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: Conducting a double-blind phase II clinical trial into the protective efficacy of a Live Attenuated Vaccine Against Salmonella Paratyphi A (VASP).

Ref: 20/R48/01a

Date: 19th January 2022

Advice of the Advisory Committee on Releases to the Environment (ACRE) 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 has been fully assessed in relation to the risks of adverse effects on human health or to the environment. ACRE therefore is content for the release to proceed.

Background

In November 2021 the Advisory Committee on Releases to the Environment (ACRE) considered a revised application from the Oxford Vaccine Group for a clinical trial involving the release of this GMO in accordance with Directive 2001/18/EC. The original application was considered by ACRE in July 2020, but due to the Covid-19 pandemic the clinical trial was not begun. The applicant submitted a revised clinical trial methodology in November 2021 to be considered by ACRE. 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.

This is the first application for deliberate release within the UK of this GMO. The GMO strain CVD 1902 *S.* Paratyphi A live oral vaccine was released previously in a single phase 1 trial conducted at the University of Maryland in the United States (NCT01129453 ClinicalTrials.gov)**.** This phase 1 study in healthy young adults (18-45 years) was designed to investigate the safety, clinical tolerability, and immunogenicity in a dose-escalating fashion of oral doses of CVD 1902. In this trial 30 recipients received the vaccine in single doses of between 1.56 x 10^6 colony forming units (CFU) and 2.25 x 10^{10} CFU. At all dosing levels, CVD 1902 was well tolerated and there were no suspected adverse effects (SAEs) attributable to the vaccine, and no halting rules were met. The study also observed that shedding was not observed in any subject beyond day 3 following vaccination, neither was any bacteraemia seen. The prophylactive efficacy of the vaccine was, however not assessed in that study, but will be in this proposed phase 2 clinical trial.

The GMO

Salmonella Typhi and Paratyphi are obligate pathogens of humans – no other host is capable of developing infections or becoming colonised. These pathogens both cause enteric fever, a significant global disease with up to 14.3 million cases and 135, 900 fatalities globally. *S.* Paratyphi A may be responsible for a quarter of all cases.

The Oxford Vaccine Group (OVG) has been undertaking controlled clinical challenge studies (more recently involving GMOs) using *Salmonella enterica* subspecies *enterica* pathovar Typhi and Paratyphi since 2010.

In this latest study the OVG team will explore the vaccination efficacy of a *S.* paratyphi A, strain CVD 1902, containing independent genetic modifications to two genetic elements. This GMO is an isogenic mutant of a wild-type *S.* Paratyphi A 9150 containing deletions in the *guaBA* chromosomal operon and the *clpX* gene. The purpose of the genetic modification is to construct a growth deficient attenuated *S*. Paratyphi A strain to act as a live oral vaccine. The resulting strain has an LD50 that is more than 6 logs greater than the wild type *S.* Paratyphi strain.

The Clinical Trial

The proposed phase II clinical trial is aimed at determining the relative protective effect of two doses of CVD 1902 given 10 days apart compared to placebo in a double-blind trial, involving between 66-76 participants in total. The maximum dose given to each participant will be 1.7 x 10^{11} cfu; with a minimum dose of 2 x 10^{10} cfu. Their health will be closely monitored, with 4 visits at

intervals of 7 days during the vaccination period. Challenge tests will begin 28 days following the second vaccine dose, followed by daily monitoring for 14 days afterwards. All study participants will have follow-up visits up to 1 year post challenge. The size and duration of this trial is such that the investigators have outlined in their application that it may take up to 48 months to complete. However, with the current global situation around the coronavirus pandemic it is unclear when they may feasibly begin the study, therefore the application seeks consent to run until September 2028.

All individuals challenged with the wild type Paratyphi organism 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). Following challenge with the wild type organism (28 days following last vaccine dose) they will be monitored daily for 14 days by the study team. Blood and stool cultures will be taken at each visit. For a week following each vaccination and during the challenge period (until day 21 post challenge) participants will be asked to measure their temperature twice daily and record solicited symptoms on an electronic diary, unsolicited symptoms can be recorded at any time up to 28 days after challenge.

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, such as training in hygiene measures for volunteers and comprehensive, extended monitoring protocols, which will be employed in order to minimise these risks.

ACRE was reassured to see that the applicant had included appropriate treatment contingency arrangements to cover development of chronic Paratyphi carriage post vaccination/challenge as well exclusion criteria to protect vulnerable groups. 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.

January 2022