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 **Spain**
(b) Notification number **B/ES/17/10**
(c) Date of acknowledgement of notification **22/03/2017**
(d) Title of the project **Phase II extension study of CaspaCIDe T cells (BPX-501) from an HLA-partially matched family donor after negative selection of TCR αβ+T cells in pediatric patients affected by hematological disorders**

(e) Proposed period of release **From 01/07/2017 to 01/07/2019 (Approximately 2 years)**

2. Notifier

Name of institution or company: **Bellicum Pharmaceuticals, Inc.**
2130 West Holcombe Blvd, Houston
Texas, 77030 USA

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 …

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

T cells obtained from haploidentical donor

- **Genus: Homo**
- **Species: Homo Sapiens**

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

The GMO is stable when stored in liquid nitrogen vapor for up to 12 months. Once thawed, the GMO is stable for 30 minutes at room temperature.

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) **IT, GB**

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 (X) No **()**

If yes:

- Member State of notification USA
- Notification number B/../../…Not applicable

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

No environmental impact is expected from the administration of ex vivo transduced, donor T cells administered intravenously to patients in a clinical trial. The viral vector used for transduction is replication deficient and the cells have tested negative for replication competent virus. The ex vivo transduction of T cells occurs in a controlled Good Manufacturing Practices facility.

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

1. Recipient or parental organism characterization:

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

(select one only)

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

animal

- mammals **(X) human T cells**
- insect (.)
- fish (.)
- other animal (.)
  (specify phylum, class) …

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 cells**

3. Geographical distribution of the organism *Not Relevant (NR)*

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

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

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

4. Natural habitat of the organism ***T cells are blood cells, thus the common habitat of the GMO is the human body***

(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 relevant

5. (a) Detection techniques
- ***Polymerase Chain Reaction*** (***PCR)***
- ***Flow cytometry for detection of specific surface markers***

(b) Identification techniques
T cells are characterized by expression of CD3 marker of cell membranes

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

Yes (X) No **()**

If yes, specify
Biosafety Level 2
As regards risk classification, it is classified as a biological agent of group 2, according to the classification of the Economic Community Protection of workers exposed to biological agents (Directive 2000/54 / EC). The name of group 2 applies to agents that cause disease in humans and could constitute a hazard to workers, which are unlikely to spread to the community and for which effective treatment or prophylaxis is available.

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: ***Not relevant. The GMO is unable to reproduce***

(a) Generation time in natural ecosystems:

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

(c) Way of reproduction: **NA** Sexual….. Asexual…..

(c) Factors affecting reproduction:
Not applicable

9. Survivability
Not relevant for this product since cell survival occurs in human body only or in specific culture conditions.

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

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

(b) relevant factors affecting survivability:
Not applicable. The GMO is unable to survive in environments other than culture 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 …, 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

To provide a suicide switch that can be activated to eliminate the transduced cells in the event the T cells cause Graft-versus-host disease (GVHD). Transduced cells are selected using the CD19 marker.

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

BPZ-1001: Recombinant retroviral vector

- ***family Retroviridae***
- ***genus: Gammaretrovirus***
- ***Species: Murine leukemia-related retrovirus.***

(c) Host range of the vector

GaLV envelope: broad host range (amphotropic) including human cells. The retroviral vector is not replication competent.

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

Yes **(X)** No ()

antibiotic resistance (.)
other, specify:
Truncated CD19 marker.

Indication of which antibiotic resistance gene is inserted
Not applicable, there is no antibiotic resistance gene

(e) Constituent fragments of the vector

5' LTR, 5' untranslated region, splice donor site, packaging signal, splice acceptor site, 3' LTR

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

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

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

FKBP12-F36V, linker, human caspase 9, 2A linker, truncated CD19

(b) Source of each constituent part of the insert

Engineered human FK506-binding protein containing F36V mutation, synthetic peptide linker, human caspase 9 cDNA, synthetic 2A peptide from Thosea Asigna insect virus, truncated human CD19

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

Human Caspase 9 protein to trigger apoptosis of the cell by dimerization of FKBP12-F36V and a truncated CD19 as a marker for identification of modified cells

(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)	***NA***
(ii)	family name for plants	***Homo***
(iii)	genus	***Homo sapiens***
(iv)	species	***Not applicable***
(v)	subspecies	***Not applicable***
(vi)	strain	***Not applicable***
(vii)	cultivar/breeding line	***Not applicable***
(viii)	pathovar	***Not applicable***
(ix)	common name	***Human cells***

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):
Not applicable

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 patient will receive genetically modified, allogeneic T cells.
These cells do not survive outside the body, similar to non-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

Genetic modification does not affect reproduction. Replication time of both modified and non-modified T cells is approximately 24 hrs.

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

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

Specify

The genetically modified allogeneic T cells do not contain any viral particles or RCRs and the GMO can therefore not disseminate.

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

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

Specify

The genetically modified T cells are non-pathogenic. The only difference with non-modified T cells is that they can be induced to undergo apoptosis.

2. Genetic stability of the genetically modified organism

After integration, the virus forms an integral part of donor T cells 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)
…

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
The transduced T cells can be detected using Polymerase Chain Reaction (PCR) or flow cytometry

(b) Techniques used to identify the GMO
PCR or flow cytometry

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
Conduct of a human clinical study.
The transduced T cells are administered to the patient to provide anti-viral and anti-tumor immunity after a T-cell depleted stem cell graft.

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):

Unidad de Trasplante Hematopoyético
Hospital Niño Jesús, Madrid. Spain

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

Isolated to the Stem Cell Transplant Unit of the hospital.

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

Not relevant – no proximity to protected area or biotopes.

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
Not relevant. Sections (b), (c) and (d) above are not considered relevant. Environmental release of the transduced allogeneic T cells is not intended beyond the treatment of trial subjects in the controlled conditions of a hospital transplant unit.

4. Method and amount of release

(a) Quantities of GMOs to be released:
Patients will receive 1 x 10e6 transduced T cells. A maximum of 10 patients will be treated.

(b) Duration of the operation:
The duration of the clinical trial enrolment will not exceed two years.

(c) Methods and procedures to avoid and/or minimize the spread of the GMOs beyond the site of the release
The product is shipped frozen from the manufacturer in a validated shipping container to the hospital stem cell transplant unit.
The receiving stem cell laboratory will store the product in vapor phase of liquid nitrogen in a controlled access freezer until time of infusion.
The haematology department within the hospital is a controlled environment with secure key card access.
Administration to the patient and handling of waste and patient samples will be in accordance with legal and institutional procedures of the hospital.

To minimize the chance of the contact between the GMO and the environment the following measure shall be taken:
• The hospital personnel is properly instructed on best practices on handling the product before and during the infusion, and on waste management
• Hand washing before and after administration either soap and running water or appropriate antiseptic hand cleaner.
• Standard personal protective equipment (PPE), such as overcoat, gloves, mask, and laboratory safety goggles must be worn for administration.

5. Short description of average environmental conditions (weather, temperature, etc.)
Mediterranean climate - standard 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.
The GMO has been handled at clinical sites in clinical trials since 2012, no potential environmental and human health impacts have been reported.

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	***Homo Sapiens***
(v)	subspecies	***NA***
(vi)	strain	***NA***
(vii)	cultivar/breeding line	***NA***
(viii)	pathovar	***NA***
(ix)	common name	***Human***

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)
The GMO (transduced T cell) is aimed at helping immune reconstitution of immunosuppressed patients. In case of Graft-versus-host disease (GVHD), activated T cells can be induced to apoptose by administration of rimiducid. The final GMO has no target organ; thus no interaction is applicable.

3. Any other potentially significant interactions with other organisms in the environment
No – integrated provirus cannot interact with other organisms in the environment.

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
The genetically modified T cells are not able to survive outside the patient.

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

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

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:
The transduced T cells are made with a replication defective vector, neither the insert nor the vector are capable of replication. The cells are also extensively washed before

cryopreservation which removes any free viral particles. As most functional genes have been removed from the retroviral construct, this reduces any risk of recombination events with endogenous retrovirus that could result in a reconstitution of replicative capacity. Thus gene transfer to unintended organisms is unlikely. No homology between the retroviral vector used for transduction and endogenous (retro)viruses, so therefore no likelihood of genetic exchange.

(b) from other organisms to the GMO:
No homology between the retroviral vector used for transduction and endogenous (retro)viruses, so therefore no likelihood of genetic exchange.

(c) likely consequences of gene transfer:
No gene transfer is anticipated.

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.):
The vector used to genetically modify T cells in this study has previously been used in a Phase 1 trial in the United States.
Ten pediatric patients who had undergone stem cell transplantation for relapsed leukemia were treated with the genetically modified T cells.
The T cells were detected in the peripheral blood and persisted for the duration of the study (24 months) [Zhou X et.al, Blood 2014;123:3895-3905].
No evidence of any replication competent retrovirus was detected in any subjects.

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
Transduced T cells will be monitored in patient blood using flow cytometry or PCR. Blood samples will be monitored for replication competent virus.

2. Methods for monitoring ecosystem effects
The transduced T cells will not be released into the ecosystem.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
The transduced T cells will be administered to patients and the genetic material is not expected to transfer to other organisms.

4. Size of the monitoring area (m^2)
Not relevant – the product intended use is for specific patients in hospital settings only.

5. Duration of the monitoring
Blood samples will be monitored for replication competent virus for up to 15 years.

6. Frequency of the monitoring

Patients will be monitored according to the clinical protocol for 2 years post administration. Long term follow-up will continue annually for 15 years.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
At the site of administration of the cell product to the patient, all used material will be disposed in accordance with legal and institutional procedures of the hospital.
Areas and equipment where manipulation occurs are cleaned after manipulation with disinfecting and decontaminating agents.

2. Post-release treatment of the GMOs
The genetically modified T cells will be infused into the patient.

3. (a) Type and amount of waste generated
At the site of administration of the cell product to the patient, waste is limited to residual cells remaining in the infusion bag, syringes and gloves.

3. (b) Treatment of waste
- ***All waste is treated as biohazardous waste and is transported and disposed in accordance with legal and institutional procedures of the hospital.***
- ***Sharps are collected and disposed of in sharps containers.***

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
- ***The GMO is to be manipulated in a restricted area only and under specific procedures.***
- ***Standard policies and procedures are in place at hospitals and research institutions for the treatment of medical waste in the event of accidental spillage.***
- ***Hospital procedures should be followed for monitoring staff in event of needle stick, the immune system will eliminate the foreign T cells.***

2. Methods for removal of the GMO(s) of the areas potentially affected
Standard hospital procedures for cleaning of areas potentially exposed to blood products. The GMO is sensitive to all hospital cleaning/disinfection agents (e.g. chlorine bleach), autoclaving, or heat treatment, identical to what would be used to treat any blood products.

In case of accidental spillage on surfaces:
- *Continue wearing personal protective equipment such as overcoat, gloves, mask and lab safety*
- *Put on a second pair of gloves.*
- *Cover spill with absorptive paper towels.*
- *Spray/soak with disinfectant.*
- *Remove after immersion time of 30 minutes. Use forceps if sharps have been produced and dispose sharps into a sharps container. Dispose paper towels and gloves in waste bag.*

• Dispose all waste, including gloves, as potentially infectious medical waste.
• Disinfect and wash hands with soap and water

In case of accidental spillage on clothing:
• Remove all contaminated clothing and put into laundry bin.
• Disinfectant skin surfaces that were in potential contact.
• Remove gloves and discard as potentially infectious medical waste.
• Re-dress with clean clothes.
• Close bin with contaminated clothing and have it laundered according to the hospital procedure for clothing potentially contaminated with infectious biological material

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 are monitored for adverse events and severe adverse events (SAE) as prescribed in the clinical trial protocol.
All serious adverse events will be recorded and evaluated by the hospital staff and the study promoter, and will be reported to health authorities when appropriate.

Standard hospital procedures for unexpected exposure to blood products will be followed, such as removal of contaminated clothing, disposal of gloves and disinfectant washing of skin surfaces.

The transduced T cells are not viable outside the body of the patient.