PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a) Member State of notification: Germany
(b) Notification number: B/DE/09/PEI984
(c) Date of acknowledgement of notification: 10/11/2009
(d) Title of the project: A Phase 1/2, Proof-of-Principle, Multi-Center, Open-Label, Single-Arm, Non-randomized Clinical Study to Assess Safety and Efficacy of a Tumor Vaccine Consisting of Genetically Modified Allogeneic (Human) Tumor Cells for the Expression of IL-7, GM-CSF, CD80 and CD154, in Fixed Combination with a DNA-based Double Stem Loop Immunomodulator in Patients with Advanced Renal Cell Carcinoma (ASET Study)

(e) Proposed period of release: 2010/12/14 until approximately 2015/06/30 (two years after the inclusion of the final patient)

2. Notifier

Name of institution or company:

Mologen AG
Fabeckstr. 30
D-14195 Berlin
Germany

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid	(.)
RNA virus	(.)
DNA virus	(.)
bacterium	(.)
fungus	(.)
animal	
- mammals	(.)
- insect	(.)
- fish	(.)
- other animal	(.)

specify phylum, class …

Name of the GMO: MGN1601-W1 (genetically modified and irradiated human cells)

(b) Identity of the GMO (genus and species)

Human renal cell carcinoma cells are transduced with human genes coding for GM-CSF, IL-7, CD80 and CD154 by use of MIDGE vectors. Thereafter, the transduced cells are irradiated. The resulting GMO (MGN1601-W1) is used for the preparation of the cell-based vaccine MGN1601.

(c) Genetic stability – according to Annex IIIa, II, A(10)

Recipient renal cell carcinoma cells are transiently genetically modified, then irradiated and thereafter stored at < -140°C until use for the preparation of the cell-based vaccine. Irradiation leads to chromosomal damage which can not be repaired and therefore, induce apoptotic death of cells.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

Yes (.) No (x)

If yes, insert the country code(s) …

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?

Yes (.) No (x)

If yes:

- Member State of notification …
- Notification number B/../../…

Please use the following country codes:
Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

Yes (.) No (x)

If yes:

- Member State of notification …
- Notification number B/../../…

7. Summary of the potential environmental impact of the release of the GMOs.

GMO within MGN1601 consist of human renal cell carcinoma cells genetically modified with GM-CSF, IL-7, CD80 and CD154 by use of MIDGE vectors. In contrast to other vectors MIDGE vectors are unable to be multiplied by organisms. GMO within MGN1601 are unable to survive longer than a few days and are unable to multiply due to irradiation. MGN1601 is applied intradermally to patients within a clinical trial. Spread of GMO is therefore excluded.

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:

(select one only)

viroid (.)
RNA virus (.)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (.)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class) …

other, specify: a human renal cell carcinoma cell line was established from renal cell carcinoma tumor material.

2. Name

(i)	order and/or higher taxon (for animals)	Primates
(ii)	genus	Homo
(iii)	species	sapiens
(iv)	subspecies	…
(v)	strain	Caucasian, renal cell carcinoma
(vi)	pathovar (biotype, ecotype, race, etc.)	…
(vii)	common name	…

3. Geographical distribution of the organism: Not applicable

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes (.) No (.) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:
(i) Yes (.)

If yes, indicate the type of ecosystem in which it is found:

Atlantic ..
Mediteranean ..
Boreal ..
Alpine ..
Continental ..
Macaronesian ..

(ii) No (.)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?
Yes (.) No (.)

(d) Is it frequently kept in the country where the notification is made?
Yes (.) No (.)

4. Natural habitat of the organism: Not applicable

(a) If the organism is a microorganism

water (.)
soil, free-living (.)
soil in association with plant-root systems (.)
in association with plant leaf/stem systems (.)
other, specify …

(b) If the organism is an animal: natural habitat or usual agroecosystem:

5. (a) Detection techniques

(b) Identification techniques

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
Yes (x) No (.)
If yes, specify
Vaccine cells Biosafety level 1

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (x) Not known (.)

If yes:

(a) to which of the following organisms:

humans (.)
animals (.)
plants (.)
other (.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC
Not applicable

8. Information concerning reproduction
GMO within MGN1601 are unable to divide because they are irradiated.

(a) Generation time in natural ecosystems:

…

(b) Generation time in the ecosystem where the release will take place:

…

(c) Way of reproduction: Sexual .. Asexual ..

(c) Factors affecting reproduction:

…

9. Survivability

GMO within MGN1601 are irradiated and therefore, unable to survive longer than a few days due to severe chromosomal damage.
Additionally, GMO within MGN1601 will be destroyed by the immune system of the patient receiving the vaccine cells.

(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify …	

(b) relevant factors affecting survivability:

…

10. (a) Ways of dissemination

Not applicable

(b) Factors affecting dissemination

Not applicable

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)

…, B/../../…

C. Information relating to the genetic modification

1. Type of the genetic modification

(i)	insertion of genetic material	(x)
(ii)	deletion of genetic material	(.)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify …	

2. Intended outcome of the genetic modification
The inserted genes of GM-CSF, IL-7, CD80 and CD154 lead to expression of the corresponding proteins by the transduced cells resulting in the local enrichment of these proteins at the site of vaccination and in modulation of the patients' immune system.

3. (a) Has a vector been used in the process of modification?
Yes (x) No (.)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?
Yes (x) No (.)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid (.)
bacteriophage (.)
virus (.)
cosmid (.)
transposable element (.)
other, specify: MIDGE (Minimalistic Immunogenically Defined Gene Expression), a non-augmentable, linear vector produced biotechnologically from plasmids containing only the expression cassette and single stranded loops. The vector does neither contain an origin of replication nor sequences for selection markers (e.g. resistance to antibiotics).

(b) Identity of the vector
pMOK plasmids are used as starting material for the manufacture of MIDGE vectors. All lots of MIDGE vectors are controlled for identity by different methods during quality control.

(c) Host range of the vector
Not applicable

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype
Yes (.) No (x)

antibiotic resistance (.)
other, specify …

Indication of which antibiotic resistance gene is inserted
…

(e) Constituent fragments of the vector
CMV promoter, respective insert, poly adenylation site

(f) Method for introducing the vector into the recipient organism

(i)	transformation	(.)
(ii)	electroporation	(x)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify …	

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i)	transformation	(.)
(ii)	microinjection	(.)
(iii)	microencapsulation	(.)
(iv)	macroinjection	(.)
(v)	other, specify …	

6. Composition of the insert

(a) Composition of the insert
Human GM-CSF coding sequence or
Human Il-7 coding sequence or
Human CD80 coding sequence or
Human CD154 coding sequence

(b) Source of each constituent part of the insert
The respective coding sequences were amplified by PCR from a human cDNA library. The resulting DNA fragment was isolated and inserted into the plasmid pMOK by use of the multiple cloning site.

(c) Intended function of each constituent part of the insert in the GMO
GM-CSF: recruitment of APC (immunomodulation)
IL-7: growth factor for T cells (immunomodulation)
CD80: co-stimulating molecule (immunomodulation)
CD154: co-stimulating molecule (immunomodulation)

(d) Location of the insert in the host organism

-	on a free plasmid	(.)
-	integrated in the chromosome	(.)
-	other, specify: on a free MIGE vector	

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No (x)
If yes, specify …

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

viroid	(.)	
RNA virus	(.)	
DNA virus	(.)	
bacterium	(.)	
fungus	(.)	
animal		
- mammals	(x)	
- insect	(.)	
- fish	(.)	
- other animal	(.)	
(specify phylum, class)		…
other, specify	…	

2. Complete name

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	…
(iv)	species	…
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

Eukaryota; Vertebrata; Mammalia; Primates; Homo sapiens

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

Yes (.) No (x) Not known (.)

If yes, specify the following:

(b) to which of the following organisms:

humans	(.)
animals	(.)
plants	(.)
other	..

(c) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism

Yes (.) No (.) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):

…

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?

Yes (.) No (x)

If yes, specify …

5. Do the donor and recipient organism exchange genetic material naturally?

Yes (.) No (x) Not known (.)

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?

Yes (x) No (.) Not known (.)

Specify: Genetically modified and irradiated vaccine cells in MGN1601 will die within a few days. Additionally, vaccine cells will be eliminated by the immune system of the treated patient.

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?

Yes (x) No (.) Unknown (.)

Specify: genetically modified vaccine cells are unable to proliferate due to irradiation. As the used MIDGE vectors contain no origin of replication and are unable to multiply even within a host.

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?

Yes (x) No (.) Not known (.)

Specify: The GMO are no longer able to disseminate due to induction of apoptosis by irradiation and, therefore, limited life span.

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?

Yes (.) No (x) Not known (.)

Specify: recipient renal cell carcinoma cells are non pathogenic per se and still non-pathogenic after genetic modification.

2. Genetic stability of the genetically modified organism

Due to the irradiation (induction of chromosomal damage and, therefore, apoptosis) GMO within MGN1601 survive only a few days. Additionally, GMO given to patients show an improved immunogenicity and are destroyed by the immune system of the treated patients.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?

Yes (.) No (x) Unknown (.)

(a) to which of the following organisms?

humans (.)
animals (.)
plants (.)
other …

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)
…

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
GMO is applied intradermally to patients and thereafter degraded by the immune system of the patient. Transmission of GMO to other persons or organisms is not possible. Therefore, it is not intended to check the GMO in the environment.

(b) Techniques used to identify the GMO
Vector sequences can be identified by use of specific PCR. Additionally, serum samples of treated patients will be repeatedly withdrawn to check for vector sequences.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
Clinical trial: A Phase 1/2, Proof-of-Principle, Multi-Center, Open-Label, Single-Arm, Non-randomized Clinical Study to Assess Safety and Efficacy of a Tumor Vaccine Consisting of Genetically Modified Allogeneic (Human) Tumor Cells for the Expression of IL-7, GM-CSF, CD80 and CD154, in Fixed Combination with a DNA-based Double Stem Loop Immunomodulator in Patients with Advanced Renal Cell Carcinoma (ASET Study).
Potential benefit: clinical response to advanced renal cell carcinoma due to immunomodulation of the patient's immune system induced by the vaccine cells.

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?
Yes (.) No (x)
If yes, specify:

3. Information concerning the release and the surrounding area
Not applicable

(a) Geographical location (administrative region and where appropriate grid reference):
…

(b) Size of the site (m^2): … m^2
(i) actual release site (m^2): … m^2
(ii) wider release site (m^2): … m^2

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
…

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
…

4. Method and amount of release

(a) Quantities of GMOs to be released:
0.7 – 1.5 E7 vaccine cells (GMO) per dose. Maximum 312 doses during the phase 1/2 clinical trial.

(b) Duration of the operation:
2010/12/14 until approximately 2015/06/30 (two years after the inclusion of the final patient)

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
- The investigational product (including GMO) will be handled strictly in accordance with the description in the study protocol.
- The investigational product will be administered by the person in charge from the study site staff and only to subjects participating in the study.

5. Short description of average environmental conditions (weather, temperature, etc.)
Application of MGN1601 will be performed at room temperature to the patients.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.
No impact to human health (regarding the GMO in general) or to the environment is expected.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable)
(i) order and/or higher taxon (for animals) …
(ii) family name for plants …
(iii) genus …
(iv) species …
(v) subspecies …
(vi) strain …
(vii) cultivar/breeding line …
(viii) pathovar …
(ix) common name …

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

Renal cell carcinoma cells expressing GM-CSF, IL-7, CD80 and CD154 are expected to modulate the immune system of the patients, thereby enhancing the immune response against the tumor cells of the patient.

3. Any other potentially significant interactions with other organisms in the environment
No interactions with other organisms are possible or expected.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes (.) No (x) Not known (.)
Give details
…

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established
GMO cannot become established in foreign ecosystems because the GMO is unable to divide due to irradiation and unable to survive longer than a few days. Additionally, the vaccine cells are destroyed by the immune system of the patient.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO
Not applicable

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	…
(iv)	species	…
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:
Not expected

(b) from other organisms to the GMO:
Not expected

(c) likely consequences of gene transfer:
Not expected

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):
Not applicable.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
Not applicable

H. Information relating to monitoring

1. Methods for monitoring the GMOs
Serum samples of treated patients are repeatedly taken and checked for the presence of vectors by specific PCR.

2. Methods for monitoring ecosystem effects
Not applicable

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
Not applicable

4. Size of the monitoring area (m^2)
Not applicable … m^2

5. Duration of the monitoring
Up to 48 hours after the 8^{th} application.

6. Frequency of the monitoring
After first and 8^{th} application

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Not applicable.

2. Post-release treatment of the GMOs
Not applicable

3. (a) Type and amount of waste generated
Empty syringes (2 per dose).

3. (b) Treatment of waste
Used syringes and needles will be stored in dedicated containers at the study site in locked rooms with restricted access only for responsible persons. In reasonable time intervals and at the end of the study, used study medication has to be returned to MOLOGEN and destroyed by autoclaving.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
Not applicable

2. Methods for removal of the GMO(s) of the areas potentially affected

After accidental application of GMO in the surrounding (e.g. on the floor) the cell suspension will be soaked with alcohol soaked paper towel, and, thereafter, the area will be disinfect. Used paper towels will be sent to the sponsor (together with the empty syringes).

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread
   Not applicable

4. Plans for protecting human health and the environment in the event of an undesirable effect
   Not applicable