APPLICATION FOR CONSENT TO RELEASE A GMO – ORGANISMS OTHER THAN HIGHER PLANTS

PART A2: DATA OR RESULTS FROM ANY PREVIOUS RELEASES OF THE GMO

Give information on data or results from any previous releases of this GMO by you either inside or outside the European Community [especially the results of monitoring and the effectiveness of any risk management procedures].

Celladon's CUPID Phase 1/2 clinical study CELL-001, "A Phase 1/2 Trial of Intracoronary Administration of MYDICAR® (AAV1/SERCA2a) in Subjects with Heart Failure Divided into Two Stages: Stage One Open-Label, Sequential Dose-Escalation Cohorts and Stage Two Randomized, Double-Blind, Placebo-Control, Parallel Cohorts)" has been completed, with the last subject having completed the final study contact in the long-term follow-up portion of the study in August 2012. The analysis of the clinical data supports progression into advanced clinical studies.

The CUPID Phase 2b clinical study CELL-004, "A Phase 2b, Double-Blind, Placebo-Controlled, Multinational, Multicenter, Randomized Study Evaluating the Safety and Efficacy of Intracoronary Administration of MYDICAR® (AAV1/SERCA2a) in Subjects with Heart Failure", is ongoing.

MYDICAR® has been studied in 51 subjects in a phase 1/2, multicenter trial of a single intracoronary administration of AAV1/SERCA2a (Protocol No. CELL-001, CUPID Phase 1/2 Trial). [1-3] The phase 1 design was an open-label study of 4 ascending doses in 12 subjects (3 subjects per cohort). The Phase 2 study design was a randomized, double-blind, placebo-controlled study in 39 subjects who received one of 3 different doses of MYDICAR® or placebo. The mode of administration was antegrade epicardial coronary artery 10-minute infusion into the left and/or right coronary artery via percutaneous catheter. All subjects had advanced systolic HF (New York Heart Association Class III), chronic ischemic or non-ischemic cardiomyopathy, LVEF ≤30-35% and VO_2max ≤16-20 mL/kg/minute. All subjects enrolled in the study were on stable optimal HF therapy, including a diuretic, angiotensin-converting enzyme (ACE) inhibitor (or angiotensin-receptor blocker [ARB] if ACE intolerant) and beta blocker; had resynchronization therapy, if indicated, at least 6 months prior to enrollment and; had an implantable cardioverter defibrillator (ICD). Treatment with either MYDICAR® or placebo was on top of maximal optimized HF therapy.

Only patients with undetectable NAbs against AAV1 (titer <1:2), which can block entry of the vector into the target cells [1, 2, 4], were eligible for the Phase 2 study. Patients were pre-screened in a separate feeder protocol (Protocol No. CELL-002).

All subjects completed 12 months of careful observation unless discontinued for a terminal event (death, LVAD implant, heart transplant) and then entered quarterly long-term follow-up for an additional 2 years. The last subject completed the last contact of the long-term follow-up in August 2012.

Phase 2 of the CUPID Phase 1/2 study showed a favourable safety signal and demonstrated early indications of efficacy. Pre-specified adjudicated cardiovascular-related events in high dose MYDICAR®-treated subjects versus placebo subjects were either delayed or had a substantially reduced frequency or both.[3] Importantly, no increases in adverse events, disease-related events, laboratory abnormalities, or arrhythmias were observed in any of the treated subjects compared to those receiving placebo.[5, 6]

PART A3: DETAILS OF PREVIOUS APPLICATIONS FOR RELEASE

Give details of any previous applications to release the GMO made to the Secretary of State under the 2002 Regulations or to another Member State under the Deliberate Release Directive 2001/18/EC.

No applications have previously been made to the Secretary of State under the 2002 Regulations. Celladon has applied for approval of deliberate release of the GMO under Directive 2001/18/EC in Belgium, Germany, Netherlands and Sweden. Approvals were issued in Sweden. Approvals are pending in Belgium, Germany and Netherlands.

PART A4: RISK ASSESSMENT AND A STATEMENT ON RISK EVALUATION

The wtAAV virus is not associated with any diseases in humans and none of its close relatives cause any known diseases in animals. [7] AAV1/SERCA2a is replication defective, contains no viral genes and does not induce pro-inflammatory cytokines. [8] The SERCA2a protein is a fully human, intracellular, endoplasmic protein that is naturally expressed and does not represent a foreign antigen. Unlike adenoviral vectors, vectors manufactured from AAV contain no viral genes, further increasing their safety. With administration of AAV1/SERCA2a to humans, the only foreign proteins which the immune system will be exposed to are the viral AAV1 capsid proteins.

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 (cardiac tissue) 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 intracoronary delivery of AAV1/SERCA2a, rAAV 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. Based on animal studies and clinical studies of other AAV gene therapy agents, it is expected that rAAV concentrations will decrease quickly over time. While rAAV is extensively biodistributed and shedding is known, the virus is nonpathogenic and risks are estimated to be very low. [9]

Since rAAV is non-replicating, even in the presence of adenoviral helper virus, there is no reason to believe that the added DNA will spread from the human subject to other persons or to the environment. Therefore, there do not appear to be risks to health care providers, family members, or other persons that come in contact with MYDICAR®-treated subjects.

1. Likelihood of the GMO to become persistent and invasive in natural habitats under the conditions of the proposed release(s).

   AAV1/SERCA2a cannot become persistent or invasive in any habitats under any conditions because it contains no viral genes and is completely replication incompetent.

2. Any selective advantage or disadvantage conferred to the GMO and the likelihood of this becoming realised under the conditions of the proposed release(s).

   AAV1/SERCA2a is replication incompetent so it cannot have any selective advantage over the parental virus AAV1. The AAV1/SERCA2a genome is an expression cassette containing the non-oncogenic gene for the fully human SERCA2a protein. The SERCA2a protein is an ATP-dependent Ca^{2+} pump that belongs to a ubiquitous motif in higher organisms that is not associated with the infectivity of any pathogens.

3. Potential for gene transfer to other species under conditions of the proposed release of the GMO and any selective advantage or disadvantage conferred to those species.

   The GMO cannot replicate and therefore its ability to disperse in the environment is extremely limited. While there are innumerable extremely low frequency scenarios for recombination of DNA within humans and other organisms, in the environment there are no selective advantages conferred by the completely gutted AAV1/SERCA2a vector that can be transferred to any potential pathogens. The parent AAV is non-pathogenic, the AAV1/SERCA2a genome has no viral genes, AAV1/SERCA2a is completely replication incompetent and the SERCA2a transgene is a ubiquitous Ca^{2+} ion transporter involved only in the muscle contraction/relaxation cycle. SERCA2a would not be expected to confer a growth advantage to any cell and only confers an advantage to cellular functioning where normal expression is abnormally deficient as in heart failure.

4. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO and target organisms (if applicable).

   There are no potential immediate or delayed environmental impacts because there are negligible opportunities for AAV1/SERCA2a to interact with non-target organisms. If such an unlikely event were to occur, AAV1/SERCA2a is replication incompetent and would not spread. Expression of huSERCA2a in any exposed organism would provide no growth advantage.

   Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO with non-target organisms, including impact on

population levels of competitors, prey, hosts, symbionts, predators, parasites and pathogens.

The absence of nearly all viral DNA in the GMO and the complete inability to replicate makes any impact on organisms in the environment exceeding unlikely.

5. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release(s).

   AAV1/SERCA2a preparation and administration occurs within the hospital investigational pharmacy and catheterization laboratory, which are operated under regulated standard practices for containment of potential biosafety level 1 and level 2 pathogens. Clinical studies using rAAV vectors have been performed worldwide in more than 700 patients with an excellent safety profile, and there have been no known immediate or delayed effects on human health due to direct and indirect interactions of the GMO and persons working with, coming into contact with, or in the vicinity of the GMO release(s). The possible health effects of persons exposed to AAV1/SERCA2a by coming into contact with a treated patient is negligible.

6. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any product derived from it, if it is intended to be used as animal feed.

   Not applicable. Neither the GMO nor any product derived from it is intended to be used as animal feed.

7. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release(s).

   The GMO parent organism is a nonpathogenic organism found in humans and primates it is not involved in any biogeochemical processes.

8. Possible immediate and/or delayed, direct and indirect environmental impacts of the specific techniques used for the management of the GMO where these are different from those used for non-GMOs.

   The techniques used for the management of the GMO related waste in the hospital are all accepted standard practices for example, autoclaving, incineration or disinfection with 10% household bleach solution.

PART A5: ASSESSMENT OF COMMERCIAL OR CONFIDENTIALITY OF INFORMATION CONTAINED IN THIS APPLICATION

Not applicable. Information is not confidential.

PART A6: STATEMENT ON WHETHER DETAILED INFORMATION ON THE DESCRIPTION OF THE GMO AND THE PURPOSE OF RELEASE HAS BEEN PUBLISHED

Information on the construction and release of the MYDICAR® has been published.

References

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6. Kawase, Y., D. Ladage, and R. Hajjar, Rescuing the Failing Heart by Targeted Gene Transfer. J Am Coll Cardiol, 2011. 57(10): p. 1169–80.
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