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

PART B: INFORMATION ABOUT THE RELEASE APPLICATION TO BE INCLUDED ON THE PUBLIC REGISTER

B.1. The name and address of the applicant

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For the first trial: "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"

Celladon Corporation
12760 High Bluff Drive, Suite 240
San Diego, CA 92130-2019
United States

For the second trial: "Investigation of the safety and feasibility of AAV1/SERCA2a gene transfer in patients with chronic heart failure and a left ventricular assist device"

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B.2. A general description of the genetically modified organisms in relation to which the application is being made

AAV1/SERCA2a (MYDICAR®) is an experimental gene transfer agent comprised of a vector and a human gene. The vector is derived from adeno-associated virus serotype 1. The human gene is ATP2A2 which codes for the SERCA2a protein a calcium ion pump that is essential for heart muscle cells to complete the contraction and relaxation cycle of a heartbeat. All of the viral genes have been removed from the virus and replaced with an expression cassette for the SERCA2a protein. The expression cassette is packaged inside an AAV1 viral capsid which is composed of three viral capsid proteins.

MYDICAR® is a recombinant adeno-associated viral vector (rAAV), which consists of an AAV serotype 1 capsid and the human SERCA2a cDNA flanked by Inverted Terminal Repeats (ITRs) derived from AAV serotype 2. The SERCA2a protein is the only protein expressed after MYDICAR® treatment, and is a fully human, intracellular, endoplasmic protein that is naturally expressed in cardiomyocytes. MYDICAR® refers to AAV1/SERCA2a drug product intended for intracoronary (IC) administration by percutaneous delivery.

B.3. The location at which the genetically modified organisms are proposed to be released

The GMO will be infused at up to 4 clinical trial centres in the UK. The UK national (OS) grid reference of the proposed sites of release provided in the table below.

Site	Principal Investigator	Address	National Grid Reference
1	Alexander Richard Lyon, M.D., MA, BM BCh, MRCP, Ph.D.	Royal Brompton and Harefield NHS Foundation Trust London SW3 6NP Tel: 020 7351 8827 Fax: 020 7351 8829	**TQ 26977 78395**
2	Dr. Mark Petrie, M.D., MBChB	Golden Jubilee National Hospital Cardiology Dept. Beardmore Street Clydebank G81 4HX Glasgow	**NS 4126 6673**
3	John J V McMurray, M.D., FRCP, FESC, FACC, FAHA, FRSE	British Heart Foundation Cardiovascular Research Centre University of Glasgow 126 University Place G12 8QQ Glasgow	Patients to be dosed at Site #2, above, **NS 4126 6673**
4	Prof. John G. F. Cleland, M.D., FACC	Cardiovascular & Respiratory Studies, University of Hull Castle Hill Hospital Cottingham, HU165JQ Kingston-Upon-Hull	Patients to be dosed at Site #1, above, **TQ 26977 78395**
5	Dr Nicholas R. Banner, M.D. FRCP, FESC	Dept of Cardiology Harefield Hospital Hill End Road, Harefield Middlesex UB9 6JH	**TQ 05166 90857**
6	Mr Steven Tsui, M.D., FRCS	Dept of Cardiothoracic Surgery Papworth Hospital Papworth Everard Cambridge CB23 3RE	**TL 28746 62837**

B.4. The purpose for which the genetically modified organisms are proposed to be released (including any future use to which they are intended to be put)

The study objectives are to determine the safety and efficacy of a single intracoronary infusion of MYDICAR® added to an optimal heart failure (HF) regimen in patients with ischemic or dilated cardiomyopathy and NYHA class III/IV symptoms of HF by reducing

the frequency and/or delaying HF-related hospitalizations compared to placebo-treated patients.

The principle aim of the LVAD study is to determine 1) the safety and feasibility 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.

In a previous phase 2 study advanced HF patients who were on maximal, optimal heart failure (HF) regimen were studied. Relative to the placebo group, MYDICAR®-treated subjects had a significant decrease in the frequency of all cardiovascular (CV)-related adverse events per subject, including both a reduced number and reduced duration of CV-related hospitalizations. This was supported by decreased symptoms of HF, augmented functional status, decreased natriuretic peptide levels, beneficial reverse remodelling of the left ventricle, as well as improving clinical outcomes. Additionally, MYDICAR® demonstrated an excellent safety profile.

Advanced HF patients generally face a poor outcome and poor quality of life. The target population for MYDICAR® is experiencing worsening of their disease and frequent HF-related hospitalizations. A new treatment option for this patient population which reduced recurrent HF-related hospitalizations and improvement in signs and symptoms of HF could be of significant benefit, not only by reducing deaths from HF, but also by improving quality of life, and reducing cost of care for HF for both individual patients and the health care system as a whole. The current study has been designed to confirm the results of the CUPID phase 2 study and serve as the basis for establishing an efficacy indication for HF based on a reduction in the frequency and/or delaying HF-related hospitalizations.

In the Phase 2b study a total of approximately 200 subjects will be enrolled in up to 50 sites worldwide. The current study is ongoing in the United States, Sweden and Denmark, and planned for Belgium, Germany, The Netherlands, Poland and the United Kingdom.

For the LVAD study trial a total of about 24 patients will be enrolled at two sites in the UK, the Harefield Hospital in Middlesex and the Papworth Hospital in Cambridge.

B.5. The intended dates of the release

Enrollment for the Phase 2b study is expected to continue through 2013. Enrollment in the UK is anticipated to begin in the first quarter of 2013. It is anticipated that 16 to 20 patients will be enrolled in the UK for this study. For the LVAD study enrollment is anticipated to begin in the first quarter of 2013 and continue for 24 months. A total of 24 patients will be enrolled in the LVAD study.

B.6. The environmental risk assessment

The wtAAV virus is not associated with any diseases in humans and none of its close relatives cause any known diseases in animals. Human exposure to AAV worldwide is

ubiquitous with over 90% of the European population already exposed to AAV before leaving adolescence. The recombinant AAV used in this study AAV1/SERCA2a is replication defective, contains no viral genes and does not induce pro-inflammatory cytokines. The SERCA2a protein is a fully human, intracellular, endoplasmic protein that is naturally expressed and does not represent a foreign antigen. Unlike other vectors including 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.

Extensive preclinical safety and biodistribution testing conducted on AAV1/SERCA2a and other AAV vectors, in addition to the previous phase 1 and phase 2 studies of MYDICAR® and data from hundreds of patients in clinical trials of other AAV vectors suggests is well tolerated at exposures that are many orders of magnitude higher what can be imagined from worst case exposures due to spills or shedding.

Since rAAV is completely replication deficient, even in the presence of helper virus, there is no reason to believe that it 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.

B.7. The methods and plans for monitoring the genetically modified organisms and for responding to an emergency

Patent monitoring: 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 (as deemed necessary), and then just before discharge from the hospital. In the Phase 2b study patients will be monitored every three months during the first 12 month active study period for adverse events, given laboratory tests including; haematology and blood chemistries, cardiac enzymes, urinalysis and given a physical examination, an ECG and health assessments. The subsequent 12 month long-term follow-up with 3 month evaluations will monitor any serious adverse events. Safety oversight will be provided by a qualified Medical Monitor reviewing all serious adverse events, an independent Data Monitoring Committee responsible for monitoring safety of

the study and Clinical Endpoint committee that will review and categorize all clinical events.

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.

All patients will be monitored for any suspected immune reactions to the infusion, tested as indicated using a sensitive assay for cell-mediated immune responses and treated as required. Patients will be instructed on the care and dressing of the puncture site.

The investigational product will be handled and administered using aseptic technique and in accordance with Standard/Universal practices for handling potentially biohazardous materials. All waste will be treated as biohazardous materials. Accidental spills will be contained and disinfected with 10% household bleach (5000 ppm sodium hypochlorite).