



Clinical trial results: Proof of Concept Study of Eurartesim® in Patients with Imported Uncomplicated Plasmodium Vivax Malaria Summary

EudraCT number	2013-003763-56
Trial protocol	IT ES NL DE
Global end of trial date	23 November 2016

Results information

Result version number	v1 (current)
This version publication date	11 July 2020
First version publication date	11 July 2020

Trial information

Trial identification

Sponsor protocol code	ST3073-ST3074-DM13-001
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Alfasigma S.p.A.
Sponsor organisation address	Via Ragazzi del '99, Bologna, Italy,
Public contact	Giovanni Valentini - Medical Expert, Alfasigma S.p.A., 0039 0691393916,
Scientific contact	Giovanni Valentini - Medical Expert, Alfasigma S.p.A., 0039 0691393916,

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	21 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 November 2016
Global end of trial reached?	Yes
Global end of trial date	23 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of an Eurartesim® treatment course in patients with imported uncomplicated P. vivax malaria. The efficacy will be primarily assessed as uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 21 of follow-up.

Protection of trial subjects:

This study was conducted in accordance with the World Medical Association Declaration of Helsinki and ICH Topic E6, Guideline for Good Clinical Practice

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2014
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	Spain: 2
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	27
EEA total number of subjects	25

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	26
From 65 to 84 years	0

Subject disposition

Recruitment

Recruitment details:

All patients were recruited from seven study centers of four countries: Italy (Rome, Brescia and Reggio Emilia), Germany (Munich and Berlin), Spain (Barcelona) and Switzerland (Bern)

Pre-assignment

Screening details:

Subjects screened for inclusion= 29; Subjects enrolled= 27

Period 1

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

Blinding implementation details:

This was an open label study not requiring blinding conditions

Arms

Arm title	Eurartesim® oral film coated tablet
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Eurartesim® (320/40mg PQP/DHA) film coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Each patient received a specific amount of drug according to his/her body weight once a day for 3 consecutive days. In case the patient was hospitalized, appropriately trained personnel administered the study treatment. Outpatients were instructed to take Eurartesim® with a dose regimen of 1 administration every 24 hours over a period of 3 days, i.e. at Day 0 at the hospital under medical supervision, then after 24 hours (Day 1) and after 48 hours (Day 2) from the first administration. The daily dose of Eurartesim® was administered with water and without food (between meals) over 3 consecutive days for a total of 3 doses taken at the same time each day.

Number of subjects in period 1	Eurartesim® oral film coated tablet
Started	27
Completed	20
Not completed	7
Major violation due to age < 18	1
Lost to follow-up	5
Subj. left the hospital w/o medical authorization	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description:	
The reporting group corresponds to the Intention to Treat (ITT) population that includes all patients taking at least one dose of the study drug.	

Reporting group values	Overall trial	Total	
Number of subjects	27	27	
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	26	26	
Age continuous			
Units: years			
arithmetic mean	35.26		
standard deviation	± 13.52	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	18	18	

Subject analysis sets

Subject analysis set title	Per protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population includes all patients who took the complete treatment and who did not meet any major protocol violations. The PP Population is the primary population for the efficacy analysis

Subject analysis set title	Per protocol (PP) baseline
Subject analysis set type	Per protocol

Subject analysis set description:

In order to be able to complete the mandatory statistical analysis section also for a single arm clinical trial a "PP baseline subject analysis set" has been created.

Reporting group values	Per protocol (PP)	Per protocol (PP) baseline	
Number of subjects	22	22	
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	22	22	
Age continuous			
Units: years			
arithmetic mean	36.77	36.77	
standard deviation	± 13.83	± 13.83	
Gender categorical			
Units: Subjects			
Female	7	7	

Male	15	15	
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End points

End points reporting groups

Reporting group title	Eurartesim® oral film coated tablet
Reporting group description:	-
Subject analysis set title	Per protocol (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	The Per Protocol (PP) population includes all patients who took the complete treatment and who did not meet any major protocol violations. The PP Population is the primary population for the efficacy analysis
Subject analysis set title	Per protocol (PP) baseline
Subject analysis set type	Per protocol
Subject analysis set description:	In order to be able to complete the mandatory statistical analysis section also for a single arm clinical trial a "PP baseline subject analysis set" has been created.

Primary: Proportion of Subjects with Uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 21

End point title	Proportion of Subjects with Uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 21
End point description:	
End point type	Primary
End point timeframe:	Day 21

End point values	Per protocol (PP)	Per protocol (PP) baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: Subjects	18	0		

Statistical analyses

Statistical analysis title	Efficacy endpoints analysis
Statistical analysis description:	The efficacy analysis was performed in the ITT and PP populations; however, given the nature of the study, the latter one was primary. The analysis for all the efficacy endpoints was descriptive. In addition, 95% Confidence Interval (CI) was computed with reference to the proportion of patients having Day 21 Uncorrected ACPR. The Confidence Interval for the primary end-point had a precision of 5%.
Comparison groups	Per protocol (PP) v Per protocol (PP) baseline

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other ^[1]
Parameter estimate	Percentage
Point estimate	81.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	59.7
upper limit	94.8

Notes:

[1] - In order to complete the mandatory statistical section for a single arm clinical trial the following data have been imputed: 1) the "PP baseline subject analysis set" is considered one group and the "PP subject analysis set" another group and, consequently, the n° of subjects in this analysis is 22 and not 44; 2) for the "PP baseline subject analysis set" the n° of subjects with uncorrected ACPR has been indicated as 0, as at baseline the n° of aparasitaemic subjects in the PP population was 0.

Secondary: Proportion of Aparasitaemic Subjects at Day 1

End point title	Proportion of Aparasitaemic Subjects at Day 1
End point description:	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Aparasitaemic Subjects at Day 2

End point title	Proportion of Aparasitaemic Subjects at Day 2
End point description:	
End point type	Secondary
End point timeframe:	
Day 2	

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Aparasitaemic Subjects at Day 7

End point title	Proportion of Aparasitaemic Subjects at Day 7
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End point description:

End point type	Secondary
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End point timeframe:

Day 7

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	21			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Aparasitaemic Subjects at Day 21

End point title	Proportion of Aparasitaemic Subjects at Day 21
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End point description:

End point type	Secondary
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End point timeframe:

Day 21

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Aparasitaemic Subjects at Day 42

End point title	Proportion of Aparasitaemic Subjects at Day 42
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End point description:

End point type	Secondary
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End point timeframe:

Day 42

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Afebrile Subjects at Day 1

End point title	Proportion of Afebrile Subjects at Day 1
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End point description:

End point type	Secondary
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End point timeframe:

Day 1

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Afebrile Subjects at Day 2

End point title	Proportion of Afebrile Subjects at Day 2
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End point description:

End point type	Secondary
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End point timeframe:

Day 2

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	22			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Afebrile Subjects at Day 7

End point title	Proportion of Afebrile Subjects at Day 7
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End point description:

End point type	Secondary
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End point timeframe:

Day 7

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	21			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Afebrile Subjects at Day 21

End point title	Proportion of Afebrile Subjects at Day 21
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End point description:

End point type	Secondary
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End point timeframe:

Day 21

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Afebrile Subjects at Day 42

End point title	Proportion of Afebrile Subjects at Day 42
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End point description:

End point type	Secondary
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End point timeframe:

Day 42

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects with Uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 42

End point title	Proportion of Subjects with Uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 42
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End point description:

End point type	Secondary
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End point timeframe:

Day 42

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects with Treatment Failure (TF) at Day 21

End point title	Proportion of Subjects with Treatment Failure (TF) at Day 21
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End point description:

End point type	Secondary
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End point timeframe:

Day 21

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects with Treatment Failure (TF) at Day 42

End point title	Proportion of Subjects with Treatment Failure (TF) at Day 42
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End point description:

End point type	Secondary
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End point timeframe:

Day 42

End point values	Per protocol (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall trial

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	ITT/Safety population
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Reporting group description:

The Intention to Treat (ITT) population includes all patients taking at least one dose of the study drug. This population is used for the safety analysis. As for the safety data presentation, it is referenced as Safety Population.

Serious adverse events	ITT/Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	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	14 / 27 (51.85%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Hepatic enzyme increased			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Transaminases abnormal			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Transaminases increased			

subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1 1 / 27 (3.70%) 1 1 / 27 (3.70%) 1 4 / 27 (14.81%) 5		
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Skin and subcutaneous tissue disorders			

Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1 1 / 27 (3.70%) 1 1 / 27 (3.70%) 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? Yes

Date	Interruption	Restart date
23 November 2016	A total of 100 male and female patients satisfying the inclusion criteria and presenting none of the exclusion criteria had to be enrolled in the study. However, the study was prematurely interrupted due to a very low rate of recruitment.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A total of 100 male and female patients satisfying the inclusion criteria and presenting none of the exclusion criteria had to be enrolled in the study. However, the study was prematurely interrupted due to a very low rate of recruitment.
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Notes: