WRAIR IRB
WRAIR # 2350 Approval expires 14 Sep 2017
Version 2.0, 28 Oct 2016B Signed HSPB
Earlier Versions Invalid

Title of Research Study: A Phase 1, First-in-Human, Double-blinded, Randomized, Placebo-controlled Trial to Evaluate the Safety, Reactogenicity, and Immunogenicity of an Alum Adjuvanted Zika Virus Purified Inactivated Vaccine (ZPIV) in Healthy Flavivirus-Naïve and Flavivirus-Primed Volunteers

Study Location: Walter Reed Army Institute of Research (WRAIR) Clinical Trials Center (CTC), Silver Spring, MD, USA

Doctor in Charge of Study: Dr. Leyi Lin, MAJ, MC, USA

Study Contact Information: Phone: 301-319-9320 or email: Usarmy.detrick.medcom-wrair.mbx.clinical-trials@mail.mil

Study Population: This study will enroll 75 healthy male and non-pregnant, non-breastfeeding female volunteers, also called subjects, between the ages of 18 and 49 who live in the DC Metro Area.

Study Period: Approximately 14-25 months, depending on your group assignment and the number of vaccines you receive. You will have 20-23 study visits during this time (including 17 to 20 clinic visits and three scheduled follow-up contacts by phone call). A subset of volunteers (up to 10 per group) will be eligible to receive a third ZPIV vaccination and followed for an additional 6 months.

Purpose of Study: This *research* study will test an *experimental* vaccine (ZPIV) against the Zika virus to learn about its safety (side effects) and how your immune system responds after receiving this experimental vaccine or placebo alone, or after you receive an FDA approved vaccine against a similar virus.

Experimental Vaccine and Placebo: ZPIV (Puerto Rico PRVABC59 strain) administered at 5 mcg per dose mixed with a substance called Alhydrogel® (aluminum hydroxide) which is used in vaccines to improve immune response – also called an adjuvant. The placebo will be normal saline (0.9% sodium chloride) which is sterile salt water. Both placebo and ZPIV are given by injection into the muscle of your upper arm (deltoid).

Study Details: This study is a single-center, double-blinded, placebo-controlled, (you and the research staff won't know if you receive the experimental ZPIV vaccine or salt water placebo) first-in-human, Phase 1 study to learn about the safety, reactogenicity, and immunogenicity of two doses of alum adjuvanted ZPIV administered 28 days apart. The study will enroll 75 flavivirus naïve (no evidence of prior exposure to viruses similar to Zika) volunteers divided into 3 equal groups sequentially, starting with Group 1 followed by Group 2 and then Group 3. Screening will occur within 28 days of first vaccination. Each group will include 20 ZPIV recipients (including sentinel subjects) and 5 placebo recipients.

Group 1 - Two sentinel subjects will be enrolled first and will receive ZPIV "open-label" (you and the researchers will know you received the vaccine and not the placebo). After the sentinel subjects have been followed for a week, the next 23 volunteers (18 ZPIV, 5 placebo) will be randomly placed into Group 1. Group 1 volunteers will receive two doses of ZPIV or placebo administered IM on Days 1 and 29.

Group 2 – Enrollment starts with the identification of two sentinel subjects, and the randomization of 23 volunteers (18 ZPIV, 5 placebo) into Group 2 (Japanese Encephalitis vaccine priming). All will

WRAIR IRB
WRAIR # 2350 Approval expires 14 Sep 2017
Version 2.0, 28 Oct 2016B Signed HSPB
Earlier Versions Invalid

receive a two-dose regimen of the Japanese Encephalitis vaccine IXIARO® (Valneva) given by injection into the muscle of your upper arm (deltoid) 28 days apart. Three months after the second IXIARO® dose, the two sentinel subjects will receive ZPIV "open-label", after a week of follow up, the rest of the subjects will receive ZPIV 28 days apart.

Group 3 – Enrollment starts with the identification of two sentinel subjects, and the randomization of 23 volunteers (18 ZPIV, 5 placebo) into Group 3 (Yellow Fever vaccine priming). All will receive one dose of Yellow Fever vaccine YF-VAX® (Sanofi Pasteur) given by injection into the subcutaneous tissue of your upper arm. Three months later, the two sentinel subjects will receive ZPIV "open-label", after a week of follow up, the rest of the subjects will receive ZPIV 28 days apart.

A subset of volunteers (up to 10 ZPIV recipients per group) will be eligible receive a third ZPIV vaccination. Depending on you group assignment; you may receive up to five vaccinations in total.

Study Procedures:

Screening visit (within 28 days of first vaccination):
Learn about the research study & sign consent forms
Meet with study doctor for medical history & physical exam including vital signs
Blood collection & urine pregnancy test (females)

Vaccination visits:
Meet with study doctor to report any new or changed medical information or symptoms
Brief physical exam including vital signs
Blood collection & urine pregnancy test (females)
Receive vaccination
30 minute observation after the vaccine during which you will learn about how to record any symptoms you may experience at home using a form called a memory aid

Follow up Visits:
Return memory aid
Brief physical exam including vital signs
Meet with study doctor to report any new or changed medical information or symptoms
Blood collection

Phone Call Follow up (scheduled):
Report any new or changed medical information or symptoms

Please carefully consider the inclusion and exclusion criteria listed below to help you decide if volunteering to participate in this study is right for you:

To be eligible for the study, you must:

- Be a male or non-pregnant, non-breastfeeding female between the ages of 18 and 49 years, at the time of screening and enrollment
- Be willing and able to read, sign, and date the informed consent document and willing and able to comply with study requirements, including being available for follow-up visits for the entire study.
- Have a means to be contacted by phone

WRAIR IRB
WRAIR # 2350 Approval expires 14 Sep 2017
Version 2.0, 28 Oct 2016B Signed HSPB
Earlier Versions Invalid

- Have a body mass index (BMI) ≥18.1 and <35.0 kg/m^2
- Have acceptable screening laboratory findings within 28 days before enrollment.
- Be in good health based on the investigator's clinical judgment
- If a woman of childbearing potential (meaning that you are neither post-menopausal for two years nor surgically sterile), have a negative urine pregnancy test at screening and a negative urine pregnancy test immediately prior to each vaccination.
- If a woman of childbearing potential, agree to use an acceptable method of contraception from one month (30 days) prior to the first vaccination until at least 60 days after the last vaccination
- If a female subject, agree to not donate eggs (ova, oocytes) from the start of screening period until at least 60 days after receiving the last ZPIV vaccination.
- Agree to refrain from donating blood or blood products throughout your participation in the study.

You may not be in the study if you have:

- Plans to become pregnant or if you are currently pregnant or breast-feeding.
- Plans to travel to an area with active Zika, Dengue, Yellow Fever, or Japanese encephalitis virus transmission during the study of if you have returned from an endemic area with these diseases within 30 days of screening.
- A history of vaccination with a licensed or investigational flavivirus vaccine or if you have been diagnosed with a flavivirus infection or disease.
- Plan to receive a licensed flavivirus vaccine or participate in another flavivirus vaccine trial during the study.
- A positive blood test for Dengue, Zika, Yellow Fever or West Nile Viruses.
- A confirmed positive blood test for HIV, Hepatitis C, or Hepatitis B.
- Known or suspected congenital or acquired immunodeficiency of recent history or current use of immunosuppressive therapy.
- History of organ or stem cell transplantation or a history of cancer other than squamous cell or basal cell skin cancer (unless there has been surgical excision that is considered to have achieved a cure)
- A history of chronic or acute severe neurologic condition and/or a history of thyroidectomy or thyroid disease requiring medication during the last 12 months.
- Diabetes mellitus type 1 or 2, including cases controlled with diet.
- Had major psychiatric illness during the last 12 months and/or a current or past history of substance abuse that the investigator believes would preclude participation
- A history of chronic disease or condition including: autoimmune disease, hypercholesterolemia, chronic hepatitis or cirrhosis, chronic pulmonary disease, chronic renal disease, and chronic cardiac disease including hypertension even if medically controlled
- Tattoos, scars, or other marks on both deltoid areas that would, in the opinion of the investigator, interfere with assessment of the vaccination site
- A history of chronic urticaria (recurrent hives)

WRAIR IRB
WRAIR # 2350 Approval expires 14 Sep 2017
Version 2.0, 28 Oct 2016B Signed HSPB
Earlier Versions Invalid

- A known allergy or history of anaphylaxis or other serious reaction to a vaccine or vaccine component, which includes: protamine sulfate, eggs or egg products, chicken protein, gelatin, sorbitol, aminoglycosides (e.g., neomycin and streptomycin), or any of the constituents of the study vaccines including alum
- Had major surgery (per the investigator's judgment) in the month prior to screening or plan to have major surgery during the study.
- Received blood products or immunoglobulin in the 3 months prior to screening or plan use during the course of the study.
- Donated a unit of blood within 8 weeks before Day 1 or plans to donate blood during the course of the study.
- Received live attenuated vaccine from 30 days before Day 1 until 30 days after the last vaccination.
- Received killed or inactivated vaccine from 14 days before Day 1 and until 14 days after the last vaccination. You may receive inactivated seasonal influenza vaccine 14 days prior or 30 days after each study vaccination (JE, YF, or ZPIV).
- Severe allergy or anaphylaxis to latex.
- Received experimental therapeutic agents within 3 months prior to the first study vaccination or plans to receive any experimental therapeutic agents during the course of the study.
- History of thymus disorder including myasthenia gravis, thymoma, or prior thymectomy.
- Received experimental therapeutic agents within 3 months prior to the first study vaccination or plan to receive any experimental therapeutic agents during the course of the study
- Plans to participate or are currently participating in another clinical study
- An acute illness or temperature ≥100.4 °F on any vaccination day (ZPIV and priming vaccinations) or within 48 hours of planned vaccination.
- In the investigator's opinion, a condition that would limit your ability to complete the study and/or cannot communicate reliably or are unlikely to adhere to the study requirements.
- Not willing to allow storage of your blood samples for future research.

For more information on this study or to schedule an appointment to be screened, please call or email the WRAIR Clinical Trials Center using the contact information below and provide the following information to the staff:

Note: *This information is entered into our secure database and is not shared with outside sources.*

1. Name
2. Date of Birth
3. Gender – M or F
4. Phone number
5. Email address
6. How you heard about the WRAIR CTC

WRAIR Clinical Trials Center
503 Robert Grant Ave Silver Spring, MD 20910
Phone: 301-319-9320
Email: usarmy.detrick.medcom-wrair.mbx.clinical-trials@mail.mil
Hours: Monday – Friday 6:00 am – 2:30 pm