Advisory Committee on Releases to the Environment

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

Advice of the Advisory Committee on Releases to the Environment to Welsh ministers under section 124 of the Environmental Protection Act 1990

Details of the notification

Notifier: Prokarium Ltd

Reference: 19/DR/001/W

Notification: A Phase I, randomised, double-blind, placebo-controlled, parallel group dose escalation study to evaluate the safety, tolerability and immunogenicity of three doses of a potential oral enteric fever vaccine containing two GMOs (ZH9 & ZH9PA).

ACRE is satisfied that sufficient information of the requisite quality has been submitted by the applicant to demonstrate that the release of this GMO under the conditions of the trial will not have any adverse effect on human health and the environment. ACRE therefore sees no reason for the release not to proceed.

Background

In July 2019, ACRE considered an application from Prokarium Ltd for a clinical trial involving the release of these two GMOs in accordance with Directive 2001/18/EC. ACRE has previously reviewed the risk assessment associated with the release of one of the GMOs (ZH9). Members assessed the environmental risks (including risks to humans who have not been administered this GM vaccine) associated with the release of both GMOs under the conditions of the trial set out in the application. No public representations were received on this trial.

The GMO

The parent strain is a modified (attenuated) derivative of *Salmonella enterica* subspecies *enterica* serovar Typhi strain Ty2 (abbreviated to S. Typhi Ty2). The attenuation results from the deletion of two genes: (i) the aroC gene, which encodes chorismate synthase, an enzyme involved in the biosynthesis of aromatic compounds; (ii) the ssaV gene, which encodes a structural component of Salmonella pathogenicity island 2. These mutations have the effect of reducing the duration of shedding compared to the wild type. The

attenuated strain is called ZH9 and ACRE has previously reviewed the risk assessment for this GMO.

The other GMO relating to the present application results from the following genetic modifications to strain ZH9: 1) replacement of the H:d allele of the flagellin component *fliC* with the H:a allele; 2) deletion of the gene encoding *rfbE* which converts abequose to tyvelose; 3) to replace the *rfbE* gene with the *wbdR* gene (an acetylase) as a spacer to maintain the expression of full length LPS-O sidechains. The overall effect of these modifications is essentially a simple replacement of two surface antigens with similar molecules.

The clinical trial

The purpose of the study is to investigate the safety of, and immune responses to ascending doses of the GMOs (or placebo) in healthy participants. The clinical protocol will be submitted to the MHRA as part of a clinical trials application. In summary, a maximum of 45 participants will be divided into three groups, receiving either placebo, novel GM ZH9PA at two different doses, or a mixture of the ZH9 (the parent GMO) and ZH9PA. The highest dose level of ZH9PA and ZH9 given to each participant will be 1 x 10^{10} CFU. Thus a maximum of 30 participants will be administered GMOs. The maximum release of the GMO ZH9PA in the study overall will be no more than 2.5 x 10^{11} CFU. The maximum release of the parent ZH9 in the study overall will be no more than 1.2 x 10^{11} CFU.

Comment

ACRE is familiar with this type of release, having previously reviewed the risk assessment of proposed trials with similar GMOs in 2011, 2015, 2017 and earlier this year (2019). ACRE considers that the GMOs in the present application are well characterised and the attenuation mechanisms are established and well understood. The risk of reversion to wild type is considered to be negligible.

A potential route of environmental exposure is from the sewage system since post-administration shedding from stools is known to occur. However, the existing mechanisms in place, notably the separation of sewage and potable water supplies, are sufficient to ensure that the distribution and dissemination of the GMO (and the wild type Salmonella typhi) would be controlled effectively. This is supported by the fact that typhoid is not spread by infected travellers returning to the UK. It is possible that some of the shed organisms could enter environmental niches other than the sewage system, e.g. soil and water bodies, if a breach of the sewage system were to occur or if faecal samples containing the GMO were disposed of via facilities that do not involve a mains sewage system. However, the applicant has previously provided robust data showing negligible persistence of the parental GMO strain under other environmental scenarios. From this data and data from other related clinical trials, ACRE is satisfied with the evidence that the GMO, once outside human hosts, is not capable of replication and does not persist in the environment and there is therefore negligible risk to human health and the environment from such routes of exposure.

Additional potential routes of environmental exposure include incorrect treatment of waste and poor bathroom hygiene on the part of participants. The applicant was considered to have treated these issues thoroughly. In summary, all waste materials will be treated as ‘clinical waste’ and the volunteers will be instructed to maintain strict personal hygiene during the study and proper hand washing techniques will be taught.

The applicant will also impose participant exclusion criteria to avoid the risk of transmission to vulnerable groups and the public.

In conclusion, the applicant has submitted a good quality dossier, characterizing the potential hazards, and demonstrating that appropriate risk management measures are in place to ensure that any risk to human health and the environment is negligible.

September 2019