BN ImmunoTherapeutics, Inc.
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INFORMATION FOR THE PUBLIC

BNIT-PRV-301: A Randomized, Double-blind, Phase 3 Efficacy Trial of PROSTVAC-V/F ± GM-CSF in Men With Asymptomatic or Minimally Symptomatic Metastatic, Castrate-Resistant Prostate Cancer

European Notification Number
B/BE/11/BVW2

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1. REGULATORY FRAMEWORK AND AUTHORISATION PROCEDURE

To acquire the necessary authorization from the competent Minister, the company BN ImmunoTherapeutics, Inc submitted an application dossier to the competent authority. On the basis of the advice of the Biosafety Council, the competent minister could grant permission to the company BN ImmunoTherapeutics, Inc to conduct experiments with recombinant vaccine PROSTVAC-V/F as stipulated in the application B/BE/11/BVW2.

The release will take place at locations in Brussels and Roeselare as a consequence of clinical trials conducted at

- Dr. Thierry Gil, Institut Jules Bordet, Rue Héger Bordet 1, 1000 Bruxelles, Belgium
- Dr. Filip Van Aelst, Heilig Hart Roeselare, Wilgenstraat 2, 8800 Roeselare, Belgium

It is expected to start in June 2012 and to be completed by January 2015.

2. DESCRIPTION OF THE GENETICALLY MODIFIED MICRO-ORGANISM (GMM)

PROSTVAC-V/F is a live attenuated viral vector-based investigational vaccine product that is comprised of two component viral vectors, to be used together in a prime-boost vaccination regimen: (1) PROSTVAC-V: Recombinant vaccinia virus that contains a modified gene encoding human prostate-specific antigen (PSA) and genes encoding three human immunological costimulatory molecules: B7.1, intracellular adhesion molecule-1 (ICAM-1), and leukocyte function-associated antigen-3 (LFA-3) (or TRIad of COstimulatory Molecules, TRICOM™); and (2) PROSTVAC-F: Recombinant fowlpox virus that co-expresses the same four human genes as PROSTVAC-V.

PROSTVAC-V: Genus: Orthopox Virus
Species: Vaccinia

PROSTVAC-F : Genus: Avipox Virus
Species: Fowlpox

3. TYPE AND PURPOSE OF THE ENVISAGED TRIAL

The objective of the proposed research is to confirm the safety and efficacy of PROSTVAC-V/F for the treatment of men with asymptomatic or minimally symptomatic, metastatic, castrate-resistant prostate cancer in a Phase 3 cinical trial (BNIT-PRV-301). The clinical trial will be conducted in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Estonia, France, Germany,

Iceland, Israel, Lithuania, Mexico, Netherlands, Panama, Puerto Rico, Poland, Russia, Spain, Switzerland, United Kingdom and United States.

The study will enroll 1200 subjects globally and it i will be conducted at standard healthcare facilities where oncology therapies are commonly administered. Within Belgium, the study will take place at 2 clinical sites:

- Dr. Thierry Gil, Institut Jules Bordet, Rue Héger Bordet 1, 1000 Bruxelles, Belgium
- Dr. Filip Van Aelst, Heilig Hart Roeselare, Wilgenstraat 2, 8800 Roeselare, Belgium

It is anticipated that approximately 18 subjects will be enrolled at the sites.

4. RESEARCH/DEVELOPMENT ACTIVITIES

Nonclinical Studies of PROSTVAC-VF
PROSTVAC-V and -F, and related pox virus vaccines have been tested in mouse, rabbit and non-human primate models as well as in a number of *in vitro* experiments. No biologically significant changes or signs of untoward toxicological effects were noted in either rodent or non-human primate safety studies.

Clinical Studies of PROSTVAC-V/F
PROSTVAC-V and PROSTVAC-F have been evaluated in eight clinical trials in the United States. These agents have been administered to over 300 men. No evidence for contact transmission was observed in any clinical trial. The most common adverse reactions were injection site reactions.

5. POTENTIAL BENEFITS OF THE PLANNED RELEASE

Prostate cancer is the second leading cause of cancer deaths in men in the United States. According to the American Cancer Society, approximately 200,000 new diagnoses of, and 28,000 deaths from prostate cancer occur each year in the United States (Jemal 2009).

The intent of vaccination with PROSTVAC is to induce an immune response to PSA, and other prostate- and tumor-specific antigens. This response may provide a long-term benefit in overall survival, which was observed in the Phase 2 trial. At this time, however, it is unknown whether PROSTVAC will provide this benefit to any patients participating in the Phase 3 trial until after the study is completed and the data are analyzed. Benefits from participation in this trial may include the potential boosting (or acquisition) of protective immunity against smallpox and monkeypox. Patients will be under constant medical observation for the duration of the study. Knowledge that will be gained from this trial about the treatment of prostate cancer may be beneficial for other patients with this disease

6. ASSESSMENT FOR POTENTIAL RISKS FOR HUMAN HEALTH AND THE ENVIRONMENT

Potential Risks to Human Health

PROSTVAC-V and PROSTVAC-F do not exhibit any known phenotypic changes (e.g., changes in virulence or growth advantage) that would increase their risk to the environment relative to their nonrecombinant parental pox viruses, which are derived from licensed vaccines. Thus, the added human transgenes have not fundamentally altered the inherent properties of the viruses. In addition, the analysis of viral shedding, transmission, persistence in the environment, and other potential issues indicates that the risk of any significant impact of PROSTVAC-V/F on the environment is low.

Viral shedding studies of smallpox vaccine indicate that nonrecombinant vaccinia virus is shed transiently from the site of vaccination and rarely from other sites (*Cooney, 1991; Cummings, 2008; Friedman, 1962, Frey, 2002; Kim,2005; Klote, 2005; Koplan,1975*). Clinical studies of recombinant vaccinia viruses, including PROSTVAC-V, have demonstrated viral shedding only at the site of vaccination (*Arlen, 2007; Brysiowicz, 1996; Cooney, 1991; Graham, 1992; Mukherhjee, 2000; Scholl, 2000; Scholl, 2003).* Subcutaneous vaccination with vaccinia virus results in reduced viral shedding relative to vaccination by scarification (*Roberts, 1932; Henderson, 1939; Cherry, 1977; Connor, 1977*). Bandaging contains the virus at the vaccination site, further minimizing release into the environment (*Talbot, 2006*).

Contact transmission of vaccinia-based smallpox vaccine is rare (*Neff, 2002; CDC, 2004*). No secondary transmission of recombinant pox viruses, including PROSTVAC-V and PROSTVAC-F, to contacts has been reported in humans. However, PROSTVAC-V and PROSTVAC-F are live viruses and, as such, retain the potential for transmission. Consequently, healthcare personnel who have direct contact with contaminated dressings or other infectious material from participants in clinical studies are instructed to adhere to appropriate infection control measures and can be offered vaccination with vaccinia vaccine. In addition, study exclusion criteria exclude subjects from participation if they have close or household contact with individuals at risk for exposure to vaccinia virus. Use of appropriate infection control measures, such as covering the vaccination site and washing hands after contact with the vaccination site, will prevent transmission.

Fowlpox virus does not replicate in human cells *(Somogyi, 1993)*. Consequently, viral shedding in humans is limited and appears to be confined to the vaccination site. These agents are not known to cause disease in healthy adult humans and are of minimal potential hazard to personnel and the environment under ordinary conditions of use. They can be handled safely in the laboratory using techniques generally acceptable for nonpathogenic material.

Pox viruses cannot propagate without a permissive host organism. In a permissive host, pox virus infections are transient, lasting up to several weeks (*Fenner, 1988*). Pox viruses do not integrate into the genome of the infected cell.

Vaccinia and fowlpox viruses are stable when stored frozen or when lyophilized under carefully controlled conditions (*Fenner, 1988*). Under normal environmental conditions, however, these viruses lose viability within days or weeks (*Essbauer, 2007; Mahnel, 1987; Mahl, 1975; McDevitt, 2007; Newman, 2003; Pastoret, 1996; Sidwell, 1966*). In addition, pox viruses are readily inactivated by a number of common disinfectants and cleaning agents (*Erterpi, 2009*).

Recombinant vaccinia and fowlpox viruses are currently commercially available and widely distributed in the environment as veterinary vaccines (*Meeusen, 2007*). No environmental issues associated with the use of these recombinant vaccines have been reported.

Potential risks linked to the expression of the inserts

PROSTVAC-V and PROSTVAC-F are recombinant vaccinia and fowlpox virus, respectively, each of which co-expresses a human prostate-specific antigen (PSA) gene and genes encoding three human immunological costimulatory molecules: B7.1, intercellular adhesion molecule-1 (ICAM-1), and leukocyte function-associated antigen-3 (LFA-3) (designated TRIad of COstimulatory Molecules, or TRICOM™). In more than 300 patients treated with this product, no adverse events related to the expression of any of the TRICOM inserts was observed. Moreover, as subjects in the proposed trial are all patients with metastatic castration-resistant prostate cancer (mCRPC), all had undergone a prostatectomy at an earlier state of disease thereby eliminating any risk for an autoimmune response related to PSA expression.

In addition, several single- or repeat-dose murine and Rhesus monkey immunotoxicity studies were conducted under GLP conditions to evaluate whether an autoimmune response to self antigens, in the context of costimulation, would be safe. There were no treatment-related autoimmune or immunotoxicity effects seen in any of the murine studies conducted with related vaccines that incorporated murine analogs of the three co-stimulatory molecules in TRICOM. In addition there were no biologically significant, vaccine related adverse findings from studies regarding clinical observations, body weight, hematology, clinical chemistry, or gross pathology in the studies conducted in rhesus monkeys utilizing related vaccines incorporating human TRICOM.

Potential Risks to the Environment
PROSTVAC-V/F will be administered in an appropriately controlled clinic environment by subcutaneous injection. The PROSTVAC-V or placebo vaccination site will be covered with a sterile, nonadherent dressing. For the PROSTVAC-F or placebo, the injection site will be covered with a sticking plaster.

Routes by which the product may potentially enter the environment include the following:

- Shedding of virus from study subjects who have received the vaccine;
- Accidental, inappropriate disposal of the product into the sewer
- Breach of container integrity during shipping and storage
- Accidental exposure to the vaccine by personnel involved in preparation and administration of the vaccine at the site of use or handling during shipping.

An analysis of these potential routes for exposure is described in the sections below, including the appropriate measures in place during the conduct of the study to mitigate the potential for environmental exposure to occur, and mitigation of adverse impacts in the event of any environmental exposure.

PROSTVAC-V and PROSTVAC-F are live vaccines and require a host cell to replicate. They can only remain viable following infection and proliferation in an appropriate host organism.

PROSTVAC-V

Vaccinia virus has no known natural habitat and the origins of vaccinia virus in nature and as a vaccine are unknown. Thus, despite the extensive worldwide use of smallpox vaccine, vaccine escape into the environment seems to be at best a rare event.

Stability in the Environment

Vaccinia virus is relatively stable when stored at low temperatures. Pox viruses have the capacity to survive for considerable periods in dried material such as detached vaccination scabs. They are also are relatively stable when stored frozen or lyophilized under carefully controlled conditions. However stability decreases significantly as temperature is increased. Under normal environmental conditions, PROSTVAC-V and PROSTVAC-F are expected to lose viability within days or weeks.

Viral Shedding

Release of PROSTVAC-V into the environment as a consequence of shedding after immunization of study subjects is unlikely. Although PROSTVAC-V is a replicating vaccinia virus, it is administered subcutaneously. Lesion formation at the vaccination site is considered an indirect measure of viral shedding (*Rotz, 2001; Lane, 2003*). Consequently, the lack of lesion formation after administration of PROSTVAC-V is expected to reflect a significantly reduced level of shedding as compared with vaccination by scarification.Bandaging and proper care of the vaccination site should minimize the likelihood of viral shedding after subcutaneous administration of PROSTVAC-V.

PROSTVAC-F

Avipox viruses are distributed worldwide and cause disease in domestic, pet and wild birds of many species. Transmission of virus can occur through a break in the skin or, more commonly, when vectored by biting insect such as mosquitoes and mites. Aerosols generated from infected birds or the ingestion of contaminated food or water, have also been implicated as a source of transmission. These viruses are highly host specific.

Stability in the Environment

There are few published studies on the persistence of avipox viruses in the environment. However, persistence in the environment and other environmental issues have not been reported as a result of the use of licensed recombinant fowlpox based products.

Destruction of GMM Containing Material
All unused study vaccine will be returned to BNIT's central storage depot in the UK or disposed of at the clinical site upon authorization of BNIT. All biomedical waste generated during the conduct of the study will be discarded into appropriate biohazard waste containers and disposed of at the study site according to site procedures. Any unexpected release or spills of PROSTVAC-V and PROSTVAC-F will be decontaminated using detergent-based cleaners or 10% Clorox.

Training Requirements
All health professionals participating in the study will be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. Clinical sites will be thoroughly evaluated to ensure that the facilities are sufficient for storing and administering the vaccine, as well as having the appropriate facilities for the collection and storage of human specimens. Additionally, all clinical site personnel involved in the handling or administration of study vaccine will be trained accordingly.

Emergency Situations
Procedures are in place to avoid and/or minimize the spread of PROSTVAC-V and PROSTVAC-F by controlled containment of PROSTVAC-V and PROSTVAC-F during transport and at the clinical sites.

In the event that the contents of the vaccine vial are accidentally released and come in contact with shipping materials, exposed skin, clothing or laboratory surfaces, standard safety precautions will be used. Contaminated materials will be placed in biohazard safety bags and disposed of as biohazard waste. Surfaces in contact with vaccinia will be thoroughly cleaned with an appropriate disinfectant. Sites of skin contact will be cleaned with standard detergents appropriate for hand washing.

Accidental transmission of vaccinia virus to a clinic staff member or a member of the patient's family or friends will be reported.

This notification concerns a deliberate release of GMM for experimental purposes. Therefore, the use of this material for any other purpose is prohibited.

7. RESPONSIBILITIES OF THE NOTIFIER

The consent that could be given to the notifier by the competent Minister stipulates that the notifier takes complete civilian liability regarding the damage that could be caused by the deliberate release to the health of humans, animals or environment.

8. INSPECTION BY THE PUBLIC AUTHORITIES

Inspectors are in charge of inspecting the trials for compliance with the conditions specified in the consent and to investigate potential breaches of the consent. In case where mismanagement or fraud is identified specific sanctions will be imposed.

9. ACTIVITY REPORT

At the end of the trial an activity report prepared by the notifier needs to be delivered to the competent authority. The activity report includes at least the following data:

- the site and period of release
- the precise nature of the actually released GMMs
- the aim(s) of the trial
- the measures that were taken to prevent unwanted release of transgenic material
- if applicable, the measures that were taken to protect the subject during administration of the GMM-containing study drug
- if applicable, the measures that were taken to protect the relatives of the treated patients
- the measures that were taken to protect the workers who had to manipulate the GMM-containing material
- the method used for the destruction of the unused or contaminated material
- the results obtained during the trial

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11. GLOSSARY

"genetic modification" in relation to an organism means the altering of the genetic material in that organism in a way that does not occur naturally by mating or natural recombination or both
"organism" means a biological entity capable of replication or of transferring genetic material and includes a micro-organism, but does not include a human or a human embryo

12. CONTACT

If you have any comment on the public dossier or our activities or wish to obtain additional information on the deliberate release, please contact us at the following address.

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You can also have access to a summary of the notification (SNIF) on the web site of the Joint Research Centre of the European Commission (http://gmoinfo.jrc.it/). Comments can be addressed to the Commission via this web site.