ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

Applicant: Liverpool School of Tropical Medicine

Application: **SNEAS** Clinical Trial: Experimental Human Pneumococcal Challenge Model (EHPC): **S**treptococcus Pneumoniae **N**asopharyngeal **E**xperimental carriage clinical trial of **A**ttenuated **S**trains – proof of concept in healthy volunteers

Ref: 18/R51/01

Date: July 2018

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

In July 2018 ACRE considered an application from the Liverpool School of Tropical Medicine for a clinical trial involving the release of genetically modified bacterium *Streptococcus pneumoniae* in accordance with Part B of Directive 2001/18/EC. Members assessed the environmental risks (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. No public representations were received on this trial.

The application was for a strain 6B of *S pneumoniae* which had been genetically modified such that different combinations of virulence genes were deleted to produce four different GMOs, (each with two different virulence genes removed). Initially two of these attenuated GM versions of *S pneumoniae* will be administered via nasal inoculation to trial volunteers.

The purpose is to measure rates of colonisation and the potential to protect against re-challenge with the wild type bacterium.

The UK ACDP has classed the wild type *S pneumoniae* as a category 2 pathogen. It is only found as a commensal micro-organism of the human oropharynx and/or nasopharyngeal - there is no environmental reservoir. It is not a commensal of non-human mammalian species, with the exception of horses, which are colonised by a subset of *S. pneumoniae* strains that do not include the 6B strain. Its natural competitors include all other human nasopharyngeal commensals, including other naturally occurring S. pneumoniae strains.

The GMOs

Four different modified strains of *S. pneumoniae* were created for the trial. In the first instance only two will be administered (alongside the wild type and negative controls). In the event that either or both do not generate an immune response, either or both of the alternative strains will be introduced to the study.

For each GMO, two chromosomally encoded genes have been deleted and replaced with genes encoding resistance to kanamycin and spectinomycin. The identity of the genes which have been deleted in each of the four strains was provided to ACRE in a confidential Appendix due to IP protection requirements.

Each of the deleted genes is either known or thought to play a role in the pathogenicity/virulence of wild type *S pneumoniae*. A key assumption of the risk assessment was that each GMO would be attenuated in virulence in comparison to the wild type, and that the risks to human health and the environment associated with the release are thus likely to be lower. Key data supporting this hypothesis was provided in the form of inoculated mouse infection models.

As part of its consideration of the molecular biology of the GMOs, ACRE asked the applicant to clarify certain aspects related to the genetic control elements used to direct antibiotic resistance gene expression, and to expand on the rationale for selecting one of the GMOs for the study.

The clinical trial

The clinical trial will be based on the established Experimental Human Challenge Model (**EHPC**) developed at the Liverpool School of Tropical Medicine. It will involve nasal administration of two double GM mutant attenuated *S. pneumoniae* strains in healthy human volunteers n=150 (including control arms). Volunteers will be inoculated in the Accelerator Research Clinic (ARC) in Liverpool School of Tropical Medicine then return to the wider community following each appointment. They will have the bacteria (8x104 *S. pneumoniae* CFU in 0.1ml saline) inoculated into their nose. Nasal wash fluid and blood samples will be collected at follow up visits to measure rates of colonisation and shedding.

An interim analysis will determine whether there is an immune response to either attenuated strain. If no immune response is present in one or both of the attenuated GM

strain arms then the IDSMC (Independent Data And Safety Monitoring Committee) may advise to replace the attenuated strain with one or both of the reserve attenuated strain(s). Six months post-administration, all volunteers will be challenged by intranasal inoculation of wild type *S. pneumoniae* (6B) to see whether the immune response to colonisation with the GM strain prevents subsequent colonisation with the wild type.

As part of its consideration of the clinical aspects of the trial, ACRE asked the applicant to clarify certain points concerning the frequency of monitoring of shedding.

Comment

Overall ACRE considered that the applicant had provided a thorough and well-presented dossier in support of its application. The post–administration monitoring procedures were considered to be appropriate for the GMO in question and the description of waste treatment and disposal procedures were compliant with GMO legislation.

In conclusion ACRE considers that the information presented in the risk assessment submitted by the applicant, demonstrates that the risks posed to human health and the environment, by the proposed releases in this trial, are negligible.