Safety, Tolerability and Plasmodium falciparum transmission-reducing activity of R0.6C vaccine adjuvanted with Alhydrogel alone or combined with Matrix-M in healthy malaria-naïve adults in the Netherlands

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Primary safety objective: 1) To evaluate safety of R0.6C immunizations in healthy malaria-naïve volunteers in four dose-adjuvant combinations.Primary efficacy objective:1) To assess transmission reducing activity (TRA) to mosquitoes in the standard...

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

Summary

ID

NL-OMON51178

Source
ToetsingOnline

Brief title
STOP-TRANS

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: EU H2020 project Optimalvax

Intervention

Keyword: Malaria, Plasmodium falciparum, Transmission, Vaccine

Outcome measures

Primary outcome

Primary safety endpoints:

1) The number of serious adverse events and solicited and unsolicited grade 3 adverse events possibly, probably or definitely related to the vaccine in the period from first R0.6C administration up to 84 days after the last immunization.

Primary efficacy endpoints:

1) The functional TRA in the standard membrane feeding assay of volunteer sera collected two weeks after the fourth R0.6C immunization (I4+14), compared to baseline (I1-1) within each of the four dose-adjuvant groups.

Secondary outcome

Secondary safety endpoints:

1) The number of solicited and unsolicited grade 1 and 2 adverse events possibly, probably or definitely related to the vaccine in the period from first R0.6C administration up to 84 days after the last immunization.

Secondary efficacy endpoints:

1) The TRA at other timepoints (I1+14, I2+14, I3+14, I3+111 [I4-1], and I4+84)

compared to baseline (I1-1) in each of the four dose-adjuvant groups.

2) The anti-6C antibody quantity in volunteer sera collected two weeks after

fourth R0.6C immunization (I4+14) and at other time points (I1+14, I2+14,

I3+14, I3+111 [I4-1], and I4+84) compared to baseline (I1-1) in each of the

four dose-adjuvant combinations, as determined by ELISA.

Study description

Background summary

Malaria, a disease caused by Plasmodium parasites, is one of the most important infectious diseases worldwide. After a period of success in global malaria control, progress has stalled in 2015-2018. The availability of a transmission blocking vaccine would be a critical step to move towards malaria elimination[1, 2]. The R0.6C fusion protein, consisting of the N-terminal region of Glutamate Rich Protein GLURP (R0) and the 6-cysteine C-terminal fragment of the well-established Pfs48/45 antigen (6C), is a lead candidate for a transmission blocking vaccine.

Study objective

Primary safety objective:
1) To evaluate safety of R0.6C immunizations in healthy malaria-naïve volunteers in four dose-adjuvant combinations.
Primary efficacy objective:
1) To assess transmission reducing activity (TRA) to mosquitoes in the standard membrane feeding assay of sera after full course of R0.6C immunizations in each of the four dose-adjuvant combinations.

Secondary safety objective;
1) To evaluate tolerability of R0.6C immunizations in healthy malaria-naïve volunteers in four dose-adjuvant combinations.
Secondary efficacy objectives:
1) To assess the dynamics of TRA in the standard membrane feeding assay of sera collected during and after R0.6C immunizations in each of the four dose-adjuvant combinations.
2) To assess the dynamics of anti-6C antibody quantities during and after R0.6C immunizations in each of the four dose-adjuvant combinations.

Study design

R0.6C is a first-in-human phase I, open-label, single-site, dose escalation study to determine the safety, tolerability and transmission reducing activity of the R0.6C vaccine in two different adjuvant combinations.

Intervention

Each of the study arms will receive four intramuscular vaccinations on days 0, 28, 56 and 168 with R0.6C adsorbed to Alhydrogel alone (Groups 1-4A), or combined with an additional adjuvant Matrix-M (groups 1-4B). Dose escalation with the two adjuvant arms will take place in parallel: first, a sentinel group (1A and 1B, n=3 per arm) will receive the low dose of 30µg R0.6C; subsequently the additional subjects (groups 2A and 2B, n=5 per arm) will receive the low dose of 30 µg R0.6C; if considered safe, a sentinel group (3A and 3B, n=3 per arm) will receive the high dose of 100µg R0.6C; and finally, the remainder of subjects will receive the high dose of 100µg R0.6C (groups 4A and 4B, n=5 per arm).

Study burden and risks

There are no individual benefits to participating in this study. In case that the vaccine is effective, vaccination campaigns will reduce the risk of transmission in a population. Subjects will not be protected against malaria after participating. The vaccine platform (Lactococcus lactis expressed recombinant protein vaccine) and both adjuvants (Alhydrogel, Matrix M) have been used extensively before. However, R0.6C has not been administered in humans before, therefore there is a theoretic risk of novel side effects to occur. Participating in this trial includes the discomfort of R0.6C vaccine administrations with potential adverse reactions, multiple blood sampling tests, follow-up visits, physical examinations, screening for HIV, Hepatitis B and Hepatitis C, pregnancy tests (for females), filling out a diary and abiding to all study rules.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Subject must sign written informed consent to participate in the trial.
2. Subject is a male or non-pregnant and non-lactating female age >= 18 and <= 55 years and in good health.
3. Subject is able to understand planned study procedures and demonstrate comprehension of the protocol procedures and knowledge of study by passing a quiz (assessment of understanding).
4. In the opinion of the investigator, the subject can and will comply with the requirements of the protocol.
5. Subjects are available to attend all study visits and are reachable by phone throughout the entire study period from day -1 until day 224 (end of study).
6. The subject will remain within reasonable travelling distance from the study center from day -1 until day 7 after each R0.6C administration and agrees not to travel to a malaria-endemic area during the study period
7. Subject agrees to their general practitioner (GP) being informed about participation in the study and agrees to sign a form to request the release by their GP, and medical specialist when necessary, of any relevant medical information concerning possible contra-indications for participation in the study to the investigator(s).
8. The subject agrees to refrain from blood donation to Sanquin or for other purposes throughout the study period according to current Sanquin guidelines.
9. Female subjects of non-childbearing potential may be enrolled in the study. All subjects of childbearing potential must agree to use continuous adequate contraception until 2 months after completion of the study. Female subjects must agree not to breastfeed from 30 days prior to R0.6C administration until 2 months after completion of the study. Female subjects must have a negative

pregnancy test at the inclusion visit.

Exclusion criteria

1. Acute or chronic disease at time of R0.6C administration, clinically significant pulmonary, cardiovascular, hepatic, renal, neurological or immunological functional abnormality, as determined by medical history, physical examination or laboratory screening tests:
a. Acute disease is defined as the presence of a moderate or severe illness with or without fever. For subjects with an illness on the day of R0.6C administration, the vaccination may be postponed up to 7 days.
b. Fever is defined as an oral, axillary or tympanic temperature >= 38.0°C.
c. Any abnormal and clinically significant baseline laboratory screening tests of ALT, AST, creatinine, hemoglobin, platelet count or total white blood cell count, as defined in the protocol according to the FDA Toxicity Grading Scale for Healthy Adult and Adolescent Subjects Enrolled in Preventative Vaccine Clinical Trials (appendix 1).
2. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years.
3. Chronic use of i) immunosuppressive drugs, 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.
4. 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.
5. Screening tests positive for Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV), Hepatitis C Virus (HCV).
6. Use of any other investigational or non-registered product (drug or vaccine) during the study period.
7. Known hypersensitivity to macrolides.
8. Participation in any other clinical study involving an investigational product in the 30 days prior to the start of the study or during the study period.
9. Receipt of any other vaccination within 30 days prior to or up to 14 days after any R0.6C vaccination. Exceptions are made for vaccination against influenza and the novel coronavirus SARS-CoV2.
10. Any history of malaria, positive serology for P. falciparum, or previous participation in any malaria (vaccine) study or CHMI.
11. Body weight > 115 kg
12. Being an employee or student of the department of Medical Microbiology of the Radboudumc at the time of screening, or a person otherwise related to the investigator.
13. 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 affects the interpretability of the trial results.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	17-05-2021
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	R0.6C

Ethics review

Approved WMO Date:	29-01-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	29-04-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	02-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-07-2021
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
EudraCT	EUCTR2021-000017-17-NL
ClinicalTrials.gov	NCT04862416
CCMO	NL76664.000.21