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 Northern Ireland ministers under section 124 of the Environmental Protection Act 1990

Details of the notification

Notifier: Prokarium Ltd

Reference: 15/R47/01/NI

Notification: Development of a Combination Vaccine Against Typhoid Fever and Enterotoxigenic Escherichia Coli (ETEC): A Phase 1, Single Centre, Randomised, Double-Blind, Placebo-controlled Clinical Trial to Evaluate the Safety and Immunogenicity of the Oral Live Attenuated Vaccine based on the “Vaxonella” platform technology (Typhetec) at three ascending dose levels

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

At its meeting in March 2015, ACRE considered an application from Prokarium Ltd 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 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 was genetically modified to remove its ability to infect and colonise humans by deleting 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 deletions mean that

although the GMO is unable to infect and colonise human hosts, it should still have the capacity to act as a vaccine and stimulate an immune response. Previous clinical trials have demonstrated an absence of the symptoms of typhoid fever and bacteraemia following inoculation. In addition, these mutations ensure that the duration of shedding following administration of the product is limited.

The GMO has also been modified to contain the plasmid pTYPHETEC which encodes a number of potential antigenic determinants that are intended to raise an immune response to enterotoxigenic E.coli (ETEC).

The clinical trial

A maximum of 45 volunteers will be included in the study and randomised to one of five treatment groups, to receive the GMO at three different dose levels, placebo or a licensed typhoid fever vaccine. A maximum of 27 volunteers will receive three doses of the GMO. The GMO will be diluted in sodium bicarbonate solution, with the possible addition of ascorbic acid and aspartame, for oral administration. The highest dose level of the GMO given to each volunteer will be 5 x 1010 CFU.

The three doses will be administered at 21 day intervals. Inoculated volunteers will leave the health care facilities to join the wider community soon after administration of the vaccine. Stool samples will be taken at day 63 to confirm that the subjects are no longer shedding. In the unlikely event that a positive culture is obtained, then those subjects will be asked to return for a repeat sample on day 70. If this second sample is also positive, subjects will be treated with a course of antibiotics. Following completion of the course of antibiotics subjects will be monitored until two consecutive samples are negative.

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

The GMO is well characterised at the molecular level and the attenuation mechanisms underlying the deletions of the aroC and ssaV genes are established and well understood. The risk of reversion to wild type is considered to be negligible due largely to the presence of the sizeable attenuating deletions. Also, S. typhi exhibits very low levels of competence for DNA uptake and recombination. The absence of antibiotic markers and mobilisation factors on the pTYPHETEC plasmid are effective measures to prevent unintended DNA transfer.

A potential route of environmental exposure is from the sewage system since 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 provided robust data on the persistence of the parental GMO strain under other environmental scenarios. The presence of the pTYPHETEC plasmid is known to have a slightly negative effect on the metabolic efficiency. It is therefore highly unlikely to afford any increase in competitive ability. From this data and other clinical trials, ACRE concludes 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 other such routes of exposure.

A further potential route of environmental exposure is at the point of administration. The applicant was considered to have treated this issue thoroughly. All waste materials will correctly be treated as ‘clinical waste’. In addition, the applicant has proposed volunteer exclusion criteria as a risk management measure to prevent transmission of the GMO to vulnerable groups. These are identified as follows; female participants who are pregnant or lactating, clinical or social workers with direct contact with young children or highly susceptible patients, commercial food handlers and; household contact with a young child and/or with someone who is immunocompromised. 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.

There are no specific plans to investigate shedding profiles as part of this trial. However, it would be helpful to produce this information alongside any efficacy data, especially if the product is to go further along the regulatory pathway towards full commercialisation.

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.

20 April 2014