A clinical study to assess the safety and feasibility of relapsing P. vivax controlled human malaria infection through experimental sporozoite infection of healthy malaria-naïve UK adults, and to characterise parasite growth and immune responses to primary and relapsing P. vivax infection

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Primary ObjectiveTo assess the safety, feasibility and frequency of relapsing P. vivax PvW1 infection after experimental sporozoite-administered Controlled Human Malaria Infection (CHMI)Secondary ObjectivesTo assess the immune response to primary...

Ethical review	Approved WMO
Status	Pending
Health condition type	Protozoal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON57368

Source
ToetsingOnline

Brief title
BIO-006

Condition

- Protozoal infectious disorders

Synonym
malaria, Plasmodium vivax

Research involving
Human

Sponsors and support

Primary sponsor: University of Oxford
Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: CHMI, P.vivax, relapse infection

Outcome measures

Primary outcome

- Safety of primary and relapsing P. vivax infection following

sporozoite-administered CHMI as measured by (S)AE occurrences

- Primary P. vivax infection following sporozoite-administered CHMI as measured

by detectable parasitaemia by qPCR +/- clinical symptoms

- Frequency of P. vivax relapse infections as measured by number of malaria

episodes confirmed by qPCR occurring within a 6-month follow-up period after

treatment of primary infection, and time to relapse infection

Secondary outcome

- Serological response to a panel of P. vivax antigens by ELISA

Study description

Background summary

Plasmodium vivax is the second-most important malaria parasite and has a significant disease and health burden. Relapse infections account for most cases of P. vivax malaria. The elimination of P. vivax hypnozoites is therefore

an essential component in the pursuit of malaria eradication. However, the current drugs available are not fit for this purpose due to contraindications, polymorphisms associated with poor metabolism, and partial efficacy. Novel drug therapies against hypnozoites are required. In addition, P. vivax vaccine candidates must be able to demonstrate efficacy in preventing the development of hypnozoites in order to have a meaningful impact on P. vivax incidence and onwards transmission. Current in vitro strategies for investigating new drug and vaccines are hampered by an inability to produce a long-term culture of P. vivax parasite, while *real world* studies of relapsing P. vivax disease are confounded by an unquantifiable contribution from primary reinfections and heterologous relapses. We therefore need new controlled research methods to improve our understanding of homologous hypnozoite reactivation, and provide a platform for the development of novel therapies (curative or preventative) against relapsing P. vivax malaria.

Study objective

Primary Objective
To assess the safety, feasibility and frequency of relapsing P. vivax PvW1 infection after experimental sporozoite-administered Controlled Human Malaria Infection (CHMI)

Secondary Objectives
To assess the immune response to primary and relapsing P. vivax PvW1 infection

Study design

non-randomized, open-label experimental study

Intervention

All participants undergo CHMI with P.vivax infected Anopheles mosquitoes. They also receive Malarone or Riamet as treatment against the blood stage of malaria. They receive this after CHMI and after recurrent infections. At the end of the study, they are treated with Primaquine.

Study burden and risks

-Mosquito bites: Participants will undergo CHMI by mosquito bites. Mosquito bites may cause local inflammatory reactions with redness, itching, swelling, scaling and/or tenderness. Topical anti-histamine cream for use twice daily for 3 days post-mosquito bite will be dispensed to both participants on the day of CHMI. Serious allergic reactions including anaphylaxis have not been seen in CHMI studies to date, but could theoretically occur. For this reason, participants will be inoculated in an area where Advanced Life Support trained physicians and defibrillator are immediately available.

-Phlebotomy: The approximate scheduled total blood volume drawn over the study period will be 477ml. Participants will never donate 470mL of blood in one sitting; the maximum volume they will donate in a single visit is 83mL so we would not expect them to report a high frequency of symptoms at the time of or just after blood donation. They will be closely monitored at all times of blood donation, and haemoglobin will be checked regularly, as described in the study procedures. Although the additional effect of malaria infection on potential anaemia is acknowledged, we are confident that the anticipated total blood volume should not compromise our participants.
Venepuncture: There may be minor bruising, local tenderness, pre-syncopal symptoms or syncope (rarely) associated with venepuncture or cannulation. To reduce these risks, venepuncture and cannulation will be performed by appropriately trained staff members.
-Risk of other infections: The challenge agent: PvW1 has been produced from a prospectively screened and infected donor with a universal blood group who passes all criteria for blood donation. All procedures related to producing the blood inoculum were done under strict quality assurance. The inoculum has been used safely in 37 malaria-naïve participants in the UK and in 8 participants in the Netherlands. The plasmosium infected mosquitoes will be created by the Radboud University Medical Center (RUMC) in Nijmegen, where healthy participants will be inoculated with PvW1. These participants will undergo similar stringent safety testing. This will include screening for blood borne infections (HIV, Hepatitis B and Hepatitis C), West Nile virus (a mosquito borne disease found in Western Europe) by PCR test, and other relevant mosquito borne diseases if indicated by travel history. The blood of these participants will then be fed to mosquitoes, which will have been reared under carefully controlled laboratory conditions. It is these laboratory-reared mosquitoes which will bite the participants in our study in order to infect them with PvW1. Due to this extensive repertoire of safety testing that has been performed the risk of transmission of any infections other than PvW1 to our participants is extremely low.
-P.vivax malaria: The main risk of P. vivax malaria are symptoms of systemic inflammation, such as fatigue, fever, headache, and myalgia. It is commonly characterized as *benign tertian malaria* because, in contrast to P. falciparum malaria, the risk of complications in healthy adults with a recently acquired infection is extremely low. Relapse infections may occur at any time during the study period and the exact number to be expected is unknown. This uncertainty will be emphasised to participants. They will be advised to contact the study team if they develop any symptoms of relapse malaria infection so that prompt treatment may be initiated.
-Relapsing P. vivax malaria following Primaquine treatment: Infection with P. vivax malaria carries a risk of ongoing relapsing disease if anti-hypnozoite treatment is suboptimal. This risk is minimised by giving participants a 14-day course of high-dose Primaquine treatment (30mg once daily) at the end of in-person follow-up. In addition we will screen participants for their ability to metabolise Primaquine effectively by checking CYP2D6 genotype. Only participants who demonstrate *high-metaboliser* status will be enrolled into

the study. After completion of Primaquine treatment, participants will be followed up by email fortnightly until 1 year following CHMI and then annually thereafter until the End of Study (5 years following CHMI).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Healthy, malaria-naïve adult aged 18 to 45 years
• Able and willing to provide informed consent to participate in the study
• Able and willing (in the opinion of the Investigator) to comply with all study requirements
• Participants of childbearing potential only: must practice continuous highly effective contraception until 3 months after completion of Primaquine treatment
• Normal G6PD screen

Exclusion criteria

• Red blood cells negative for the Duffy antigen/chemokine receptor (DARC)
• CYP2D6 genotype suggestive of poor or intermediate metabolism of Primaquine
• History of clinical malaria (any species) or previous participation in any malaria vaccine trial or CHMI
• Pregnancy, lactation or intention to become pregnant during the study
• Any clinically significant abnormal finding on biochemistry or haematology blood tests, or clinical examination.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2025
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	26-03-2025
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
CCMO	NL88438.091.24