

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**

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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/17/PEI3136 |
| (c) Date of acknowledgement of notification | 11/07/2017 |
| (d) Title of the project | A Phase I/II, Open-Label, Non-Randomized, Multicentre, Dose Escalation Clinical Trial with Control Group to Evaluate the Safety, Feasibility and Preliminary Efficacy of PRAME TCR modified T cells, MDG1011, in Subjects with High Risk Myeloid and Lymphoid Neoplasms |
| (e) Proposed period of release | From December/14/2017 until 2022 |

2. Notifier

Name of institution or company:

Medigene AG
Lochhamer Straße 11
D-82152 Planegg/Martinsried
Germany

3. GMO characterization

(a) Indicate whether the GMO is a:

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

specify phylum, class: Chordata, Mammalia

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

The GMO is used as Investigational Medicinal Product (IMP) and consists of patient-autologous human CD8⁺ T cells transduced ex vivo with a γ -retroviral self-inactivating (SIN) vector containing the cDNA of the HLA-A*02:01 restricted PRAME-specific T cell receptor (TCR).

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

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.

The release of the transduced autologous T cells is limited to single patient administration in a hospital setting. An environmental impact is not expected, as the GMO is not viable outside the patient or outside very specific, controlled culture conditions. According to the environmental risk assessment the GMO (investigational medicinal product) will not reach the environment at large.

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

The GMO is derived from peripheral blood lymphocytes of humans. The recipient organism is the patient from which the CD8⁺ T cells were derived (autologous setting). The CD8⁺ T cells are transduced ex vivo with the γ -retroviral vector encoding for a PRAME specific TCR. The transduced, autologous CD8⁺ T cells constitute the final GMO to be administered by intravenous infusion into the specific patient.

1. Recipient ~~or parental~~ organism characterization:

The recipient organisms are autologous CD8⁺ T cells transduced ex-vivo with the γ -retroviral vector encoding for a PRAME specific TCR.

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

(select one only)

viroid (.)

RNA virus (.)

DNA virus (.)

bacterium (.)

fungus (.)

animal

- mammals (X)

- insect (.)

- fish (.)

- other animal (.)

(specify phylum, class) Chordata, Mammalia

other, specify ...

2. Name

- | | | |
|-------|---|--------------|
| (i) | order and/or higher taxon (for animals) | - |
| (ii) | genus | homo |
| (iii) | species | homo sapiens |
| (iv) | subspecies | - |
| (v) | strain | - |
| (vi) | pathovar (biotype, ecotype, race, etc.) | - |
| (vii) | common name | human |

3. Geographical distribution of the organism

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

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

(i) Yes (X),

following questions are not applicable to human

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

Atlantic	..
Mediterranean	..
Boreal	..
Alpine	..
Continental	..
Macaronesia	..

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

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

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

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:
Human

5. Detection and identification techniques

(a) Detection techniques
Common techniques of blood cell analysis

(b) Identification techniques
Common techniques of blood cell analysis

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

The recipient's autologous T cells from which the GMO is derived are patient-specific and are not viable outside the patient from which the cells were derived. Autologous blood leukapheresis source material is controlled for viral adventitious agents as per country specific guidance's.

However, patient autologous T cells material will be handled in the intended phase I/II trial as potentially containing infectious agents as it cannot completely be excluded that a potential for such agents may be present.

Instruction for transport, handling and disposal are defined for the clinical trial material including instructions in case of accidental release of the IMP. Nevertheless, the environmental conditions outside the host are substantially different and not appropriate for survival of the GMO.

8. Information concerning reproduction

Not applicable for human T cells

- (a) Generation time in natural ecosystems:

Retroviral transduced human T cells do not generate in natural ecosystem

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

The genetically modified T cells will not be released in an ecosystem, outside of the patient.

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

Not applicable

- (c) Factors affecting reproduction:

In laboratory conditions: antigen-stimulus, growth medium/factors, temperature, pH

In respective patient: antigen stimulus, growth factors

The environmental conditions (temperature, pH, UV, and biophysical and biochemical conditions) outside the human host are substantially different and not appropriate for its reproduction.

9. Survivability

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

Not applicable, it is impossible for TCR gene modified T cells or viral SIN vectors to survive in the environment.

- | | | |
|--------|------------------------|-----|
| (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:

The recipients' autologous T cells are patient-specific and are not viable outside the host. Proper culture conditions (media, pH, temperature) in the presence of antigen and/or growth factors are required for the survival. The environmental conditions outside the host are substantially different and not appropriate for its survival (temperature, pH, UV, and a change in the biophysical and biochemical conditions). The cells can be inactivated e.g. by heat or formaldehyde.

10. (a) Ways of dissemination

Transmission of modified T cells can only happen by accidental injection. No dissemination in the environment is possible due to fast inactivation. The retroviral vector is replication incompetent; it is not expected that co-replication or reversion to virulence could occur.

The genetically-modified CD8⁺ T cells are not able to survive, disseminate in and/or displace other organisms.

(b) Factors affecting dissemination

The modified T cells can only amplify in the donor. The human immune system protects from dissemination of foreign T cells by allo-response and elimination of the respective T cells.

The factor that could lead to the dissemination of retroviruses is the emergence of replication competent retroviruses (RCR). This risk has been minimized with modifications made to the vector and the manufacturing process. The absence of RCR is nevertheless assessed at the end of the manufacturing process of the Vector.

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/././...

None

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

Grafting PRAME specificity onto patient's T cells for adoptive T-cell therapy of cancer. PRAME-specific TCR-transduced T cells are provided as a personalized T-cell immunotherapy to patients with multiple myeloma (MM), acute myeloid leukemia or myelodysplastic syndrome, whose tumors express the PRAME antigen.

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 ...

(b) Identity of the vector

Replication-deficient MMLV-based γ -retroviral vector: (gamma-RV) MP71

(c) Host range of the vector

The vector is MMLV-based and pseudotyped by GALV-env and can thereby transduce dividing human and animal cells, e.g. patient autologous T cells stimulated with CD3/28.

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes (X) No (.)

- antibiotic resistance (.)
- other, specify

- Selection of PRAME TCR (transgene) positive T cells by Vβ1 specific flow cytometry
- PRE element, detectable by polymerase chain reaction

Indication of which antibiotic resistance gene is inserted
None

(e) Constituent fragments of the vector

The transgene is under the control of the short promoter for elongation factor-1α (EF1α) (EFS promoter). In addition, 5′ and U3 deleted 3′ LTRs from the moloney murine leukaemia virus (MMLV), a packaging signal (psi+) and a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) are part of the sequence.



STRUCTURE	INTENDED PURPOSE
5′-LTR	5′-LTR
Δ3′-LTR	3′-LTR with a deleted U3 region
PSI+	Packaging signal
EFS	Short version of the elongation factor-1α (EF1α) promoter
TCRα & TCRβ	Therapeutic genes encoding for the TCR T4.8-1-29 α- and β- chain
P2A	Porcine teschovirus-1 2A self-cleaving peptide
WPRE	Woodchuck hepatitis virus posttranscriptional regulatory element

(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 into CD8+ autologous T cells |

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

TCRα and TCRβ chain genes are combined by the porcine teschovirus-1 2A self-cleaving peptide (P2A). The introduced TCR is minimally murinized to reduce the chance of mispairing events with endogenous human TCR chains.

(b) Source of each constituent part of the insert
Human and murine

(c) Intended function of each constituent part of the insert in the GMO
see section 4 (e) above

(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:

2. Complete name

(i) order and/or higher taxon (for animals) ...
(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 human

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**)

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 (.) No (X) Not known (.)

Specify: The GMO consists of genetically modified CD8⁺ T cells. No influence on cell survival is expected from the vector or the insert contained in the vector. The only phenotypic modification is the expression of the specific transgene by the modified T cells.

- (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: The GMO consists of genetically modified CD8⁺ T cells. No influence on reproduction is expected from the vector or the insert contained in the vector.

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

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

Specify: The GMO consists of genetically modified CD8⁺ T cells. No influence on dissemination is expected from the vector or the insert contained in the vector.

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

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

Specify: The GMO consists of genetically modified CD8⁺ T cells. The genetic modification of hematopoietic stem cells with this vector will not result in any changes in the pathogenicity of the genetically modified cells for the environment.

2. Genetic stability of the genetically modified organism

The PRAME TCR is introduced in the T cells by retroviral gene transfer. After chromosomal integration the gene modified autologous T cells are genetically stable and the vector is an integral part of the host DNA.

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)

The replication-deficient retroviral vector genome is integrated in the T-cell genome. No new viral particles can be generated in the final host T cells since the gag, pol and env genes and all accessory elements are absent from this viral vector. The transgene inserted in the retroviral vector does code for a human TCR, no pathogenic factors, cytokine-coding sequences, oncogenes, antibiotic resistance genes or otherwise hazardous inserts are present in the integrated vector.

Furthermore, genetically modified CD8⁺ T cells 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 is unlikely for several reasons: (a) the vector has a SIN configuration limiting the possibility for replication (b) CD8⁺ T cells are transduced ex vivo with infectious particles and (b) the cultured cells are extensively washed before reinfusion into the patient therefore limiting passive administration of infectious particles.

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 un-controlled environmental conditions.

- (b) Techniques used to identify the GMO

Identity is ensured by detection of PRAME TCR (transgene) positive T cells by Vβ1 specific flow cytometry and detection of PRE element by polymerase chain reaction. The sequence of the integrated vector between 5'LTR and 3'LTR is identical to the sequence as was specified by the transgene plasmid.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
Gene Therapy Medicinal Product.
The GMO (genetically modified CD8⁺ T cells) is an Investigational Medicinal Product (IMP) intended to be infused under an autologous setting to patients enrolled in a phase I/II clinical trial.
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: The final GMO is not released in the environment; it is released under highly controlled conditions, in a limited number of patients at defined authorized clinical study sites (Hospitals).
3. Information concerning the release and the surrounding area
 - (a) Geographical location (administrative region and where appropriate grid reference):
The IMP (PRAME-specific TCR-transduced T cells) will be manufactured by authorized GMP manufacturer in Germany and released by a qualified person (QP):
The final drug product is not released into the environment, but infused into a patient in a hospital setting. The clinical phase/I/II trial will be conducted in Germany.
 - (b) Size of the site (m²):

	typical hospital surrounding
(i) actual release site (m ²):	~ 20 m ²
(ii) wider release site (m ²):	... m ²
 - (c) Proximity to internationally recognized biotopes or protected areas (including drinking water reservoirs), which could be affected:
No environment beyond the site of the release the (clinical trial site(s)) should be affected by the release. Personal protective equipment will be used to avoid exposure to PRAME TCR T cells of the medical personnel involved in the administration of the product.
 - (d) 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:
32 patients will receive a single infusion of the Investigational Medicinal Product in a volume of 100 ml intravenously. The maximum target dose a patient might receive is 1 x 10⁷ T cells carrying the crafted TCR per kg body weight.
 - (b) Duration of the operation:
The final GMO (Investigational medicinal product) administration will last up to 30 minutes per patient.

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

Instruction for safe transport, handling and disposal of GMO containing material are defined for the clinical trial in a separate document, including measures to be in place in case of accidental releases, personal protective equipment, first aid and decontamination. Study Personnel will be trained accordingly.

The final GMO and γ -retroviral vector are not released in the environment. The final GMO is administered intravenously into the patient under standard controlled conditions for hematopoietic stem cell transplant at the clinical site. All waste is destroyed according to hospital bio-hazard disposal procedures. The GMO will be manufactured at one manufacturing site in Germany and transported to the study sites (hospitals) also located in Germany by a dedicated carrier in a sealed S1 container. The actual release will occur within a closed area with restricted personnel access. The staff involved in the release of the GMO has wide experience in stem cell transplantation and will follow Good Clinical Practice rules as in any stem cell transplantation routine. The GMO is only intended for clinical use and will be administered immediately after preparation by experienced personnel. Personnel responsible for the administration of the GMO will wear disposable gloves and masks. Standard rules for spraying, wiping, gowning up and entry of personnel/goods into the room are followed. Remaining waste will be transported in sealed containers labeled with appropriate stickers to be inactivated via autoclaving.

5. Short description of average environmental conditions (weather, temperature, etc.)
Hospital rooms have to fulfill hygiene conditions required for the treatment of immune-compromised 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 data from previous releases is available for this particular GMO.

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	human

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

The GMO, PRAME-specific TCR-transduced T cells are provided as a personalized T-cell immunotherapy to patients with multiple myeloma (MM), acute myeloid leukemia or myelodysplastic syndromes whose tumors express the PRAME antigen. For this approach patient T cells are isolated from blood samples and activated. Anti-tumor TCR is introduced using a retroviral vector. Modified T cells are expanded and re-infused into the patient. The adoptive transfer of T cells enables T-cell-based cytokine secretion and cytotoxic responses to be utilized to attack cancer cells namely multiple myeloma, acute myeloid leukemia or myelodysplastic syndrome cells. Anticipated result of interaction is positive influence on clinical parameters of disease activity, namely reduction and potentially elimination of the tumor.

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

None 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: The GMO consists of genetically modified CD8+ T cells. 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.

The only organism in which the GMO will be disseminated is the dedicated patient (T-cell donor) who receive autologous PRAME TCR T-cell product. Exposure requires direct injection of PRAME TCR T cells. Immune-suppressed individuals other than the patients will not participate in the administration of PRAME TCR T cells. Humans with a functional immune-system that accidentally got injected with PRAME TCR T cells would eliminate PRAME TCR T cells by an allo-response. Simple contact exposure to blood from treated patients will not result in transmission of PRAME TCR T cells as PRAME TCR T cells are quickly inactivated under environmental conditions.

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, administration will be done in hospital.

- | | | |
|--------|---|-----|
| (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:
None

(b) from other organisms to the GMO:
None

(c) likely consequences of gene transfer:
None

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.):
Not applicable

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
None

H. Information relating to monitoring

1. Methods for monitoring the GMOs
Monitoring of patients will include molecular analysis of minimal residual disease, patho-morphologic analysis of residual PRAME positive tumor cells, multi-parameter flow-cytometric immunological cell monitoring, q-PCR for detection of transfused T cells (pharmacokinetic analyses), sample storage for cytokine analysis and RCR-testing (retention samples). The GMO PRAME TCR (transgene) positive T cells will be detected by V β 1 specific flow cytometry, genomic integration will be followed by detection of PRE element using polymerase chain reaction. Patients will continue to be followed at regular intervals post- PRAME TCR T-cell infusion per health authority guidance as defined in the treatment protocol.
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 (m²)
Less than 30m² (hospital room). Only applicable during infusion of the GMO to the patient.
5. Duration of the monitoring
See Section H1
6. Frequency of the monitoring
See Section H1

I. Information on post-release and waste treatment

1. Post-release treatment of the site

Instruction for transport, handling and disposal are defined for the clinical trial material in a separate document. People involved in the clinical trial will be trained about the procedures and measures to be taken in case of unexpected spread/accidental release, accordingly. Additionally, 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 inactivated or destroyed according to the hospital facility bio-hazard disposal procedures. The waste is to be inactivated by autoclaving or utilization of a disinfectant prior to incineration.

3. Waste

(a) Type and amount of waste generated

Type and amount of waste is similar to what is expected during a blood transfusion. Waste mainly consists of the GMO container (cryo-storage container), infusion line, infusion catheter, dry adhesives, gloves, and disposable garments.

The estimated total amount of waste is expected to be minimal.

(b) Treatment of waste

Waste will be disposed off by trained staff in biohazard containers and will be inactivated by autoclaving or utilization of a disinfectant prior to incineration.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
Risk of dissemination after unexpected spread is regarded as very low, as the GMO is not able to survive outside of the human body and does not release replication competent viruses. Application of the GMO to patients will be done in suitable and confined areas within the respective clinical site. Accidental injury with GMO contaminated needles will induce an allo-response in the affected person with elimination of the GMO, which prevents further spread of the GMO. Emergency response is defined in the clinical protocol and is under the responsibility of Investigator and Sponsor responsible for the trial.
Instruction for transport, handling and disposal are defined for the clinical trial material in a separate document. People involved in the clinical trial will be trained about the procedures and measures to be taken in case of unexpected spread/accidental release, accordingly.
2. Methods for removal of the GMO(s) of the areas potentially affected
Decontamination procedures according standard for hospital clean rooms are regarded safe methods.
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
Target organism (human patient)
Patients treated with the GMO in the authorized clinical trial setting will be monitored regularly and followed up in line with the EMA “Guideline on follow up of patients administered with gene therapy medicinal products”. Emergency response is defined in the clinical protocol and is under the responsibility of Investigator and Sponsor responsible for the trial.
Staff
Staff handling the IMP have to follow handling instructions and protecting measurements laid down in the written instructions for the Clinical Trial and to follow hospital standards (e.g. need to wear specific clothing, gloves or surgical mask, follow standard disinfection procedures by personnel/goods into the rooms)

Due to the administration modalities the risk of accidental release is considered negligible.