ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

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

Applicant: Celladon Corporation (with separate trial sponsorship from Imperial College London and the British Heart Foundation)

Application: Application for Part B consent to carry out clinical gene therapy trials using a GM adeno-associated viral vector (AAV1/SERCA2A) expressing a human heart calcium transporter gene.

Ref: 13/R46/01 and 13/R46/01/S

Date: 25th March 2013

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 Scottish 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.

The GMO

1. ACRE recently considered an application from the Celladon Corporation for clinical trials of a GM gene therapy agent based on a replication defective, highly depleted adeno-associated virus (AAV/SERC2A) designed to improve Calcium ion transport across the cell membranes of cardiac tissue in heart failure patients. Members assessed the environmental risks associated with the release of this GMO under the conditions of the trial set out in the application, including risks to humans who have not been administered the vector[1].

2. Two studies are planned for English sites and one for Scotland. In England, one study is to be undertaken at the Royal Brompton Hospital in London where approximately 8 to 10 patients with systolic heart failure will receive the MYDICAR® product that is based on the AAV1/SER2A viral gene therapy agent. A second study will take place at two sites, the Harefield (Middlesex) and Papworth (Cambridge) heart transplant centres resulting in 16 patients who have been fitted with left ventricular assist device (LVAD) receiving the same dose of AAV1/SERCA2a as in the Brompton study. The Scottish study will take place at the Golden Jubilee National Hospital, Glasgow in 8 to 10 patients.

3. The agent administered in the gene therapy trials is a protein-encased viral capsid containing DNA for the human SERC2A gene driven by the human Cytomegalovirus immediate early enhancer/promoter (CMVie) (609 bases) and hybrid intron (319 bases). This cassette is flanked at either end by the AAV1 terminal repeat sequences (145 bp per end).

4. The wild type AAV1 virus is a small non-enveloped single stranded DNA virus that is non-pathogenic and not known to be associated with any human diseases (although over 90% of people are seropositive to AAV before entering adulthood indicating that they have been exposed).

5. The UK ACDP has not categorised wild type AAV, consequently the UK Scientific Advisory Committee on Genetic Modification states that Containment Level 1 is sufficient except in cases where a potentially harmful transgene may require higher containment. (see Section 2.6.5 of the SACGM Compendium of Guidance). The SERC2A gene is not considered harmful and thus no increase in the basic level of containment is required.

The clinical trial

6. The principal aim of the clinical trials is to evaluate and confirm the clinical safety and efficacy of the GMO gene therapy agent versus placebo added to an optimal Heart Failure (HF) regimen. Celladon believes that targeted SERCA2a transporter protein replacement in advanced HF patients will correct imbalances in Ca2+ cardiac metabolism, resulting in enhanced cardiac function and energetics, which will in turn translate to improved clinical outcomes.

7. The principal aim of the study on patients fitted with a left ventricular assist device (LVAD) is to determine 1) the safety and efficacy of SERCA2a gene transfer in patients with advanced chronic heart failure and LVAD support, 2) the magnitude of viral gene transfer to the human failing myocardium and 3) the influence of circulating neutralising antibodies to AAV1 upon myocardial gene transfer.

8. Study sites will be evaluated and personnel trained on drug assignment, receipt, dispensing, storage and accountability procedures. In addition to receiving a site initiation visit by the sponsor that reviews investigational product storage, handling, dilution and administration according to the Study Pharmacy and Interventionalist manuals, the sites will complete in-service training on use of the administration syringe pump and complete an administration ‘dry run’. Thus personnel involved in delivery of the drug will only be those familiar with procedures that minimize undue exposure to themselves and to the environment.

Administration and fate of the GMO

9. The release will be performed at the investigator’s centres, in a hospital catheterization laboratory. Subjects will be observed for a recovery period either in a room near the catheterization lab or in a normal hospital room. Release will be a single intracoronary infusion of 50ml containing $1x10^{13}$ capsid particles for each study subject.

10. After administration the puncture wound created for arterial access for the administration of investigational product will be monitored in the cardiac catheterization laboratory, during the overnight hospitalization, and then just

before discharge from the hospital. Use of an Angio-Seal vascular closure or similar medical device may be used to aid in rapid closure and sealing of the puncture site; the protocol allows radial, brachial or femoral arterial access as determined by the treating interventionist. After closure and sealing of the puncture site it will be bandaged accordingly.

11. Preclinical data indicate that the biodistribution and persistence of AAV1/SERCA2a is similar to other AAV1- and AAV2-based vectors. The persistence of vector DNA is limited to the injection/infusion site (the heart) and highly perfused tissues and decreases with dose administered and time. AAV1/SERCA2a is expected to spread to other parts of the body before it is cleared. After intra-coronary (IC) delivery of AAV1/SERCA2a, particles which are not taken up in the heart are first passed through the lung via the coronary sinus, where they are thought to be cleared by the reticuloendothelial system (RES). Based on animal studies and clinical studies of other AAV gene therapy agents, it is expected that concentrations will decrease quickly over time. In studies of AAV2 vectors in cystic fibrosis and HIV vaccines administered via aerosol or intramuscularly, respectively, at doses as high as 1×10^{13} DRP, most samples were negative and those that were positive were at less than 1/1,000,000 of the dose administered even at 2 hours after dosing. Stool and urine samples were negative for all samples. In summary shedding is to be expected to varying degrees from some patients and continuing for as long as 150 days post administration.

Waste material and excess inoculant

12. All disposable materials (including but not limited to gloves, masks, syringes, needles, catheter and tubing) that come into contact with the investigational product will be disposed of as biohazardous materials according to individual institutional practices and policies. In general the materials will be disposed of in sharps containers or biohazard bags and decontaminated by autoclave or incineration, or both.

13. The unused investigational product and vial, stopper and crimp seal can be decontaminated with a 10% aqueous solution of household bleach (5000 ppm sodium hypochlorite), autoclaved or incinerated according to institutional practice. Following decontamination, materials will be disposed of as biohazardous waste. If excess investigational product is destroyed by bleach it can be poured down a sink with running water or otherwise in compliance with local and institutional disposal and cleaning procedures. Non-disposable materials, equipment and surfaces will be decontaminated with a 10% solution of household bleach. Some non-disposables may be autoclaved.

Detection methods and monitoring

14. The GMO can be identified by qPCR. The PCR primers only detect the transgene sequence within the GMO. The primers are designed to detect a 106 bp fragment in the SERCA2a transgene in the GMO. The donor (human) DNA in humans is not detected because there is an intervening 1.1 kb intron. The primers do not hybridise to the recipient DNA. The assay has been shown to detect less than 30 DNA copies in blood and tissue. The sensitivity and reliability of the assay in other matrices should be similar.

15. The health of patients enrolled in the study will be monitored for two years, or longer, over the course of the study. On Day 0, subjects will undergo cardiac catheterization and angiography, followed by infusion of investigational product. In the Phase 2b study at Months 1, 3, 6, 9 and 12 (12-Month Active

Observation Period), subjects will undergo a battery of safety, efficacy and economic assessments, followed by quarterly visits (Months 15, 18, 21, 24, etc.) in the Long-Term Follow-Up for collection of information on clinical events and resource utilization until the last enrolled subject completes 12 months of observation and at least 180 adjudicated HF-related hospitalizations have occurred, whichever comes later. All subjects will be observed and followed for a minimum of 24 cumulative months. The 24 cumulative months includes the amount of time in the 12-Month Active Observation Period plus the amount of time in Long-Term Follow-Up.

16. In the LVAD study subjects will be monitored weekly including a clinical evaluation, record of all medications and blood tests. Then subjects will be monitored monthly to month 6 including a clinical evaluation, record of all medications and blood tests followed by an annual follow up including a clinical evaluation and record of all medications for 10 years. While some viral shedding by subjects following administration is expected, there is negligible risk from shedding and exposure of family members or other casual contacts from infectious AAV1/SERCA2a so shedding and effects will not be monitored in the present study.

17. However, prior to submission of the Marketing Approval Application for MYDICAR Celladon will conduct a vector shedding study to monitor vector shedding in an open label study. qPCR assay for vector DNA in saliva, buccal swab, urine, and faeces Day 1, Day 3, Day 7; followed by weekly for 1 month, and then monthly for 3 months until there are two consecutive negative results.

Comment

18. ACRE discussed the application for Deliberate Release of the AAV/SERC2A GMO gene therapy agent at its committee meeting on the 7th February 2013.

19. ACRE agree that the genetic composition of the viral product is well characterised and the methods used to produce the inoculant are such that the actual GMO delivered to the patients would be as described in the application. ACRE note that, although low levels of the antibiotic resistance genes used in the intermediates of production of the gene therapy agent are detected by PCR, this does not present any significant risk.

20. The risk of recombination and replication of the AAV/SERC2A virus is negligible since the viral genome has had virulence genes and other sequences removed (only 6% of the genome was present) and the virus can only be propagated in the presence of a ‘helper’ virus.

21. Data on the likely amounts and timing of shedding are limited to studies in which the same or a very similar vector was used to carry *different* human genes. The lack of robust data on shedding would normally be a significant issue (and ACRE would certainly want to see more information if the application reached the Market Authorisation Application phase). However, taking into account the likely amounts of shed vector and that AAV1/SERC2a is a non-pathogenic, non-replicating entity, encoding a human gene, the risk from shedding is considered negligible for the purposes of the current trials. This is because even if small amounts of vector were shed as expected, the ‘biological containment’ inherent to it would make this essentially an environmental ‘dead-end’, ie incapable of replication in the environment.

22. Overall ACRE is satisfied that the application should be allowed to proceed as is it content that potential risks to the environment and non-patient humans have been sufficiently considered and that the appropriate risk management procedures have been described and will be applied.