Safety and protective efficacy of chemoprophylaxis and sporozoite immunization with Plasmodium falciparum NF135 against homologous and heterologous challenge infection in healthy volunteers in the Netherlands

Published: 25-06-2018
Last updated: 04-01-2025

Primary Objective: To determine the safety and tolerability of NF135.C10 sporozoite immunization under chemoprophylaxisSecondary Objectives:• To determine the dose-dependent protective efficacy of NF135.C10 CPS-immunization against homologous...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44351

Source
ToetsingOnline

Brief title
CPS135

Condition

- Other condition
- Protozoal infectious disorders

Synonym
Plasmodium falciparum; malaria

Health condition

Malaria infectie

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: MVI

Intervention

Keyword: Controlled Human Malaria Infection, Malaria, Plasmodium falciparum, Sporozoite immunization

Outcome measures

Primary outcome

Frequency and magnitude of adverse events after NF135.C10 CPS immunization

Secondary outcome

Secondary study endpoints

• Time to blood stage parasitemia detectable by qPCR after malaria challenge

infection

• Sterile protection after controlled human malaria infection

Exploratory study endpoints

• The phenoptype and cytokine profile of P. falciparum specific T cell

responses induced by NF135.C10 CPS immunization

• The antigen specificity of T cell responses induced by NF135.C10 CPS

immunization

• The antigen specificity and/or functionality of P. falciparum specific

antibodies induced by NF135.C10 CPS immunization

• The phenotype and/or function of innate and semi-innate immune responses to NF135.C10 CPS immunization and/or CHMI, including γδT cells, invariant T cells, antigen presenting cells, NK cells and granulocytes

• Epigenetic profiles of innate immune cell subsets, with emphasis on both activation (H3K4me3, H3K4me1, H3K27Ac) and repression (H3K9me3, H3K27me) markers

• RNA transcriptome profiling through whole mRNA-sequencing, PCR and/or microarray

Study description

Background summary

Malaria, a disease caused by the parasite Plasmodium, is one of the world*s major infectious diseases. Ultimately, the key to malaria control and hopefully eradication would be an effective vaccine. Chemo-Prophylaxis and Sporozoite immunization (CPS) has repeatedly shown to be an extremely efficient regimen for induction of long lasting sterile homologous protection. However, it provided only 20% and 10% sterile protection against heterologous NF135.C10 and NF166.C8 clones, respectively. We propose to make use of the increased liver infectivity of NF135.C10, to increase the late liver stage load without the need for increasing the number of sporozoites administered. The presumably generated higher titers and broader repertoire of specific antibodies can increase heterologous protection.

Study objective

Primary Objective: To determine the safety and tolerability of NF135.C10 sporozoite immunization under chemoprophylaxis

Secondary Objectives:
• To determine the dose-dependent protective efficacy of NF135.C10 CPS-immunization against homologous controlled human malaria infection
• To determine the protective efficacy of NF135.C10 CPS-immunization against heterologous NF54 controlled human malaria infection

• To assess the longevity of protective immunity after NF135.C10 CPS-|mmunization against homologous challenge (cohort A).

Exploratory Objectives:
• To analyse P. falciparum specific T cell responses in NF135.C10 CPS-immunized volunteers
• To delineate the antibody repertoire directed against P. falciparum in NF135.C10 CPS-immunized volunteers
• To evaluate changes in phenotype and function of innate and semi-innate immune cells following NF135.C10 immunization
• To explore the (innate) immunology of early malaria infection, with specific attention to γδ-T cells, monocytes, antigen presenting cells and natural killer cells
• To analyse changes in epigenetic and transcriptome profiles of (innate) immune cells after NF135.C10 CPS immunization and/or after malaria infection

Study design

In an open label, randomized, controlled clinical trial a maximum of 52 volunteers will be allocated to receive either three immunizations with 15 NF135.C10 infected Anopheles mosquitoes (n=30), 3 immunizations with 5 NF135.C10 infected mosquitoes (n=10) or no immunizations (n=12). Immunizations will be perfomed under mefloquine prophylaxis in cohort A. Volunteers of cohort B will be treated with artemether/lumefantrine on day 7 after each immunisation.

Nineteen weeks after the last immunization, all volunteers will be challenged either by the bites of 5 NF135.C10 or 5 NF54 infected mosquitoes. After challenge infection, volunteers will be followed up on an out-patient basis once daily for qPCR and safety lab measurements from day 6 until day 21 post challenge. All volunteers will be treated with a curative regimen of Malarone, either at the time of detection of blood stage parasitemia (for treatment criteria see paragraph 8.3.3), or 28 days after challenge infection. All volunteers will be checked for parasites after treatment.

One year after the last immunization, if >50% of immunized volunteers were protected in cohort A, the protected volunteers will undergo a second homologous CHMI. During the immunization and challenge phases, blood will also be drawn for exploratory immunology and parasitology objectives. These samples will be analyzed by Radboudumc and its collaborators.The total study period will last a maximum of 14 months.

Three reserve volunteers will be recruited per cohort. If one of the volunteers is not fit to participate in the study before the first immunization, another volunteer who passed screening will be included as replacement. To allow for subjects intolerant of mefloquine to leave the study prior to the first CPS immunization without impacting the study sample size, three reserve volunteers for cohort A will also begin mefloquine prophylaxis. If they are not used to

replace a withdrawn volunteer, these reserve volunteers will stop mefloquine prophylaxis after the third dose.

Intervention

1. CPS immunization

On the first day of the study, all study subjects of cohort A will be seen by the investigators to initiate mefloquine prophylaxis. All volunteers will receive 250mg mefloquine once a week according to a standard prophylactic regime. They will receive four doses prior to the first CPS immunization. 3 weeks after initiation of mefloquine prophylaxis, subjects will receive CPS immunization with bites from 5 or 15 NF135.C10 P. falciparum infected A. stephensi mosquitoes, depending on allocation. This procedure will be repeated three times at four week intervals. Volunteers of cohort A will continue mefloquine prophylaxis throughout CPS immunization and for four weeks after the last immunization.
Volunteers of cohort B will receive CPS immunization with bites from 15 NF135.C10 P. falciparum infected A. stephensi mosquitoes. Volunteers will be treated with artemether/lumefantrine on day 7 after each immunization.

Mosquitoes will be prepared by technicians of the Radboudumc malaria unit and placed in identical boxes, numbered to correspond with the participant*s study code. Treatment allocation will not be blinded. The infections will be performed by placing a box containing mosquitoes on the forearm of the volunteer. Directly after the feed, the mosquitoes will be dissected by a technician of the mosquito unit. This will be done to assure that the mosquito has fed and the presence of sporozoites in the salivary glands of the mosquitoes. Exposure will be repeated until the exact number of infected mosquito bites has been reached.

In a previous study, the prophylactic dose of mefloquine was sufficient to overcome bites of 15 NF54 infected mosquitoes (Bijker, Schats et al. 2014), and the sensitivity of NF135.C10 to mefloquine is similar to NF54. As long as there are volunteers present in the mosquito unit, there will be supervision of one of the clinical investigators. Another clinical investigator will be on call, in case of emergency. Emergency aid kits will be present and readily available at any location, whenever there are volunteers present. All volunteers will be seen by the trial clinicians on days 6 - 10 after each immunization for safety assessments. In cohort A, on days 7-9 after each immunization blood will be taken for thick smears. A thick smear will also be performed in any volunteer with a temperature above 38.0° Celsius after immunization. In cohort B, all volunteers will start artemether/lumefantrine treatment on day 7 after each immunization. Blood will be drawn for prospective qPCR on day 6 through 10 after the first immunization. On day 10 after the second and third immunization, blood will be taken for thick smears.

Throughout the entire trial, blood will be drawn on day 6 through 10 after each immunization for (retrospective) qPCR in volunteers from cohort A and B.

2. Controlled Human Malaria Infection
Nineteen weeks after the last CPS immunization, all immunized subjects plus naïve controls will undergo malaria challenge infection. On the challenge day, all subjects will be exposed to the bites of five NF135.C10 or NF54 strain P. falciparum infected mosquitoes. Mosquito feeding will be allowed for 10 minutes. Volunteers will receive a local treatment (tripelennamine crème) for mosquito bites and will be observed for 15 minutes after the feed. Directly after the feed, the mosquitoes will be dissected by a technician of the mosquito unit. Exposure will be repeated until five infected mosquitoes have fed on each volunteer.

After malaria challenge infection subjects will be observed closely according to an intensive out-patient follow-up schedule including frequent safety analyses. From the sixth day until the twenty-first day post-CHMI, assessments of parasite densities using qPCR will be performed once daily. qPCR assessment of parasite densities will be performed directly in volunteer samples. As soon as a qPCR is deemed positive for malaria parasites, the technician will inform the trial clinician. Treatment will be initiated after a single positive qPCR. If treatment has to be initiated, the trial clinician will contact the volunteer who will return to the clinic to receive atovaquone/proguanil treatment. Subjects will also visit the study site for a follow-up visit on day 1, 2 and 3 after treatment (TD+1, 2 & 3). All subjects will be seen for a final control visit on day 35 after CHMI.

During the entire study period subjects will be instructed to call the trial physicians at any time if they experience symptoms. The trial physician can decide to initiate any additional diagnostics (including safety laboratory evaluations and/or diagnostics for malaria parasites) or treatment at all times. For unexpected laboratory abnormalities, the laboratory test will be repeated. If there is any ambiguity regarding the decision to include or exclude a volunteer, the study physician or the clinical supervisor will discuss the case with the local safety monitor and make the final decision after that, if necessary with consultation of a specialist. If volunteers prove to be eligible, they will be invited to the next visit.

3. Treatment with Malarone.
All volunteers will be treated with Malarone® based on the predetermined criteria mentioned above. The treatment will consist of the drug Malarone® (atovaquon/proguanil). Dosing will be as follows: once daily 4 tablets of 250/100mg, during three days according to Dutch SWAB guidelines. This drug has been chosen because of its fast clinical response and the few side-effects. Furthermore, it has not been reported to have any cardiac side-effects. During treatment, complaints of malaria infection will be treated symptomatically. In addition to specific treatment with Malarone®, symptomatic treatment will be

administered at the discretion of the study physician.
During and one day after Malarone® treatment qPCR is performed directly in collected blood samples. If qPCR remains positive on day three after Malarone® treatment (usually the result of parasite debris remaining in the bloodstream) a thick blood smear will be performed to confirm the absence of intact malaria parasites.

4. Re-challenge infection
Approximately 10 months after the last CPS immunization of cohort A, if >50% of immunized volunteers were protected in cohort A, immunized and protected volunteers will undergo a second challenge infection to assess the duration of homologous protection.

Study burden and risks

There is no benefit expected for subjects participating in this study. The risk to subjects after exposure to P. falciparum infected mosquitoes in this trial will be minimized by adherence to the inclusion/exclusion criteria and close clinical monitoring, which ensures that subjects with malaria are detected and treated early.
The risks associated with CPS immunizations are those related to exposure to P. falciparum infected mosquitoes and those associated with taking mefloquine. In this part of the trial, the risk of developing clinical malaria is low, as volunteers in cohort A will be taking standard mefloquine prophylaxis. Any volunteer with a positive thick smear during the immunization phase will be treated with treated with Malarone®.
All volunteers in cohort B will be treated with artemether/lumefantrine on day 7 after each immunisation. Mefloquine is a marketed medication registered for use as a malaria prophylactic agent for Plasmodium strains sensitive to it. Common side effects include sleeplessness and vivid dreaming (>10%), psychiatric symptoms such as fear and depression (1-10%), headache (1-10%) and gastro-intestinal symptoms (1-10%).
The risks of a CHMI for malaria-naïve subjects include the discomfort sustained by mosquito bites, the discomfort associated with periodic blood draws and the risk of acquiring clinical P. falciparum malaria.
Mosquito bites are known to cause mild discomfort associated with mosquito feeding. A small amount of inflammation and pruritus typically accompanies the bite of the insect. Anaphylaxis to the bite of a mosquito is extremely rare and has never been reported after CHMI. While significant allergic reactions are extremely rare, in the event of an allergic reaction, epinephrine, anti-histamines, on-call physician and resuscitation equipment are available on site. The Radboudumc, an established site for CHMIs, is fully equipped to manage anaphylaxis and any other medical emergency.
Frequent blood draws will be necessary to closely monitor the subjects and to perform qPCR for early detection of P. falciparum parasitemia after challenge infection. Universal precautions will be maintained for the protection of the volunteer and the study personnel during venapuncture. Throughout this study,

the amount of blood collected will be maximally 500 mL during the immunization period and 500 mL during each challenge period. This amount is similar to widely accepted guidelines used by the Sanquin blood bank.
Intensive follow-up with qPCR performed on samples taken once daily will allow for detection of parasites at a very early stage. As therapy will be initiated at this early stage, dangerously high levels or prolonged duration of parasitemia that would put the subject at undue risk, will not occur. Severe malaria has never been described in a CHMI. Mild malaria symptoms include headache, myalgia, fever, chills, sweats, nausea, vomiting, and diarrhoea. Researchers at the Radboudumc have extensive experience with the care of clinical malaria.
Although subjects often become symptomatic with mild malaria after CHMI, rapid diagnosis by qPCR and treatment quickly attenuates the illness so that the infection does not place the subject at undue risk. Additional information about the potential risks associated with CHMI and a summary of relevant reported Serious Adverse Events is given in section 1.5 and section 13 of the protocol.

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 agrees to abide strictly thereby.
3. Subject is able to communicate well with the investigator and is available to attend all study visits.
4. The subject will remain within the Netherlands during the challenge period, not travel to a malaria-endemic area during the study period, and is reachable (24/7) by mobile telephone throughout the entire study period.
5. Subject agrees to inform his/her general practitioner about participation in the study and to sign a request to release by the General Practitioner (GP), and medical specialist when necessary, any relevant medical information concerning possible contra-indications for participation in the study.
6. 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.
7. For female subjects: subject agrees to use adequate contraception and not to breastfeed for the duration of study. Acceptable forms of contraception include: established use of oral, injected or implanted hormonal contraceptives; intrauterine device or intrauterine system; barrier methods (condoms or diaphragm with additional spermicide); male partner*s sterilisation (with appropriate post-vasectomy documentation of absence of sperm in the ejaculate); true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
8. Subject agrees to refrain from intensive physical exercise (disproportionate to the subjects usual daily activity or exercise routine) during the malaria challenge period.
9. Subject agrees to avoid additional triggers that may cause elevations in liver enzymes including alcohol from baseline up to 1 week post treatment.
10. Subject has signed 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, 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), or active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV).
1.6 Chronic use of i) immunosuppressive drugs, ii) antibiotics or antimalarials, 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 History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years.
1.8 Any history of treatment for severe psychiatric disease by a psychiatrist in the past year.
1.9 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 inclusion, or positive urine toxicology test for cannabis at inclusion.
2. For female subjects: positive urine pregnancy test at screening or at inclusion.
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 Mefloquine, Malarone or artemether-lumefantrine, 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 90 days 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 of the Radboudumc or the department of Internal Medicine.
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
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-04-2019
Enrollment:	52
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	25-06-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	08-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-08-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-09-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-01-2021
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
Other	clinicaltrials.gov (NCT03813108)
CCMO	NL63594.091.17

Study results

Date completed: 01-02-2021

Results posted: 08-02-2022

Summary results
Trial ended prematurely

First publication
29-09-2021