ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

Advice on an application for deliberate release of a GMO for research and development purposes

Applicant: BN ImmunoTherapeutics Inc

Application: Application for Part B consent from BN ImmunoTherapeutics Inc to release live attenuated genetically modified *vaccinia and fowl pox viruses* for use in Phase III randomised, double blind clinical trials.

Ref: 12/R44/01/NI

Date: 4 January 2013

Advice of the Advisory Committee on Releases to the Environment under section 124 of the Environmental Protection Act 1990 to Ministers of the Northern Ireland Executive

ACRE is satisfied that sufficient information of the requisite quality has been submitted by the applicant to demonstrate that the release of this GMO under the conditions of the trial will not have any adverse effect on human health and the environment. ACRE therefore sees no reason for the release not to proceed.

Background

At its meeting in November 2012, ACRE considered an application from BN ImmunoTherapeutics Inc (BNIT) for a clinical trial in Northern Ireland involving the release of these GM live attenuated vaccines to optimise immune responses against prostate cancer tumour cells. ACRE assessed previous applications for these vaccines for sites in England, Scotland and Wales at its meetings in December 2011 and October 2012. Members assessed the environmental risks[1] including risks to humans who have not been administered this GM vaccine, associated with the release of this GMO under the conditions of the trial set out in the application.

The GM vaccines

PROSTVAC-V and PROSTAC-F are therapeutic vaccines that have been developed by BNIT using a modified attenuated vaccinia virus (PROSTVAC-V) and modified fowl pox virus (PROSTVAC-F). Both GMOs contain the same transgenes.

[1] ACRE's role is to give statutory advice to Ministers in the UK and devolved administrations on the risks to human health and the environment from the release and marketing of genetically modified organisms (GMOs). This does not include consideration of risks to volunteers in clinical trials.

PROSTVAC-V is a recombinant vaccinnia virus that co-expresses a human prostate-specific antigen (PSA) gene and genes encoding three immunological costimulatory molecules: B7.1, intracellular adhesion molecule-1 (ICAM-1) and leukocyte function-associated antigen-3 (LFA-3). Together these are referred to as TRICOM. The parental vaccinia virus (TBC-Wy) is an attenuated virus that was derived from the seed stock of virus used to produced a smallpox vaccine (Dryfax).

PROSTVAC-F is a recombinant fowlpox vaccine that co-expresses the same four transgenes as PROSTVAC-V. The parental fowlpox virus is derived from a USDA licensed poultry vaccines used widely for vaccinating chickens against fowlpox.

The modification induces anti-prostrate serum antigen (PSA) immune responses that results in the eradication of PSA-expressing tumour cells. Host cells infected with the vaccinia virus are short lived (days). These immune responses to PSA are boosted by multiple immunisations with the recombinant fowlpox virus PROSTVAC-F.

The clinical trial
This is a Phase III randomised, double blind trial to investigate efficacy and immune responses in men with asymptomatic or minimally symptomatic metastatic, castrate-resistant prostate cancer. A trial at 1 site in Northern Ireland is proposed with approximately 3 subjects. Consents were previously issued in January 2012 for 10 sites in England and 1 in Wales, and in December 2012 for 12 further sites in England and 1 in Scotland. The vaccines PROSTVAC-V/F will be administered as 7 subcutaneous vaccinations over a 5 month period. In week 1 the dose given to patients will be $2x10^8$ pfu of PROSTVAC-V. In weeks 3, 5, 9, 13, 17 and 21, $1x10^9$ pfu of PROSTVAC-F will be injected (as a boost to the PROSTVAC-V vaccination). All patients will be vaccinated in the clinic/hospital setting according to local regulations.

Inoculated patients will be leaving the health care facilities to join the wider community soon after administration of the vaccine. The applicant has proposed exclusion criteria to minimise transmission of the GMO, particularly to individuals at risk of exposure to vaccinia virus. To minimise accidental transmission of the GMO to other individuals the patients will be advised of appropriate control measures such as covering the vaccination site, washing hands after contact with the vaccination site and instructions regarding the disposal of all associated waste.

Comment

In coming to its conclusion ACRE has considered the molecular characterisation of the GMO, its stability, potential routes of environmental exposure and proposed risk management measures and monitoring.

ACRE noted that the parental, non-recombinant strain of the vaccine virus was derived from the same seed stock as the Dryfax vaccine, which was used to vaccinate humans against small pox for over 200 years. The applicants have demonstrated through neurovirulence tests in mice that it is more attenuated than the mix of vaccinia viruses comprising the Dryfax vaccine. The parental strain of the fowlpox virus is a USDA licensed poultry vaccine widely used for vaccinating chickens against fowlpox. The committee concluded that there was a history of safe use.

ACRE considered that the GMOs were well-characterised. The parental strain of PROSTVAC-F is highly attenuated and the insertion of the human genes into the coding region of a gene that has homology to the ankyrin repeat gene family would mean that it would be very unlikely to revert to the full virulence of the wild type virus. The committee concluded that, given the evidence on the characteristics of these viruses they are very unlikely to recombine with each other or with other viruses or to insert into the genome of the host cell.

ACRE considered the potential routes for exposure of the GMOs to the environment including through shedding, disposal of contaminated materials including dressings and the inappropriate disposal of the GMOs into the sewage system and needle stick injuries. The committee concluded that in terms of shedding and likely duration of shedding that this would be restricted to the site of vaccination and minimised through intramuscular injection and in the case of PROSTVAC-V through bandaging the wound. ACRE noted that the exclusion criteria proposed for patients by the applicant will significantly reduce the likelihood of complications and that shedding from other sites is unlikely. ACRE noted that, in the case of the PROSTVAC-V vaccine, patients would have been vaccinated against smallpox previously. Consequently, patients are unlikely to develop sequel and replication is unlikely because the patients' immune systems will react against the vaccine.

ACRE discussed the procedure proposed by the applicant for disposal of contaminated material including dressings associated with the wound-site. The Committee concluded that, whilst the risk to the environment and human health would be negligible if this material were disposed of in the sewer system or via municipal waste, alternative procedures to those proposed should be put in place that would be more likely to result in higher compliance. ACRE recommends that rather than requiring patients to return material to the clinic they should instead be required to disinfect material using a suitable disinfecting agent prior to its disposal in containers provided for each patient.

ACRE considered the clinical study set up more broadly – to ensure that environmental exposure is minimised. The applicant has proposed that all clinical site staff follow WHO guidelines for the prevention of transmission of infectious agents. ACRE discussed the potential for transmission to healthcare staff involved during the trial and in particular through needle stick injury. ACRE considered that the risk of harm was negligible. However the Committee recommends, given that the management of waste on each site may vary, the applicant should consider each site individually, and put in place localised guidelines based on existing mechanisms already in place.

The applicant has proposed strict study exclusion criteria for the trial to minimise the risk of transmission of the GMO to either patients or the patients' close household contacts considered to be potentially vulnerable groups identified as follows; persons with active or a history of eczema or other eczematoid skin disorders; those with other acute, chronic or exfoliative skin conditions; pregnant or nursing women; children less than one year of age; and immunodeficent or immunosuppresed persons including those with HIV infection. ACRE agreed with the exclusion criteria proposed by the applicant.

ACRE considered that overall the applicant had provided a good quality dossier, which provided sufficient evidence for an assessment of potential risks. ACRE concluded that this assessment demonstrated that the risks posed to human health and the environment, by the proposed releases in this trial, are negligible.

Items arising from Public Representations

No representations were received from the public.