Advisory Committee on Releases to the Environment

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

Applicant: The Oxford Vaccine Group

Application: Exploring the bottleneck hypothesis of the pathogenesis of bacteraemia in an ambulatory outpatient experimental human experimental infection of Salmonella Typhi

Ref: 18/R48/01

Date: 4 February 2019

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 January 2019 ACRE considered an application from the Oxford Vaccine Group for a clinical trial involving the release of this GMO in accordance with 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 trial is very similar to one previously assessed by ACRE in July 2016 (ref 16-R48-01). The same GMO will be released in this 2019 trial, with the principal difference being that some participants will receive both the GMO and the wild type organism in the same dose (ie simultaneously) at a 1:1 ratio. The purpose of the study is to investigate the bottleneck hypothesis of gut-based bacterial infections which suggests that it may be only a single bacterium which crosses the gut lining to cause a bloodstream infection.

The GMO

Salmonella Typhi is an obligate pathogen of humans – no other host is capable of developing infections or becoming colonised. To produce the vaccine for this clinical trial, S. Typhi (Quailes strain) was genetically modified such that the three genes responsible for producing typhoid toxins were deleted from its genome. The primary outcome of the trial will be to determine the proportion of participants who develop bacterial infection after giving them either the wild type S. Typhi Quailes strain (WT) or a typhoid toxin-deficient isogenic mutant of S. Typhi Quailes strain (named SB6000) or a combination of both strains. The data gathered will provide important information regarding the mechanism of infection following oral challenge with S. Typhi.

The Clinical Trial

The study is expected to involve a maximum of 15 participants. Administration will be via the oral route and there is an expectation that faecal shedding of the GMO will occur in some participants at low levels. All individuals challenged with the GMO will be treated with a one week course of oral antibiotics, either at the time of acute infection or at Day 14 (whichever is sooner). Monitoring will take place for the duration of the clinical study. After receiving the relevant dose, participants will leave the health care facility but will be monitored daily for the first 14 days. The procedure for visits will depend on whether the participant develops infection or not.

If enteric fever is diagnosed, blood and stool sampling will be performed at 6, 12, 24, 48, 72 and 96 hours post diagnosis. Following completion of antibiotic treatment and confirmed clearance of the GMO in stool samples, participants will be monitored by way of long term follow-up visits at one, three, six and 12 months. The applicant has proposed volunteer exclusion criteria as a risk management measure to prevent transmission of the GMO to vulnerable groups. To minimise accidental transmission of the GMO to surfaces or to other individuals, the volunteers will be instructed to maintain strict personal hygiene during the study and proper hand washing techniques will be taught.

Comment

Following a detailed consideration of the dossier, ACRE concluded that the environmental risk assessment provided by the applicant was generally very thorough, and included a helpful consideration of the risks to human health and the environment as well as a good description of appropriate measures which will be employed in order to minimise these risks. ACRE was satisfied that sufficient evidence had been provided to demonstrate that the risk to human health and the environment, by the proposed releases in this trial is

negligible. In conclusion 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.

February 2019