PRESENTATION OF THE RESULT OF DELIBERATE RELEASE INTO THE ENVIRONMENT OF GENETICALL Y MODIFIED ORGANISMS

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

- *The report format shall be completed by the notifier.*
- *The notifier shall fill in the report format according to the proposed form (tick boxes and/or, as far as possible, specific keywords to use in text fields).*
- *The notifier shall illustrate as much as possible the reported data by means of diagrams, figures and tab les. Statistical data could also be provided*
- *where relevant.*
- *In the case of multi-sites, multi-events and/or multi-annual 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.*

1. General information

1.1. European notification number: B/NL/07/011

1.2. Member State of notification: The Netherlands

1.3. Date of consent and consent number: 03-07-2008, IM 07-011

2. Report status

2.1. Please indicate whether, according to Article 3 of the present Decision, the current report is:

☒ the final report
☐ a post-release monitoring report; ☐ final ☐ intermediary

3. Characteristics of the release

3.1. Scientific name of the recipient organism:
Homo sapiens

3.2. Transformation event(s) (acronym(s)) or vectors used (if transformation event identity not available):
The Allovectin-7® medicinal product is not a GMO per se. It is an investigational gene therapy medicinal product consisting of a purified plasmid DNA (pDNA) drug substance formulated with a synthetic cationic lipid/neutral colipid delivery system (DMRIE-DOPE) in an injection vehicle consisting of 0.9% sodium chloride supplemented with 10 µg/mL glycerin. The pDNA drug substance, designated VCL-1005, is derived from the commonly used laboratory cloning vector pBR322. The VCL-1005 pDNA contains an antibiotic resistance gene and a bacterial origin of DNA replication, and is manufactured

at Vical's facility in the U.S. by growth in Escherichia coli (E. coli) cultures maintained under antibiotic selection with kanamycin. The final pDNA drug substance contained in Allovectin-7® is an acellular product free of contaminating bacteria or viruses.

In a prior correspondence from a representative of the EMEA it was confirmed that Allovectin-7® is not classified as a GMO, but falls under the GMO legislation as a gene therapy medicinal product administered to humans.

For the purposes of this notification, the VCL-1005 pDNA component of Allovectin-7® is considered to be the active component of the GMO.

3.3. Unique identifier, if available:
VCL-1005 pDNA

3.4. Please provide the following information:

Geographicallocation(s) (administrative region and, where appropriate, grid reference)	Identity (*) and approximate quantity of GMO per event actually released (virusparticles or bacteria per ml)	Duration of the release(s) (from *(d/m/y) - until (d/m/y)*)
Groningen, 9713 GZ	Per injection 2 mg of the GMO. Multiple injections per patient. Total of 4 patients.	01-01-2009 – 31-12-2010 (end of multicenter trial on 12-08-2013)
(*) Vectors used.		

4. *Any kind of product that the notifier intends to notify at a later stage*

4.1. Does the notifier intend to notify the released transformation event(s) as product(s) for placing on the market under Community legislation(s) at a later stage?

☐ Yes ☒ No ☐ Unknown to date

If yes, indicate the country(ies) of notification:

If yes, specify for which use(s):

☐ Import
☐ Cultivation (e.g. seedfplanting material production)
☐ Food
☐ Feed
☐ Pharmaceutical use (or processing for pharmaceutical use)
☐ Processing for:
  ☐ Food use
  ☐ Feed use

☐ Industrial use
☐ Others (specify):.....

5. *Type(s) of deliberate release(s)*

Please select the main type(s) (in boxes) as well as subtype(s) of the release(s). In the case of multi-sites, multi-events and/or multiannual release(s), please provide a general overview of the type(s) of deliberate release(s) which has/have been carried out for the full duration of the consent. Please tick the appropriate type(s):

5.1. Deliberate release(s) for research purposes ☒

5.2. Deliberate release(s) for development purposes ☐

☐ Event screening
☐ Proof of concept ([1])
☐ Agronomie performances (e.g. efficiencyfselectivity of plant protection product, yield capacity, germination capacity, erop establishment, plant vigour, plant height, susceptibility to climatic factorsfdiseases, etc.) (specify)
☐ Altered agronomie properties (e.g. diseasefpestfdroughtffrost-resistance, etc.) (specify)
☐ Altered qualitative properties (prolonged shelf-life, enhanced nutritional value, modified composition, etc.) (specify)
☐ Stability of the expression
☐ Multiplication oflines
☐ Hybrid vigour study
☐ Molecular farming ([2])
☐ Phyto-remediation
☐ Others (describe):.....

5.3. Official testing ☐

☐ Variety registration on a national variety catalogue
  ☐ DUS (= Distinctness, Uniformity and Stability)
  ☐ VCU (= Value of Cultivation and Use)
☐ Others: (specify):.....

5.4. Herbicide authorization ☐

5.5. Deliberate release(s) for demonstration purposes ☐

5.6. Seeds multiplication ☐

5.7. Deliberate release(s) for *biosafety/risk* assessment research ☐

☐ Vertical gene transfer studies
  ☐ Out-crossing with conventional crops
  ☐ Out-crossing with wild relatives

([1]) For example, testing the new trait under environmental conditions .

([2]) *'Molecular farming'* means the production of substances (for instance, proteins, pharmaceuticals) by plants, which have been genetically modified for a particular trait. *'Molecular farming'* could be defined as well as the production of plant-synthesised pharmaceuticals, plant-made pharmaceuticals, plant-based proteins production, etc.

☐ Horizontal gene transfer studies (gene transfer to micro-organisms)
☐ Management of volunteers
☐ Potential changes in persistence or dispersal
☐ Potential invasiveness
☐ Potential effects on target organisms
☐ Potential effects on non-target organisms
☐ Observation of resistant relatives
☐ Observations of resistant insects
☐ Others: (describe) :.....

5.8. Other(s) type(s) of deliberate release(s): ☐
(describe).....

6. *Method(s), result(s) of the release, management and monitoring measure(s)* in *respect of any risk* to *human health* or *the environment*

6.1. Risk management measure(s)

Please report the risk-management measures, which have been used to avoid or minimize the spread of the GMO(s) outside the site(s) of release, and in particular those measures
- *which were not originally notified in the application,*
- *which were applied in addition to the conditions in the consent,*
- *which the consent required only under certain conditions,*
- *for which the consent allowed the notifier a choice among different measures.*

There were no risk-management measures provided by the competent authority.

6.1.1. *Emergencyplan(s)*

Indicate:
(a) if the release proceeded as planned:
☒ Yes
☐ No (describe for which reason, e.g. vandalism, climatic conditions, etc.): ..... .

(b) if measures according to the emergency plan(s) (Article 6(2)(a)(vi) and Annex III.B of Directive 2001/18/EC) had to be taken:
☒ No
☐ Yes (describe): ....

6.2. Post-release monitoring measures

Due to the fact that the current report format can be used for the final and post-release monitoring report(s), the notifier is asked to clearly make the difference between both types of report through this section 2 of Chapter 6.

Please indicate whether

☐ **the post-release monitoring plan will start** (in the case of a final report)

☐ **the post-release monitoring plan is ongoing** (in the case of an intermediary post-release monitoring report),

☐ **the post-release monitoring plan has been completed** (in the case of the final post-release monitoring report),

☒ **no post-release monitoring plan has to be fulfilled.**

6.3. Plan for observation(s)/method(s) involved

In this section the observation plan and the methods used to collect the effects, which have to be reported under the next section (section 6.4), need to be specified. Any amendments or modifications to the plan as proposed in the application and the Summary notification information format (SNIF) part B need to be specified in detail.

During the time between the notification and the final report submission, new scientific insights or methods may be developed which cause a change in the methods used. In particular these modifications need to be specified under this section.

Describe the used observation plan regarding the GMO release:

A post-injection clinical evaluation of trial subjects (vital signs and symptom-directed exam) was performed after each administration. Periodic evaluations were performed at scheduled visits throughout the duration of treatment.

6.4. Observed effect(s)

6.4.1. Explanatory note

All results of the deliberate release(s) in respect of any risk for human health or the environment shall be stated, without prejudice to whether the results indicate that any risk is increased, reduced or remains unchanged.

The main objectives of the information given in this section are:

- *to confirm or invalidate any assumption regarding the occurrence and impact of potential effect(s) of the GMO(s) which was/were identified in the environmental risk assessment,*
- *to identify effect(s) of the GMO(s) which was/were not anticipated in the environmental risk assessment.*

*The observed **effect(s)/interaction(s)** of the GMO(s)*

- *with respect to any risk to human health,*
- *with respect to any risk to the environment*

shall be reported under this section.

Particular attention shall be drawn to unexpected and unintended effect(s).

Indications as regards the effects, that the notifier may have to report, are provided hereunder. The effects have obviously to be considered in the light of the crop, the new trait, the receiving environment as well as the conclusions of the environmental risk assessment, which is carried out on a case-by-case basis.

In order to structure the information and to facilitate an efficient search within the given information, the notifier shall use, as far as possible, specific keywords to fill in the text fields under Chapter 6, especially sections 6.4.2, 6.4.3 and 6.4.4. A most updated list of those specific keywords is available on the Internet at http://gmoinfo.jrc.it

6.4.2. Expected effect(s)

This section concerns 'Expected effects', that is to say, potential effects which were already identified in the environmental risk assessment of the notification and could therefore be anticipated.

Notifiers should supply data from the deliberate release(s) which validate the assumptions made in the environmental risk assessment.

From the environmental risk assessment the competent authority of The Netherlands concluded that there were no expected effects which would be harmful for humans and environment.

6.4.3. Unexpected effect(s) ([3])

'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.*

No unexpected effects occurred.

6.4.4. Other information

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

inapplicable.

7. Conclusion

In this chapter, the notifier should specify the conclusions drawn and the measures taken or to be taken on the basis of the results of the release with regard to further release(s) and, where appropriate, make reference to any kind of product the notifier intends to notify at a later stage.

The information provided in this report is not considered confidential in accordance with Article 25 of Directive 2001/18/EC.
This does not prevent the competent authority from requiring additional information from the notifier, both confidential and non-confidential.
In the case of confidential data, it should be provided in an Annex to the report format, with a non-confidential summary or general description of these data, which will be made available to the public.

The 390-subject trial, in which the notifier participated, failed to demonstrate a statistically significant improvement vs. first-line chemotherapy. Therefore the trial was terminated on August 12, 2013.

([3]) Without prejudice to Article 8 of Directive 2001/18/EC as regards handling of modifications or new information.