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Safety and immune response of the malaria vaccine, R21/Matrix-M™, in Thai adults

Submission date 08/10/2023	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 18/10/2023	**Overall study status** Completed	[X] Statistical analysis plan [X] Results
Last Edited 28/10/2024	**Condition category** Other	[_] Individual participant data

Plain English summary of protocol

Background and study aims

Malaria is still a big problem globally, causing a lot of sickness and death. Plasmodium falciparum, the germ that causes malaria, is tricky to deal with because it has many ways to avoid the body's defenses. This makes it tough to create vaccines that work well and don't cost too much. We need vaccines that can stop 75% of malaria cases, as the World Health Organization wants.

One new vaccine called R21 is showing promise. It's made by combining Hepatitis B and parts of the malaria germ. This vaccine has been tested and found to be safe for people, with only a few minor side effects like fever. After a year, it was still working well, preventing malaria in 77% of cases. People who got this vaccine had a lot of anti-malaria antibodies in their blood, even more with a higher dose.

Now, we want to test this vaccine in Thailand to make sure it's safe and works in Asian people. We also want to check if it still works when given with malaria medicines. This will help us use the vaccine along with other efforts to eliminate malaria in the region. In short, we're going to study R21 in Thai adults to see if it's safe and works, even when given with malaria drugs.

Who can participate?

Healthy volunteers aged 18 - 55 years

What does the study involve?

This is a Phase 2 study, meaning it's the second step in testing a new medical treatment. It's open-label, which means both the patients and the doctors know which treatment the patients are getting.

Before joining the study, all potential volunteers will have a screening visit, where doctors make sure they meet the requirements to participate. They'll get a number, and if they qualify, they'll be given a case record form for their information.

At the first visit, they'll do a physical check-up, take blood for testing, and perform other assessments. If the patients meet all the conditions and none of the exclusions, they'll be assigned to one of three groups and get their first vaccine or medication.

The study participants will be watched closely for at least 30 minutes after getting the vaccine or medication. If there are any problems, they can get medical help right away.

There will be more visits after the first one, where they'll check the patients' health, take more blood for testing, and provide any necessary treatments. The study will be done openly, which means everyone knows which group the patients are in.

What are the possible benefits and risks of participating?
Study Benefits:
The information gathered from this research will contribute to the development of a vaccine against P. falciparum malaria. This vaccine could potentially aid in halting the spread of malaria and the development of resistance to malaria treatments in the area.

Phlebotomy Risk:
Getting blood drawn might result in minor bruising, local tenderness, or feeling a bit lightheaded.

R21/Matrix-M™ Vaccination Risk:
Common side effects observed in previous trials of the R21/Matrix-M™ vaccine include pain, swelling, redness, and tenderness at the injection site, as well as general symptoms like a low-grade fever, fatigue, muscle pain, headache, and feeling unwell. In rare cases, serious allergic reactions to vaccine components could occur, although this hasn't been reported in earlier studies with this vaccine in adults. There's also a theoretical concern about immune-related diseases, but no clear link between the vaccine and autoimmune diseases has been established.

Dihydroartemisinin/piperaquine (DHA-PIP) Risk:
DHA-PIP is a common treatment for uncomplicated malaria and is usually safe. Possible side effects include upset stomach, dizziness, headache, and disturbed sleep. These side effects are generally mild and occur in a small percentage of people. There's no strong evidence that DHA-PIP can significantly affect heart rhythms at typical doses.

Primaquine (PQ) Risk:
Primaquine, like other similar medicines, can lead to the breakdown of red blood cells in people with a certain genetic condition (G6PD deficiency), but the dose given in this study is considered safe even for those with this condition. Primaquine may cause stomach-related symptoms when taken in high doses for a long time, but this study uses a low dose that is not associated with these side effects.

Where is the study run from?
University of Oxford (UK) and Mahidol University (Thailand)

When is the study starting and how long is it expected to run for?
August 2022 to September 2023

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Lorenz von Seidlein, Lorenz@tropmedres.ac

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05252845

Protocol serial number
MAL22001

Study information

Scientific Title
A randomized, open label, single centre, phase 2 trial of the malaria vaccine, R21/Matrix-M™, to assess safety and immunogenicity of the vaccine in Thai adults

Study objectives
Malaria remains one of the leading causes of morbidity and mortality worldwide. Plasmodium falciparum is a complex pathogen with numerous immune evasion mechanisms which has added layers of complexity to the development of safe and protective vaccines. There remains an urgent need to identify and develop more protective and more affordable vaccine candidates that could achieve the World Health Organization (WHO) goal of 75% efficacy against clinical malaria.

R21 is a novel pre-erythrocytic candidate malaria vaccine. R21 includes Hepatitis B surface antigen (HBsAg) fused to the C-terminus and central repeats of the circumsporozoite protein of P. falciparum (CSP), which self-assemble into virus-like particles in yeast. R21 lacks the excess HBsAg found and comprises only fusion protein moieties.

R21/MatrixM™ (MM) had a favourable safety profile and was well tolerated. The majority of adverse events were mild, with the most common event being fever. None of the serious adverse events were attributed to the vaccine. At one year, vaccine efficacy remained high, at 77%. Participants vaccinated with R21/MM™ showed high titres of malaria-specific anti- Asn-Ala-Asn-Pro (NANP) antibodies 28 days after the third vaccination, which were almost doubled with the higher adjuvant dose. Titres waned but were boosted to levels similar to peak titres after the primary series of vaccinations after a fourth dose administered one year later.

Currently, there are no safety and immunogenicity data for the use of R21/MatrixM™ in Asian populations. This trial will generate the required data for the use of this vaccine in Asia. For integration with the current targeted malaria elimination (TME) activities, which provide mass drug administrations at months M0, M1, and M2, it would be most efficient and practical to provide the vaccine at the same intervals.

In summary: The investigators propose to conduct a safety and immunogenicity trial of R21 /MatrixM™ in Thai adults. The major aims of this study are to
1) assess the safety and immunogenicity of R21/MatrixM™ in Thai adults
2) confirm that the co-administration of antimalarial drugs with the malaria vaccine R21 /MatrixM™ does not reduce the immunogenicity of the vaccine and
3) assess the absorption and pharmacokinetics of antimalarial drugs piperaquine, and a single low dose of primaquine (SLDPQ) when co-administered with R21/MatrixM™.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. Approved 12/10/2022, Oxford Tropical Research Ethics Committee (University of Oxford Research Services, Research Governance Ethics & Assurance Boundary Brook House, Churchill Drive, Oxford, OX3 7GB, United Kingdom; +44 (0) 1865 282106; oxtrec@admin.ox.ac.uk), ref: 9-22

2. Approved 04/08/2022, Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (420/6 Ratchawithi Road, Bangkok, 10400, Thailand; +66 (0) 2354 9100-4 ext. 1349; tmectropmed@mahidol.ac.th), ref: TMEC22-034

Primary study design
Interventional

Study design
Randomized open-label single centre Phase 2 trial

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Malaria vaccine in healthy volunteers

Interventions
A total of 120 participants will be enrolled and randomized into one of three study arms in a ratio of 5:5:2. Each arm will have 50 participants (for arm 1 and 2) and 20 participants (for arm 3). For arm 1 and 3, the eligible volunteers will be asked to come into the Hospital for Tropical Diseases as out-patient on Day 0, Day 1, Day 2, and Day 7 of Study Months 0, 1 and 2; and on Day

0 of Study Months 3 and 6. There are a total of 15 study visits.
For arm 2, the eligible volunteers will be asked to come into the hospital as out-patient on the Day 0, and Day 7 of Study Months 0, 1 and 2; and on Day 0 of Study Months 3 and 6. There are a total of 9 study visits.

(Arm 1, n=50)
R21/MatrixM™ + Dihydroartimisinin (DHA)-Piperaquine (PIP)+ primaquine (PQ)
Participant will receive R21/MatrixM™ + 3 doses DHA-PIP+PQ at Month 0, Month 1 and Month 2

(Arm 2, n=50)
R21/MatrixM™ only
Participant will receive R21/MatrixM™ standard dose at Month 0, Month 1 and Month 2

(Arm 3, n=20)
DHA-PIP+PQ only
Participant will receive 3 doses DHA-PIP+PQ at Month 0, Month 1 and Month 2

Intervention Type
Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
R21/MatrixM™, Dihydroartimisinin (DHA)-Piperaquine (PIP), Primaquine (PQ)

Primary outcome(s)
Safety measured using patient records:
1. Occurrence of solicited from the date of each vaccination to 7 days of each vaccination.
2. Occurrence of unsolicited adverse events (AEs) from the date of the first vaccination to 28 days after the last vaccination, according to the MedDRA classification.
3. Occurrence of serious adverse events (SAEs) during the whole study period, i.e. during a 6-month follow up period from the receipt of first vaccination, according to the MedDRA classification.

Key secondary outcome(s)
1. For Arms 1 and 2, the concentration of antibodies against Plasmodium falciparum circumsporozoite (anti-NANP total IgG antibody), one month after the first dose (at Study month 1), one month after the second dose (at Study month 2), one month after the third dose (at Study Month 3) and six months after the first dose (at Study Month 6).
2. Exploratory immunology endpoints including but not limited to cellular immunity at baseline, months 1, 2, 3, 6
3. For Arms 1 and 3, piperaquine levels following the administration of the antimalarials with or without vaccine

Completion date
18/09/2023

Eligibility

Key inclusion criteria

1. Participant is a healthy adult, aged 18 to 55 years (both inclusive), of Thai origin.
2. Participant is willing and able to voluntarily give informed consent to participate in the trial
3. Able, in the investigator's opinion, and willing to comply with the study requirements and follow-up.
4. Women of childbearing potential: must agree to practice continuous, effective contraception for the duration of the trial, and have a negative pregnancy test before each vaccination. (Costs for contraceptives will be reimbursed by the trial.)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
All

Total final enrolment
127

Key exclusion criteria
1. Pregnancy or breastfeeding, or planned pregnancy during the course of the study.
2. Presence of any medical condition (physical or mental) which, may place the participant at undue risk or interfere with the results of the study*. Including: serious cardiac, renal, hepatic, or neurological disease, severe malnutrition
3. Any confirmed or suspected immunosuppressive or immunodeficient condition. Including: history of splenectomy, human immunodeficiency virus (HIV) infection
4. Chronic administration (>14 days in total) of immunosuppressants or other immune-modifying drugs within six months of enrollment. Including: oral corticosteroids equivalent to prednisone > 20 mg/day (a*)
5. History of an autoimmune disease
6. Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody (b*) detected in serum.
7. HIV antibody detected in serum
8. Screening electrocardiogram (ECG) demonstrating a QTc interval ≥ 450 ms
9. Finding on safety laboratory values as defined below:
9.1. AST > 2 x upper normal limit
9.2. ALT > 2 x upper normal limit
9.3. Anaemia (Hb < 10 g/dL),
9.4. Platelets < 150,000
9.5. Total bilirubin > 2 x upper normal limit
10. Abnormalities of examination or investigations at screening. Including: hepatomegaly, right upper quadrant abdominal pain or tenderness, abnormal blood tests (as defined in the protocol

which are not listed above)
11. Positive malaria parasitaemia (RDT) at screening or baseline (Month 0, Day 0).
12. Receipt or planned receipt of an investigational medical product or participation in an interventional clinical trial during the study period
13. Contraindications to the use of artemisinins, piperaquine or primaquine*.
14. Use of medications with known potential interactions, prior allergic reactions to one or more components of the drug regimen.
15. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine (e.g. egg products)
16. History of clinically significant contact dermatitis.
17. Contraindication to intramuscular (IM) injection*
18. Administration of a vaccine not included in the study protocol within 7 days of a study vaccine (c*).
19. History of anaphylaxis post-vaccination.
20. Administration of immunoglobulins and/or any blood products during the period starting three months before the first dose of study vaccine or planned administration during the study period.

* subject to the investigator's judgement

Exceptions:
(a*) Inhaled and topical steroids.
(b*) Participation in hepatitis C vaccine study with confirmed negative HCV antibodies prior to participation in that study, and negative HCV RNA PCR at screening for this study
(c*) The following vaccinations may be administered more than 7 days before or after a study vaccination: polio, diphtheria, tetanus, pertussis, hepatitis B, Haemophilus influenzae type b, Bacillus Calmette–Guérin (BCG vaccine), measles, influenza, pneumococcal disease, COVID-19 or yellow fever

Date of first enrolment
04/01/2023

Date of final enrolment
31/03/2023

Locations

Countries of recruitment
Thailand

Study participating centre
Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
All personal details of participants will be de-identified. These data including laboratory investigation results will be stored and may be shared with other researchers to apply in their research in accordance with the MORU data sharing policy https://www.tropmedres.ac/units/moru-bangkok/bioethics-engagement/data-sharing.

IPD sharing plan summary
Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/07/2024	28/10/2024	Yes	No

Protocol file	version 2022	09/11/2022	13/10/2023	No	No
Statistical Analysis Plan	version 1.0	10/03/2023	13/10/2023	No	No