PRESENTATION OF THE FINAL RESULTS OF DELIBERATE RELEASE INTO THE ENVIRONMENT OF GENETICALLY MODIFIED ORGANISMS

IN ACCORDANCE WITH ARTICLE 10 OF DIRECTIVE 2001/18/EC

The final report format shall be completed by the notifier.

- The notifier shall fill in the report format according to the proposed form.
- The notifier shall illustrate as much as possible the reported data by means of diagrams, figures and tables.
- Statistical data could also be provided where relevant.
- In the case of multi-sites and/or multi-events release(s) the notifier shall provide a general overview of the measures taken and effects observed for the full duration of the consent.
- The space provided after each item is not indicative of the depth of the information required for the purposes of this report.
- The information provided in this report is not considered confidential in accordance with Article 25 of Directive 2001/18/EC.

1. General information

1.1. European notification number: *Number can be found on the corresponding SNIF form (i.e. year and number, B/NL/xx/xxx)*	B/NL/12/004
1.2. Member State of notification:	The Netherlands
1.3. Date of consent: *Date of issue of permit*	20-6-2013
1.4. Title of the project:	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 (CUPID Phase 2b Trial)
1.5. Name of institution or company: *i.e. legal entity = notifier*	University Medical Center Groningen
1.6. Duration of release:	Max 12 months
1.7. Period of release:	1-1-2014 until 31-12-2014

2. Characteristics of the release

2.1 Scientific name of the recipient organism: Homo Sapiens

2.2 Transformation event(s) (acronym(s)) or vectors used:
Describe the GMO(s) and/or vector(s) and insert(s) used for the modification

Genus: Dependovirus
Species: Adeno-associated virus (vector).

The AAV1/SERCA2a vector is a recombinant adeno-associated virus (rAAV) vector. It is a pseudotype of AAV serotype 1(AAV1) and is denoted as rAAV1/2. As such, the capsid proteins are from wt AAV1 and the AAV DNA (two 148 base inverted terminal repeats) is from wtAAV2.

AAV1/SERCA2a is a "gutted" AAV viral vector with an inserted transgene SERCA2a. As such, all of the viral gene-encoding sequences have been removed leaving only the two small (145 bases) AAV serotype 2 inverted terminal repeat sequences at the 3´ and 5´ ends flanking the CMV hSERCA2a-polyA expression cassette.

The intention of the modifications was to render the virus completely replication-incompetent and to make mobilization negligible if not impossible, to maintain the skeletal muscle tropism of AAV1 and to allow expression of SERCA2a. To maintain the desired tropism the vector, AAV1/SERCA2a, is an AAV2/1 pseudotype containing the capsid proteins of adeno-associated virus serotype 1 (AAV1) and the sequence for AAV2 inverted terminal repeats

SERCA2a is an intracellular Ca2+ pump located in the sarcoplasmic retucula of cardiac muscle cells. This enzyme catalyzes the hydrolysis of ATP, coupled with the translocation of calcium from the cytosol into the lumen of the sarcoplasmic reticulum, and is involved in regulation of the heart contraction/relaxation cycle. It is not a toxic or oncogenic protein. The primary objective is to up-regulate SERCA2a in patients with ischemic or dilated cardiomyopathy and NYHA class III/IV symptoms of heart failure (HF). SERCA2a genetic enzyme replacement in advanced HF patients may correct imbalances in Ca2+ cardiac metabolism, resulting in enhanced cardiac function and energetics, which will in turn translate to improved signs and symptoms of HF, quality of life and clinical outcomes.

2.3 Unique identifier, if available: AAV1/SERCA2a vector
i.e. product name or GMO name

2.4 Geographical location(s) (administrative region): Groningen, 9713 GZ

2.5 Number of test subjects: 1

2.6 Amount of GMO administered to each test subject:	One injection with a dose of 1 x 10^{13} DNase resistant particles (DRP)
2.7 Number of administrations per test subject:	One injection

3. Risk management measure(s)

Please report the risk-management measures used to avoid or minimize the spread of the GMO(s) outside the site(s) of release, and in particular those measures

- *not originally notified in the application,*
- *applied in addition to the conditions in the consent.*
- *required by the consent only under certain conditions,*
- *that the consent allowed the notifier a choice of measures.*

Answer:

Standard hospital precautions to minimize the spread of biological agents were taken, meaning administration of the product by medical trained personnel, the use of rooms which can be easily disinfected, disinfection of equipment and surfaces and controlled waste treatment.
The following risk-management measures were taken (as required by the consent):

1. The patients had to use effective contraception in combination with a barrier device during the first three months after treatment.
2. The vector was not to be applied when there were clinical indications for an active viral infection.
3. The treated patients had to be excluded from donation of blood, cells, and tissues.

4. Post-release monitoring measures

Please describe here any monitoring strategies.

Answer:

There were no requirements for post-release monitoring measures.

5. Results of the foreseen and unforeseen release(s)

Consider in the following questions 5.1 through 5.4 all results of the foreseen and unforeseen release(s) in respect of any risk for human health or the environment, without prejudice to whether the results indicate that any risk is increased, reduced or remains unchanged.

5.1 Results of the study

Provide a summary of the study results in respect of any risk for human health or the environment. Include also the results of the monitoring measures (if applicable).

Answer:

One patient was treated with the GMO product in 2014. The patient died of the disease in the same year and therefore the results were incomplete. There was no correlation between the death of the patient and the treatment.

5.2 Unexpected effect(s) and adverse effects

'Unexpected effects' refer to effects on human health or the environment, which were not foreseen or identified in the environmental risk assessment of the notification. This part of the report should contain any information with regard to unexpected effects or observations relevant for the initial environmental risk assessment. In case of any observed unexpected effects or observations, this section should be as detailed as possible to allow a proper interpretation of the data.

Answer:

There were no unexpected or adverse effects relevant for the environmental risk assessment.

5.3 Unintended release of the GMO

'Unintended releases' refer to any incidents or spills with regard to the GMO that occurred during the study, where possible effect(s) on human health and/or the environment cannot be excluded. Describe these effects, including actions taken to manage the risks.

Answer:

There was no unintended release of GMO

5.4 Other information

Notifiers are encouraged to supply information, which is outside the scope of the notification but which might be relevant to the trial(s) in question. This may also include observations of beneficial effects.

Answer:

Not applicable

6 Assessment of risk following completion of release

Please provide a reflection of the risk assessment and risk management strategies carried out prior to the release in relation to the obtained results and findings of for instance monitoring and samples taken from the test subjects. Do the results of the study justify the performed environmental risk assessment and conclusion?

Answer:

There was no monitoring of shedding of the vector in this study. Therefore it is not possible to reflect on the risk management measures.

7 Conclusion

Here the notifier should elaborate on the efficacy and efficiency of all measures taken, and elaborate on the insights gained during this release. Also, specify how the gain in experience can benefit further (future) releases with respect to risk management.

Answer:

For this AAV based vector, taking the standard hospital measures to prevent spreading of the vector was sufficient as AAV is considered as non-pathogenic. There was no monitoring of shedding of the vector in this study. Therefore it is not possible to reflect on efficacy and efficiency of the risk management measures.