

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/16/PEI2572 |
| (c) | Date of acknowledgement of notification | 03/11/2015 |
| (d) | Title of the project | A single arm Phase I/II study of the safety and efficacy of gene-modified WT1 TCR therapy in patients with myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) with low blast counts failing to achieve an IWG defined response following azacitidine therapy. |
| (e) | Proposed period of release | From 30/04/2015 until 31/12/2017 |

2. Notifier

Name of institution or company: Cell Therapy Catapult

3. GMO characterisation

(a) Indicate whether the GMO is a:

- | | | |
|----------------|-----|---|
| viroid | (.) | |
| RNA virus | (.) | |
| DNA virus | (.) | |
| bacterium | (.) | |
| fungus | (.) | |
| animal | | |
| - mammals | (X) | Genetically modified autologous T lymphocytes |
| - insect | (.) | |
| - fish | (.) | |
| - other animal | (.) | |

specify phylum, class ...

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

Genus: Human

Species: Homo Sapiens

The GMO/IMP consists of patient-autologous T lymphocytes transduced ex-vivo with GMP grade modified MP71 replication defective retroviral vector containing the genes for the human Wilms Tumor antigen-1 (WT1) specific T Cell Receptor (TCR) (alpha and beta chains; pWT126-specific HLA-A*0201-restricted) for the treatment of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML). The genetically-modified Investigational Medicinal Product (IMP) is intended to recognize and lyse leukaemic cells as transgene expression in the transduced T cells results in expression of the introduced TCR at the cell surface, which efficiently re-directs the antigen-specificity of the T cell. As an additional safety feature the constant regions of the TCR alpha and beta chains have each been modified to contain an additional cysteine residue facilitating the formation of a second disulfide bond to maximise preferential pairing between the introduced TCR chains and minimise mispairing with the endogenous TCR chains. The final TCR alpha and TCR beta chain sequences were codon-optimised to enhance the efficiency of mRNA translation.

The cells will be used only for therapeutic purposes in the same patient from whom the cells were obtained (autologous application).

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

The long terminal repeat of the modified MP71 vector is derived from the Myeloproliferative Sacrcoma Virus (MPSV) and the leader sequence is derived from the Mouse Embryonic Stem Cell Virus (MESV). Ex-vivo transduction of retroviruses followed by transduced cell culture is associated with greatly reduced risks when compared with in-vivo gene therapies (Schenk et al 2007). The leader sequence was designed to increase vector safety in clinical applications. All ATG codons have been removed to decrease the risk of possible protein/peptide production and reduce the likelihood of homologous recombination with endogenous retroviral sequences. The original MP71 vector also contained a full length Woodchuck Hepatitis Response Element (WPRE), which has been removed as an additional safety measure,

Tests are performed by the manufacturer of the retroviral vector (EUFETS GmbH) to verify the identity and integrity of the vector and confirm the absence of replication competent retroviruses. The final Investigational Medicinal Product (i.e. autologous transduced T lymphocytes) is also tested in order to confirm the presence of the vector integration and expression of the WT1 TCR gene to demonstrate gene functionality prior to dosing.

Once a patient has been dosed, the IMP / patient is monitored in accordance with the protocol to record the persistence, function and phenotype of transduced infused cells.

In the unlikely event that the cells should be exposed to the environment e.g. accidentally released from their container, they would rapidly lose viability and therefore the genetic sequences would be lost and thus, genetic stability would no longer be a risk.

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

Yes (X) No ()

If yes, insert the country code(s) GB, FR, BE

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

This GMO /IMP is currently in use a Phase I/II trial currently ongoing in the UK. The trial has been approved by the competent authority, ethics committee and the Health and Safety Executive (HSE) where its use was classified as Contained Use, Category 1.

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.

The GMO consists of genetically-modified T lymphocytes that are transduced ex vivo in a GMP facility in the UK and then supplied to Germany for re-infusion into the patient via the intravenous route, therefore the risk of any impact on the environment is negligible.

In the unlikely event that the cells should be exposed to the environment e.g. accidentally released from their container, they would rapidly lose viability and therefore, the vector sequences would be lost. In addition, the MP71 vector is a replication incompetent retroviral vector, which needs no special precautions for disposal of contaminated clinical waste.

An excretion of live product or its progeny (“shedding”) by the patient is extremely unlikely (Schenk et al, 2007) possible. Vector sequences are highly unlikely to be mobilized as previously described.

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

1. Recipient or parental organism characterisation:

The parental organism is the Myeloproliferative Sacrcoma Virus (MPSV). However, only the long terminal repeat of the MPSV is present in the MP71 vector. The modified replication defective MP71 retroviral vector also contains the genes for the human Wilms Tumor antigen-1 (WT1) specific T Cell Receptor (TCR) (alpha and beta chains; pWT126-specific HLA-A*0201-restricted). The long terminal repeat of the MPSV is required for integration of the WT1 TCR alpha-2A-TCR beta-Cys-1 transgene into the host human T lymphocytes (recipient).

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

The parental organism is retroviral in origin. The retroviral content of the viral vector is the long terminal repeat of the Myeloproliferative Sarcoma Virus (MPSV).

(select one only)

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

other, specify ...

2. Name

- (i) order and/or higher taxon (for animals) Retroviridae
- (ii) genus
- (iii) species Myeloproliferative sarcoma virus
- (iv) subspecies
- (v) strain ...
- (vi) pathovar (biotype, ecotype, race, etc.) ...
- (vii) common name Retroviral vector

3. Geographical distribution of the organism

(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 ..
- Mediterranean ..
- Boreal ..
- Alpine ..
- Continental ..
- Macaronesian ..

(ii) No

(iii) Not known

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

The modified MP71 viral vector is manufactured in Germany by EUFETS GmbH, Vollmersbachstrasse 66, 55743 Idar-Oberstein, Germany. Manufacturing is performed to EU GMP requirements.

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

See 3c above.

4. Natural habitat of the organism

- (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:

Not applicable.

5. (a) Detection techniques

Both the parental organism (viral vector) and the GMO (gene modified T lymphocytes) are detected by using conventional polymerase chain reaction and flow cytometry techniques.

- (b) Identification techniques

As above.

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?

Yes (.) No (X)

If yes, specify

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
- ...

8. Information concerning reproduction

The MP71 vector is a replication incompetent retroviral vector. The GMO (transduced human T lymphocytes) will reproduce as they would without genetic modification.

- (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

Not applicable as it is impossible for gene modified T lymphocytes or the viral vector to survive in the environment.

- (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

Neither the genetically-modified T lymphocytes nor the retroviral vector are able to survive, disseminate in and/or displace other organisms. The retroviral vector is replication incompetent and has been used in a number of clinical trials without vector-related toxicity. It is not expected that co-replication or reversion to virulence could occur.

- (b) Factors affecting dissemination

...

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 pMP71 vector contains the genes for a human WT1-specific T cell receptor (TCR). Transgene expression in the transduced T lymphocytes results in expression of the introduced TCR at the cell surface, which efficiently re-directs the antigen-specificity of the T cell.

Pre-clinical studies (detailed in the IMPD) have demonstrated that the WT1 TCR-transduced T lymphocytes recognise the pWT126 peptide presented by HLA-A2 molecules on the surface of leukaemic cells resulting in cytokine production and lysis of leukaemic cells.

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 (X)
cosmid (.)
transposable element (.)
other, specify

- (c) Identity of the vector

Modified replication defective MP71 retroviral vector. Please note, the clinical use of the modified pMP71 vector (containing the genes for a human WT1-specific T cell receptor) has previously been notified in the UK via the Health and Safety Executive (HSE) for trial EUDRACT No. 2006-004950-25. The HSE Advisory Committee of Genetic Modification issued a hazard rating of Class 1 for the vector (of no or negligible risk).

- ...
 (d) Host range of the vector

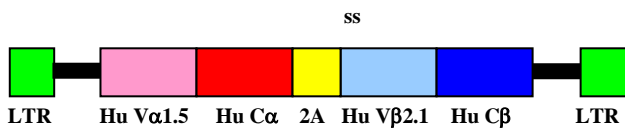
Patient's own T lymphocytes.

- (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



LTR: Long Terminal Repeat (Myeloproliferative sarcoma virus promoter)
HuVα1.5: Codon-optimised alpha chain variable region of human pWT126-specific TCR
HuCα: Codon-optimised alpha chain constant region of human pWT126-specific TCR
HuVβ2.1: Codon-optimised beta chain variable region of human pWT126-specific TCR
HuCβ: Codon-optimised beta chain constant region of human pWT126-specific TCR
2A: Self-cleaving 2A sequence derived from porcine teschovirus
ss: Additional disulphide bond

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

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

Ex vivo transduction of autologous T lymphocytes.

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

Ex vivo transduction of autologous T lymphocytes.

6. Composition of the insert

- (a) Composition of the insert

Alpha and beta chains of the human pWT126-specific HLA-A*0201-restricted T cell receptor.

As an additional safety feature the constant regions of the TCR alpha and beta chains have each been modified to contain an additional cysteine residue facilitating the formation of a second disulfide bond to maximise preferential pairing between the introduced TCR chains and minimise mispairing with the endogenous TCR chains.

- (b) Source of each constituent part of the insert

Human gene sequence

- (c) Intended function of each constituent part of the insert in the GMO

Expression of pWT126-specific HLA-A*0201-restricted T cell receptor.

- (d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (X)
- other, specify ...

- (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

Human

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 ...

Homo sapien

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 ..

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

Yes (.) No (X) 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)

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

The only phenotypic modification is the expression of the transgene by the gene modified T lymphocytes.

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

Yes (.) No (X) Not known (.)
Specify ...

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

Yes (.) No (X) Unknown (.)
Specify ...

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

Yes (.) No (X) Not known (.)
Specify ...

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

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

2. Genetic stability of the genetically modified organism

The insert is stably integrated into the genome of the cell, and does not have the capacity for mobilization. The MP71 retroviral vector is stable and does not have capacity for replication.

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 ...

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

Genetically modified T lymphocytes can only survive ex-vivo under special cell culture conditions in a CO₂ incubator at 37°C. Outside of the incubator the GMOs are not viable. Thus the environmental risk conferred by inappropriate disposal of waste or unused product or the accidental dissemination during product handling is considered to be negligible. Also an excretion of live product or its progeny (“shedding”) by the patient will not occur as the transduction of T cells occurs ex vivo within the GMP facility and no free viral particles remain in the T cell inoculum given to patients. Schenk et al (2007) published data from over 100 patients who received ex-vivo transduced retroviral gene modified therapies. No replication competent retrovirus was observed in the blood of any of these patients.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment

The final GMO is not released to the environment, and is not stable under uncontrolled environmental conditions. It is infused into the patient from whom the autologous cells were originally obtained. It is therefore not detectable in the environment.

(b) Techniques used to identify the GMO

N.A – see above

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

The final GMO is not released in the environment, the final GMO is infused to a patient enrolled in a phase I/II clinical trial with the aim of recognizing and lysing leukemic cells. The retroviral MP71 vector is used to transduce the patient’s own T lymphocytes.

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)

The final GMO is not released in the environment; it is released under highly controlled conditions, in a limited number of patients (approximately 10 patients in total). The final GMO is not viable outside the body of the specific recipient. It would be destroyed in any other recipient.

3. Information concerning the release and the surrounding area

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

The final GMO is not released in the environment but transduced cells are infused to a patient in a restricted, controlled area (clinical site). Planned participating sites are located in Dresden, Muenster, Kiel, Dusseldorf and Munich.

- (b) Size of the site (m²): ... m²
(i) actual release site (m²): ... m²
(ii) wider release site (m²): ... m²

Not applicable.

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

Not applicable.

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

Not applicable.

4. Method and amount of release

- (a) Quantities of GMOs to be released:

Trial subjects will receive an *i.v.* infusion of bulk WT1 TCR-transduced T cells ($\leq 2 \times 10^7$ /kg or up to $\leq 1 \times 10^8$ /kg if recommended by the DSMB based on emerging data). Subjects may receive a second dose of cells 4 months after their first dose if they do not achieve the defined target clinical response after the first infusion.

- (b) Duration of the operation:
Trial conduct is scheduled to start in Germany in Q1 2015 and conclude in 2017

- (c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release

Due to the nature of the GMO as autologous genetically modified T cells infused into trial subjects, the risk of any spread of GMO or hazard to the environment is considered negligible.

5. Short description of average environmental conditions (weather, temperature, etc.)

Not applicable.

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.

Not applicable.

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)	Primates
(ii)	family name for plants	Hominidae
(iii)	genus	Homo
(iv)	species	Homo sapiens
(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)

Cells obtained from human patients will be genetically modified and reintroduced into the same patient. The purpose of this is to provide a therapeutic advantage to patients suffering from AML / MDS. The GMO will target and lyse cancerous cells.

3. Any other potentially significant interactions with other organisms in the environment

None.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?

Yes (.) No (X) Not known (.)
Give details

The GMO consists of genetically modified T lymphocytes. No increased competitiveness or increased invasiveness is expected from the vector, the genetic modification or the insert contained in the vector.

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established

None

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

Not applicable.

(a) from the GMO to other organisms in the release ecosystem:

...

(b) from other organisms to the GMO:

...

(d) likely consequences of gene transfer:

...

8. Give references to relevant results (if available) from studies of the behavior and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):

None – 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

The GMO will be infused into patients suffering from AML / MDS. No other application is intended. Thus the monitoring of the GMO will occur in the patients at regular intervals post-infusion as defined in the treatment protocol. The GMO will be measured / detected by using conventional characterization techniques such as polymerase chain reaction and flow cytometry.

2. Methods for monitoring ecosystem effects

Not applicable. The GMO will not be released into the environment and could not survive outside of the intended autologous donor, where it will be monitored as described above.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms

Not applicable. The gene modified cells are incapable of donating their genetic material to other organisms as the vector is replication incompetent and the cells would not survive outside of the host.

4. Size of the monitoring area (m²)

Not applicable

5. Duration of the monitoring

Not applicable.

6. Frequency of the monitoring

Not applicable.

I. Information on post-release and waste treatment

1. Post-release treatment of the site

The site/place of the GMO administration will be cleaned according to standards cleaning methods for handling of biological hazard materials

2. Post-release treatment of the GMOs

All IMP waste, as well as any material that came into contact with the IMP will be destroyed according to the hospital facility bio-hazard disposal procedures.

3. (a) Type and amount of waste generated

Needles, syringes, cotton balls, disposable plasticware, gloves, and disposable garments. Sharps (needles etc.) will be stored in different specific containers appropriately labelled.

The estimated total amount of waste is expected to be minimal (less than 1000 ml).

3. (b) Treatment of waste

Waste will be collected and disposed of (by incineration) in line with site specific procedures.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

Patients will be dosed within a suitable and confined area within the clinical site. Thus, any accidental spread will be limited to this space or the personnel involved in the production or administration of the GMO. The GMO cannot survive outside the body of the patient therefore limiting the risk of dissemination. Accidental stick injury with a needle contaminated with the GMO will not lead to a spread of the GMO as the immune system of the affected person will destroy the GMO as soon as this comes in contact with human serum (donor and product must be same patient).

All of the people involved in the trial will be trained about the procedures and measures to be taken in case of accidental release.

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

The site will be cleaned and sterilized in line with site-specific procedures.

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. The GMO cannot survive outside of the body of the intended recipient and thus presents no additional risks.

References (supplied in CTA)

Schenk-Braat E.A.M. et al (2007). An inventory of shedding data from clinical gene therapy trials. *The Journal of Gene Medicine*. **9**: 910-921.