

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

Bavarian Nordic, POX-MVA-011, Amendment #5, 10-Sep-2007**A Multicenter, Open-Label, Controlled Phase II Study To Evaluate Safety And Immunogenicity Of MVA-BN® (IMVAMUNE®) Smallpox Vaccine In 18-55 Year Old Naive And Previously Vaccinated HIV Infected Subjects With CD4 Counts \geq 200 – 750/ μ L****CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY**

Principal Investigator:	Ian Frank, MD	(215) 662-7419
Sub Investigators	Stuart Isaacs, MD	(215) 662-2473
Coordinators:	Joseph Quinn, RN	(215) 349-8092
	Randee Silverman, RN	(215) 349-8092

24 Hour Emergency Number (215) 662-6059 Ask for the Immunodeficiency Program Doctor on call

WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH?

You are being invited to voluntarily take part in a smallpox vaccine research study for the prevention of the disease smallpox. Before agreeing to participate in this research study, it is important that you read and understand the following description of the study. If you are not completely truthful regarding your current medical conditions and your medical history, you may harm yourself and others by participating in this study.

Please read the information provided below carefully, and do not hesitate to ask the investigator or staff members any questions you may have. If you volunteer to take part in this study, you will be one of about 550 people. Up to 50 volunteers will be enrolled at the University of Pennsylvania.

WHO IS DOING THE STUDY?

This study is being done in up to 35 study centers in the U.S. and Puerto Rico, the University of Pennsylvania is one of them. The University of Pennsylvania is receiving financial support from Bavarian Nordic the sponsor of this trial to assist in the conduct of this research study. The study is funded by the National Institutes of Health (NIH) as well as the US Department of Health and Human Services (HHS). Dr. Ian Frank is conducting this study at the University of Pennsylvania. There may be other people on the research team assisting at different times during the study.

WHAT IS THE PURPOSE OF THIS STUDY?

The world was declared free of smallpox in 1980. General routine vaccinations for smallpox were stopped in the US in 1971. Because of the recent concern of biowarfare and bioterrorism throughout the world, the United States government is making efforts to improve its ability to protect its citizens in the event of a bioterrorist attack with the possible use of the smallpox virus (Variola major virus). Because the approved smallpox (vaccinia) vaccine Dryvax® is contraindicated for immune compromised subjects such as subjects with HIV infection due to potential severe side effects, there is a medical need for a safer vaccine for this population.

The purpose of this research study is to compare the safety and tolerability of a new investigational smallpox vaccine called MVA-BN® in HIV infected subjects to healthy (HIV) negative subjects. In addition the induction of an immune response (the body's defense system) against smallpox in subjects with HIV infection will be compared to healthy subjects. There will be two vaccinations given.

MVA-BN® is a live virus vaccinia vaccine, but unlike Dryvax®, the vaccine traditionally used for smallpox vaccination, this virus has been weakened and is not able to propagate ("replicate") in humans. The

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vaccine causes the body to have an immune response (antibodies) without causing a vaccination sore or scar. MVA-BN® is supplied by a Danish/German company called Bavarian Nordic.

MVA-BN® is an investigational [not approved by the US Food and Drug Administration (FDA)] vaccine developed by Bavarian Nordic to be given as an injection with a short needle below the skin of the upper arm.

In the future, if a small pox vaccine were to be made available to the public, participation in this study would not prevent you from receiving it.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The research procedures will be conducted at the Infectious Disease Division/MacGregor Clinic on 3 Silverstein at the Hospital of the University of Pennsylvania. The study may last up to 39 weeks in total (see Table I) from the time you are first seen at the study site until the follow up which will either be conducted as a visit (for the first 165 subjects included in the study or if decided by the investigator for safety reasons) or as a telephone follow up (telephone call from your doctor). During the active phase of the study, you will need to have blood drawn and be seen in the clinic. This means that you will need to come to the clinic for 6 regular visits plus a follow up visit or follow up phone call (see Table II). Only if clinically indicated, additional visits in the clinic could be scheduled. The regular study visits will usually take no more than 1 - 1½ hours each.

WHAT WILL I BE ASKED TO DO?

You can participate in the study if you meet the conditions in one of the three different groups and if you are willing to participate by attending all study visits as shown in Table I below:

Table I: Overview on study groups

	Group 1	Group 2	Group 3
Subjects	Healthy Previously smallpox vaccinated or not	HIV infected Previously not smallpox vaccinated	HIV Infected Previously smallpox vaccinated
No. of subjects	90	360	100
Age	18-55 years		
Study Duration	Up to 39 weeks		
No. of Visits to clinic	6 or 7*		
No. of blood samples taken	6 or 7*		

*7 visits will be done in case followup will be performed as a clinic visit rather than a telephone call

The study visits take place according to the following schedule:

Table II

Visit	Blood draw scheduled (amount)	ECG scheduled
Screening	X (28 ml or about 2 tablespoons)	X
Visit 1, Day 0	X (77 ml or about 5 tablespoons)	
Visit 2, Week 2	X (92 ml or about 6 tablespoons)	X
Visit 3, Week 4	X (72 ml or about 5 tablespoons)	
Visit 4, Week 6	X (92 ml or about 6 tablespoons)	X
Visit 5, Week 8	X (87 ml or about 6 tablespoons)	(X)
Follow up at 26 -30 weeks after Visit 3 Follow up visit OR telephone follow up	X (up to 92 ml or 6 tablespoons)	(X)

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Explanation: X= To be performed; (X)= To be performed only if the investigator decides to do so

Once you have been assigned to a group the study staff will give you a schedule of your return visits up to the 6 month visit or the telephone follow up.

Your participation is described in the following section. If you agree to join the study, you will be assigned to one of the three groups depending on whether you have HIV infection or not and whether you have been vaccinated against smallpox in the past.

You will receive vaccinations at Day 0 and Day 28 as an injection under the skin (shot).

Screening Visit (Visit SCR)

Within 28 days prior to vaccination you will have a screening visit carefully checking to see if you are eligible for participation in the study.

You will complete a health history form and have a physical examination which will include your vital signs. Also during this visit, approximately 2 tablespoons (28 ml) of blood will be drawn and you will be asked to give a urine sample for laboratory examination. An electrocardiogram ("ECG") will be performed to check your heart and for female participants a serum (blood) pregnancy test will be done to make sure you are not pregnant.

Your screening blood will be tested for a general health screening (blood, heart, kidney and liver health) and for hepatitis B. Test for hepatitis C and HIV will only be done for healthy (not HIV infected) subjects (Group 1). New knowledge of positive HIV status may cause psychological stress, discrimination from other people or other unknown inconveniences. If your blood tests positive for HIV, a qualified person will provide counseling to you. The test results will be reported to the Public Health Department using your name as required by law. Your test results will be coded and therefore your identity will not be revealed to anyone outside the research staff working on the study except as explained above. This is the legal obligation of the medical personnel as required by law.

Immunization and Visits

If you are eligible for study participation as determined during screening, and are chosen to be vaccinated in this study you will have blood samples taken up to five or six more times (see Table II). Only in case of further follow up examinations additional blood draws could be scheduled.

Blood samples are scheduled as shown in Table II above. The amounts of blood taken at each visit during the active phase of the study varies between 72 (about 5 tablespoons) and 92 ml (about 6 tablespoons).

At every visit during the study and also at the follow-up visit, you will have a short physical examination and your vital signs will be taken.

An ECG will be performed at visits 2 and visit 4. Only if the investigator decides that it is needed further ECGs will be done at study visit 5 and at the follow up visit scheduled six month after the last study vaccination. If you have been included in the extension study (after about 165 subjects were already included in the study before you), only a telephone call from your doctor will be done for follow-up visit.

If you are a female, you will have a urine pregnancy test done to make sure you are not pregnant before you will receive each of your vaccinations and at the final visit.

Vaccination with MVA-BN®

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MVA-BN® is given as a shot with a short needle into the upper arm. The vaccine in this research study will be given under the skin (“subcutaneously ,SC”).

You will receive a vaccination of MVA-BN® at study visit 1 and study visit 3.

After each Vaccination

You will remain in the clinic for ½ hour after each vaccination to be observed by the study center staff. Following each vaccination, you will be asked to keep a diary card to record your temperature orally and document symptoms each day for 7 days or longer if symptoms persist. You will receive a thermometer and a ruler to measure possible reactions at the vaccination site. The study personnel will explain to you how to measure and how to keep records in the diary. You will need to bring your diary to every clinic visit.

Remaining visits

The study staff will examine the vaccination site. They will also review your diary card with you and ask if you had any changes in your health or experienced any problems since your last visit. Please see Table II for the visit schedule.

Diary Card

You will be given a diary card at visits 1 and 3. The study staff will review the diary card with you so that you understand how to complete it. Please bring the diary card to each visit. It will be collected at visits 2 and 4.

Blood for Tests Done During the Study

With the blood taken before and during the study tests are performed to examine general health parameters (blood, heart, kidney and liver health) and immune responses induced by the vaccine. Vaccination site will be examined at visits 2 and 4. Please see Table II for amount of blood drawn during the study. You might also be asked to have laboratory tests between regular visits if you have side effects to the vaccine. Your blood will be identified by code; your name will not be used. Portions of your samples taken during the study will be stored / analyzed at University of Pennsylvania, a central laboratory, and the laboratory of Bavarian Nordic.

ARE THERE REASONS WHY I SHOULD NOT TAKE PART IN THIS STUDY?

You cannot participate in the study if you meet certain conditions which will be evaluated and discussed with you by the study doctors or nurses. For example if you:

- Have an acute febrile disease
- Take or apply certain medication like steroids
- Are allergic against certain antigens, e.g. hen egg or aminoglycoside antibiotics

If you are a female, you can not participate in this study if you are pregnant, breastfeeding or plan to become pregnant within 28 days after your final vaccination. Females of childbearing potential, including women who are abstinent, must agree to use an approved form of birth control for 30 days before vaccination and throughout the study period following the study vaccination. Acceptable contraception methods are restricted to abstinence, barrier contraceptives (condom, diaphragm), intrauterine contraceptive devices, or licensed hormonal products.

There may be harm to an unborn child if you were to participate in the research during pregnancy. If you are pregnant, or become pregnant, you cannot participate in this research. If you are sexually active during your participation in the research, you must use approved measures to avoid becoming pregnant.

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Volunteers who become pregnant will only have safety bloods drawn and blood for antibody testing and will be asked to keep all of their scheduled follow-up visits. Until your pregnancy is over, we will ask you for information about your health and the health of your baby.

If you are planning to participate in another study, you must tell the investigator who will decide if it is OK for you to participate in more than one study at the same time.

The study doctors or nurses will review with you those things which may prevent you from participating in the study.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

Immunization with MVA-BN®

The vaccine has been used in clinical trials in more than 1500 subjects. Very common after vaccination were pain, soreness, redness, itching and swelling at the vaccination site. Less frequent were headache, malaise (general feeling of being unwell), fever, chills, dizziness and diarrhea. Rash, sweating, muscle or joint pain, sore throat, nausea, fatigue and swollen lymph nodes were reported only in few or single cases. The majority of the symptoms were mild to moderate and all resolved within a few days.

A vaccine which is based on the same virus as MVA-BN® has been tested in clinical trials in 75 HIV infected subjects in Europe. In these studies up to 5 times higher dose of the vaccine as used in this trial has been used. The side effects of the vaccinations were similar to those described above with MVA-BN® in healthy subjects.

As with all vaccines or drugs, you could have an allergic reaction - a rash, hives or even difficulty breathing. Allergic reactions can be dangerous; therefore, the study center staff will watch you for 30 minutes after each vaccination. There may be other side effects from MVA-BN®, even serious ones that are not yet known. Therefore, it is important that you report any side effects to the study staff. You will keep a daily diary card to record any side effects you might have for seven days after each vaccination.

The vaccination with a smallpox vaccine could possibly have an increased risk to those with cardiac disease, such as chest pain caused by heart problems (angina), poor heart muscle blood circulation (Coronary Artery Disease) or prior heart attacks (myocardial infarction, MI).

Bovine (cow) - derived materials are used in the manufacture of the vaccine used in this research study. These materials were obtained from a country, which has had Bovine Spongiform Encephalopathy (BSE, also called "mad-cow disease") in cows. Eating beef products from countries with BSE has been associated, on very rare occasion, with the development of a fatal brain disease called variant Creutzfeldt-Jakob disease (vCJD, the human disease related to BSE). No evidence exists that vaccines have contributed to any cases of vCJD. Two panels of experts reported to the FDA that they consider the risk of getting this brain disease from vaccines (while it could happen in theory) to be extremely small. The conclusion was based, in part, on information about the materials and the processes used during production of the vaccines.

Blood Drawing

Blood drawing may cause pain and bruising, bleeding, and rarely infection at the site where the blood is taken. Sometimes, being stuck with a needle causes people to feel lightheaded or even faint. Rarely does infection occur where you were stuck with the needle. You may also feel light-headed or faint when the blood is being drawn.

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There may be few risks to you if your blood samples are used in future research. A possible risk might be release of information from your study records (loss of confidentiality). Reports about future research done with your samples will not be put in your study record.

Pregnancy

Women must have a negative pregnancy test before each vaccination and agree to use an approved method of birth control or be known to be sterile because possible effects of the vaccine on the unborn child are not known. Acceptable contraception methods are restricted to abstinence, barrier contraceptives (condom, diaphragm), intrauterine contraceptive devices, or licensed hormonal products.

There is always a chance that any medical treatment can harm you, and the treatment in this study is not different. We will do everything we can to keep you from being harmed. In addition to the risks listed above, you may experience a previously unknown risk or side effect.

Subject's Responsibilities:

While you are in this study it is important that you do the following:

- Come to your study visits as scheduled.
- Fill out your diary card as indicated completely and honestly and bring it to the clinic at each visit.
- Tell the study staff of any health problems you are having even if you think they are not important.
- Tell the study staff if you wish to stop being in the study and if so, come back for the final visit.

It is very important that you follow the instructions given to you by the Study Center.

WILL I BENEFIT FROM TAKING PART IN THIS STUDY?

There is no known benefit to you by being vaccinated with MVA-BN®. The benefit to society is the possible development of a safe vaccine against smallpox. It is currently not known if you are protected against smallpox after vaccination with MVA-BN®.

There will be no direct benefit to you from any future studying of your samples. We may learn more about smallpox or similar diseases: how to prevent them, how to treat them, how to cure them.

Should a product be developed resulting from (blood or tissue) samples obtained from the research, there are no present plans to share any monies obtained from the sale of the product with you.

DO I HAVE TO TAKE PART IN THE STUDY?

Participation is voluntary. You may refuse to participate. If you choose to participate, you can change your mind at any time and withdraw from the study. In either case you will not lose any benefits or rights to which you are entitled. Your participation in this study can be terminated if it is determined by the study doctor to be in your best interest of if you fail to follow all directions.

If you do decide to no longer participate in the study after you have been enrolled, you will be asked to come to the clinic for a final examination.

IF I DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

Currently, vaccination for smallpox is not available to the general population. Therefore, the only alternative is to not participate in this study.

WHAT WILL IT COST ME TO PARTICIPATE?

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There are no direct costs to you to participate in this study. All costs for the required study visits, examinations, laboratory procedures, and vaccines will be covered by Bavarian Nordic, the sponsor of the study.

The University of Pennsylvania is not allowed to bill your insurance company, Medicare or Medicaid for the medical costs of procedures done strictly for research. The sponsor has agreed to pay all research costs.

WHO WILL SEE THE INFORMATION THAT I GIVE?

All information collected during the study will be maintained in a confidential manner and in compliance with regulations enacted pursuant to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Your name will not appear in any publication or presentation of the data collected during this study. You hereby authorize that all records and data relating to your participation in this study, including medical information, may be used or disclosed by Dr. Frank for purposes of conducting and administering this research study, and for regulatory review purposes. This information may be disclosed to Bavarian Nordic, its legally authorized representatives and agents, participating Institutional Review Boards, the US Food and Drug Administration (FDA), Department of Health and Human Services (HHS), National Institutes of Health (NIH), international drug regulatory authorities, or other involved regulatory agencies. You acknowledge that any and all records or information related to your participation in the study shall remain part of the study even if you withdraw from the study.

Individuals not signing this Informed Consent and the separate Authorization for Use and Disclosure of Health Information (HIPAA) form may not participate in this research study. The HIPAA form explains what PERSONAL HEALTH INFORMATION (PHI) will be collected and to whom it can be disclosed.

In the rare event that your information is required to be disclosed by law to another entity, Bavarian Nordic cannot assure that confidentiality of your information will be maintained.

CAN MY TAKING PART IN THE STUDY END EARLY?

Your participation in this study is voluntary. You may refuse to participate. If you choose to participate, you can change your mind at any time and withdraw from the study. In either case, you will neither be penalized nor lose any benefits to which you are otherwise entitled. Your participation in this study can be terminated if it is determined by your study doctor to be in your best interests or if you fail to follow all directions.

If you quit or are withdrawn, you will be asked to come to the clinic for a final examination.

The individuals conducting the study may need to withdraw you from the study. This may occur if you are not able to follow the directions they give you, if they find that your being in the study is more risk than benefit to you, or if the agency funding the study decides to stop the study early for a variety of scientific reasons.

WHAT HAPPENS IF I GET HURT OR SICK DURING THE STUDY?

In the event of any physical injury resulting from the research procedures, medical treatment will be provided without cost to you. There is no program for compensation either through the University of Pennsylvania or Bavarian Nordic. If the injury is related to the investigational product/procedure, the Sponsor may reimburse for medical expenses incurred by you as a result of participation in the study.

You or your third party payer, if any, may be billed for medical expenses associated with this study only if they are deemed medically necessary and if such expenses would have been incurred independent of the study.

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You will not be giving up any of your legal rights by signing this consent form.

WILL I RECEIVE ANY PAYMENT?

You will be compensated \$ 100 for each scheduled study visit you complete up to a total of \$600 or \$700 to compensate you for your time and travel for taking part in this study. If any additional (unscheduled) visits are requested or will become necessary for safety reasons, each of these visits will be reimbursed with \$100 as well. There will be no reimbursement for the telephone follow-up. Study personnel will pay the compensation for each study visit directly after the visit by AMERICAN EXPRESS traveler checks.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. You will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

If you wish further information regarding your rights as a research subject, you may contact the Director of Regulatory Affairs at the University of Pennsylvania by telephoning (215) 898-2614. If you ever have questions pertaining to your participation in this research study or about research-related injuries, you may contact the investigators or study nurse listed on the first page of this form.

SIGNATURE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below. You will be given a copy of this consent form to take home with you.

Participant's Name (print)

Participant's Signature

Date/Time

Study Staff Obtaining Consent (PRINT)

Study Staff Signature and Date