Protocol Registration and Results System

Protocol Registration and Results Preview

This is a rough approximation of how the Protocol Registration and Results will appear on the ClinicalTrials.gov public web site.

Study of Malaria Vaccine RTS,S/AS01E in Plasmodium Falciparum-infected and Uninfected Adults Pre-treated With Anti-malarial Therapy

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04661579

Recruitment Status: Completed
Results First Posted: *
First Posted: *
Last Update Posted: *

* Date not available in PRS

Sponsor:

PATH

Collaborators:

US Army Medical Research Directorate-Africa - Walter Reed Army Institute of Research
GlaxoSmithKline
Kenya Medical Research Institute
FHI Clinical SA Proprietary Limited
DF/Net

Information provided by (Responsible Party):

PATH

Study Description

Brief Summary:

The main goal of this study is to assess the efficacy of RTS,S/AS01E, a candidate vaccine against malaria caused by Plasmodium falciparum (P. falciparum), in adults positive for P. falciparum at the start of the study, but treated with anti-malarial medications to clear the parasite before receiving multiple doses of the vaccine. The goal is to overcome the reduced vaccine efficacy (hypo-responsiveness to the vaccine) reported in actively or chronically infected adults.

Condition or disease	Intervention/treatment	Phase
Plasmodium Falciparum	Biological/Vaccine: Malaria Vaccine RTS,S/AS01E Biological/Vaccine: Abhayrab rabies vaccine Drug: Dihydroartemisinin-piperaquine (DHA/Pip) Drug: Artemether / Lumefantrine Drug: Primaquine	Phase 2

Detailed Description:

PATH and GlaxoSmithKline (GSK) are committed to developing a malaria vaccine to help reduce the burden of malaria disease in children and contribute to malaria elimination. GSK has developed a candidate vaccine against malaria caused by P. falciparum called RTS,S/AS01E. The vaccine has been shown to be safe in multiple trials and efficacy data in pediatric populations has led to a pilot implementation program in three African countries including Kenya. The RTS,S/AS01E vaccine mechanism of action is presumed to work on the initial sporozoite and liver stages of P. falciparum infection through neutralization of the circumsporozoite (CS) antigen on parasites invading after a mosquito bite in individuals immunized with the RTS,S/AS01E vaccine. In order to inform whether a vaccine such as RTS,S/AS01E may have a future role in malaria elimination, it will be important to establish vaccine efficacy in adults in Sub-Saharan Africa who are reservoirs of parasites and who contribute to ongoing malaria transmission. However, in previous trials, the vaccine has been less effective in adults who have had malaria before. There are probably multiple reasons for this, but one possible reason that is probably very important is that prior infection with malaria or an infection with malaria for long periods, even without symptoms of the disease, can prevent the vaccine from working properly.

This study postulates that treatment of infection prior to immunization can reset the immune response leading to an improved vaccine efficacy. To evaluate this hypothesis, the study will recruit 5 groups. Groups 1 and 4 will have asymptomatic infection with P. falciparum as measured by a

or the comparator rabies vaccine, respectively, with the primary objective of evaluating the vaccine efficacy of RTS,S/AS01E relative to the rabies vaccine in this context. Groups 2 and 5 will be negative for asymptomatic infection with P. falciparum as measured by a highly sensitive PCR assay and will be treated with antimalarial medications prior to immunization with RTS,S/AS01E or the comparator rabies vaccine, respectively, with the secondary objective of evaluating the vaccine efficacy of RTS,S/AS01 relative to the rabies vaccine in this context. Group 3 will have asymptomatic infection with P. falciparum as measured by a highly sensitive PCR assay but will not be treated with antimalarial medications prior to immunization with the RTS,S/AS01E vaccine; the immunological profile of this group and groups 1 and 2 will be evaluated as part of secondary and exploratory objectives. Other secondary objectives include safety assessments.

The study will include an initial immunization period (vaccine given on 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations) followed by 6-12 months of follow-up (varying based on the number of events),

Study Design

Study Type:	Interventional
Actual Enrollment:	620 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment Three groups (Groups 1, 2, and 3) will be administered RTS,S/AS01E on a 0, 1, 7 month schedule with Dose 3 delivered as a 1/5th fractional dose. Two groups (Groups 4 and 5) will be administered a comparator vaccine on a 0, 1, 7 month schedule.
Masking:	None (Open Label)
Primary Purpose:	Other
Official Title:	A Phase 2b Randomized, Open-label, Controlled, Single Center Study in Plasmodium Falciparum-infected and Uninfected Adults Age 18-55 Years Old in Kenya to Evaluate the Efficacy of the Delayed, Fractional Dose RTS,S/AS01E Malaria Vaccine in Subjects Treated With Artemisinin Combination Therapy Plus Primaquine
Actual Study Start Date:	November 6, 2020
Actual Primary Completion Date:	June 22, 2022
Actual Study Completion Date:	August 17, 2022

Arms and Interventions

Arm	Intervention/treatment
Experimental: Group 1: Positive Parasitemia; Anti-malarial treatment + RTS,S/AS01E Vaccine Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with dihydroartemisinin-piperaquine (DHA/Pip) plus low dose primaquine (LD PQ) 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a course of artemether/lumefantrine (A/L) plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Biological/Vaccine: Malaria Vaccine RTS,S/AS01E RTS,S/AS01E vaccine 0.5 mL, containing 25 µg protein comprising circumsporozoite protein (CS) and hepatitis B surface antigen (RTS,S), 25 µg monophosphoryl lipid (AMPL), 25 µg Quillaja saponaria 21 (QS21) in a liposomal formulation) for the first two immunizations. One-fifth dose RTS,S/AS01E vaccine was used for the third immunization. Drug: Dihydroartemisinin-piperaquine (DHA/Pip) Dihydroartemisinin (120 mg or 160 mg based on weight) and piperaquine tetraphosphate (960 mg or 1280 mg based on weight) mg) administered once a day for 3 days. DHA/Pip is a long acting anti-malarial used to clear asexual stage and young gametocyte parasites. Drug: Artemether / Lumefantrine Artemether (80 mg) and lumefantrine (480 mg) administered twice a day for 3 days. Coartem is a short-acting artemisinin combination therapy used to provide clearance of blood stage parasites in order to establish a clean baseline for determination of vaccine efficacy. Other Names: • Coartem® Drug: Primaquine One dose of 15 mg primaquine. Low dose primaquine (LD PQ) is used to clear mature gametocytes of P. falciparum.

RTS,S/AS01E Vaccine Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	RTS,S/AS01E vaccine 0.5 mL, containing 25 µg protein comprising circumsporozoite protein (CS) and hepatitis B surface antigen (RTS,S), 25 µg monophosphoryl lipid (AMPL), 25 µg Quillaja saponaria 21 (QS21) in a liposomal formulation) for the first two immunizations. One-fifth dose RTS,S/AS01E vaccine was used for the third immunization. Drug: Dihydroartemisinin-piperaquine (DHA/Pip) Dihydroartemisinin (120 mg or 160 mg based on weight) and piperaquine tetraphosphate (960 mg or 1280 mg based on weight) mg) administered once a day for 3 days. DHA/Pip is a long acting anti-malarial used to clear asexual stage and young gametocyte parasites. Drug: Artemether / Lumefantrine Artemether (80 mg) and lumefantrine (480 mg) administered twice a day for 3 days. Coartem is a short-acting artemisinin combination therapy used to provide clearance of blood stage parasites in order to establish a clean baseline for determination of vaccine efficacy. Other Names: • Coartem® Drug: Primaquine One dose of 15 mg primaquine. Low dose primaquine (LD PQ) is used to clear mature gametocytes of P. falciparum.
Experimental: Group 3: Positive Parasitemia; RTS,S/AS01E Vaccine Participants with detectable P. falciparum parasitemia at baseline did not receive any anti-malarial medications to clear parasites. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations. This group is included only for immunological assessment and not for vaccine efficacy.	Biological/Vaccine: Malaria Vaccine RTS,S/AS01E RTS,S/AS01E vaccine 0.5 mL, containing 25 µg protein comprising circumsporozoite protein (CS) and hepatitis B surface antigen (RTS,S), 25 µg monophosphoryl lipid (AMPL), 25 µg Quillaja saponaria 21 (QS21) in a liposomal formulation) for the first two immunizations. One-fifth dose RTS,S/AS01E vaccine was used for the third immunization.
Placebo Comparator: Group 4: Positive Parasitemia; Anti-malarial Treatment + Rabies Vaccine Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with dihydroartemisinin-piperaquine (DHA/Pip) plus low dose primaquine (LD PQ) 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a three-day course of artemether/lumefantrine (A/L) plus LD PQ was administered. Participants received 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.	Biological/Vaccine: Abhayrab rabies vaccine Abhayrab rabies vaccine, 0.5 mL, contains 2.5 IU rabies antigen. Drug: Dihydroartemisinin-piperaquine (DHA/Pip) Dihydroartemisinin (120 mg or 160 mg based on weight) and piperaquine tetraphosphate (960 mg or 1280 mg based on weight) mg) administered once a day for 3 days. DHA/Pip is a long acting anti-malarial used to clear asexual stage and young gametocyte parasites. Drug: Artemether / Lumefantrine Artemether (80 mg) and lumefantrine (480 mg) administered twice a day for 3 days. Coartem is a short-acting artemisinin combination therapy used to provide clearance of blood stage parasites in order to establish a clean baseline for determination of vaccine efficacy. Other Names: • Coartem® Drug: Primaquine

	(LD PQ) is used to clear mature gametocytes of P. falciparum.
Placebo Comparator: Group 5: No Parasitemia, Anti-malarial Prophylaxis + Rabies Vaccine Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.	Biological/Vaccine: Abhayrab rabies vaccine Abhayrab rabies vaccine, 0.5 mL, contains 2.5 IU rabies antigen. Drug: Dihydroartemisinin-piperaquine (DHA/Pip) Dihydroartemisinin (120 mg or 160 mg based on weight) and piperaquine tetraphosphate (960 mg or 1280 mg based on weight) mg) administered once a day for 3 days. DHA/Pip is a long acting anti-malarial used to clear asexual stage and young gametocyte parasites. Drug: Artemether / Lumefantrine Artemether (80 mg) and lumefantrine (480 mg) administered twice a day for 3 days. Coartem is a short-acting artemisinin combination therapy used to provide clearance of blood stage parasites in order to establish a clean baseline for determination of vaccine efficacy. Other Names: • Coartem® Drug: Primaquine One dose of 15 mg primaquine. Low dose primaquine (LD PQ) is used to clear mature gametocytes of P. falciparum.

Outcome Measures

Primary Outcome Measure:

1. Time to First PCR-detectable Malaria Infection During the Active Detection of Infection (ADI) Phase in Groups 1 and 4 [Time Frame: The active detection of infection phase began 2 weeks after the third vaccination (approximately week 30) for up to 35 weeks. Participants provided blood samples every 21 days during the ADI phase for PCR assays.]

   Participants were actively monitored for malarial infection starting 2 weeks after the third vaccination. Blood samples were assayed using a highly sensitive polymerase chain reaction (PCR) (Plasmodium falciparum/ Pan-Plasmodium 18S ribosomal ribonucleic acid (rRNA) laboratory developed test [LDT]) that can detect sub-clinical parasitemia at the US Army Medical Research Directorate-Africa (USAMRD-A) / Kenya Medical Research Institute (KEMRI) laboratories in Kisumu, Kenya. A positive PCR result from blood samples collected during the ADI was recorded as a positive event for the presence of P. falciparum blood stage infection.

   The time to first malaria infection is expressed in terms of rate of first malaria infection, that is, the number of malaria infection events reported over the time period elapsed until the event occurred (i.e. events per Persons Year at Risk [PYAR]) for each group.

Secondary Outcome Measures:

1. Time to First PCR-detectable Malaria Infection During the Active Detection of Infection Phase in Groups 2 and 5 [Time Frame: The active detection of infection phase began 2 weeks after the third vaccination (approximately week 30) for up to 35 weeks. Participants provided blood samples every 21 days during the ADI phase for PCR assays.]

   Participants were actively monitored for malarial infection starting 2 weeks after the third vaccination. Blood samples were assayed using a highly sensitive PCR (Plasmodium falciparum/ Pan-Plasmodium 18S rRNA LDT) that can detect sub-clinical parasitemia. A positive PCR result from blood samples collected during the ADI phase was recorded as a positive event for the presence of P. falciparum blood stage infection.

   The time to first malaria infection is expressed in terms of rate of first malaria infection, that is, the number of malaria infection events reported over the time period elapsed until the event occurred (i.e. events per Persons Year at Risk [PYAR]) for each group.

2. Number of Participants With Serious Adverse Events (SAEs) [Time Frame: From first dose to end of study, up to 65 weeks.]

   An adverse event is any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure.

   A serious adverse event is any adverse event that:

   - Resulted in death,
   - Was life-threatening,
   - Resulted in disability/incapacity,

- Resulted in disability/incapacity.
- Resulted in a congenital anomaly and / or birth defect.

3. Number of Participants With Solicited Local and Systemic Adverse Events (AEs) [Time Frame: Within 7 days after each vaccination.]

   Solicited AEs are pre-specified local and systemic AEs that occur relatively more frequently or are known to be associated with immunization, which are monitored actively as potential indicators of vaccine reactogenicity.

   Solicited local and general AEs were collected among RTS,S vaccinated groups in the first 50 participants enrolled in Groups 1 and 2 and all participants enrolled in Group 3 (Reactogenicity Cohort) for seven days (day of vaccination and six subsequent days) after each dose of vaccine.

   Local (injection site) adverse events are defined as:

   - Pain at injection site
   - Swelling at injection site

   Systemic adverse events are defined as:

   - Fever (temperature ≥ 37.5°C)
   - Headache
   - Gastrointestinal problems
   - Fatigue
   - Muscle ache

4. Number of Participants With Unsolicited Adverse Events [Time Frame: Within 28 days after each vaccination.]

   An adverse event is defined as any untoward medical occurrence in a study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure.

   Unsolicited AEs are any AEs reported spontaneously by the participant, observed by the study staff during study visits or those identified during review of medical records or source documents. Solicited AEs with an onset after the seven-day solicitation period were also considered unsolicited AEs.

5. Geometric Mean Titer of Anti-Plasmodium Falciparum Circumsporozoite (CS) Antibodies in Groups 1, 2, and 3 [Time Frame: Baseline, Day 29 (28 days after first vaccination), Day 57 (28 days after second vaccination), Day 197 (24 weeks after second vaccination), and Day 225 (28 days after third vaccination)]

   The RTS,S antigen consists of sequences of both the P. falciparum circumsporozoite protein and hepatitis B surface antigen.

   Antibody levels against P. falciparum circumsporozoite (CS) protein central repeat region (NANP) were measured from blood samples of participants in Groups 1, 2 and 3 using standard enzyme-linked immunosorbent assays (ELISA) at Walter Reed Army Institute of Research (WRAIR), in Silver Spring, MD, United States.

6. Anti-Plasmodium Falciparum Circumsporozoite (CS) Antibody Avidity Index in Groups 1, 2, and 3 [Time Frame: Baseline, Day 29 (28 days after first vaccination), Day 57 (28 days after second vaccination), Day 197 (24 weeks after second vaccination), and Day 225 (28 days after third vaccination)]

   Antibody levels against P. falciparum circumsporozoite (CS) protein central repeat region (NANP) measured by standard enzyme-linked immunosorbent assays (ELISA) for participants in Groups 1, 2 and 3. To measure antibody-antigen avidity (strength of binding) ELISA was performed with and without urea (to dissociate the antigen-antibody complex).

   The avidity index is calculated by dividing the serum titer obtained in the presence of the urea by the serum titer without urea.

7. Geometric Mean Titer (GMT) of Anti-Hepatitis B Surface Antigen (HBsAg) Antibodies in Groups 1, 2, and 3 [Time Frame: Baseline, Day 29 (28 days after first vaccination) and Day 225 (28 days after third vaccination)]

   The RTS,S vaccine antigen consists of sequences of both the P. falciparum circumsporozoite protein and hepatitis B surface antigen, hence anti-HBsAg antibodies were also measured.

   Anti-hepatitis B surface antigen antibodies were assessed at the International AIDS Vaccine Initiative Human Immunology Laboratory (IAVI-HIL) at Imperial College, London, UK, using a commercially available ELISA kit.

Eligibility Criteria

Ages Eligible for Study:	18 Years to 55 Years
Sexes Eligible for Study:	All
Gender Based:	No
Accepts Healthy Volunteers:	Yes

Criteria