

Study Title: Phase 1 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Hantaan and Puumala Virus DNA Vaccines, pWRG/HTN-M(x) and pWRG/PUU-M(s2), for Prevention of Hemorrhagic Fever with Renal Syndrome Administered to Healthy Adult Volunteers Using the TDS-IM Electroporation Delivery Device

Purpose of the Study: This is an early phase study and is intended to assess two experimental vaccines: Hantaan virus DNA and Puumala virus DNA vaccines. The study looks at safety and the ability to produce antibodies or proteins made by the body to protect against infection. This means if you were exposed to these viruses, your body would be able to more quickly respond to either prevent or lessen the effects of the infection. These vaccines have been given to humans before.

This study will use a device to give the injections, called the Tri-Grid Delivery System for intramuscular injection (TDS-IM), rather than a standard needle and syringe for an intramuscular (IM) injection. The TDS-IM is a handheld, fully automatic electronic device, which has been used in other clinical studies for several years. The device uses a brief electrical impulse to give the injection, and volunteers have noted a mild muscle spasm at the injection site (similar to the reaction you get when a health provider checks your knee reflex during a physical exam). Volunteers have also noted a brief, mild discomfort from needle penetration into the skin similar to that of a standard intramuscular vaccination (such as the “flu shot”). This study will be the first time these particular vaccines are administered with this device.

This study is using this device because it enables safe and consistent delivery of the vaccine. It increases the amount of vaccine allowed into the cells; they “open the pathway” into the cells. This allows an increased uptake of vaccines compared to other delivery types. Both the increased uptake and consistency of getting the vaccine into the cells play an important role in how well a vaccine works. In surveys by the manufacturer of the device, volunteers felt the delivery mechanism was acceptable and tolerable.

To participate in this study you must be:

- Between the ages of 18 and 49
- Healthy
- Not pregnant or lactating and willing to use reliable contraception for the duration of the study

You cannot participate in this study if you have:

- History of prior infection with any hantavirus virus (including screening blood test of prior exposure), or prior participation in a HTNV or PUUV virus vaccine trial
- Clinically relevant medical history or abnormality on the physical examination, such as a history of immunodeficiency or use systemic corticosteroids, immunosuppressive, antiviral, anticancer, or other medications considered to be significant by the study investigator
- Have an acute or chronic medical condition requiring the care of a physician, such as diabetes, heart disease, rheumatologic illness, cancer, or substance abuse, that in the opinion of the investigator would make it unsafe for you to participate

- History of a neurological disorder, including seizures or epilepsy
- Occurrence of even one episode of fainting within the previous 12 months
- Obscured injection sites so the investigator would not be able to see injection reactions (e.g., tattoos or scarring covering the upper outer arms)
- Too much skin and fatty tissue over top of the muscles at the injection sites (on your upper outer arms), so that an injection cannot be successfully be given to you using the device in this study
- If you are female, and are either pregnant, breast-feeding or planning pregnancy from screening until 6 months after the final injection
- Receipt of immunoglobulin or any blood products 4 months prior to enrollment
- Participation in another clinical trial of an investigational product currently or within the past 30 days or expected participation during this study
- Receipt or planned receipt of any approved vaccine within the period 30 days prior to the first injection through the period 60 days after Study Day 70 (~6 month period in total)
- History of severe local or systemic reactions to injection or a history of severe allergic reactions

Study Duration: The study is expected to last up to 14 months for each volunteer with most volunteers completing the study in 8 to 11 months. Each volunteer will attend up to 18 study visits (including screening) during this period, with most subjects completing approximately 15 study visits.

Background Information: The vaccines are targeted against infection from Hantaan and Puumala viruses. These viruses belong to the genus (family) Hantavirus and are found worldwide, including the United States. The viruses are found in infected rodent urine, feces, and saliva in both rural and urban areas. Humans are exposed by bites from infected animals, breathing in dust from infected animal droppings or coming in contact with excrement through mucous membranes (nose and/or mouth) and broken skin. Hantavirus does not make animals sick but can cause illness in humans. There may be no symptoms cause symptoms similar to the flu, or become much more serious, causing hemorrhagic fever with kidney syndrome (severe blood loss with kidney-related problems) and can lead to death.

Currently, there is no vaccine licensed by the U.S. Food and Drug Administration (FDA) for this infection so research is being done to develop a vaccine that would work for people who live or travel to areas of exposure. Vaccines are given to people to try to prevent or lessen the effect of an infection or disease.

Study Information: We plan to enroll up to 27 volunteers in the study, who will be divided into 3 groups of 9 volunteers. Each group will receive the same vaccine IM throughout the study. You will be randomly assigned to one of the 3 groups: one group will receive the HTNV DNA vaccine, one group the PUUV DNA vaccine, and one group both the HTNV DNA and PUUV DNA vaccines. Each group will receive the injections at 3 time points; study Days 0, 28, and 56. You will not know which group you are in during the study but may find out after the study is

completed. Each vaccinated subject will be followed for a period of 240 days and complete 14 study visits.

An additional 3 volunteers will be enrolled as alternates, who will participate if a previously enrolled volunteer is unable to continue to Study Day 70. The alternates are asked to come in on scheduled injection days (0, 28, and 56) and Study Day 70.

All visits are at the WRAIR Clinical Trials Center (CTC) and occur from 0630–1200, unless other arrangements are made in advance.

- Briefing (1): Takes approximately 30–45 minutes and involves coming to the CTC to learn about the study in detail and signing the informed consent
- Screening (1): Takes approximately 30–45 minutes and involves a medical history and physical exam with a doctor, collection of blood for safety tests and Hantavirus exposure and urinalysis for kidney function tests. Women will also have a urine pregnancy test.
- Injection (3): Takes about 1.5–2 hours and involves a brief physical exam, collection of blood and urine, injection, and paperwork
- Follow-up visits (11): Takes approximately 20–30 minutes and involves a brief physical exam, collection of blood, and a review of any symptoms that occurred

Compensation: Volunteers will be financially compensated for their time and effort.

- Enrolled vaccine volunteer (spread over 14 visits): \$1,725
- Alternate who does not enroll (spread over 4 visits): \$225
- Alternate who enrolls: Dependent on time of enrollment