Safety and protective efficacy of genetically modified Plasmodium berghei (Pb(PfCS@UIS4)) malaria parasites in healthy volunteers

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Phase 1Primary objective:To determine the safety and tolerability of administration of Pb(PfCS@UIS4) to healthy volunteers delivered by infectious mosquito bites.Secondary objective:Immunogenicity of Pb(PfCS@UIS4) as assessed by ELISA and IFA....

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

Summary

ID

NL-OMON45576

Source
ToetsingOnline

Brief title
PbVac

Condition

- Protozoal infectious disorders

Synonym
Malaria, Plasmodium falciparum

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: Path-MVI

Intervention

Keyword: genetically modified parasite, malaria, Plasmodium falciparum, vaccine

Outcome measures

Primary outcome

Phase 1 (Safety)

Primary endpoints:

* Frequency and magnitude of adverse events in study groups.

* Presence of parasitemia after exposure to Pb(PfCS@UIS4), as assessed by thick smear.

Phase 2 (Efficacy)

Primary endpoints:

* Frequency and magnitude of adverse events after multiple exposures to Pb(PfCS@UIS4).

* Time to parasitemia after CHMI with the wild-type NF54 P. falciparum strain, as detected by qPCR.

Secondary outcome

Secondary endpoints:

* Immunogenicity of Pb(PfCS@UIS4) as assessed by ELISA and IFA.

Study description

Background summary

Malaria is caused by Plasmodium (P.) parasites and is one of the major infectious diseases in the world, with a tremendous impact on the quality of life, significantly contributing to ongoing poverty in endemic countries. Whole organism malaria vaccine approaches generate high-level (>90%) protection against malaria in humans through i) immunization with sporozoite forms of the parasite attenuated by irradiation or ii) when sporozoites are administered together with a chemoprophylactic dose of chloroquine[1, 2] In the underlying study, a genetically modified P. berghei parasite is used. P. berghei is one of the four Plasmodium species that causes malaria in rodents. The hypothesis is that immunization of humans with P. berghei will induce a cross-species immune response without the risk of a breakthrough infection. To further increase the potential for protective efficacy, the P. falciparum circumsporozoite (CS)-protein gene has been integrated in the P. berghei parasite, generating a genetically modified P. berghei parasite, abbreviated as Pb(PfCS@UIS4).

Study objective

Phase 1
Primary objective:
To determine the safety and tolerability of administration of Pb(PfCS@UIS4) to healthy volunteers delivered by infectious mosquito bites.

Secondary objective:
Immunogenicity of Pb(PfCS@UIS4) as assessed by ELISA and IFA.

Exploratory objective:
To analyse immune responses in volunteers immunized by Pb(PfCS@UIS4).

Phase 2
Primary objective:
To determine the safety, tolerability and protective efficacy of immunization with Pb(PfCS@UIS4) against Controlled Human Malaria Infection (CHMI) by mosquito bite.

Secondary objective:
Immunogenicity of Pb(PfCS@UIS4) as assessed by ELISA and IFA.

Exploratory objective:
To analyse immune responses in volunteers exposed to Pb(PfCS@UIS4).

Study design

Study design:
Multicenter, open label, adaptive design, study
Phase 1
* (Group 1 and 2): dose escalation, safety trial (n=6)

* (Group 3): dose escalation, safety trial (n=12)
Phase 2
* (Group 3): protective efficacy trial
* (Group 4): infectivity control group, challenge 1 (n=6)
* (Group 5): infectivity control group, challenge 2 (n=6)

Intervention

Phase 1
Group 1: exposure to bites of 5 Pb(PfCS@UIS4) infected mosquitoes
Group 2: exposure to bites of 25 Pb(PfCS@UIS4) infected mosquitoes
Group 3: exposure to bites of 75 Pb(PfCS@UIS4) infected mosquitoes

Phase 2
Group 3: 3-4 immunisations with bites of 75 Pb(PfCS@UIS4) infected mosquitoes and 1-2 challenges with bites of 5 Pf infected mosquitoes
Group 4: exposure to bites of 5 Pf- infected mosquitoes, challenge 1
Group 5: exposure to bites of 5 Pf- infected mosquitoes, challenge 2

Study burden and risks

Please refer to question E4 for the burden of the volunteers.
Please refer to question E9 for the possible risks related to participation.
Please refer to Section 12 of the Clinical Trial Protocol for a risk assessment.

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. Subject is aged * 18 and * 35 years and in good health. ;2. Subject has adequate understanding of the procedures of the study and is able and willing (in the investigator*s opinion) to comply with all study requirements.;3. Subject is willing to complete an informed consent questionnaire and is able to answer all questions correctly.;4. Subject is able to communicate well with the investigator and is available to attend all study visits, lives in Rotterdam or in proximity to the trial centre (can be on site within 1 hour) or is willing to stay in a hotel close to the trial centre during part of the study (phase 1: from day of immunization to day 12 post-immunization; phase 2: from day of immunization to day 8 post-immunization. ;5. The subject will remain within the Netherlands from day -1 until day +28 after immunization during phase 1; from day -1 until day 12 after each immunization during phase 2, and during the challenge period, will not travel to a malaria-endemic area during the study period, and is reachable (24/7) by mobile telephone throughout the entire study period. ;6. Subject agrees to their general practitioner being informed and contacted about their participation in the study and agrees to sign a form to request the release by their General Practitioner (GP), and medical specialist when necessary, to the investigator(s), of any relevant medical information concerning possible contra-indications for participation in the study. ;7. The subject agrees to refrain from blood donation to Sanquin or for other purposes throughout the study period and for a defined period thereafter according to current Sanquin guidelines (3 years minimum, depending on serology).;8. For female subjects: subject agrees to use continuous adequate contraception** and not to breastfeed for the duration of study. ;9. Subject agrees to refrain from intensive physical exercise (disproportionate to the subject*s usual daily activity or exercise routine) during the malaria challenge period. ;10. Subject agrees to avoid additional triggers that may cause elevations in liver enzymes including alcohol from baseline up to 1 week post treatment.;11. Subject has signed written informed consent to participate in the trial.

Exclusion criteria

1. Any history, or evidence at screening, of clinically significant symptoms, physical signs or abnormal laboratory values suggestive of systemic conditions, such as cardiovascular, pulmonary, renal, hepatic, neurological, dermatological, endocrine, malignant, haematological, infectious, immunodeficient, psychiatric and other disorders, which could compromise the health of the volunteer during the study or interfere with the interpretation of the study results. These include, but are not limited to, any of the following. ;1.1. Body weight <50 kg or Body Mass Index (BMI) <18 or >30 kg/m2 at screening. ;1.2. A heightened risk of cardiovascular disease, as determined by: an estimated ten year risk of fatal cardiovascular disease of *5% at screening, as determined by the Systematic Coronary Risk Evaluation (SCORE); history, or evidence at screening, of clinically significant arrhythmia*s, prolonged QT-interval or other clinically relevant ECG abnormalities; or a positive family history of cardiac events in 1st or 2nd degree relatives <50 years old. ;1.3. A medical history of functional asplenia, sickle cell trait/disease, thalassaemia trait/disease or G6PD-deficiency. ;1.4. History of epilepsy in the period of five years prior to study onset, even if no longer on medication. ;1.5. Screening tests positive for Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) ;1.6. Chronic use of i) immunosuppressive drugs, ii) antibiotics, iii) or other immune modifying drugs within three months prior to study onset (inhaled and topical corticosteroids and oral anti-histamines exempted) or expected use of such during the study period. ;1.7. Any recent or current systemic therapy with an antibiotic or drug with potential anti-malarial activity (chloroquine, atovaquone-proguanil, arthemether-lumefantrine, sulfadoxine-pyrimethamine, doxycycline, tetracycline, piperaquine, benzodiazepine, flunarizine, fluoxetine, tetracycline, azithromycin, clindamycin, erythromycin, hydroxychloroquine, etc.) (allowable timeframe for use at the Investigator*s discretion).;1.8. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years. ;1.9. Any history of treatment for severe psychiatric disease by a psychiatrist in the past year. ;1.10. History of drug or alcohol abuse interfering with normal social function in the period of one year prior to study onset, positive urine toxicology test for cocaine or amphetamines at screening or at inclusion, or positive urine toxicology test for cannabis at inclusion. ;2. For female subjects: positive urine pregnancy test at screening and/or at the baseline visits, including baseline of immunizations (I-1) and or baseline before CHMI (C-1).;3. Any history of malaria, positive serology for P. falciparum, or previous participation in any malaria (vaccine) study. ;4. Known hypersensitivity to or contra-indications (including co-medication) for use of sulfadoxine-pyrimethamine, piperaquine, chloroquine, Malarone®, artemether-lumefantrine, primaquine or history of severe (allergic) reactions to mosquito bites.;5. Receipt of any vaccinations in the 3 months prior to the start of the study or plans to receive any other vaccinations during the study period or up to 8 weeks thereafter.;6. Participation in any other clinical study in the 30 days prior to the start of the study or during the study period. ;7. Being an employee or student of the department of Medical Microbiology and Infectious Diseases of the Erasmus MC or Radboudumc, or the department of Internal Medicine of the Radboudumc or Havenziekenhuis. ;8. Any other condition or situation that would, in the opinion of the investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-05-2017
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism

Ethics review

Approved WMO Date:	31-01-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-03-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2017
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2017-000315-17-NL
CCMO	NL60019.000.17
Other	will follow