ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

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

Applicant: International AIDS Vaccine Initiative

Application: Application for Part B consent from International AIDS Vaccine Initiative to release live, attenuated, genetically modified Sendai virus SeV-G(NP) for use as a vaccine in Phase I randomised, double blind clinical trials.

Ref: 12/R45/01

Date: 5 December 2012

Advice of the Advisory Committee on Releases to the Environment under section 124 of the Environmental Protection Act 1990 to the Secretary of State for Environment, Food and Rural Affairs and Ministers of the Welsh Assembly Government.

ACRE is satisfied that the information provided by the applicant in accordance with the current regulations on the Deliberate Release of GMOs, demonstrates that the 'release' of this GMO under the conditions of the trial will not have an adverse effect on human health or the environment. ACRE therefore sees no reason for the release not to proceed.

Background

At its meeting in November 2012, ACRE considered the application from the International AIDS Vaccine Initiative (IAVI) for a Phase I clinical trial of a live attenuated GM vaccine (SeV-G(NP)), designed to raise an immune response against HIV. 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 vaccine is based on the Sendai virus which is a member of a large family of viruses (the paramyxoviridae family) that are common causes of respiratory tract infection in rodents. Sendai virus and other members of the paramyxoviridae family are classified in the Mononegavirlaes Order. Non-GM Sendai virus has been safely used in previous clinical trials to raise an immune response to human Para-Influenza Virus type I. In the present trial, the virus will have been modified to express the Gag gene from HIV in order to raise an HIV-specific immune response. The objective of

[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.

the trial is to evaluate the safety and immunogenicity of the SeV-G(NP) vaccine in healthy adult volunteers. It will be administered via intranasal inoculation.

The SEV-G(NP) vaccine is based on a live Sendai virus which is severely attenuated in comparison to the wild type. The HIV-1 Gag gene has been inserted into the viral genome. The six native Sendai virus genes will function as normal in inoculated individuals ensuring the virus interacts and replicates within local mucosal membranes. The heterologous expression of the Gag protein will occur as part of this process. The mucosal tissues are expected to generate antibodies specific to the Sendai virus, human para-influenza I and Gag protein (the potential antigenic determinant of an immune response to HIV).

The clinical trial also involves inoculation with a second GM vaccine (Ad35-GRIN) that was not considered as part of the ACRE assessment. This is because Ad35-GRIN vaccine will be administered intramuscularly and is replication incompetent. It will not therefore be released into the environment. (see also below)

The clinical trial

The clinical trial will be duplicated in three countries: England, Kenya and Rwanda. The English site is the St. Stephens Centre (HIV Clinical Trials Unit, Chelsea and Westminster Hospital Foundation). A maximum of 72 volunteers will be included in the London study.

This is a dosage-escalation study. Safety and tolerability of SeV-G(NP) will be evaluated by a Safety Review Board (SRB) four weeks after vaccine administration for all volunteers receiving the first vaccination of the lower dosage level (Group A). The trial will then proceed to the higher dosage level in Groups B, C and D. Groups B, C and D are planned to be enrolled simultaneously. The SRB will then review the blinded safety data from the first one-third of volunteers from Groups B and D after they receive the high dose of SeV-G(NP) and will recommend to the Sponsor whether or not to continue enrolment of the remaining volunteers in Groups B, C and D.

Group	Vaccine/ Placebo	Month 0	Month 4
Part I			
A	12/4	SeV $2x10^7$	Ad35
Part II			
B	12/4	SeV $2x10^8$	Ad35 $1x10^{10}$
C	12/4	Ad35 $1x10^{10}$	SeV $2x10^8$
D	12/4	SeV $2x10^8$	SeV $2x10^8$

Comment

In coming to its conclusion ACRE first considered the question of whether the administration of the secondary GMO vaccine Ad35-GRIN constituted the Deliberate Release or the Contained Use of a GMO. ACRE were satisfied that because Ad35-GRIN vaccine will be administered intramuscularly and is replication incompetent there will be no release of this organism to the environment.

The following comments are therefore relevant to ACREs assessment of information pertaining to the GMO vaccine Sev-G(NP). This is in regard to it's molecular and biological aspects as well as it's stability, potential routes of environmental exposure and proposed risk management measures and monitoring.

Following a discussion of the data on the molecular characterisation of the GMO vaccine, ACRE agreed that it had been well characterised at the molecular level and it was sufficiently different to the wild type to enable easy identification. Given that the virus remains inside the infected cell until lysis, and also that it is replication incompetent, it already has a high level of 'biological containment'. It was noted that the HIV Gag protein inserted into the viral genome had been modified to reduce normal functionality such that it would not form cellular clumps of Gag protein.

The Sev-G (NP) vaccine virus was noted to be clearly attenuated with respect to it's virulence and there was no expectation of any significant replication. Whilst shedding from the nasal cavities represents one of the most likely routes of environmental exposure, ACRE noted that similar previous studies with non-recombinant Sendai virus had failed to detect SeV in specimens collected from the nasal cavities of the trial volunteers. ACRE considered that the applicants had described the thorough and appropriate management of conditions and measures to minimise any potential exposure within the area of administration, including the treatment of waste, description of protective equipment and low risk to non-patients. The procedures were considered to be well documented and ACRE were unable to identify any additional routes of potential environmental exposure other than those considered and described. ACRE were also satisfied that the applicants had considered the post-administration risk of environmental exposure and that the duration and frequency of monitoring of patients was sufficient, as subjects would be closely monitored and appropriately assessed and treated should they develop signs or symptoms of GMO infection.

ACRE discussed the applicant's description of the use of 10% bleach in cleaning procedures and in the management of spills and noted that this should in fact be described as using a preparation where the 'in use' dilution is given in parts per million of available chlorine. This should be used at a concentration appropriate to the specific use (e.g. cleaning post procedure or management of spill) in accordance with local NHS trust infection control policy.

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.