Safety and protective efficacy of genetically attenuated Pf*b9*slarp (PfSPZ-GA1) malaria parasites in healthy volunteers

Published: 13-09-2016
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The study is divided in Stage A and BGA1 stage A1. To determine the safety and tolerability of direct venous inoculation of PfSPZ-GA1 in healthy volunteers.GA1 stage B Primary objective:1. To determine the safety, and tolerability of PfSPZ-...

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

Summary

ID

NL-OMON46209

Source
ToetsingOnline

Brief title
GA1

Condition

- Protozoal infectious disorders

Synonym
Malaria, Plasmodium falciparum

Research involving
Human

Sponsors and support

Primary sponsor: Sanaria

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Controlled Human Malaria Infection, Genetically attenuated parasite, Malaria, Vaccine

Outcome measures

Primary outcome

GA1 stage A:

Primary endpoints:

* Presence of blood stage parasites after inoculation with PfSPZ-GA1 as

assessed by qPCR

* Frequency and magnitude of adverse events in study groups

GA1 stage B:

Primary endpoints:

* Frequency and magnitude of adverse events in study groups

Secondary outcome

GA1 stage B:

* Presence of parasitemia after controlled human malaria infection with the

wild-type NF54 strain, as detected by qPCR

Study description

Background summary

Malaria 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) sporozoite administration together with a chemoprophylactic dose of chloroquine[1;2]. In rodents, genetically attenuated parasites (GAPs) have been shown to induce protective immune responses equal to, or even greater than, those induced by irradiated sporozoites[3;4]. Radboudumc and LUMC along with the industrial US-based partner Sanaria have created a human GAP (Pf*b9*slarp), where 2 genes have been removed from the parasite genome in order to ensure complete life-cycle arrest in the liver. Pf*b9*slarp and the equivalent rodent malaria GAP (Pb*b9*slarp) have been evaluated in preclinical safety studies showing a favourable safety profile and the induction of sustained protection. These GAP show complete attenuation (i.e. complete growth arrest) in the liver, confirming its safety profile. In addition, low dose immunizations of the rodent GAP Pb*b9*slarp induced complete and sustained protection in mice[5]. Pf*b9*slarp sporozoites have now been manufactured by Sanaria as an aseptic, purified, cryopreserved vaccine product referred to as PfSPZ-GA1. Lots produced during engineering runs have demonstrated (1) an attenuated phenotype with no evidence of breakthroughs in vitro and (2) efficient blood stage culture/gametocyte generation, development in mosquitoes and sporozoite production, indicating suitability for manufacturing.

Study objective

The study is divided in Stage A and B

GA1 stage A
1. To determine the safety and tolerability of direct venous inoculation of PfSPZ-GA1 in healthy volunteers.

GA1 stage B
Primary objective:
1. To determine the safety, and tolerability of PfSPZ-GA1
Secondary objective:
2. To determine the short term protective efficacy of PfSPZ-GA1 against Controlled Human Malaria Infection (CHMI) by mosquito bite.

Study design

Stage A: Phase I trial
Stage B: Phase I trial, placebo controlled double blind multi center

Intervention

Intervention per group:
Stage A
1. Once infection with 1.35x10^5 PfSPZ-GA1

2. Once infection with 4.5x10^5 PfSPZ-GA1
3. Once infection with 9.0x10^5 PfSPZ-GA1

Stage B
4. 3 immunisations with 9.0x10^5 PfSPZ-GA1, followed by a CHMI
5. 3 immunisations with 4.5x10^5 PfSPZ-GA1, followed by a CHMI
6. 3 immunisations with 4.5x10^5 PfSPZ Vaccine, followed by a CHMI
7. 3 immunisations with saline, followed by a CHMI

Study burden and risks

Please refer to question E4 for the burden for participants.
Please refer to question E9 for the risk for participants.
For a risk analysis, please refer to chapter 13 of the clinical trial protocol.

Contacts

Public
Sanaria

Medical Center Drive 9800
Rockville MD 20850
US
Scientific
Sanaria

Medical Center Drive 9800
Rockville MD 20850
US

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, 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 and be reachable by phone (24/7). From day 28 till day 35 after each infection subjects have to be reachable by phone (24/7) throughout this 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 GP, and medical specialist when necessary, any relevant medical information concerning possible contra-indications for 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 current Sanquin guidelines (3 years minimum, depending on serology).
7. Non-pregnant, non-lactating females of reproductive potential (i.e., have a uterus and are neither surgically sterilized nor post-menopausal) should agree to use adequate contraception and not to 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 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, 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:
1.1 Body weight <50 kg or Body Mass Index (BMI) <18.0 or >30.0 kg/m2 at screening
1.2 A heightened risk of cardiovascular disease, defined as: 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 first or second degree relatives (according to the system used in medical genetics) <50 years old.
1.3 Functional asplenia, sickle cell trait/disease, thalassaemia trait/disease or G6PD deficiency.
1.4 History of non-febrile seizure at any time prior to study onset, even if no longer on medication

1.5 Positive HIV, HBV or HCV screening tests.
1.6 Chronic use of i) immunosuppressive drugs, ii) antibiotics, iii) or other immune modifying drugs within three months prior to study onset (excluding inhaled and topical corticosteroids and incidental use of oral anti-histamines) 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 five 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 prior to infection or positive urine toxicology test for cannabis at baseline prior to infection.
2. For female subjects: positive urine pregnancy test at screening or prior to immunization or prior to infection.
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 atovaquone, proguanil 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 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 or Infectious Diseases of the Radboudumc or the LUMC.
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:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-05-2017
Enrollment:	67
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism
Product type:	Medicine
Brand name:	PfSPZ Vaccine

Ethics review

Approved WMO Date:	13-09-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-01-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-01-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-02-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	16-08-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-08-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-10-2017
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	EUCTR2016-000893-39-NL
CCMO	NL56657.000.16
Other	volgt

Study results

Date completed:	25-10-2018

Results posted:	09-12-2019
Actual enrolment:	67

First publication
02-12-2019