

Phase 1 with Sporozoite Challenge Open-Label Dose-Escalation Safety, Reactogenicity, Immunogenicity, and Efficacy of the Vaccine Candidate *Plasmodium falciparum* Malaria Protein (FMP012), an *E coli*-Expressed Cell-Traversal Protein for Ookinetes and Sporozoites (*Pf*CelTOS), Administered Intramuscularly with GLA-SE Adjuvant in Healthy Malaria-Naïve Adults

1. Study Objective: This study is being conducted to evaluate the safety and effectiveness of an experimental malaria vaccine. This new vaccine is made up of two parts. The first part is called FMP012 and it is designed to look like a part of the malaria parasite. The second part is called GLA-SE, and is the component to boost the body's immune response to FMP012.

2. Has this vaccine been tested in humans before? The FMP012 portion of the vaccine has not been tested in humans before; however, the GLA-SE portion has been tested in humans and has not been found to cause serious side effects.

3. Study Duration: The active portion of the study will be up to 11 months for vaccinated subjects (up to 3 months for screening and 8 months for vaccination and follow-up), and approximately 6 months for non-immunized controls (up to 3 months for screening and 3 months for the malaria challenge and follow-up). There will also be 2 follow-up phone calls at 6 and 12 months after the final vaccination.

4. Number of People in the Study: There are two groups: 30 who will receive 3 vaccinations and 6-12 controls, who will not receive vaccinations, for a total of 36-42

5. Study Background: Malaria is a parasitic disease transmitted by mosquitoes. It is a significant cause of death and disability in tropical areas of Africa, Asia, Oceania (Pacific islands) and Latin America. Humans become infected when they are bitten by infected mosquitoes. People don't feel well with this disease – its effects are similar to Influenza with symptoms such as fever, headache, body aches, upset stomach and diarrhea. Therefore, this disease impacts people and communities due to lost time in the home, at work and school. A vaccine against this parasite would be a major contribution to public health. The US Army is at the forefront of malaria vaccine research and development because soldiers are deployed to areas with malaria. In the current proposed study, we want to evaluate the safety of a new anti-malarial vaccine developed by scientists at WRAIR.

6. Brief review of inclusion / Exclusion criteria

Inclusion:

- Men and non-pregnant, non-lactating women, civilian or military
- ages 18-50 (inclusive)
- in good health

- no plans to travel to a country with malaria throughout the study
- low cardiac risk (based on NHANES I criteria and screening electrocardiogram (EKG))

Exclusion:

- History of malaria or receipt of an investigational malaria vaccine
- Recent travel to *P. falciparum* endemic area within the past three months
- Heart, lung, liver, or kidney disease (high blood pressure, diabetes)
- Neurologic disease
- Splenectomy
- History of sickle cell disease or other blood diseases
- Positive for HIV, hepatitis C, or hepatitis B
- Use of investigational drug or non-registered vaccine within 30 days before the first vaccination
- Use of any licensed vaccine within 7 days before the first vaccination (we recommend that you get any approved preventive vaccines that you need during the study, but ask that you schedule them for at least seven days before or after the study vaccination day)
- Allergic reaction to a vaccine (vaccine group)
- Pregnancy or planned pregnancy during the study time period
- Use of certain prescription medications
- Inability to make all follow-up appointments
- Active duty military volunteers will require approval from their supervisory chain
- Alcohol or drug abuse
- Any other significant finding that in the opinion of the clinical investigators would make participation in the study unsafe

7. Study Plan:

Screening

A person who wants to enroll in the study will be screened to ensure they are eligible to participate. Screening includes:

- A detailed explanation of the study
- Completion of the informed consent documents
- Brief medical history and physical exam
- ECG – a painless test that measures the electrical activity of your heart

- Urine pregnancy test and blood tests

Vaccination

- There are 3 vaccinations given at 0, 4, and 8 to 16 weeks.
- The vaccine is given through a needle into a muscle in your upper arm.
- You will be required to come in for several follow-up visits after each vaccination.
- A study physician will see you at each visit, and you will have blood drawn at several visits. Volunteers in the control group will not receive vaccinations.
- A urine pregnancy test will be performed for all women before each vaccination

Challenge

- All vaccinated volunteers will have their blood tested for antibodies against the FMP012 protein after but there are no blood tests to see if the vaccine will prevent malaria. The only way to see if the vaccine is effective is by a malaria challenge. If less than 50% of people in a group develop antibodies, that group will not be challenged. The challenge involves being bitten by mosquitoes infected with the malaria parasite. The mosquitoes are contained in a small cup with a screen on top. This procedure doesn't hurt, but your arm may itch later, as with any mosquito bite. You may develop malaria from the mosquito bite.
- A urine pregnancy test will be performed for all women before the challenge
- Post-challenge and Hotel Phase
- Volunteers will need to return to the Clinical Trials Center every other day in the first 5 days after the challenge to provide blood for testing. They will then return every day on days 6-9.
- Starting the night of the ninth day after the challenge, volunteers will need to check in to a specific hotel each night to stay for a maximum of 10 days to allow for rapid assessment and treatment by study staff. The reason is that this is the period of time you are most likely to become sick with malaria.
 - Each morning, you will be seen by a study physician and have a small amount of blood drawn to test for malaria.
 - Each afternoon, a study staff member will call to see how you feel and relay the test results to you.
 - You will only have to sleep at the hotel, but you can come and go for work and outside activities as long as you return for your clinical visits.
- The symptoms of malaria include fever, chills, headache, fatigue, vomiting, diarrhea, muscle aches, and stomachache.
- If you do develop malaria, you will be treated with either a medication called Chloroquine or a medication called CoartemTM (artemether/lumefantrine) that you take by mouth for 3 days. Both of these drugs are FDA-approved. The medication is expected to completely cure the malaria.

Post Hotel Phase

- Volunteers will also be required to return to the Clinical Trials Center for follow-up visits for approximately 3 months after the challenge.
- Each volunteer will have a unique schedule, based on whether or not you develop malaria.
- Blood will be drawn at some of these visits.

8. Risks to the Volunteers may include:

Note: Study staff have methods to decrease or limit most, if not all, side effects

- From vaccinations: this vaccine has not been administered to humans, however typical side effects from vaccines are redness, swelling, and soreness at the site of injection. There may be other unknown side effects.
- From challenge: local reaction at the site where mosquitoes bite, side effects from the FDA approved anti-malaria medication (such as upset stomach, nausea, diarrhea, tiredness, ringing in ears)
- From malaria: fever, chills, headache, fatigue, vomiting, diarrhea, muscle aches, and stomachache
- From blood draws: bruising at the site
- Loss of confidentiality: If you participate in this study, there is a chance that limited information about you may be disclosed to persons outside of this study to include: representatives of the USAMRMC, USAMMDA, the Food and Drug Administration (FDA), and the WRAIR Institutional Review Board (IRB). These representatives may have access to review research records as part of their responsibility to protect humans in research but they must also maintain confidentiality of your records within the limits of the law.

9. Payment:

- Payments will be made for blood drawn during the study (\$100 per blood draw plus \$25 for screening) but not for transportation or other expenses.
- Vaccination plus challenge: compensation may range up to \$4025 to \$4625 for volunteers who participate in both the vaccination and challenge portions, depending on if, and when they become positive for malaria
- Control (Unvaccinated) volunteers: approximately \$2225, depending on when they become positive for malaria.
- Active duty personnel will be paid \$50 per blood draw, unless the visits occur during off duty hours or they are on leave. In that case, they will be paid the same as non-military personnel.

10. Study Setting: Outpatient