CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER INFORMED CONSENT

STUDY TITLE: A Phase I, Randomized, Placebo Controlled, Double-Blind, Dose Escalation Trial to Evaluate the Safety and Immunogenicity of an Andes Virus DNA Vaccine for the Prevention of Hantavirus Pulmonary Syndrome Using the Pharmajet Stratis® Needle-Free Injection System in Normal Healthy Adults

STUDY NUMBER: DMID Protocol # 16-0119

WHO IS IN CHARGE OF THE RESEARCH?
Dr. Grant Paulsen is the research study doctor in charge of this study at Cincinnati Children's Hospital Medical Center (CCHMC). He may be reached by phone on the 24hr. Study line at 513-636-7699.

Cincinnati Children's Hospital is being paid by the National Institutes of Health (NIH) Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), to do this study.

Aldevron is the company who is making the study vaccine that was developed by the Department of Molecular Virology, US Army Medical Research Institute of Infectious Diseases.

INTRODUCTION
We are asking you to be in a research study so that we can learn new information that may help others. If you decide not to be in this study, we will still take good care of you. If you decide to be in this study, you may change your mind at any time during the study and you can stop being in the study. Take all the time you need to make your choice. Ask us any questions you have. It is also okay to ask more questions after you decide to be in the study. You can ask questions at any time.

WHY ARE WE DOING THIS RESEARCH?
Hantavirus Pulmonary Syndrome (HPS) is a severe, sometimes fatal, respiratory disease in humans caused by infection with hantaviruses. Andes virus is one of the types of hantavirus that causes HPS. Hantaviruses are found everywhere in the world, including the United States. Hantaviruses are spread to humans through bites from infected rodents, breathing in dust from infected animal droppings, or having contact with infected droppings through nose, mouth, or broken skin. Infected people may have no symptoms, or they may have mild flu-like illness or a severe, possibly life-threatening illness.

One of the ways we can try and stop HPS is with vaccines. This study will test an experimental Andes Virus (ANDV) DNA vaccine to see if it is safe and can protect against HPS. Experimental means the vaccine has not been approved by the US Food and Drug Administration (FDA).

Vaccines are given to people to stop them from getting sick from a virus. Vaccines work by telling your body to make proteins called "antibodies". Antibodies help your body fight infections. The vaccines used in this study work by using non-Andes viruses to carry genes (coded instructions) that tell the body to make "antibodies" against Andes virus proteins. The vaccine is not a living virus, it does not contain human DNA, and cannot cause hantavirus infection. In this study, the Andes Virus vaccine will be injected into your arm muscles using the Pharmajet Stratis® Needle-Free Injection System. This system uses compressed air (instead of a needle) to quickly push the vaccine through the skin and into the arm muscle.

WHO SHOULD NOT BE IN THE STUDY?
You cannot be in this study if:

- You are younger than 18 years of age or older than 49 years of age.
- You have ever had a Hantavirus vaccine, have had HPS, lived or traveled (more than 2 weeks) to Chile, Brazil or Argentina (countries where Hantavirus illness is most common) in the past 3 years.
- You plan to travel to Chile, Brazil or Argentina within 6 months of last study vaccine.
- You have had a severe reaction to a past vaccine.
- You are allergic to gentamicin, tobramycin, neomycin, streptomycin
- You have problems fighting off infections, or you have Hepatitis B, Hepatitis C, or HIV.
- You know that you have Type I or II diabetes.
- You are female and are pregnant or breastfeeding.
- You are in other research studies.

There may be other reasons you cannot be in this study, and the study doctor will review these with you.

WHAT WILL HAPPEN IN THE STUDY?
You will get a handout so you will know what will happen at each study visit. The research staff will explain each visit to you. You will be able to ask questions and you can take the handout home with you.

Screening Visit
First you will come to the clinic for a screening visit(s) to see if you qualify to be in this study. You will be asked to read and sign a consent form and will be given a copy. We will ask questions to make sure you are healthy enough to be in the study.

At the Screening Visit:

- We will ask you questions about your:
  - age, race and ethnic group
  - any past or present illnesses, hospitalizations, surgeries and medicines you are taking including past vaccines
- We will measure your height, weight, blood pressure, temperature and heart rate.
- We will perform a physical examination
- Trained staff will collect about 1 tablespoon of your blood from a vein to test for:
  - Healthy blood cell counts and to be sure your liver and kidneys are healthy
  - Pregnancy in women – if pregnant you will not be able to join the study
  - Hepatitis B, Hepatitis C, HIV infection
    * If you have a blood test that is positive for Hepatitis B, Hepatitis C, or HIV, the results must be reported to the local health authorities according to state law.
- We will collect a urine sample to test for protein and opiate drugs (like heroin, morphine, and codeine).

If these tests are normal and you meet all other study requirements, you may enroll into the study.

Approximately 48 healthy adults will participate in this study. If you qualify and you decide you want to be in the study, you will come to our clinic about 14 or more times over the next 12 months. You will receive the study vaccine or placebo at 4 of the clinic visits. Please review the handout for study visit details.

These are the things that will happen to you while in the study:

Medical History: We will ask you about your past and present illnesses, hospitalizations, surgeries, medicines and vaccinations

Physical Exam and Vital Signs: We will measure your temperature, heart rate, blood pressure, height and weight. You may have a physical exam if anything has changed in your health.

Pregnancy Test: If you are a woman and able to have children, we will test your urine before each vaccine visit to be sure you are not pregnant.

Blood Tests: Trained staff will collect 1 to 7 tablespoons of your blood from a vein at each study visit to see if the study vaccines have caused any changes in your blood counts, liver or kidneys. Also, we will be collecting blood to test how your body is responding to the vaccines. Extra tubes of blood will be collected at 3 study visits. By being in this study, all blood tests are collected for research only.

By giving consent to be in this study you also give permission to allow the extra tubes of blood and any leftover blood samples from any study visits to be stored indefinitely at Cincinnati Children's or another facility that the National Institutes of Health chooses. These blood samples will be used for research only. They will not be sold, or used to make new cell lines or for genetic testing of inherited diseases. They may be used for genetic testing for vaccine responses to help develop new vaccines, or in new or different laboratory tests, or to study other infections. If the study doctors perform genetic testing, results will be part of research records and will not become part of your medical record and will not be shared with your doctor. There will be no identifying information used in reporting or publications of any future testing results. The results of this testing will not be reported to you or your doctor, and will not benefit you. The samples might be shared with researchers at other study centers.

Vaccination: There are 4 groups in this study. You will be put into one of 4 groups by chance (like flipping a coin). You will get 3 or 4 Andes Virus vaccines or a placebo depending on which group you are in. The placebo in this study is a sterile, salt water solution made for injecting into people. There are also 2 different doses of vaccine for this study; 2 milligrams (mg) and 4mg. Approximately half of all the participants will receive 2mg of the study vaccine and the other half will receive 4mg. A few participants will receive placebo for all of the doses. You will get 2 injections using the PharmaJet Stratis® Needle-Free Injection System each time there is a vaccine visit; one each in the muscle of your right and left upper arms. You will stay in the research clinic **for 30 minutes** after each vaccine to be watched for any immediate vaccine reaction.

Since this is the first time this vaccine has been tested in humans, the Andes Virus vaccine will be given to two people at the 2mg dose and two people at the 4mg dose to make sure there are no unexpected or serious side effects. This is standard practice for testing new vaccines. For all other participants, neither you nor the study staff will know which vaccine you received. If there is an emergency, your study doctor will be able to find out.

Vaccine Groups:

Group	**Vaccine 1** Day 1	**Vaccine 2** Day 29	**Vaccine 3** Day 57	**Vaccine 4** Day 169
1	2 mg Andes Vaccine or placebo	2 mg Andes Vaccine or placebo	Placebo	2 mg Andes Vaccine or placebo

2	2 mg Andes Vaccine or placebo	2 mg Andes Vaccine or placebo	2 mg Andes Vaccine or placebo	2 mg Andes Vaccine or placebo
3	4 mg Andes Vaccine or placebo	4 mg Andes Vaccine or placebo	Placebo	4 mg Andes Vaccine or placebo
4	4 mg Andes Vaccine or placebo	4 mg Andes Vaccine or placebo	4 mg Andes Vaccine or placebo	4 mg Andes Vaccine or placebo

Memory Aid: You will be given a memory aid, thermometer, and ruler. You will fill out the memory aid every day for 7 days after each vaccine. The study staff will give you instructions and teach you how to do this. You will take your temperature about the same time every day and write it down. You will also write down any symptoms you have.

Unscheduled Visits: You may be asked to come back to the clinic at other times if there is a need to do so. Your medical history, medicines, memory aid and any safety questions may be reviewed. The study doctor may examine you and your vital signs and, blood may be drawn to be sure you are safe.

Stopping the Study Early: You may decide at any time not to be in the study, the study may be stopped, or your doctor may decide that it is not in your best interest to continue in this study. If this occurs, you will be asked to come back to the clinic for a final visit. Your medical history, medicines, memory aid and any safety questions may be reviewed. The study doctor may examine you and your vital signs and, blood may be drawn to be sure you are safe.

WHAT ARE THE GOOD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?
Being in this study may not help you right now. We hope that we will learn more about whether the ANDV vaccine is safe and what dose to use.

WHAT ARE THE BAD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?
General Risks and Discomforts
While in this study, you are at risk for some side effects. There may be other risks, discomforts, or side effects that are unknown at this time. The study team will discuss these with you.

From the Vaccine:
Getting an injection in your arm muscle may cause pain and some people may feel like fainting. We will carefully clean your arm and all vaccines are given with new, clean needles and syringes.

Vaccines can cause the following:

Mild symptoms where you get the injection in your arms such as:

- Pain or tenderness
- Redness
- Warmth
- Lump or swelling
- Bruise
- Pain with arm movement
- Skin color change where injection given

General body symptoms such as:

- Tiredness
- General unwell feeling
- Headache
- Body aches/muscle/joint pain
- Fever, chills/shivering/sweating
- Nausea

The PharmaJet Stratis® Needle-Free Injection System:
You may feel pressure or some pain when the device is firmly pushed against your arm for the injection. Some people feel nothing when the vaccine is given while others have a feeling like the snap of a rubber band against the skin. The injection site may show some mild redness, tenderness, swelling or itching even if you do not receive the vaccine.

Possible, but unproven risks related to DNA vaccines include:

- damage to the cells in your body
- your body makes antibodies to the DNA in the vaccine
- the vaccine DNA inserts itself into your body's DNA
- the vaccine DNA inserts itself into a bacteria inside your body causing that bacteria to be resistant to some antibiotics
- the vaccine DNA inserts itself into a virus in your body leading to the formation of a new virus.

None of these possible risks of DNA vaccines have been seen in laboratory tests in humans so far. While no vaccine for Hantavirus infection has been tested in humans, other DNA vaccines against related hantaviruses in the same family as Andes virus have been tested for safety in humans as part of clinical studies. People in those DNA vaccine studies have experienced tiredness mild headache, muscle aches, bruising, pain, redness and swelling at the injection site.

Allergic Reactions:
Vaccines can cause a severe allergic reaction. Such reactions are rare and would happen within a few minutes to a few hours after the shot is given. Signs of a severe allergic reaction can include rash, hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, and weakness.

It is possible that the DNA vaccine might cause you to have a stronger reaction if you are exposed to a similar disease in the future. This has been seen with other vaccines but not with other hantavirus vaccines to date.

Blood draws
Blood draws can cause pain or bruising where the needle goes into the vein or you may feel like fainting when your blood is drawn. Although it is rare, some people have gotten an infection from having their blood drawn. To lower this risk, we will clean the skin where the blood will be drawn and use brand new needles and supplies.

What are the bad things that can happen if you become pregnant in the study?
Because the risks to an unborn baby or a pregnant mother are unknown at this time, you should not become pregnant while you are in this research study. If you are a woman and choose to have sex with a man, you must agree to use birth control from 30 days before the first study dose until 90 days after the last dose of vaccine. The staff will review the types of birth control you may use during the study. You should notify your study doctor immediately if you become pregnant. If you do become pregnant, the study staff will ask your permission to continue to follow you during your pregnancy. We may ask you to come for study visits and we will collect blood samples for the research. We will also check on the health of your baby

once born. If you are a woman, you should not donate eggs until 90 days after receiving the last dose of vaccine.

If you are a man and choose to have sex with a woman, you must agree not to father a child from receipt of the first study dose until 90 days after the last dose of vaccine. The staff will review the types of birth control you may use during the study. Men must also agree to not donate sperm for 90 days after receiving the last dose of vaccine.

There may be other risks, discomforts, or side effects that are unknown at this time.

WHAT OTHER CHOICES ARE THERE?
Instead of being in this study, you can choose not to be in it.
If you work at Children's Hospital and decide you do not want to participate or if you withdraw from the study, it will not affect your job or employment in any way.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE?
You will be registered in the Cincinnati Children's Hospital Medical Center's (CCHMC) computer system as a research patient. We will keep a copy of this consent form in your research chart. To keep your information private and confidential, CCHMC and/or the study doctor will:

- use code numbers instead of your name in your study chart
- limit the people who can see your study records
- not identify you in any records or articles published about the study findings

By signing this consent form, you are giving permission for parts of your medical and research records related to this study to be reviewed by:

- Cincinnati Children's Hospital Medical Center
- The study doctor and CCHMC research staff who are part of the study
- The CCHMC Institutional Review Board and the Office for Research Compliance and Regulatory Affairs
- The sponsoring company: National Institutes of Health (NIH) or authorized representative
- Your personal healthcare provider

The Food and Drug Administration (FDA) may choose to review your records since they are in charge of studies of experimental unapproved vaccines.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

To help us protect your privacy, we have a Certificate of Confidentiality from the National Institutes of Health (NIH). The researchers can use this Certificate to legally refuse to give information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except for reporting of communicable diseases to State and local health departments.

The Certificate of Confidentiality:

- will not be used to prevent disclosure to state or local authorities for information required by local or state law.

- cannot be used for information in your medical records.
- does not prevent disclosure of your information to the NIH, Food and Drug Administration (FDA), or federal funding agency.
- does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research.

If you give your consent to release information to a medical care provider, an insurer, or other person to receive research information, then the researchers will not withhold that information.

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?
The study doctor will tell you if they find out about new information from this or other studies that may affect whether or not you want to stay in this study.

WILL YOU BE PAID TO BE IN THIS RESEARCH STUDY?
It will not cost you anything to be in this study. You or your insurance company with not be charged for the lab tests, study visits and other study tests. You will receive about $1000.00 for completion of all the required study visits as described in the study visit handout. If you do not complete all the study visits, you will be paid for those that have been completed.

Your study payment will be on a reloadable debit card called Clincard. We will give you a handout explaining how to use the card. Because you will be paid for your study participation, we are required by the Internal Revenue Service (IRS) to collect and use your social security number (SSN) or taxpayer identification number (TIN) in order to track the amount of money that we pay you. You will need to complete a Federal W-9 form and this form will be kept in the CCHMC business office. If you move, you will need to complete another W-9.

Blood collected for this research may result in the development of a product that could be patented or licensed. You will not be paid if this happens.

WHO DO YOU CALL IF YOU HAVE QUESTIONS, PROBLEMS OR ARE INJURED?
If you have questions, concerns, or complaints about this research study or want to report a research-related injury, you can contact the study doctor, Dr. Grant Paulsen at 513-803-5458 or on the 24hr line at 513-636-7699.If you have general questions about your rights as a research patient in this research study, or questions, concerns, or complaints about the research, you can call the Cincinnati Children's Hospital Medical Center Institutional Review Board at 513-636-8039. You can also call this number if the research staff could not be reached, or if you wish to talk to someone other than the research staff.

In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH or the Federal Government. Cincinnati Children's Hospital Medical Center makes all decisions about compensation and/or medical treatment for physical injuries that happened during or were caused by being in this research study case by case.

WHAT ELSE SHOULD YOU KNOW ABOUT THE RESEARCH?
Being in the research study is your choice. You can say "Yes" or "No". It is OK to say "No". If you say "Yes" now and change your mind later that is also OK. You can stop being in the research study at any time.

If you want to stop being in the research study, all you have to do is tell Dr. Paulsen or someone else on the study staff.

FUTURE CONTACT

We may want to contact you in the future to see if you would be interested in participating in future studies. At this time, you may decide whether or not you want to be contacted. If and when you are contacted, you can decide if you want to participate in any of the other studies and will sign another consent form to participate in those studies. Your decision regarding future contacts will not affect your participation in this study.

_____ **YES, I may** be contacted about future studies.
(Initials)

_____ **NO, I may not** be contacted about future studies.
(Initials)

SIGNATURES

The research team has discussed this study with you and answered all your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research, you will document your permission by your signature below.

You will receive a copy of this signed document for your records.

_____
Printed Name of Research Participant

_____ _____
Signature of Research Participant Indicating Consent — Date

_____ _____
Signature of Individual Obtaining Consent — Date