Safety and preliminary protective efficacy of genetically attenuated Pf*mei2 (GA2) malaria parasites in healthy Dutch volunteers

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Phase 1 • Primary objective: to determine the safety and tolerability, including the attenuation phenotype of a novel late-arresting GAP, named GA2 parasite, administered by sequentially increasing numbers of mosquito bites.• Secondary objective: to...

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

Summary

ID

NL-OMON51062

Source
ToetsingOnline

Brief title
GA2

Condition

- Protozoal infectious disorders

Synonym
Malaria, parasitaire ziekte

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Bontius Stichting

Intervention

Keyword: Controlled human malaria infection, Immunisation, Malaria, Plasmodium falciparum

Outcome measures

Primary outcome

Primary endpoints:

Phase 1:

• Number of volunteers with blood-stage parasitaemia after exposure to the GA2 parasite, as assessed by qPCR.

• Number and magnitude of adverse events (AEs) and serious adverse events (SAEs).

Phase 2:

• Number of volunteers protected against CHMI after immunisation with the GA2 parasite.

• Number and magnitude of AEs and SAEs.

Secondary outcome

Secondary endpoints (Phase 1 and Phase 2):

• Kinetics of cellular and humoral immune response of volunteers exposed to the GA2 and GA1 parasite.

Study description

Background summary

Malaria is one of the most common infectious diseases worldwide, affecting as many as 228 million people and causing 405.000 deaths each year. Given the rising resistance of both parasites against anti-malarial drugs and mosquitoes against insecticides, the goal of defeating malaria is becoming more elusive and an alternative to existing tools of eradications is urgently needed. One promising possibility is the development of a vaccine against the disease.

Among the different approaches to vaccine development, attenuated sporozoite (ASp) vaccines for Plasmodium falciparum (Pf) malaria stand out for their high (>90%) protective efficacy in human trials. There are different types Pf ASp vaccines, namely radiation attenuated sporozoites (RAS) and genetically attenuated parasites (GAP).
The way RAS and GAP work is that they prime the immune system for recognition of the wild-type (WT) parasite at a later time point. The parasites used for vaccination interrupt development in the pre-erythrocytic liver stages (RAS and GAP), allowing for recognition by the immune system while at the same time also avoiding the debilitating symptoms of clinical malaria.

Recently, a new GAP, the GA2 parasite (Pf*mei2), lacking one gene and arresting development during the late liver-stage, was created. The advantage of the GA2 parasite is that, by arresting development at a later stage than RAS and previous GAPs, it may allow for prolonged antigenic exposure to the immune system and thus have more powerful immunogenic properties. The hope is then that the GA2 parasite will have good protective efficacy and be a suitable vaccine candidate.
The GA2 phenotype closely resembles the *sporozoites under chemoprophylaxis strategy*, whereby live sporozoites are administered under chloroquine or mefloquine prophylaxis cover, which has previously shown to very efficiently induce immunity in healthy malaria-naïve individuals.
The scope of this trial is to evaluate the safety and tolerability of GA2 parasite in humans and to test its preliminary protective efficacy against controlled human malaria infection (CHMI). Moreover, immunological responses elicited by the GA2 parasite will be compared to those elicited by one of its predecessors, the GA1 parasite (Pf*b9*slarp).

Study objective

Phase 1
• Primary objective: to determine the safety and tolerability, including the attenuation phenotype of a novel late-arresting GAP, named GA2 parasite, administered by sequentially increasing numbers of mosquito bites.
• Secondary objective: to analyse the humoral and cellular immune response of healthy volunteers exposed to the novel late-arresting GA2 parasite.

Phase 2
• Primary objective: to determine the safety, tolerability and the preliminary protective efficacy of the novel late-arresting GA2 parasite against CHMI.

• Secondary objective: to analyse and compare the cellular and humoral immune response of healthy volunteers exposed to the late-arresting GA2 or the early-arresting GA1 parasite.

Study design

This will be a first-in-human, double-blind, randomized clinical trial of the GA2 parasite in healthy, malaria-naïve male and female volunteers. Recruitment and follow-up will take place at the LUMC, exposure to parasites by mosquito bites will take place at RUMC.

Phase 1 will be an open label, dose escalation, safety trial in two cohorts of volunteers to assess safety, tolerability and attenuation phenotype (lack of breakthrough blood-stage infections) of the GA2 parasite.
21 volunteers will participate in Phase 1 in two different cohorts: six individuals in the first cohort and 15 individuals the second cohort.
Volunteers in Cohort 1 and Cohort 2 will be exposed to 15 and 50 GA2-infected mosquito bites respectively. End of follow-up in Phase 1 will be six months after the last exposure to the GA2 parasite.

Phase 2 will be a double-blind, randomized trial aimed at assessing the preliminary protective efficacy of the GA2 parasite.
30 volunteers will participate in Phase 2 and will be randomly allocated to either of three groups: 15 volunteers in Group 1 will be exposed to bites of GA2-infected mosquitoes, 10 volunteers in Cohort Group 2 will be exposed to bites of GA1-infected mosquitoes and five volunteers in Group 3 will be exposed to uninfected mosquitoes and serve as infectivity controls. Immunization by exposure to mosquito bites will be repeated three times at intervals of 28 days. Three weeks after the last immunization, all volunteers will undergo CHMI by five bites of mosquitoes infected with WT PfNF54 sporozoites. As soon as blood stage parasitaemia is detected by qPCR (equal to or more than 100 parasites per ml) or 28 days after CHMI at the latest, volunteers will be treated with a curative regimen of antimalarials (atovaquone/proguanil or, alternatively, artemether/lumefantrine), dosed according to local hospital guidelines. End of follow-up in Phase 2 will be six months after CHMI.

Intervention

Phase 1: six volunteers will be allocated to Cohort 1 and will be exposed to 15 bites of GA2-infected mosquitoes. If this dose is safe and there are no breakthrough blood-stage infections, 15 volunteers will be allocated to Cohort 2 and will be exposed to 50 bites of GA2-infected mosquitoes. If this dose is safe and there are no more than five (30%) breakthrough blood-stage infections, the trial will proceed to the next phase.

Phase 2: 30 volunteers will be allocated to three groups in a double-blind

randomized fashion. Group 1 will consist of 15 volunteers who will be exposed to 50 GA2 infected mosquitoes, Group 2 will consist of 10 volunteers who will be exposed to 50 GA1 by 50 mosquito bitess and Group 3 will consist of five volunteers who will be exposed to 50 uninfected mosquito bites. Exposure to either intervention will be repeated three times at 28-day intervals. Three weeks after the last exposure, all volunteers will undergo CHMI with five (WT) PfNF54-infected mosquitoes.

Recruitment and follow-up of all volunteers will take place at the Leiden University Medical Centre (LUMC). Exposure to mosquitoes in Phase 1 and 2 for the purpose of immunisation and the CHMI will take place at Radboud University Medical Centre (RUMC). All exposed volunteers will be followed closely for possible breakthrough blood infections by testing for the presence of parasitaemia by qPCR. As soon as a breakthrough blood-stage infection develops or at the latest at 28 days after exposure to the GA2 parasite in Phase 1 or 28 after CHMI in Phase 2, all volunteers will be treated with a curative regimen of atovaquone/proguanil or, alternatively, artemether/lumefantrine. Six months after the inoculation, a final visit will take place to assess immune responses.

Study burden and risks

Benefits: There are no direct benefits for volunteers. Volunteers will still be advised to take regular malaria chemoprophylaxis when travelling to malaria endemic areas in the future.

Risks: Risks for volunteers in both studies are related to:
• Potential breakthrough blood-stage infection after exposure to the GA2 parasite;
• Systemic AEs related to exposure to the GA2 and GA1 parasites;
• Local AEs related to mosquito bites;
• Potential blood-stage infection after CHMI;
• Side effects of antimalarial treatment.

Burden:
Volunteers will have to visit the trial centre on 26 occasions for Phase 1 and on 37 occasions for Phase 2. In Phase 1, the maximum cumulative amount of blood collected will be 500 ml for each volunteer. In Phase 2, the maximum amount of blood collected will be 500 ml in four months with an additional 75 ml six months after CHMI per volunteer. In addition, physical examinations will be performed when clinically indicated and volunteers will be asked to complete a diary of AEs on a daily basis.
Burden for volunteers is related to the frequent visits, frequent venapuncture, itching after mosquito bites and potential symptoms after immunisation or CHMI.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

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 agrees to abide strictly thereby.
3. Subject is able to communicate well with the investigator, is available to attend all study visits.
4. Furthermore, the subject will remain within the Netherlands from day -1 till day +28 after each parasite exposure. After exposure to parasites, subjects have to be reachable by phone (24/7) from day -1 until day 35.
5. Subject agrees that his/her general practitioner (GP) will be informed about participation in the study.
6. 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 Sanquin guidelines (three years minimum, depending on serology).

7. Non-pregnant, non-lactating, fertile (i.e., have a uterus and are neither surgically sterilized nor post-menopausal) female subjects agree to use adequate contraception and to not breastfeed for the duration of study.
8. Subject agrees to refrain from intensive physical exercise (disproportionate to the subjects* usual daily activity or exercise routine) for twenty-one days following each immunization and during the malaria challenge period.
9. Subject signs informed consent.

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, immune-deficient, psychiatric or 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:
a. Body weight <50 kg or Body Mass Index (BMI) <18.0 or >30.0 kg/m2 at screening.
b. A heightened risk of cardiovascular disease, defined as:
i. An estimated ten-year risk of fatal cardiovascular disease of >=5% at screening, as determined by the Systematic Coronary Risk Evaluation (SCORE).
ii. History, or evidence at screening, of clinically significant arrhythmia*s, prolonged QT-interval or other clinically relevant ECG abnormalities; or
iii. A positive family history of cardiac events in first- or second-degree relatives (according to the system used in medical genetics) <50 years old.
c. Functional asplenia, sickle cell trait/disease, thalassemia trait/disease or G6PD deficiency.
d. History of epilepsy in the period of five years prior to study onset, even if no longer on medication.
e. Positive HIV, HBV or HCV screening tests.
f. Chronic use of i) immunosuppressive drugs, ii) antibiotics, iii) or other drugs that might have an influence on the immune system (excluding inhaled and topical corticosteroids and incidental use of oral anti-histamines), within three months prior to study onset or expected use of such during the study period.
g. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past five years.
h. Any history of treatment for severe psychiatric disease by a psychiatrist in the past year.
i. 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 prior to exposure to parasites or positive urine toxicology test for cannabis prior to exposure to parasites.

2. For female subjects: breastfeeding, or positive urine pregnancy test at screening or prior to immunization or prior to CHMI.
3. Any history of malaria, positive serology for Pf, or previous participation in any malaria (vaccine) study or CHMI.
4. Known hypersensitivity to or contra-indications (including co-medication) for use of atovaquone/proguanil or artemether/lumefantrine, or history of severe (allergic) reactions to mosquito bites.
5. Receipt of any vaccinations in the three months prior to the start of the study or plans to receive any other vaccinations during the study period or up to eight weeks thereafter. Exceptions are made for influenza vaccination and, if it becomes available during the study period, for vaccination against the novel coronavirus SARS-COV2.
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 Parasitology, Medical Microbiology or Infectious Diseases of the LUMC or RUMC.
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 or would compromise the integrity of the data.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	13-09-2021
Enrollment:	51
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism
Product type:	Medicine
Brand name:	GA1 parasite
Product type:	Medicine
Brand name:	GA2 parasite

Ethics review

Approved WMO Date:	29-01-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-07-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	22-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-04-2022
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	EUCTR2020-005646-41-NL
ClinicalTrials.gov	NCT04577066
CCMO	NL75577.000.21

Study results

Date completed:	22-12-2022

Results posted: 11-12-2023

First publication
11-12-2023