PART B1 – B7: INFORMATION ABOUT RELEASE APPLICATION FOR THE PUBLIC REGISTER

Department for Environment, Food and Rural Affairs

PART B: INFORMATION ABOUT THE RELEASE APPLICATION TO BE INCLUDED ON THE PUBLIC REGISTER

B1 The name and address of the applicant

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B2 A general description of the genetically modified organisms in relation to which the application is being made

Adenovirus serotype 4 (Ad4) belongs to the family of Adenoviridae, is frequently the causative agent for conjunctivitis or pharyngoconjunctival fever and is responsible for acute respiratory disease (ARD) among susceptible populations worldwide. Adenovirus serotype 4 is a non-enveloped, icosahedral virion, 70-90nm in diameter containing a double-stranded linear DNA genome. Adenovirus 4 transmission predominantly occurs via short-range droplets and aerosols, and via direct contact with contaminated fomites with self-inoculation onto mucous membranes. Transmission can also be mediated by faecal-oral and occasionally water transmission.

The genetically modified organism to be used in this study is based on the "parental wild-type" Ad4 virus vaccine that has been safely orally administered to more than 10 million U.S. recruits. The "parental wild-type" vaccine is attenuated by oral administration and protects against Ad4 respiratory disease. The "parental wild-type" vaccine has been modified by insertion of a gene sequence encoding an HIV-1 envelope glycoprotein (CN54 gp150). This has been inserted downstream of the intact E3 region between the E3B poly A sequence and the L5 fiber gene. The study vaccine (Ad4-EnvCN54) will be administered orally at the dose of 10^{10}VP. Studies of the "parental wild-type" oral replication competent Ad4 vector have detected rectal, but not respiratory, shedding for up to 28 days after administration. The Ad4 virus can only replicate in humans and there are no other reservoirs of infection.

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Transmission of the vaccine strain to secondary contact is extremely rare and reported to only occur in less than 0.1% of close household contacts.

B3 The location at which the genetically modified organisms are proposed to be released

This is a single site Phase 1 clinical study that will take place at the site listed below:

Address
NIHR / Wellcome Trust Imperial CRF Imperial Centre for Translational and Experimental Medicine, Imperial College Healthcare NHS Trust, Hammersmith Hospital, Du Cane Road, London, W12 0HS

Healthy male and female volunteers between the age of 18 and 50 will be recruited. Fifty four volunteers will be vaccinated as per the vaccine schedule in the study protocol, and then released to commence their normal daily activities after observations in the ICRF.

B4 The purpose for which the genetically modified organisms are proposed to be released (including any future use to which they are intended to be put).

The objective of the proposed research is to investigate and evaluate the immunogenicity, safety and tolerability of oral Ad4 vector expressing HIV-1 CN54 (Ad4-EnvCN54) when combined with different boosting options (MVA-CN54 and CN54rgp140) designed to optimize systemic and mucosal approaches in healthy volunteers. The study will be conducted in the United Kingdom only.

The current vector is based on the “parental wild-type” adenovirus vaccine strain. The wild type vaccine has been modified by insertion of a gene sequence encoding a HIV-1 envelope glycoprotein-150 CN54 strain (97CN001, GenBank AX149771.1). This has been inserted downstream of the intact E3 region between the E3B poly A sequence and the L5 fiber gene. This is the only manipulation of the parental vaccine strain.

The Ad4-EnvCN54 vaccine vector is formulated as white enteric-coated capsules for oral administration and can only replicate in human cells and

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there is no other known host capable of supporting the replication of Ad4. The genetically modified organism is being used as an oral vaccine to an induce immune response to the HIV-1 envelope glycoprotein, the primary target for protective antibodies produced by the gastrointestinal tract. Should this genetically modified vaccine be shown to be safe and effective in inducing appropriate immune response in this small phase I clinical trial (54 volunteers), future studies will assess its protective efficacy in larger phase II studies that are typically performed using several hundred volunteers.

B5 The intended dates of the release.

Enrollment of the Ad4HIV clinical study will commence MAR_2017. The active treatment period of the clinical trial is approximately 6 months. The date of final release will be once approximately 54 volunteers have completed their full vaccine schedule visits at the designated site in the United Kingdom (see list of site in section B3).

B6 The environmental risk assessment.

The study vaccine Ad4-EnvCN54 encodes rgp150 HIV-1 membrane expressed trimeric envelope protein subtype C CN54 that will be administered orally.

Study volunteers will be carefully monitored during the study protocol for any signs of symptoms of treatment-emergent toxicity by means of a focused physical exam, hematology, serum chemistry panels, recording adverse events, concomitant medications and viral shedding. Study volunteers will also be monitoring for their immune responses following administration of the vaccines through the collection of blood samples and pre-defined time points throughout the clinical study.

The Ad4 parental vaccine protects against respiratory disease and is attenuated by the oral route of delivery. In a recent Phase 1 re-licensure study faecal shedding of the Ad4 vaccine was detected between 7 and 21 days post vaccination in 27% of vaccinees. However viral shedding did not occur at any other site including urine and upper respiratory tract.

Procedures are in place to avoid and/or minimize the spread of the GMO by controlled containment during transport and at the clinical sites and by minimizing the potential of secondary transmission to vulnerable populations through exclusion criteria defined in the study protocol. Transmission of the vaccine strain to secondary contact is extremely rare and reported to only occur in less than 0.1% of close household contacts. Volunteers will be educated as to the care after using the toilet, bathing, possible side effects, and minimization of contact with vulnerable populations and household contacts, in order to further decrease the potential for spread and/or environmental exposure.

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In brief, there are no perceived hazards to the environment. The "parent wild-type" Ad4 oral vaccine has been administered orally to more than 10 million U.S. military recruits for over 45 years without environmental concerns (Radin JM, Clin Infect Dis. 2014; 59:962). Ad4 is only able to replicate in humans and has no other host. The encoded transgene is non-functional and provides no advantage or change in pathogenicity

Adenovirus serotype 4 is a non-enveloped, icosahedral virion, 70-90nm in diameter containing a double-stranded linear DNA genome, and is rapidly inactivated by exposure to ultraviolet light and bleach-based products. In addition to chemical agents, Ad4-EnvCN54 is inactivated by exposure to ultraviolet light.

Response to accidental release of capsule contents includes containment of the source of spill or leak and decontamination of affected surfaces with detergent-based cleaners or 10% bleach-based disinfectants. All contaminated materials will be treated as infectious waste and incinerated according to local institutional protocols.

B7 The methods and plans for monitoring the genetically modified organisms and for responding to an emergency.

The release of the study vaccine Ad4-EnvCN54 as described in this application is not expected to result in adverse environmental impact. Data that support this assessment include the following:

Comparability of parental and recombinant viruses
Adenovirus serotype 4 is comparable to its corresponding "parental wild-type" non-recombinant parental virus, with respect to growth characteristics and stability in the environment. The added HIV-1 DNA has not fundamentally altered the inherent properties of the recombinant virus. Therefore, Ad4-EnvCN54 has not acquired any known phenotypic properties that would increase their risk to the environment beyond those associated with the use of the corresponding non-recombinant parental virus.

Minimal risk of gene transfer
Adenovirus replication takes place entirely in the human gastrointestinal tract and is not integrated into the human hosts DNA. Adenovirus 4 tropism for mucosal surfaces of the GI tract initiates replication in submucosal tissues, thus maximizing effective expression of native HIV envelope trimers on the surface of infected cells (Alexander et al. PLoS One. 2013). This localized mucosal expression of native envelope has the strongest potential to induce potent immunity to strengthen defences. As a result, it is not subject to events that could lead to rearrangement or recombination in volunteers participating in the clinical study. The Ad4 virus is cleared from the host within several

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days of administration of the attenuated virus.

Minimal risk of viral shedding

Administration of Ad4 orally attenuates the virus. In a recent Phase 1 re-licensure study Ad4 vaccine virus shedding was not detected in throat swab specimens from any vaccine. However, faecal shedding of the Ad4 vaccine was detected between 7 and 21 days post vaccination in 27% of vaccinees. Viral shedding of Ad4 cannot be contained, but instead minimized by educating volunteers on the importance of hand washing procedures after using the bathroom.

Minimal risk of contact transmission

Administration of Ad4 orally attenuates the virus. Risk of transmission is reduced by use of universal precautions by healthcare workers and educating of volunteers in proper hygiene and proper care during the course of the clinical study.

Minimal risk of environmental persistence

Adenovirus 4 is readily inactivated by a number of detergents; thus, accidental spills can be contained and are not likely to result in spread of the study vaccine Ad4-EnvCN54 into the environment. The general environment is highly unlikely to support persistence of these viruses, which require human-to-human contact to propagate. There is no evidence for persistence of the "parent wild-type vaccine" which is routinely administered under deliberate release without any environmental control measures.

Precedent for environmental recombinant Adenoviruses

The "parent wild-type" Ad4 vaccine is currently commercially available and widely distributed in the United States. The "parent wild-type" vaccine has a substantial safety record having been administered orally to more than 10 million US military recruits without safety concerns (Radin et al. Clin Infect Dis. 2014).

No environmental issues associated with the use of these recombinant vaccines have been reported.