ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

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

Applicant: Southampton University

Application: Experimental challenge of the human nasopharynx with recombinant *Neisseria lactamica* expressing the meningococcal type V autotransporter protein, *Neisseria* Adhesin A (*Nad*A)

Ref: 17/R50/01

Date: September 2017

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 experimental trial not to proceed.

Summary

In September 2017, ACRE considered an application from Southampton University for an experimental clinical trial, involving the release of this GMO (recombinant *Neisseria lactamica*) in accordance with Part B of Directive 2001/18/EC. ACRE were assisted in their deliberations by Professor Paul Langford of Imperial College London. No public representations were received.

The application included a risk assessment for a proposed 'first-in-humans' clinical trial involving two similar genetically modified strains of *Neisseria lactamica*. Since patient safety and ethical considerations are outside of its remit, ACRE paid particular attention to the potential risks to humans who have *not* been administered the GMOs.

ACRE's opinion is that the risk assessment is scientifically robust and comprehensively describes the risks associated with the trial. ACRE also agrees that the proposed risk management measures are appropriate for minimising the risk to human health and the environment.

In coming to its conclusion, ACRE considered that little attention should be given to the control strain since this was phenotypically identical to the wild type and therefore did not pose any additional risk. However, several issues were discussed in detail which were related to the potential for transgene expression in the other GM strain to confer increased fitness and persistence in comparison to the wild type. Based on these discussions, ACRE suggested several clarifications and additions should be made to the applicant's risk assessment for completeness as follows: the applicant should clarify the precise sequence of events that will be taken in the event that monitoring identifies a significantly unexpected phenotype which might impact on transmissibility (especially within the first 2 weeks post administration). Quantitative comparisons of colonisation frequencies should also be made between the control (wild type) and GMO throughout the monitoring period. Participants who are still carrying the GMO at the 90 day mark should be treated with ciprofloxin to clear it from the body.

In summary, ACRE considers that the applicant has provided an excellent dossier, which provides sufficient evidence for an overall assessment of potential risks. ACRE concludes that this assessment demonstrates that the risks posed to human health and the environment, by the proposed experimental trial, are negligible.

Background

Neisseria lactamica (*Nlac*) is a gram-negative diplococcus bacterium with a habitat restricted to the human naso-pharynx. It is recognised as a non-pathogenic, commensal human organism. The UK ACDP has not categorised *Nlac*, therefore the wild type is considered to be a Group 1 biological agent under the European Economic Community classification for the protection of workers with biological agents [Directive 2000/54/EC].

It has long been known that carriage of *Nlac* confers a level of natural immunity to *Neisseria meningitidis (Nmen),* the causal agent of the infectious disease meningitis. Recent attempts have been made to enhance this natural immunity by inoculating volunteers with *Nlac* and studying the effectiveness of the immune response. The present Part B application from Southampton University represents the next stage of these experiments aimed at further investigating the parameters that enable *Nlac* to confer immunological protection against *Nmen*.

The clinical study involves using *Nlac* which has been genetically modified to give a control strain and an 'effector' strain. In both the control and 'effector' strain, the endogenous copy of the β-galactosidase has been deleted. In the control strain it has been replaced with a single copy of the β-galactosidase gene under the control of the promoter from the *Nlac lst* gene (which codes for α-2,3-sialyltransferase). In the 'effector' strain the endogenous β-galactosidase gene has been replaced with a double-gene cassette containing i) β-galactosidase under the control of the promoter from the *Nlac lst* gene and ii) a copy of the *nad*A adhesin gene from *Nmen* under the control of a constitutive hybrid promoter based on

the *por*A/*por*B genes from *Nmen*. The expectation is that the *nad*A-expressing strain will have an enhanced ability to colonise the naso-pharynx of trial volunteers and elicit an immune response which may protect against meningococcal acquisition (in comparison to the control strain).

Risk management and monitoring

The trial has an enrolment target of 44 participants, half of which will receive the control strain and half the *nad*A-expressing strain. Both GMOs will be delivered by intra-nasal inoculation. Prior to administration, all volunteers involved in the study will be admitted to the NIHR Wellcome Trust Clinical Research Facility. They will remain here for five days post-administration, and will be subject to 24hr clinical observation during this time. They will then be discharged for follow-up and monitoring as outpatients for a total of 90 days.

Enrolment to the trial will be subject to the following exclusion criteria: pre-existing carriage of *Neisseria spp* (assessed 7 days prior to inoculation), and any condition or medication causing immunosuppression in the volunteer or in their household or occupational contacts.

Following administration, the fate of both GM bacterial strains will be closely monitored at regular intervals, when volunteers will provide nasal wash and throat swab samples to the trial organisers. This will enable measurement of the frequency and level of colonisation. The potential for environmental shedding and onward transmission will be assessed from colony counts of micro-organisms detected from volunteers either using an air sampler or expiration onto a mask, as well as by collecting nasal wash and throat swab samples from 'close contacts' of the volunteers (eg bedroom sharers) at two weeks post-administration. The body's immunological response to the GMO's will also be studied by analysing volunteer blood samples for antibody production.

Since onward transmission of the GMO's to non-participants could occur, in order to minimise its likelihood, volunteers will be required to avoid frequenting social gatherings (pubs and clubs etc) for two weeks post-administration, when the likelihood of onward transmission is highest. In addition, volunteers and very close contacts of the volunteers, such as bedroom sharers, will be taught and required to practice strict infection control behaviours. Furthermore an independent Data Safety Monitoring Board (DSMB) will be established prior to the start of the study to provide real-time oversight of safety and trial conduct. The DSMB will have access to data and, if required, will monitor these data and make recommendations to the study investigators on whether there are any ethical or safety reasons why the study should not continue. The DSMB will be notified immediately if the study team have any concerns regarding the safety of a participant or the general public (e.g. if a participant develops disease).