INFORMATION FOR THE PUBLIC

A Phase 2b, Double-Blind, Placebo-Controlled, Multinational, Multicentre, Randomized Study Evaluating the Safety and Efficacy of Intracoronary Administration of MYDICAR® (AAV1/SERCA2a) in Subjects with Heart Failure

PROTOCOL N°: CELL-004

European notification number: B/BE/12/BVW2

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The release of genetically modified organisms (GMOs) in the environment is strictly regulated at European level by directive 2001/18/EC of 112 March 2001 repealing directive 90/220/EEC and at Belgian level by a new Royal Decree, "regulating the deliberate release and/or marketing of GMOs or products that contain GMOs into the environment" repealing the Royal Decree of 18 December 1998. The transposition procedure is still ongoing for the moment.

To ensure the safe use of GMOs, the provisions of the Royal Decree above stipulate that the release of GMOs for experimental aims is prohibited without prior consent from the competent Minister. The decision is based on a thorough evaluation of the biosafety of the planned release, which is conducted by the Biosafety Advisory Council, composed of different Scientific Committees grouping independent experts from Belgian universities and governmental institutes.

To acquire the necessary authorization from the competent Minister, the company Celladon Corporation (Celladon) submitted an application dossier to the competent authority. ON the basis of the advice of the Biosafety Council, the competent minister could grant a permission to Celladon to conduct experiments with AAV1/SERCA2a, recombinant AAV vector consisting of a single-stranded cDNA encoding the human SERCA2a flanked by Inverted Terminal Repeats derived from AAV serotype 2 and the capsid from AAV serotype 1 (MYDICAR®) as stipulated in the application B/BE/12/BVW2.

The release will take place at up to three clinical trial centres in Belgium and Flanders:

OLV Hospital Aalst
Cardiovascular Centre
Dr. Jozef Bartunek
Moorselbaan 164
9300 Aalst

U.Z. Gasthuisberg
Department of Cardiology
Dr. Walter Droogné
Herestraat 49
B3000 Leuven

Brussels Heart Centre
Clinique Saint-Jean
Department of Cardiology
Dr. Marc Castadot
32 Boulevard du Jardin Botanique
1000 Brussels

A total of 15 patients are planned for treatment beginning in 4Q2012. Enrolment is planned for 16 months following start of the study. Up to 5 patients are planned to enrol at each of the following sites, for a total of 15 patients. Patients will be randomized in parallel in a ratio of 1:1, MYDICAR® to matching placebo (buffer without the active ingredient). Administration consists of a single intracoronary infusion for each patient, with a total of 8 to 9 patients expected to be randomised to receive the GMO over the study period.

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1. GENERAL INFORMATION

1.1 Description of the Genetically Modified Micro-Organism (GMM)

Genes contain the information that tells the body's cells what to do. Gene transfer is the process of delivering new genes into a person to compensate for the person's lack of a protein coded by the gene. Researchers are trying to learn more about it to see if it works to treat certain health problems. Gene transfer is experimental.

Genes can be transferred through a virus, using the virus's natural ability to deliver genetic material into cells. The researchers first remove all the genes from the virus so that it is less likely to cause disease. Then they add the new gene, which they hope will be delivered to the target cell when the virus carrying the gene attaches to the cell. If the gene reaches the cell, it may be able to start making the protein that the body needs to treat the disease being studied. The virus with its own genes removed and replaced with the gene to be delivered is called a vector.

AAV1/SERCA2a (MYDICAR®) is an experimental gene transfer agent made of a vector and a human gene. The vector is designed to deliver its gene to heart muscle cells following administration of to human subjects enrolled in the clinical trial to be conducted by Celladon Corporation. The vector in MYDICAR® is a virus made from adeno-associated virus (AAV) and the human gene SERCA2a. The AAV virus is not known to cause disease in humans. AAV is also replication defective, which means that it cannot duplicate without the presence of a helper virus. In addition, the virus vector in MYDICAR® has been modified in a way that will not allow it to multiply.

The gene that the virus delivers to the heart muscle cells makes a type of protein called an enzyme. Enzymes are substances produced by the body to speed up chemical reactions. The gene transfer method in this clinical trial is intended to add copies of the gene for an enzyme called SERCA2a to the heart muscle cells of heart failure patients who are enrolled in the trial. In heart failure, a patient's own heart muscle cells don't make enough of the SERCA2a enzyme. The enzyme is important for the cycling of calcium inside of the cell. Proper calcium cycling is important for the heart to contract with maximum efficiency. In heart failure, there are lower levels of this enzyme in heart muscle cells which makes the heart not contract as well as it should. Study doctors have found that increasing the enzyme in the heart muscle cells of animals with heart failure improves heart function.

1.2 Type and Purpose of the Envisaged Trial

The purpose of this trial is to test whether an experimental gene transfer agent called MYDICAR® will help to improve the clinical outcome in subjects with heart failure by reducing the frequency of heart failure-related hospitalizations as compared to subjects who randomly received placebo. The purpose is also to confirm the safety and the efficacy of MYDICAR®.

To properly evaluate the good and bad effects of MYDICAR®, the trial is designed to compare the effects of adding the experimental gene transfer agent or placebo (an inactive

substance) to the treatment that the patient is currently receiving for his or her heart failure.

A total of about 200 heart failure patients will be enrolled in the trial in the U.S. and in Europe. About 12 to 24 of these patients will live in Belgium. Subjects will be randomly assigned (like the flip of a coin) to either MYDICAR® or placebo, and will have an equal chance of being assigned either. This means that if about half of patients receive MYDICAR®, a total of about 6 to 12 patients in Belgium will receive MYDICAR®.

The study is double-blind, which means that neither the subject or study doctor will know until the study is done whether the subject received MYDICAR® or placebo. However, this information is available to the study doctor if needed in an emergency.

2. RESEARCH/DEVELOPMENT ACTIVITIES

2.1 Previous Development Activities

In clinical trials performed in the United States, there were no major safety issues in 37 subjects who received the same or lower doses of MYDICAR® as planned in this trial. Subjects who received the same dose as in this study were admitted to the hospital for heart failure less often than subjects who received placebo. In addition, the subjects who received this dose tended to be more stable with their heart failure condition. These were small studies and the results may not necessarily be the same in this study.

2.2 Knowledge and Experience Obtained in Previous Development Activities

Nonclinical studies (in animals) and early clinical studies (in humans) suggest that MYDICAR® has the potential to help patients whose heart failure continues to worsen even with all treatments that are currently available. Most conventional treatments for heart failure do not fix the underlying cause. It is believed that a single treatment with MYDICAR® will provide continuous delivery of the SERCA2a enzyme in advanced heart failure patients, potentially leading to improvement. The possible benefits of MYDICAR® may include a longer life, improvement or stabilization of the function of the heart, and/or reduced frequency or duration of hospital stays.

2.3 Future Activities

The planned study, CELL-004, "A Phase 2b, Double-Blind, Placebo-Controlled, Multinational, Multicentre, Randomized Study Evaluating the Safety and Efficacy of Intracoronary Administration of MYDICAR® (AAV1/SERCA2a) in Subjects with Heart Failure," is designed to confirm the safety and efficacy of a single intracoronary infusion of MYDICAR® in a specific group of heart failure patients by reducing the frequency and/or delaying HF-related hospitalizations compared to placebo-treated patients.

Future clinical studies will also be conducted to confirm the safety and effectiveness of the treatment. These studies may be conducted in a larger number of people or in different patient populations.

3. BENEFITS

Heart failure patients that participate in this study will be patients whose heart failure is not getting better despite optimal medical therapy for their disease. Earlier studies support the safety of MYDICAR® as an experimental gene transfer agent for the treatment of advanced heart failure, but it is far too early to say whether the treatment will be safe and effective or how long the effectiveness may last.

Information from this study may benefit future patients with heart failure.

4. RISKS

4.1 Risks to Subjects

In previous studies, MYDICAR® was studied in a total of 51 subjects with advanced heart failure. Of those, 37 subjects received the same or a lower dose than that being used in this trial, and 14 subjects received placebo. The following is a list of adverse events that occurred at a higher rate than subjects who received placebo (inactive agent). Most of the adverse events were of mild or moderate severity; those indicated with an asterisk (*) were severe. At this early stage of development, it is hard to say whether MYDICAR® is the direct cause of these events or whether these events are part of the underlying condition of heart failure. The known risks of MYDICAR® are still limited and there may be unexpected adverse events not listed that might occur.

These adverse events occurred the most often (≥5%) in order of frequency (highest to lowest):

- Ventricular tachycardia, an abnormal heart rhythm (16% vs. 14% in placebo);
- Low level of potassium in the blood (16% vs. 0% in placebo);
- Too much fluid in the blood (14% vs. 7% in placebo);
- Nasal congestion (11% vs. 7% in placebo);
- Low blood pressure (11% vs. 7% in placebo);
- Ventricular fibrillation, an abnormal heart rhythm (8% vs. 7% in placebo);
- Fall (8% vs. 7% in placebo);
- Low level of sodium in the blood (8% vs. 0% in placebo);
- Muscle spasms, sudden, involuntary contractions of a muscle (8% vs. 0% in placebo);
- Decrease in kidney function (8% vs. 0% in placebo);
- Shortness of breath (8% vs. 7% in placebo);
- Shortness of breath upon exertion (5% vs. 0% in placebo);
- Clicking, rattling or crackling noises in the lungs (8% vs. 0% in placebo);
- Arrhythmia (5% vs. 0% in placebo);
- Cardiogenic shock (failure of the heart to pump effectively)(5% vs. 0% in placebo);
- Abnormal manner in walking (5% vs. 0% in placebo);
- Herpes (5% vs. 0% in placebo);
- Viral infection (5% vs. 0% in placebo);
- Flu (5% vs. 0% in placebo);
- Eye injury (5% vs. 0% in placebo);

- Increased bilirubin which might indicate damage to the liver or a blood disorder (5% vs. 0% in placebo);
- Increased creatine phosphokinase which might indicate a breakdown of muscle (5% vs. 0% in placebo);
- Groin pain (5% vs. 0% in placebo);
- Fainting(5% vs. 0% in placebo);
- Productive cough (5% vs. 0% in placebo);
- Nose bleeds (5% vs. 0% in placebo); and
- Bruising (5% vs. 0% in placebo).

These adverse events occurred less often (3%):

- Cardiac disorders: chest pain, abnormal heart rhythms*, heart and kidney failure*, blood clot in the heart, cardiac aneurysm (thinning, stretching or bulging of the wall of the heart), and palpitations (skipped beat or rapid beating of heart).
- Gastrointestinal disorders: bloating or increased pressure in stomach, stomach pain, build-up of fluid in the abdomen, stomach discomfort, ulcer, bleeding ulcer*, blood in stool, inflammation of the pancreas and jaundice (yellow colour of skin).
- Infections: yeast infection, skin infection, central line infection*, infection in stomach with bacteria that causes ulcers*, herpes, pneumonia*, and upper respiratory infection (infection in nose, throat and lungs).
- Metabolism and Nutrition Disorders: excessive weight loss, decreased appetite, dehydration, diabetes, water retention and high level of lipids/cholesterol in the blood.
- Muscle, Bones and Connective Tissue Disorders: bone disorder and bursitis (swelling of the fluid-filled sac that lies between a tendon and skin or bone).
- Nervous System Disorders: wrist tremor, stroke, worsening brain function from liver not working properly, reduced sense of touch, neurological symptoms, involuntary eye movement, restless leg syndrome, drowsiness and mini-stroke.
- Mental Health: alcoholism, clenching or grinding teeth, mental status changes and sleepwalking*.
- Kidney and Urinary Disorders: kidney failure*.
- Respiratory and Chest Disorders: asthma; chronic obstructive pulmonary disease (narrowing of the airways, leading to limitation of flow of air to and from the lungs and causing shortness of breath); coughing up blood from the lungs; sore or painful throat; respiratory failure and sleep apnoea (pauses in breathing during sleep).
- Skin Disorders: bleeding underneath the skin, skin ulcer and Stevens-Johnson syndrome.
- Vascular Disorders: blood clots in a deep vein and high blood pressure.
- Other: fluid around a testicle, blurred vision, blood leaking from blood vessel to surrounding tissue, jittery feeling, swelling near injection or catheter site, swelling in hands and feet, sudden death*, blood clot at site of injection or blood draw, head injury, mouth injury, discharge from injection site, tendon injury, certain abnormal blood tests (increased uric acid which might indicate arthritis or gout, increase in clotting time of blood, increase in red blood cell volume which might indicate a type of anaemia, increase in Prostate Specific Antigen (PSA) which might indicate inflammation or cancer of the prostate gland in men, increase in liver enzymes which might indicate damage to the liver, and decrease in vitamin D), weight

increase, breast disorder, breast enlargement in males, enlarged or twisted veins in the scrotum,

In the current trial, subjects could have an immune reaction in which white blood cells attack the heart muscle or other organs or cells in the body after gene transfer. This has not occurred in previous trials and subjects enrolled in this trial will be watched for any signs or symptoms of an immune reaction. In other gene transfer studies using the same type of AAV vector with a different gene, a few subjects had an immune reaction that required treatment with a short course of steroid therapy. This is most likely to occur within 2-8 weeks of receiving MYDICAR®. If a subject has an immune reaction, the study doctor may treat the subject with certain drugs to try to stop or decrease the immune reaction. There are no assurances, though, that it can be stopped or reversed.

MYDICAR® could distribute to other organs as it did in animal studies. The risks of this are not known at this time.

In addition, subjects will develop antibodies to AAV that might prevent or complicate future gene transfer using AAV or a similar viral vector (delivery agent). Antibodies are Y-shaped proteins used by the immune system to identify bacteria, viruses, and other foreign bodies. Antibodies bind to bacteria, viruses, or other foreign bodies and help the body destroy them.

There is a very small chance that MYDICAR® could damage DNA in the subject's cells by inserting the new (SERCA2a) gene into the genes. If this happens, it could put the subject at risk for developing cancer. Two children in a gene transfer study using a very different virus vector developed cancer. The AAV vector in this study does not have the ability to grow on its own and should not be able to survive and grow within the body. No cancers have yet been found in any of the experiments in which genes have been transferred into monkeys and humans using AAV.

One risk of this study is that the AAV could have harmful effects on an unborn child. We do not know if AAV can become part of normal reproductive cells (egg or sperm). If it can, it could cause harm to foetuses conceived after the gene transfer. These harms could include birth defects, and death of the foetus or of the child after birth. To date, there have been no cases of AAV causing birth defects or harming foetuses. To prevent this risk, subjects will be asked to use birth control if necessary.

The heart failure may not improve and could even worsen during the study. The potential short- and long-term safety effects of the virus and the introduction of the gene inside cells are not known.

4.2 Risks to Health Care Providers and Family Members

There do not appear to be risks to health care providers, family members, or other persons that come in contact with MYDICAR®-treated subjects. AAV is a small, stable virus that has never been shown to cause disease in humans, even though a majority of the population has been exposed to it. Control of the most likely route of infection (i.e., via

sharps) is important and measures to reduce exposure to any aerosol generated exposure also seem appropriate.

Preparation of the investigational product is a simple dilution of small volumes in the controlled setting of an investigational pharmacy or cardiac catheterization laboratory using appropriate containment and best practices. The likelihood of unintended release is very small. The investigational product is administered as a single intracoronary infusion in a cardiac catheterization laboratory, usually located within a hospital, by a qualified attending interventional cardiologist having performed a minimum of 75 coronary interventions and 150 diagnostic procedures per year. The likelihood of the vector being transmitted to another person in this setting by experienced and trained staff practicing standard precautions while executing routine procedures is determined to be low.

4.3 Risks to the Environment

Viral vectors, including vectors derived from AAV, are frequently used in gene therapy. The risk to the environment is thought to be very low. The AAV parent virus only interacts with primates. It does not interact with other plants or animals. In addition, because the vector has no viral genes it cannot replicate under any circumstances so its persistence in the environment is limited. The consequences of the release in the environment although thought to be very low are not entirely known yet, however some data are available in the literature.[1].

5. CONTAINMENT, CONTROL AND MONITORING MEASURES

AAV is considered to be either in Risk Group 1 or Risk Group 2 by the responsible regulatory agencies across Europe and in the U.S. The Belgium Scientific Institute of Public Health assigns a maximum risk of Group 2 for humans with fully functioning immune systems. With regard to AAV vectors, most the agencies that have designated it (DE, SW, UK, US) consider vectors like the one in MYDICAR® to be Risk Group 1, however many others have not classified it. Biosafety Level 1 or 2 practices and universal precautions should be employed when recombinant AAV-based vectors are administered to humans in Belgium. These precautions consist of wearing gloves, a laboratory coat, gown or uniform and protective eyewear such as regular glasses or safety glasses. In addition, areas of storage and use should have limited access.

Accidental spill of the investigational product should be handled in accordance with the Material Safety Data Sheet, as follows:

- Gloves and protective eyewear should be worn.
- Use an absorbent material to contain/pick up the spilled solution.
- Once the absorbent is spent, place all contaminated disposables into a suitable container, seal, label and dispose as a biohazard material.
- Wash spill site with 10% bleach after material pickup is complete.

5.1 Control of GMM and Gene Spreading

Preparation of the investigational product is a simple dilution of small volumes in the controlled setting of an investigational pharmacy or cardiac catheterization laboratory using appropriate containment and best practices. The likelihood of unintended release is very small. The investigational product is administered as a single intracoronary infusion in a cardiac catheterization laboratory, usually located within a hospital, by a qualified attending interventional cardiologist having performed a minimum of 75 coronary interventions and 150 diagnostic procedures per year. The likelihood of the vector being transmitted to another person in this setting by experienced and trained staff practicing standard precautions while executing routine procedures is determined to be low.

The AAV1/SERCA2A vector system uses a replication-defective AAV1 vector, making the spread of the virus from one person to another very unlikely. Furthermore, after intracoronary delivery of AAV1/SERCA2a, AAV 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 (a network of cells and tissues found throughout the body, especially in the blood, general connective tissue, spleen, liver, lungs, bone marrow, and lymph nodes). Upon entry into the lungs, the concentrated solution infused into the heart to transfer the gene to heart tissue is rapidly diluted by the volume of blood flowing through the lungs, reducing the AAV concentration and limiting active infection of other tissue.

5.2 Genetic Stability of the GMM

The vector is stable by design in that the vector DNA is approximately the same size as the viral genome and it contains no viral genes. The investigational product's stability is assured by a well-characterized manufacturing process and extensive testing. The vector has been tested for the presence of other viruses and DNA. In addition, it is tested for identity, potency and other impurities.

5.3 Destruction of GMM-Containing Material

Any disposable surgical instruments or other materials used during the procedure will be disposed of in a manner which is also consistent with the standard practice of the institution for biohazardous materials.

The disinfectant used for decontamination is fresh 5000 ppm sodium hypochlorite in water (household bleach diluted to 10%), that is applied and left wet for a minimum of 10 minutes.

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 hazardous biological materials according to individual institutional practices and policies. In general the materials will be disposed in sharps containers or biohazard bags and decontaminated by autoclave or incineration, or both.

The unused investigational product and vial, stopper and crimp seal can be decontaminated with the 10% bleach solution. The materials can be disposed of as

biohazardous waste and the excess destroyed investigational product 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 the 10% bleach solution. Some non-disposables may be autoclaved.

5.4 Training Requirements

Administration of the investigational product will be by authorized trained personnel in a hospital catheterization lab according to good clinical practice and the study protocol. The primary mode of containment during the catheterization procedure is application of Standard/Universal Precautions for infectious materials. In the cath lab personnel performing the procedure will wear goggles, scrub suit, shoe covers, cap and mask, and gloves while support personnel will wear support personnel wear safety glasses, gown, shoe covers, cap and mask, and gloves.

All personnel involved in the direct use of the syringe pump for administration of investigational product must attend an in-service training on the proper use of the syringe pump and participate in a dry run of its setup and operation prior to infusing the first subject. The investigational sites abide by all EU, country and self-imposed guidelines regarding the conduct of clinical trials, as well as the appropriate biosafety regulations required by the EMA for gene therapy medicinal research.

5.5 Emergency Situations

The patients will be treated by qualified health care personnel in hospital departments. All involved personnel will receive detailed procedures for handling the drug, including procedures for preparation, injection, disposal and accidental spillage.

All waste resulting from the use of the product will be stored in appropriate biohazard containers. Destruction and return of materials and unused product will be according to strict procedures.

5.6 Other Containment, Control and Monitoring Measures

AAV1 requires the co-infection of a helper virus so replication in an infected host can take from 24 to 48 hours, but may never occur in the absence of an appropriate helper virus. Note that the AAV1/SERCA2a vector does not contain any viral genes and cannot replicate under any conditions.

Instructions that are provided to the clinical study site for the destruction of unused undiluted and diluted Investigational product, along with associated generated waste will be followed and documented by the hospital staff in the investigational pharmacy and in the cardiac catheterization lab. In general, treatment with a fresh 10% dilution of household bleach, autoclaving and/or incineration will be used for destruction of the GMO.

5.7 Responsibilities of the Sponsor

The consent that could be given to the study Sponsor by the competent Minister stipulates that Celladon takes complete civilian liability regarding the damage that could be caused by the deliberate release to the health of humans, animals or environment.

5.8 Inspection by the Public Authorities

Inspectors are in charge of inspecting the trials for compliance with the conditions specified in the consent and to investigate potential breaches of the consent. In cases where mismanagement or fraud is identified specific sanctions will be imposed.

5.9 Activity Report

At the end of the trial an activity report will be prepared by Celladon to be delivered to the competent authority. This activity report will include at least the following data:

- the site and period of release,
- the precise nature of the actually released GMMs,
- the aim(s) of the trial,
- the measures that were taken to prevent unwanted release of transgenic material, if applicable, the measures that were taken to protect the relatives of the treated patients, the measures that were taken to protect the workers who had to manipulate the GMM-containing material,
- the method used for the destruction of the unused or contaminated material,
- the results obtained during the trial,

6. REFERENCES

1. Brandon, E.F.A., et al., *Effect of Administration Route on the Biodistribution and Shedding of Replication-Deficient AAV2: A Qualitative Modelling Approach.* Current Gene Therapy, 2010. **10**(2): p. 91-106.

7. CONTACT

7.1 Notifier

If you have any comment on the public dossier or our activities or wish to obtain additional information of the deliberate release, please contact us at the following address.

You can also have access to a summary of the notification (SNIF) on the web site of the Joint Research Centre of the European Commission (http://gmoinfo.jrc.it/). Comments can be addressed to the commission via this web site.

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