Advisory Committee on releases to the Environment

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

Applicant: ILiAD Biotechnologies, LLC

Application: A 120 subject Phase IIb clinical trial of a GM *Bordetella pertussis* (whooping cough) BPZE1 vaccine in healthy adults.

Ref: 21/R53/01 and 22/R53/01

Date: July 2021 and reissued in May 2022

Advice of the Advisory Committee on Releases to the Environment to the Secretary of State under section 124 of the Environmental Protection Act 1990.

The Advisory Committee on Releases to the Environment (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 effect on human health or the environment. ACRE therefore sees no reason for the release not to proceed.

Background

In April 2022 ACRE considered an application from ILiAD Biotechnologies, LLC 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.

This is the second application for deliberate release within the UK of this GMO, the previous clinical trial (given consent under Defra reference 21/R53/01) is ongoing. The GMO strain BPZE1 previously underwent four human trials (two Phase I and two Phase II) as a pertussis vaccine candidate in the United States, with two of the Phase I trials being conducted simultaneously in Sweden.

B. pertussis is a strict human pathogen, that non-invasively colonizes the upper respiratory tract of humans and cannot exist outside of the host. Wild-type *B. pertussis* is endemic throughout the world and currently the disease is controlled through vaccination, with an acellular pertussis vaccine being used in the UK.

Human to Human transmission of wild type *B. pertussis* following colonisation of the respiratory tract is by aerosols, exacerbated as a result of coughing induced by the tracheal cytotoxin. Coughing response to the GM strain BPZE1 is apparently reduced by 99%, thus restricting any propensity to spread by aerosol. Therefore, BPZE1 has been classified as Biohazard Level 1 by several international authorities and has so far been administered to a total of 356 human subjects in the 4 trials referred to previously, where it was shown to be highly attenuated without any significant adverse reactions.

These clinical studies further revealed that high doses of BPZE1 (up to 10^9 CFU) does not induce whooping cough or related disease in humans. Further, the GMO is strongly attenuated and does not induce airway inflammation and, as documented in pre-clinical studies, protects against airway inflammation induced by allergens or viral infections,

The GMO

BPZE1 was made from the parental strain BPSM, which itself is a streptomycin- and nalidixic acid-resistant derivative of a wild type strain *B.pertussis* Tohama I. BPZE1 was separately mutated with respect to three gene products: *ampG*, Pertussis toxin (PT) gene (*ptx)*, and the dermonecrotic toxin (DNT) gene (*dnt*).

The three mutations each involved conjugation with suicide plasmid vectors containing the mutated or truncated gene. Subsequently, sequencing of each locus was performed to confirm the inserted genetic element was present, and finally the complete genome of BPZE1 was also sequenced. Therefore, the applicant was confident that no vector DNA remained in the final BPZE1 construction.

The net result was that BPZE1 produced less than 1% of the wild-type level of Tracheal cytotoxin (TCT), so did not appear to induce coughing and also did not produce DNT. The GMO also produces an inactivated PT such that the latter no longer expresses enzymatic ADP-ribosyl transferase activity. This thereby abolishes its toxic activity, but still allows for the needed immunologic response against the natural toxin.

Although *B. pertussis* is a strict human pathogen, other animals including laboratory mice and baboons, can be infected with high doses of wild-type organism, but they clear the infection spontaneously. BPZE1 can likewise be acquired by nasal inoculation but without evidence of disease manifestations. This is most likely due to the removal/modification of the three, key toxin-mediated genes (PTX, TCT and DNT). BPZE1 was also reported to grow slightly less well in the respiratory tract of adult mice than the parent strain BPSM.

BPZE1 is therefore a live, attenuated vaccine able to induce mucosal and systemic immunity through natural mucosal pathways. Completed clinical studies conducted to date included a total 356 human subjects exposed to BPZE1 and revealed that the GMO was strongly attenuated and did not induce airway inflammation. In fact, BPZE1 was shown to protect against airway inflammation induced by allergens or viral infections, in agreement with pre-clinical studies.

The Clinical Trial

The trial is a single site placebo-controlled, randomised challenge test study of 120 participants. Its aim is to assess the immunological response, when subsequently challenge tested with the wild-type pathogen, of BPZE1 via intranasal vaccination studies in healthy adults. The application is for a phase IIb clinical trial beginning in May 2022, aiming to recruit 120 subjects in total at the one site. The applicant is therefore asking for consent until February 2024, to allow enough time to recruit and conduct the trial with this number of subjects.

The applicant proposes, and details, the follow up protocol for monitoring clearance in vaccinates to be conducted over the course of this trial.

The potential application of BPZE1 is distinct from acellular pertussis vaccines because the latter do not work on infection/acquisition. The applicant believes that by targeting protection against acquisition/infection of wild-type *B. pertussis,* BPZE1 should contribute significantly to abrogate human to human transmission of wild-type *B. pertussis*.

Comment

Following careful consideration of this new application, ACRE were content to reissue their advice from the previous consent granted for a clinical trial of the same GM strain of *B. pertusis*, BPZE1 (Defra reference: 21/R53/01) which

was as follows:

Following a detailed consideration of the application, ACRE concluded that the environmental risk assessment provided by the applicant was 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 employed in order to minimise these risks.

Given the nature of the vaccine candidate, its level of attenuation, species (human) specificity, evidence from previous clinical trials and, very limited propensity for shed and spread, ACRE assessed it unlikely that there will be any significant impact upon the environment.

ACRE further concluded that given the evidence and arguments in the application it seemed that any environmental risk would be to non-target personnel and in particular handlers of the vaccine and vaccinators. The act of intra-nasal vaccination can for example be an irritant and induce an involuntary reaction such as sneezing. The applicant describes in some detail the precautions that will be taken including Good Clinical Practice, appropriately trained personnel, use of appropriate PPE, bespoke vaccinator devices etc. and such a risk should therefore be minimised.

ACRE considered it possible that some spread to handlers (although largely prevented by good practise) would actually be of benefit by increasing immunity and therefore reducing the propensity to transmit wild type pertussis. ACRE concluded that the trial as proposed was well designed, in that it included a clear description of follow up protocols for monitoring clearance in vaccinates. ACRE also recognised that the trial was designed to address a real issue, namely spread of B pertussis among partially vaccinated populations, and to this end should provide data of significant benefit in public health planning while presenting a negligible risk to other people, animals or the environment. ACRE therefore sees no reason for the release not to proceed.

May 2022