposed	1 / 298 (0.34%)			
occurrences (all)	2			
Malaria				
subjects affected / exposed	64 / 298 (21.48%)			
occurrences (all)	64			
Nasopharyngitis				

subjects affected / exposed	6 / 298 (2.01%)			
occurrences (all)	6			
Oral candidiasis				
subjects affected / exposed	2 / 298 (0.67%)			
occurrences (all)	2			
Otitis media				
subjects affected / exposed	3 / 298 (1.01%)			
occurrences (all)	3			
Otitis media acute				
subjects affected / exposed	2 / 298 (0.67%)			
occurrences (all)	2			
Pneumonia				
subjects affected / exposed	2 / 298 (0.67%)			
occurrences (all)	2			
Pyoderma				
subjects affected / exposed	1 / 298 (0.34%)			
occurrences (all)	1			
Rash pustular				
subjects affected / exposed	4 / 298 (1.34%)			
occurrences (all)	4			
Respiratory tract infection				
subjects affected / exposed	17 / 298 (5.70%)			
occurrences (all)	17			
Respiratory tract infection viral				
subjects affected / exposed	1 / 298 (0.34%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	16 / 298 (5.37%)			
occurrences (all)	17			
Rhinotracheitis				
subjects affected / exposed	1 / 298 (0.34%)			
occurrences (all)	1			
Skin infection				
subjects affected / exposed	1 / 298 (0.34%)			
occurrences (all)	1			
Subcutaneous abscess				

subjects affected / exposed	2 / 298 (0.67%)		
occurrences (all)	2		
Tinea capitis			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Tinea pedis			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 298 (1.01%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 298 (2.68%)		
occurrences (all)	8		
Dehydration			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported