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/12/1750
(c)	Date of acknowledgement of notification	25/10/2012
(d)	Title of the project	**Clinical Study: Treatment of Advanced Gastrointestinal Cancer in a Phase I/II trial with modified autologous mesenchymal cells MSC_apceth_101**
(e)	Proposed period of release	**From 4th quarter 2013 until 4th quarter 2015.**

2. Notifier

Name of institution or company: **apceth GmbH & Co.KG**

3. GMO characterisation

(a) Indicate whether the GMO is a:

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

specify phylum, class **phylum: chordata**
class: mammalia

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

genus: homo
species: sapiens
Genetically modified mesenchymal stem cells (somatic cells) derived from Homo sapiens.

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

During the production of the GMO, flow cytometric analysis has shown that 6 weeks after the introduction of the genetic modification the transgene is stably expressed over this period.

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.

Not applicable. MSC_apceth_101 (genetically modified MSCs) are mesenchymal stem cells derived from humans. They are not viable outside cell culture conditions or the human body.

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

1. Recipient organism characterisation:

(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) **phylum: chordata**
class: mammalia

other, specify …

2. Name

(i) order and/or higher taxon (for animals) **mammal**
(ii) genus **Homo**
(iii) species **sapiens**
(iv) subspecies
(v) strain
(vi) pathovar (biotype, ecotype, race, etc.)
(vii) common name **Mesenchymal stem cells derived from humans**

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes (.) No (**X**) 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 (**X**)
(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:

Not applicable. The GMO (MSC_apceth_101) are mesenchymal stem cells derived from humans. It is not viable outside cell culture conditions or the human body

5. (a) Detection techniques
Specific surface markers for human mesenchymal stem cells can be detected by flow cytometry techniques. The transgene can be detected by flow cytometry techniques or PCR.

(b) Identification techniques
See 5a

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

(a) Generation time in natural ecosystems:
Technically there is no "natural" ecosystem. The GMO are human mesenchymal stem cells. The generation time of naturally occurring mesenchymal stem cells in the human body is unknown. The cells are derived from human bone marrow and are isolated and expanded in cell culture. In cell culture the generation time

is approximately 48 h. The cells are genetically modified expanded further and then re-infused into patients as cancer therapy.

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

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

(c) Factors affecting reproduction:
N.A.

9. Survivability

(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 **not applicable, GMO are human mesenchymal stem cells.**	

(b) relevant factors affecting survivability:
N.A., GMO are human mesenchymal stem cells.

10. (a) Ways of dissemination
N.A., GMO are human mesenchymal stem cells.

(b) Factors affecting dissemination
N.A., GMO are human mesenchymal stem 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)

Not applicable. …, 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 GMO is generated by the retroviral transduction of mesenchymal stem cells. The retroviral vector integrates quasi randomly into the genome of host cells (MSC). The retroviral vector encodes the therapeutic transgene HSV-TK (herpes simplex virus

thymidine kinase) driven by the human RANTES promoter. HSV-TK is a prodrug converting enzyme (PCE). Furthermore, the vector encodes a selection marker (puromycin resistance gene, *pac*) under control of the constitutive human PGK promoter. This expression cassette is necessary for the selection of the transduced MSC during the in vitro production process. The selection process is used to enrich the genetically modified mesenchymal stems cells in culture, while eliminating all unmodified cells. The expanded and genetically modified mesenchymal stem cells will be infused to tumor patient within a clinical trial phase I/II.

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	**…replication in competent retroviral vector**

(b) Identity of the vector

gamma-retroviral vector (pEMTAR-bi.RANTES.tk). It is derived from the murine leukemia virus which allows stable integration into the genome of the target cell and long-term expression of transgenes. The vector is pseudotyped with the Gibbon ape leukemia virus (GALV) envelope protein

(c) Host range of the vector

Various human, porcine and non-human primate cells

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

Yes (**X**) No (.)

antibiotic resistance	(**X**)
other, specify	…

Indication of which antibiotic resistance gene is inserted

puromycin resistance gene: puromycin N-acetyl-transferase (*pac*)

(e) Constituent fragments of the vector

Retroviral vector pEMTAR-bi.RANTES.tk:

- **5' long terminal repeat derived from myeloproliferative sarcoma virus-promoter**
- **Packaging signal Ψ**
- **RANTES promoter**
- **Herpes simplex virus thymidine kinase gene (HSV-TK)**
- **human phosphoglycerate kinase promoter,**
- **Puromycin resistance gene,**
- **wPRE: woodchuck Hepatitis post-transcriptional regulatory element**
- **3' Long terminal repeat with "self inactivating" modification**

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

(i)	transformation	(.)
(ii)	electroporation	(.)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify …	**single round retroviral transduction in vitro**

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

- **RANTES promoter**
  Herpes simplex virus thymidine kinase gene
- **human phosphoglycerate kinase promoter,**
  puromycin resistance gene,

(b) Source of each constituent part of the insert

- **RANTES promoter** **Source: Homo sapiens**
- **Herpes simplex virus thymidine kinase gene** **Source: Herpes simplex virus**
- **Human phosphoglycerate kinase promoter** **Source: Homo sapiens**
- **Puromycin resistance gene** **Source: Streptomyces alboniger**

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

- **RANTES promoter**
  drives expression of HSV thymidine kinase gene
- **Herpes simplex virus thymidine kinase gene**

Therapeutic gene for cancer treatment (see section C.2)

- **Human phosphoglycerate kinase promoter**
  drives expression of puromycin resistance gene
- **Puromycin resistance gene**
  the gene is needed during the production process; it allows the enrichment of genetically modified cells during the cultivation process (see section C.2)

(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

- **Relevant information for RANTES-Promoter and PGK-Promoter (part of the INSERT)**

1. Indicate whether it is a:

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

2. Complete name

(i)	order and/or higher taxon (for animals)	**Primate**
(ii)	family name for plants	…
(iii)	genus	**Homo**
(iv)	species	**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 (.) 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 (**X**) No (.) Not known (.)
Human exchange genes with humans.

- **Relevant information for Herpes simplex virus thymidine kinase (part of the INSERT)**

1. Indicate whether it is a:

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

(specify phylum, class)

other, specify …

2. Complete name

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

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:

(c) 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 **Class 2**

5. Do the donor and recipient organism exchange genetic material naturally?
Yes (.) No () Not known (**X**)

- **Relevant information for puromycin resistance gene, *pac* (part of the INSERT)**

1. Indicate whether it is a:

viroid	(.)
RNA virus	(.)
DNA virus	( )
bacterium	(**X**)
fungus	(.)

animal

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

(specify phylum, class)

other, specify …

2. Complete name

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

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:

(d) 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 (.) Not known (**X**)

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 genetically modified mesenchymal stem cells can only survive under cell culture conditions or after infusion into a human host. It is not expected that the genetic modification will have any effect on survivability.

(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 genetically modified mesenchymal stem cells (MSC) can only reproduce themselves in optimized cell culture or after infusion into a human host. Since MSC do not transfer genetic information to other human cells, it is not expected that the genetic modification will have any effect on reproduction of the recipient.

Nevertheless, patients, who will be treated with the GMO, must agree to follow medically acceptable contraception methods during treatment and for 3 months after completion of treatment.

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

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

Specify

Mesenchymal stem cells are not viable outside the human body or cell culture. During the course of the clinical trial the genetically modified cells are destroyed by subsequent infusion of Ganciclovir. GMO will therefore not persist long-term in the patient. It is not expected that the GMO will have the possibility to disseminate after infusion into human.

Remaining GMO infusion bags, transfusion sets, etc. will be autoclaved and destroyed according to the local GMO regulations.

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

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

Specify

Mesenchymal stem cells are non pathogenic. It is not conceivable that pathogenic potential will arise due to the genetic modification.

2. Genetic stability of the genetically modified organism

The retroviral vector is stably integrated into the genome of the mesenchymal stem cell. During the production of the GMO, flow cytometric analysis has shown that 6 weeks

after the introduction of the genetic modification the transgene is stably expressed over this period in cell-culture.

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
Specific surface markers for human mesenchymal stem cell can be detected by flow cytometry techniques. The transgene can be detected by flow cytometry techniques or PCR.

(b) Techniques used to identify the GMO
See section 4 a

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 applied as therapeutic agent within a phase I/II clinical trial for the treatment of cancer patients.
The GMO is generated by retroviral transduction of mesenchymal stem cells. The vector encodes the therapeutic transgene HSV-TK (herpes simplex virus thymidine kinase) driven by the human RANTES promoter. HSV-TK is a prodrug converting enzyme (PCE). Furthermore, the vector encodes a selection marker (puromycin resistance gene, *pac*) under control of the constitutive human PGK promoter. This expression cassette is required for the selection of the transduced MSC during the *in vitro* production process.
The proposed treatment approach consists of the systemic administration of the genetically modified mesenchymal stem cells (GMO) via intravenous (i.v.) infusion into a patient suffering from advanced gastrointestinal adenocarcinoma. Subsequently, the prodrug Ganciclovir (GCV) is infused.
The current model for the mode of action is based on the following properties of MSC_apceth_101:
MSC_apceth_101 takes advantage of the intrinsic tumor tropism of human MSC, which allows them to migrate specifically to sites of tumor lesions and efficiently infiltrate tumor tissue in vivo. These cells infiltrate tumor tissues and form gap junctions with the

surrounding tumor tissue. This allows the transfer of small molecules between MSC_apceth_101 and the tumor cells and therefore, these cells can be used as delivery vehicles for therapeutic genes for tumor therapy. MSC_apceth_101 accumulates in tumor tissue after intravenous administration. Subsequently the prodrug Ganciclovir (GCV) is given and is metabolized by HSV-TK into GCV-monophosphate which in turn is phosphorylated into the active cytotoxic compound GCV-triphosphate by endogenous enzymes. The phosphorylated GCV is a nucleotide-analogue and is incorporated into DNA during replication where it leads to strand abrogation and to death of the MSC expressing HSV-TK. The activated GCV is also passed through gap junctions from the MSC to neighboring tumor cells, where it also induces cell death. This effect is termed bystander killing.
This process is restricted to the tumor tissue due to the preferential migration of MSC to injured tissue.

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

   (a) Geographical location (administrative region and where appropriate grid reference):
   Hospitals (GMO will be used as therapeutic agent to treat cancer patients)

   (b) Size of the site (m^2): **Not applicable**
   (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:
   Not applicable

   (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:

   Patients will be treated with different doses of the GMO (dose escalation). Per three weeks treatment the same dose will be administered. weekly. The maximum total dose will be 2-4 x10^6 cells per kg body weight.

   (b) Duration of the operation:
   Less than 10 minutes per infusion of a single bag and maximum two bags per infusion.

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

The genetically modified mesenchymal stem cells are not viable out side the human body. Therefore spread is impossible.

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

Clinical trial / hospital conditions

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)	…
(ii)	family name for plants	…
(iii)	genus	**Homo**
(iv)	species	**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 will be applied as therapeutic agent within a clinical phase I/II trial for the treatment of cancer patients. The GMO are autologous genetically modified mesenchymal stem cells which are reinfused to cancer patients.
The GMO is generated by the retroviral transduction of mesenchymal stem cells. The vector encodes the therapeutic transgene HSV-TK (herpes simplex virus thymidine kinase) driven by the human RANTES promoter. HSV-TK is a prodrug converting enzyme (PCE). Furthermore, the vector encodes a selection marker (puromycin resistance gene, *pac*) under control of the constitutive human PGK promoter. This expression cassette is necessary for the selection of the transduced MSC during the in vitro production process.
The proposed treatment approach consists of the systemic administration of the genetically modified mesenchymal stem cells (GMO: MSC_apceth_101) via intravenous (i.v.) infusion into a patient suffering from advanced gastrointestinal adenocarcinoma. Subsequently, the patients are treated with the prodrug Ganciclovir (GCV).
The current model for the mode of action is based on the following properties of MSC_apceth_101:
MSC_apceth_101 takes advantage of the intrinsic tumor tropism of human MSC, which allows them to migrate specifically to sites of tumor lesions and efficiently infiltrate

tumor tissue in vivo. These cells infiltrate tumor tissues and form gap junctions with the surrounding tumor tissue. This allows the transfer of small molecules between MSC_apceth_101 and the tumor cells and therefore, these cells can be used efficiently as delivery vehicles for therapeutic genes for tumor therapy. MSC_apceth_101 accumulates in tumor tissue after intravenous administration. Subsequently the prodrug Ganciclovir (GCV) is given and is metabolized by HSV-TK into GCV-monophosphate which in turn is phosphorylated into the active cytotoxic compound GCV-triphosphate by endogenous enzymes. The phosphorylated GCV is a nucleotide analogue and is incorporated into DNA during replication where it leads to strand abrogation and to death of the MSC expressing HSV-TK. The activated GCV is also passed through gap junctions from the MSC to neighboring tumor cells, where it also induces cell death. This effect is termed "bystander killing".

During the clinical trial the GMO will be inactivated in the patient because of the GCV treatment.

3. Any other potentially significant interactions with other organisms in the environment
Not applicable

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes (.) No (X) Not known (.)
Give details
Not applicable. The genetically modified mesenchymal stem cells are not viable outside the human body. During the course of the clinical trial the genetically modified cells are destroyed by the application of Ganciclovir to the patient. GMO will therefore not persist long-term in the patient.

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

Not applicable. The genetically modified mesenchymal stem cells cannot survive 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. The genetically modified mesenchymal stem cells are not viable outside the human body.

(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:
Negligible. The GMO is intended for human use within a clinical phase I/II trial. It consists of retrovirally transduced human mesenchymal stem cells (MSC). The used retroviral vector is free of replication competent viral particles and also no vectors will remain in the cell preparation which is applied to the patient. MSC not transfer genetic information to other human cells.

(b) from other organisms to the GMO:
Negligible. The GMO is intended for human use with in a clinical phase I/II trial. It consists of retrovirally transduced human mesenchymal stem cells (MSC). The only source of genetic information to be transferred to the GMO would be the patient, who has been treated with the cells. No naturally process is known that allows the exchange of genetic information between somatic cells in a human being.

…

(c) likely consequences of gene transfer:
Not applicable. Transfer does not occur.

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

General surveillance is incorporated in a monitoring plan. From the start of the clinical trial all involved clinical trial sites will be advised to keep a registry of individuals who handle MSC_apceth_101. These include all personnel handling MSC_apceth_101 until the application to the patient and also personnel involved in cleaning up large spills of MSC_apceth_101. The gathered information is retained in the hospital for fifteen years. This plan is sufficient to monitor unanticipated effects on human health in general.

Appropriate training of site personnel is performed during a site initiation visit which is a requirement before enrollment and treatment of patients and will be maintained throughout the clinical trial.

2. Methods for monitoring ecosystem effects
Not applicable. See section G.2

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
Not applicable. See section G.7

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

5. Duration of the monitoring
Patients are monitored for two months closely (so-called treatment period) and are followed up a total of 12 months.

The clinical trial sites and its personnel are monitored by a sub-contracted Clinical Research Organization (CRO) during the complete clinical trial until close-out visit. Retraining of site personnel will be performed when needed.

6. Frequency of the monitoring
During treatment with GMO (= 3 weeks) 12 visits are scheduled for patients with contact to an investigator. After each infusion with GMO the patient stays overnight at the study site and is closely monitored. The subsequent GCV-infusions on three consecutive days are also performed at the study site under supervision of an investigator.
Overall 15 visits will be performed during the treatment period and additionally 3 visits in the follow up period.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Standard hospital hygiene program (disinfection of surfaces).

2. Post-release treatment of the GMOs

3. (a) Type and amount of waste generated
- **Infusion bags which contained the GMO (up to 2 bags per infusion)**
- **Needles used for infusion (1 per infusion)**
- **Transfusion set (maximum 2 per infusion)**

3. (b) Treatment of waste
Waste contaminated with the GMO will be accounted for and returned to the sponsor, where it will be autoclaved and destroyed according to the local GMO-regulations. The transport process and waste disposal process is regulated by internal SOPs and will be documented.

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. The genetically modified MSC are not able to survive outside the human body, therefore spread cannot occur.

2. Methods for removal of the GMO(s) of the areas potentially affected
Not applicable.

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.