Proof of Concept Study of Eurartesim® in Patients with Imported Uncomplicated Plasmodium Vivax Malaria

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Primary Objective:• Uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 21.Secondary Objectives: • Proportion of aparasitaemic patients (at different visits).• Proportion of afebrile patients (at different visits).• Uncorrected...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Protozoal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON40593

Source
ToetsingOnline

Brief title
Eurartesim® in imported, uncomplicated P. vivax malaria

Condition

- Protozoal infectious disorders

Synonym
Malaria

Research involving
Human

Sponsors and support

Primary sponsor: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.
Source(s) of monetary or material Support: Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.

Intervention

Keyword: Plasmodium vivax Malaria

Outcome measures

Primary outcome

Day 21 uncorrected ACPR.

Secondary outcome

• Proportion of aparasitaemic patients at different visits.

• Proportion of afebrile patients (at different visits).

• Day 42 uncorrected ACPR.

• Proportion of patients with TF.

• Adverse Event (AE) occurrence.

• Changes from screening in haematology, biochemistry, urinalysis, vital signs.

Study description

Background summary

Eurartesim® , the drug that will be utilized in this trial, is marketed in most of the European Countries and is recommended globally by the World Health Organisation (WHO) as an option for the treatment of uncomplicated Plasmodium falciparum malaria.
Eurartesim® is a fixed-dose combination of 2 active compounds, dihydroartemisinin (DHA) and piperaquine tetraphosphate (PQP) for which substantial amount of data have been collected in patients with uncomplicated P. falciparum malaria and also several trials have provided evidence of high cure rate in patients with P. vivax malaria when these two compounds have been administered. No systematic studies have been conducted so far on efficacy and safety of the DHA+PQP treatment in patients with imported P. vivax malaria. Acquiring data is therefore of particular importance since malaria represents an important burden among all travel-acquired illnesses and also considering the number of cases due to P. vivax infection (10-20% of the imported malaria

cases).

Study objective

Primary Objective:
• Uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 21.

Secondary Objectives:
• Proportion of aparasitaemic patients (at different visits).
• Proportion of afebrile patients (at different visits).
• Uncorrected ACPR at Day 42.
• Proportion of patients with Treatment Failure (TF).

Safety and tolerability of the drug:
• Adverse Event (AE) occurrence.
• Changes from screening in haematology, biochemistry, urinalysis, vital signs.

Study design

A multi-centre, phase II, single arm trial to assess the efficacy of Eurartesim® oral formulation (320/40 mg PQP/DHA) in adult patients with uncomplicated Plasmodium vivax malaria.
One-hundred adults (males and females, age >=18 years) visiting the study clinics and for whom a diagnosis of uncomplicated P. vivax malaria (according to the WHO criteria) is confirmed, by a microscopic parasitological diagnosis and quantitative parasitaemia, and have signed an Informed Consent Form will be included in the study.
Eurartesim® tablets will be administered to the patients meeting the protocol recruitment criteria after the parasitological results of the thick and thin blood smear are known.
For the radical cure of P. vivax malaria, starting at Day 21 of the study, patients will receive an appropriate anti-hypnozoite drug regimen (to eradicate dormant hypnozoites from the liver) according to WHO guidelines and to local clinical procedures, under the responsibility of the Investigator following the local practice. All patients will have a final assessment at Day 42.

Intervention

Each patient will receive a specific amount of drug according to his/her body weight once a day for three consecutive days.
The following table reports the amount of drug and the number of Eurartesim® tablets to be administered:

Body weight (kg) Daily dose (mg) Tablet strength and number of tablets per dose
PQP DHA
24 to <36 640 80 2 x 320mg / 40mg tablets

36 to <75 960 120 3 x 320mg / 40mg tablets
75 to 100 1280 160 4 x 320mg / 40mg tablets

The daily dose will be re-administered in case of vomiting within 30 minutes from the drug administration, while half dose will be re-administered in case of vomiting occurred between 30 and 60 minutes after the drug administration. In case of repeated vomiting (the same day) the drug cannot be re-administered more than once and another drug for malaria treatment has to be adopted.

Daily dose of Eurartesim® will be administered according with the following regimen:
Day 0: hour *0*
Day 1: hour *0* + 24 hours
Day 2: hour *0* + 48 hours

The Eurartesim® film coated formulation is a 320/40 mg Piperaquine Tetraphosphate (PQP) /Dihydroartemisinin (DHA) formulation.

The drug will be taken with water and without food over three consecutive days for a total of three doses taken at the same time each day.
Each dose should be taken no less than 3 hours after the last food intake. No food should be taken within 3 hours after each dose.

Study burden and risks

Side effects following treatment with the study medications could occur. Generally, side effects (Anaemia, Headache, Asthenia, Fever, Flu, Respiratory tract infection, Loss of appetite, Dizziness, Convulsion, Heart rhythm disturbances, Cough, Vomiting, Abdominal pain, Diarrhoea, Nausea, Hepatitis, Hepatomegaly, Abnormal liver function tests, Pruritus, Arthralgia, Myalgia) are mild and short lived. In some cases, a transient alteration has been noted on the electrocardiographic tracing, but it did not cause any clinical consequence. In order to avoid an increased frequency and amplitude of such alteration, the study drug have to be administered three hours apart from food intake. The blood sampling may cause pain and swelling. You will be monitored closely after receiving treatment for malaria with the study medications for any possible side effect of the drug and will receive appropriate medical care for any problem that happens during the course of the study.

Eurartesim® and other artemisinin-based combination therapies are increasingly being used for the treatment of chloroquine resistant P. vivax malaria, moreover in case of mixed infections Eurartesim® would be effective against most of the other malaria species.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.Have read the Information for the Patient and signed the Informed Consent Form;;2.Aged >=18 years;;3.Ability to swallow oral medication;;4.Body weight comprised between 24 kg and 100 kg (included) for males and females;;5.Uncomplicated malaria with microscopically confirmed monoinfection by Plasmodium vivax or mixed infection (i.e. infection with P. vivax and other Plasmodium species);;6.Willingness to comply with the study protocol and the study visit schedule.

Exclusion criteria

1.Participation in any investigational drug study during the previous 30 days;;2.Antimalarial treatment with chloroquine and quinine within the previous 6 weeks, with piperaquine-based

compounds or mefloquine or lumefantrine within the previous 3 months and with halofantrine within the previous 30 days prior to screening;;3.Known hypersensitivity to piperaquine and/or dihydroartemisinin;;4.P. vivax/Plasmodium species asexual stage parasitaemia >= 5% RBCs (in cases of mixed infection);;5.Clinical and/or laboratory features of severe malaria according to WHO criteria (WHO 2010);;6.ECG abnormality that requires urgent management (i.e. clinically significant arrhythmias, AV block II and III degree etc.);;7.Family history of sudden death, or known congenital prolongation of the QT interval;8.Lengthening of QT interval on ECG: QTc (Fridericia*s correction) >=450 ms for males and >=470 ms for females;;9.Concomitant administration of any treatment which can induce a lengthening of QT interval (i.e. antihistamines, macrolides, etc.) and of any antimalarial drugs (for the full list of prohibited drugs refer to section 8.3);;10.Any contraindication to blood sampling (i.e. important haemorrhagic diathesis);;11.Presence of intercurrent illness or any condition (i.e. severe vomiting and dehydration) which in the judgement of the Investigator would place the patient at undue risk or interfere with the study results; ;12.Hypoglycaemia (blood glucose levels < 2.2 mmol/L or < 40 mg/dL);;13.Splenectomy;;14.Pregnant or lactating women. During the study period (Day 0- Day 42), fertile women who are sexually active must use an adequate birth control method. They should utilize oral or patch contraceptives, contraceptive implant or depot injection or an intrauterine device from at least one month before screening and during the whole study period. In all the other cases they have to agree to remain inactive or use condoms with a spermicidal agent during the study period;;15.Presence of jaundice;;16.Known renal impairment (serum creatinine > 2X the upper limit of the hospital laboratory reference range);;17.Known liver insufficiency (AST and/or ALT > 3X the upper limit of the hospital laboratory reference range);;18.Relevant anaemia (Hb< 8 g/dL).

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Eurartesim®
Generic name:	dihydroartemisinin (DHA)/piperaquine tetraphosphate (PQP)
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-02-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-01-2015
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-003763-56-NL
CCMO	NL47491.058.13