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

A. General information

1. Details of notification

(a) Norway

(b) Notification number

(c) Date of acknowledgement of notification

(d) Title of the project *A Phase 3 Randomized Study Comparing Bortezomib, Lenalidomide and Dexamethasone (VRd) followed by Ciltacabtagene Autoleucel, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA versus Bortezomib, Lenalidomide, and Dexamethasone (VRd) followed by Lenalidomide and Dexamethasone (Rd) Therapy in Participants with Newly Diagnosed Multiple Myeloma for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy*

(e) Proposed period of release: *30/09/2021 – 30/09/2036*

2. Notifier : Katarzyna Zdziarska

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3. GMO characterisation

(a) Indicate whether the GMO is a:

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

- other animal (.)

specify phylum, class Human T Cells

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

The GMO, refered to as JNJ-68284528 consists of autologous T cells genetically modified to express a synthetic chimeric antigen receptor (CAR). The CAR recognises the cell surface marker B cell maturation antigen (BCMA).

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

The parental human T cells are inherently genetically stable.

The CAR receptor is introduced in the T cells via lentiviral gene transfer. The inserted genetic material is stably integrated and is not capable of replication. After integration of the LCAR2SIN_KAN transgene into the host genome, the gene remains in the genome and is passed on to progeny of the cells when they divide.

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) *AT, BE, DK, FI, FR, DE, GR, IT, NL, NO, PT, SE*

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

Yes (X) No (.)

If yes:

- Member State of notification NL, ES, DE

- Notification number

ES: B/ES/19/16, B/ES/19/25, B/ES/18/32
NL: B/NL/19/002, B/NL/19/011, B/NL/19/012, B/NL/19/014
DE B/DE/20/PEI3934

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 (X) No (.)

If yes:

USA, Canada

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

JNJ-68284528, consists of autologous T cells genetically modified using the self-inactivating LCAR2SIN_KAN lentiviral vector to express a synthetic CAR. The CAR-T cells are designed to treat subjects with relapsed or refractory multiple myeloma. The target antigen of the receptor is B cell maturation antigen (BCMA) which is specifically expressed on malignant plasma cells.

This GMO consists of *ex vivo* transduced, autologous T cells that are prepared in a facility that meets the Good Manufacturing Practice (GMP) principles.

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 has limited viability outside the patient. According to the environmental risk assessment the GMO will not reach the environment at large. Furthermore, shedding via urine or faeces of subjects into the environment is not anticipated[1], therefore no plant or animal species are likely to be exposed.

T- cells are highly labile and do not survive on environmental surfaces. The sponsor is responsible for the healthcare management/biosafety procedures and staff are trained in managing patients and safe handling of GMOs, ultimately reducing the risk of biohazardous exposure. Personal protective equipment will be used to avoid exposure to JNJ-68284528 of the medical personnel involved in the administration of the product.The sites are responsible for the execution of the procedures provided by the sponsor. Overall, the risk of the modified CAR and/or LCAR2SIN_KAN lentiviral vector (replication incompetent), designed as a personalised investigational medicine, in combination with the control measures pose extremely low risks to other surrounding humans and the environment. Therefore, the environmental risk potential is considered negligible.

[1]*Reuter JD, Fang X, Ly CS, Suter KK, Gibbs D. Assessment of Hazard Risk Associated with the Intravenous Use of Viral Vectors in Rodents. Comparative Medicine. 2012;62(5):361-370.*

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:

viroid (.)

RNA virus (.)

DNA virus (.)

bacterium (.)

fungus (.)

animal

- mammals (X)
- insect (.)
- fish (.)
- other animal (.)

(specify phylum, class) Human

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 points not applicable for human cells) No (.)

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

Atlantic

Mediteranean

Boreal

Alpine

Continental

Macaronesian

(c) Is it frequently used in the country where the notification is made?

Yes (.) No () not applicable to human cells

(d) Is it frequently kept in the country where the notification is made?

Yes (.) No () not applicable to human cells

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. (a) Detection techniques

QC testing procedures are in place to confirm the characteristics of the patient apheresis material.

Flow cytometry and qPCR analyses of patient blood samples and CAR-T drug product will also be used to measure genetically modified T cells.

(b) Identification techniques

QC testing procedures are in place to confirm the characteristics of the patient apheresis material.

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

Yes (.) No (X)

The recipient organism is *Homo sapiens*.

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

Autologous blood apheresis source material is controlled for infectious diseases as applicable per local regulations. Patients will at least be tested for evidence of serious active viral, bacterial or uncontrolled systemic fungal infection per clinical trial protocol.

The T cells cannot survive outside of the patient from which the cells were derived. The cells do not persist or replicate in the environment.

8. Information concerning reproduction – Not applicable for human T-cells

(a) Generation time in natural ecosystems:

Not Applicable

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

Not applicable

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

Not applicable

(d) Factors affecting reproduction:

Not applicable

9. Survivability

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

Not applicable for human T-cells

(i) endospores (.)

(ii) cysts (.)

(iii) sclerotia (.)

(iv) asexual spores (fungi) (.)

(v) sexual spores (funghi) (.)

(vi) eggs (.)

(vii) pupae (.)

(viii) larvae (.)

(ix) other, specify *N/A*

(b) relevant factors affecting survivability:

The survival of human blood cells requires a complex combination of special media, temperature and CO_2. 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).

10. (a) Ways of dissemination

Human T cells can only be transmitted between individuals through injection. No dissemination in the environment is expected due to fast inactivation and lack of a natural entry route into the body.

(b) Factors affecting dissemination

The immune system of people other than the donor will eliminate the blood cells.

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)

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

Autologous T cells are genetically modified to express CARs to target malignant cells that express BCMA. This genetic modification induces CAR-T cell activation and killing of BCMA-positive 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 …

(b) Identity of the vector

A lentiviral self inactivating (SIN) VSV-G pseudotyped vector is used for the genetic modification. Although the lentiviral plasmids are designed based on the HIV-1 virus, the lentiviral vector is prepared by transient transfection of HEK-293 cells and are replication incompetent.

(c) Host range of the vector

VSV-G pseudotyped and thus able to transduce many different non-dividing human and animal cells.

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

Yes (X) No (.)

antibiotic resistance (No)

other, specify: CAR-T cells are identified by flow cytometry for CAR protein expression, and by qPCR to detect CAR transgene.

(e) Constituent fragments of the vector

The lentiviral vector is prepared by transient transfection of HEK-293 cells with a SIN vector plasmid and plasmids carrying the Env, Gag/Pol and Rev genes.

The LCAR2SIN_KAN lentiviral vector encodes a CAR consisting of the human CD8α signal peptide (SP), BCMA targeting domains, CD8α hinge and transmembrane (TM) domains, human CD137 cytoplasmic domain and human CD3ζ cytoplasmic domain. The expression of LCAR2SIN_KAN is driven/controlled by a human hEF1α promoter.

(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 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

See below in 6(c)

(b) Source of each constituent part of the insert

See below in 6(c)

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

The LCAR2SIN_KAN lentiviral vector is an HIV-1-based, lentiviral expression vector driven by a RSV promoter. The transgene is driven by a human EF1- α promoter. The vector contains all of the viral processing elements necessary for the production of replication-incompetent lentivirus, as well as elements to improve viral titer, transgene expression, and overall vector function.

The CAR was composed of the codon optimized human CD8α signal peptide (CD8α SP), the codon optimized BCMA binding domain (composed of 2 different VHH

(single domain antibodies), the human CD8α hinge, the human CD8α transmembrane domain, the CD137 (or 4-1BB) cytoplasmic domain, and CD3ζ cytoplasmic domain. The following table provides the composition of the insert, and its function.

CAR element	**Function**
CD8α SP	Signal peptide
BCMA targeting Domain	Therapeutic gene
CD8α Hinge	Ensure correct T cell receptor conformation
CD8α Transmembrane domain	
CD137 Cytoplasmic domain	Ensure correct T cell receptor function
CD3ζ Cytoplasmic domain	

(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 (X)

DNA virus (.)

bacterium (.)

fungus (.)

animal

- mammals (.)

- insect (.)
- fish (.)
- other animal (.)

(specify phylum, class) …

other, specify:

2. Complete name

(i)	order and/or higher taxon (for animals)	Viruses
(ii)	family name for plants	Retroviridae
(iii)	genus	Lentivirus
(iv)	species	Human immunodeficiency virus 1
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	HIV-1

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

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

If yes, specify the following:

(a) to which of the following organisms:

humans (X)

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 (X) No (.)

If yes, specify

Wild type HIV-1 is classified as a group 3 biological agent as per the European Economic Community classification for the protection of workers with biological agents (Directive 2000/54/EC). The group 3 designation applies to agents (1) that cause severe human disease and present a serious hazard, (2) that may present a risk of spreading to the community, but (3) there is usually effective prophylaxis or treatment available. Although the lentiviral plasmids are designed based on the HIV-1 virus, the lentiviral vector is replication deficient

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: :

(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 (X) Not known (.)

Specify:

2. Genetic stability of the genetically modified organism

The CAR receptor is introduced in the T cells via lentiviral gene transfer. The inserted genetic material is stably integrated and is not capable of replication. After integration of the LCAR2SIN_KAN vector into the host genome, the vector remains in the genome and is passed on to progeny of the cells when it divides.

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)

Not applicable for human T-cells The lentiviral vector is replication-deficient.. The transgenes inserted in the lentiviral vector do not code for pathogenicity factors, cytokine-coding sequences, oncogenes, antibiotic resistance genes or otherwise hazardous inserts.

4. Description of identification and detection methods

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

Cells transduced with the lentiviral vector are not released into the environment and are not stable under uncontrolled environmental conditions. Both Flow cytometry and qPCR methods are used for analysis of drug product and patient blood samples.

(b) Techniques used to identify the GMO

Transgene integration in the transduced cells is confirmed by multiplex qPCR.

Transgene expression in transduced cells is characterized by flow cytometry. The flow method is an orthogonal assay to demonstrate that transgene integration is associated with expression of properly folded CAR protein on the cell surface.

F. Information relating to the release

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

The GMO will be administered intravenously into subjects enrolled in the clinical studies and will be administered to subjects for the treatment of relapsed or refractory multiple myeloma.

The drug product will be manufactured in the USA.

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 administered 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 location of the clinical trial centres is known and the GMO will be administered under controlled conditions at the clinical sites. The transduced cells will be infused into a patient in a restricted, controlled area.

(b) Size of the site (m^2): Not applicable. The drug product is given to a patient via intravenous infusion in a hospital clinical environment. It is not anticipated that the GMO will be released into the environment.

(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:

No environmental sites outside the hospital room will be affected. Containment measures during the preparation and administration of JNJ-68284528 to the patients will exclude release into the environment. Personal protective equipment will be used to avoid exposure to JNJ-68284528 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:

JNJ-68284528 is administered as an intravenous infusion. The maximum target dose a patient might receive is a maximum of 2.25×10^6 CAR + viable T cells/kg. Subjects may be considered for retreatment with JNJ-68284528 with the same dose range to which they were initially assigned, or the de-escalated dose if de-escalation is required per protocol.

(b) Duration of the operation:

JNJ-68284528 will be administered to a patient following pre-conditioning chemotherapy treatment. The total time of GMO administration will be up to 90 minutes for infusion.

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

JNJ-68284528 will be administered under standard controlled conditions at the clinical site.

The sites will be provided a Safety Data Sheet on safe handling directions for JNJ-68284528, measures in case of accidental spills, personal protective equipment, first aid, decontamination and disposal. These measures are in place in order to avoid any release of JNJ-68284528 into the environment.

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.

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

This section is not applicable. The target organism is the recipient. The transduced autologous T cells are not released into the environment.

1. Name of target organism (if applicable)

(i) order and/or higher taxon (for animals) Primates

(ii) family name for plants …

(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)

It is expected that the GMO will have a therapeutic effect in patients with multiple myeloma expressing B cell maturation antigen (BCMA).

The T cells cannot spread in any natural ecosystem, since they can proliferate exclusively under specific culture condiions or in infused patients.

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

None expected.

The lentiviral vector used in the production of JNJ-68284528 has design elements that limit the potential risk for generation of replication competent lentiviruses (RCL). Furthermore, the transduced T cells are highly labile on environmental surfaces and have a very limited survival outside the human body. Therefore, no undesirable effects are 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

None, except the dedicated patients who receive JNJ-68284528. Exposure requires direct injection of JNJ-68284528. JNJ-68284528 is highly labile on environmental surfaces and have a very limited survival outside the human body.

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:

Highly unlikely

(b) from other organisms to the GMO:

Highly unlikely

(c) likely consequences of gene transfer:

Highly unlikely

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.):

No studies of the behaviours and characteristics of the GMO and its ecological impact carried out in stimulated natural environments have been performed.

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

Monitoring of patients will include multiparameter immunological cell monitoring by flow cytometry. The GMO positive T cells will be identified by quantitative PCR. Patients will continue to be followed at regular intervals post-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 (m^2)

Not applicable. The lentiviral vector and the drug product are not released into the environment.

5. Duration of the monitoring

In accordance with the clinical protocol, subjects will be monitored closely for safety and disease assessments during the post-infusion period (Day 1 to Day 100).

Post-treatment follow up starts once the post-infusion follow-up is complete (on Day 100) and lasts until end of study. In the post treatment follow-up phase, subjects will continue to be monitored for efficacy until confirmed PD, death, or withdrawal of consent.

6. Frequency of the monitoring

Following completion of the study, assessment for RCL and second primary malignancies will be collected yearly until 15 years after dosing with JNJ-68284528 on a follow-up study.

I. Information on post-release and waste treatment

1. Post-release treatment of the site

JNJ-68284528 will not be released in the environment.

The investigator is responsible for instructions and site staff training. 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 standard cleaning methods for handling of biological hazard materials supplemented by the company safety data sheet.

<u>Decontamination/cleaning measures after administration:</u>

Appropriate validated disinfection detergents and methods will be used for decontamination and disinfection in accordance with local institutional regulations and developed in line with national policies/laws.

2. Post-release treatment of the GMOs

JNJ-68284528 should not be released in the environment.

All medical waste, as well as any material that came into contact with the IMP will be inactivated or destroyed according to site procedures supplemented by the company safety data sheet. Medical waste should be decontaminated and sent off site for disposal.. Treattment of waste is detailed in section 3(b).

Patients ex vivo modified cells are not shed via excreta into the environment. No extra precautions are taken.

3. (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

To avoid potential transmission of infectious diseases, all disposable waste that has been in contact with the GMO during preparation and administration, as well as waste from sampling and sample processing, will be disposed of as specific potentially infectious hospital waste in an appropriately labelled biohazardous waste container and in accordance with local biosafety guidelines. Non-disposable materials are disinfected with appropriate validated disinfection detergents or autoclaved.

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. 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 autoimmune response in the affected person with elimination of the GMO, which prevents further spread of the GMO. 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

See response to J.1

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

Patients treated with the GMO in the authorized clinical trial setting will be monitored regularly. 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).