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	Netherlands
(b)	Notification number	B/NL/17/005
(c)	Date of acknowledgement of notification	05-07-2017
(d)	Title of the project	A Phase 2, Single-Arm, Multi-Cohort, Multi-Center Trial to Determine the Efficacy and Safety of JCAR017 in Adult Subjects with Aggressive B-Cell Non Hodgkin Lymphoma
(e)	Proposed period of release	From 01/12/2017 until 31/12/2021

2. Notifier

Name of institution or company:
Celgene Corporation, 86 Morris Avenue, Summit, New Jersey 07901

3. GMO characterisation

(a) Indicate whether the GMO is a:

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

other, specify (kingdom, phylum and class) Human

(b) Identity of the GMO (genus and species)
JCAR017 is a second generation CAR T cell construct comprised of autologous CD4+ and CD8+ T cells expressing a CD19-specific CAR consisting of an scFv binding domain derived from the FMC63 murine CD19-specific mAb fused to the 4-1BB and CD3ζ chain signaling domains.

(c) Genetic stability – according to Annex IIIa, II, A(10)
The sequences encoding the CD19 targeting CAR are introduced to the T cells via transduction with a replication incompetent self-inactivating lentivirus. Due to integration of the viral vector into the host genome, the CAR sequences will be present as a stable, integral part of the host DNA in transduced cells during the duration that the cells persist following infusion.

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; DE; DK; ES; FI; FR; GB; IT; NO; 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 FR
- Notification number Unknown

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 US
- Notification number Not applicable

7. Summary of the potential environmental impact of the release of the GMOs.
The potential environmental impact of the release of JCAR017 is very low. The release of JCAR017 is limited to patient administration in hospital settings and will not reach the environment at large.

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

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

Excretion of vector used to manufacture JCAR017 ("shedding") by the patient is extremely unlikely (Schenk-Braat et al, *J Gene Med* 2007; 9: 910-921; Bear et al, *Molecular Therapy*

2012; vol.20 no.2: 246-249). Vector sequences are highly unlikely to be mobilized as previously described.

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

1. Recipient or parental organism characterisation:

(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)	

other, specify

2. Name

(i)	order and/or higher taxon (for animals)	Homo sapiens
(ii)	genus	
(iii)	species	
(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 not applicable to humans

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

Atlantic	..
Mediteranean	..
Boreal	..

Alpine ..
Continental ..
Macaronesian ..

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

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

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

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
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
Autologous blood leukapheresis source material is controlled for viral adventitious agents as per country specific guidances. Patients will at least be tested for HIV, HBV and HCV prior to blood donation and excluded from the clinical study if tested positive.

8. Information concerning reproduction
Not applicable for transduced human T cells in the recipient.

(a) Generation time in natural ecosystems:

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

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

(c) Factors affecting reproduction:

9. Survivability
Not applicable, gene modified T lymphocytes cannot survive in the environment.

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

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

(b) relevant factors affecting survivability:
Human T cells require complex solutions, environmental, and physical controls in order to survive outside the human body. Without these controls and in the general environment human T cells will not survive.

10. (a) Ways of dissemination
Human T cells can only be transmitted between individuals through infusion or injection. Due to the inability for the human T cells to survive in the general environment, no dissemination is expected to occur.

(b) Factors affecting dissemination
Should the human T cells be infused or injected into an individual other than the donor, it is expected that the recipient's immune system will eliminate the 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
JCAR017 product is comprised of autologous CD4+ and CD8+ T cells transduced via a lentiviral vector to express a CD19-specific CAR consisting of an scFv binding domain derived from the FMC63 murine CD19-specific mAb fused to the 4-1BB and CD3ζ chain signaling domains. JCAR017 CAR T cells target CD19+ B-cell malignancies and are effectively redirected toward recognition and lysis of CD19-expressing target cells including malignant 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
The ZRX-014-LV vector is a replication incompetent self-inactivating lentiviral vector.

(c) Host range of the vector
The ZRX-014-LV vector is amphotropic and has a wide host range that can infect more than one species or cell culture line.

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

Yes (X) No (.)

antibiotic resistance (.)
other, specify
Detection of integrated ZRX-014-LV vector is analyzed by qPCR method. A DNA standard curve is used to quantify the amount of ZRX-014-LV amplified, and the number of ZRX-014-LV vector integrations per genome is calculated. Albumin is used as a housekeeping gene to determine the number of genomes present in the sample.
The reported value is the number of ZRX-014-LV vector integrations per genome as a part of release specifications (known as VCN: vector copy number).

Indication of which antibiotic resistance gene is inserted

(d) Constituent fragments of the vector
The CD19-specific CAR fragment encodes an N-terminal leader peptide of the human GMCSF receptor alpha chain signal sequence to direct surface expression, CD19-specific scFv derived from the IgG1 murine monoclonal antibody FMC63, Human IgG4 hinge and human CD28 transmembrane region, Human 4-1BB T cell costimulatory element, Human Cytoplasmic tail of human CD3zeta for T cell activation, T2A linker peptide, and EGFRt, a truncated non-functional human epidermal growth factor receptor type I transmembrane polypeptide.

(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
The CD19-specific CAR insert encodes an N-terminal leader peptide of the human GMCSF receptor alpha chain signal sequence to direct surface expression, CD19-specific scFv derived from the IgG1 murine monoclonal antibody FMC63, Human IgG4 hinge and human CD28 transmembrane region, Human 4-1BB T cell costimulatory element, Human Cytoplasmic tail of human CD3zeta for T cell activation, T2A linker peptide, and EGFRt, a

truncated non-functional human epidermal growth factor receptor type I transmembrane polypeptide.

(b) Source of each constituent part of the insert

Name	Source	Function
N-terminal leader peptide of GMCSF receptor alpha chain signal sequence	Human	Directs surface expression
CD19-specific scFv (FMC63)	Murine	CD19 specific antigen receptor
IgG4 hinge and CD28 transmembrane region	Human	Trans-membrane domain
4-1BB costimulatory element	Human	T cell co-stimulation
Cytoplasmic tail of CD3zeta	Human	T cell activation
T2A	Virus	Self-cleaving linker polypeptide
EGFRt transmembrane polypeptide	Human	Truncated human EGFR polypeptide for identification of transduced cells

(c) Intended function of each constituent part of the insert in the GMO
See response to 6 (b).

(e) Location of the insert in the host organism

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

(f) 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 (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	…
(iii)	genus	Lentivirus
(iv)	species	HIV Murine and human
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

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 (.) 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 sequences encoding the CD19 targeting CAR are introduced to the T cells via transduction with a replication incompetent self-inactivating lentivirus. Due to integration of the viral vector into the host genome, the CAR sequences will be present as a stable, integral part of the host DNA in transduced cells during the duration that the cells persist following infusion.

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 ZRX-014 lentiviral vector is a replication incompetent self-inactivating vector. For this it not capable of making more viral progenies of itself that would result in the spread of a replicating virus or recombination with other retroviruses. The ZRX-014 viral vector uses a split-genome third-generation system where the plasmids encoding the segments and genes

required to form the viral vector are segregated onto separate plasmids: the envelope glycoprotein (not derived from a lentivirus) is on one plasmid, the *gag* and *pol* genes on another plasmid (derived from HIV-1), the *rev* gene on another plasmid (derived from HIV-1) and the transfer genome encoding the transgene on a separate plasmid (derived from HIV-1 but self-inactivating due to a deletion in the 3'LTR). These sequences are provided *in trans* via transfection of plasmids into the HEK-293T cell line which allows for only transient expression of these constructs during the viral vector production stage. The risk for RCL is even further reduced by retaining the Rev-dependence of the viral vector: Rev is required for export of the RNA genome transgene from the nucleus into the cytoplasm for protein expression and packaging. Since Rev is provided only *in trans* and since the Rev protein is not packaged in the virus the chance that a lentiviral RNA genome can continue its nuclear export in transduced cells is highly unlikely. Finally, the self-inactivating nature of the vector means that expression off of the LTR is significantly reduced due to the 3'LTR deletion and the absence of the HIV-1 *tat* gene (normally required for LTR-driven transcription).

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
Following administration of the product, patients are monitored for persistence of JCAR017 using qPCR.

(b) Techniques used to identify the GMO
The techniques used to identify JCAR017 include qPCR and Flow Cytometry.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
The final GMO is not released in the environment, the final GMO is infused to a patient enrolled in a clinical trial with the aim of recognizing and lysing malignant cells.

The purpose of the release is to conduct a multi-center clinical trial to determine the efficacy and safety of JCAR017 in adult subjects with B-cell Non Hodgkin lymphoma.

Chimeric antigen receptor (CAR) T cells are a new therapeutic approach to patients with Non Hodgkin lymphoma. Early clinical data have found this therapy to be tolerable and have shown high overall and complete response rates.

JCAR017 treatment is not expected to have any significant environmental effects.

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):
Erasmus Medical Center (Erasmus MC), Rotterdam, Netherlands

(b) Size of the site (m^2): The entire Erasmus MC covers thousands of m^2
(i) actual release site (m^2): hospital room of 15 to 20 m^2
(ii) wider release site (m^2): None
Administration of JCAR017 will take place in a hospital room.

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
None

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
None

4. Method and amount of release

(a) Quantities of GMOs to be released:
JCAR017 will be administered as one flat dose of 1 x 10^8 CAR+ T cells.

(b) Duration of the operation:
Administration of JCAR017 is expected to take approximately 30 minutes.

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

Celgene will provide a JCAR017 Product Administration Manual to all participating sites; all product handling should be carried out as per the Product Administration Manual. Any product waste and potentially contaminated materials after administration must be disposed as outlined in the Product Administration Manual per the institution's biohazard disposal safety measures in place for bloodborne pathogens or potentially infectious patient material. This destruction will be clearly documented and kept available in the records. These procedures and containment measure will ensure safe handling and prevention of any release into the environment.

5. Short description of average environmental conditions (weather, temperature, etc.)
JCAR017 will be administered in a hospital room setting at room temperature.

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.
Clinical research with JCAR017 is ongoing in the United States. The potential environmental and human health impacts from the release of JCAR017 as described in this form are consistent with those associated with previous releases carried out.

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)	Human
(ii)	family name for plants	…
(iii)	genus	…
(iv)	species	…

(v) subspecies …
(vi) strain …
(vii) cultivar/breeding line …
(viii) pathovar …
(ix) common name …

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)
JCAR017 CAR T cells are used in the treatment of patients with B-cell malignancies. When injected into the patient JCAR017 cells effectively recognize and target CD19+ B-cells (including the malignant B-cells),and upon binding, induce the lysis of CD19-expressing target cells.

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

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established
None

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

(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:
Not applicable

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 behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.) have been performed.

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
As JCAR017 is administered as a single course of treatment, subjects are followed on study for 2 years after the final JCAR017 infusion for safety and efficacy evaluations. Because this protocol involves gene transfer, long-term follow-up for retroviral vector safety and long-term survival will continue for up to 15 years after the final JCAR017 infusion.

In the long term follow up, subjects will undergo a routine (semi-annual or annual) physical examination and medical history, including concomitant medications and AEs, with particular attention paid to features possibly related to retrovirus-associated events such as new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or autoimmune disorder, or new incidence of other hematologic disorders. Bone marrow examinations may be performed to evaluate or confirm remission status. In addition, laboratory studies will be performed to evaluate routine safety endpoints, JCAR017 vector persistence, and RCL.

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

5. Duration of the monitoring
See response to H.1.

6. Frequency of the monitoring
See response to H.1.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Celgene will provide a JCAR017 Product Administration Manual to all participating sites; all product handling should be carried out as per the Product Administration Manual. Any product waste and potentially contaminated materials after administration must be disposed as outlined in the Product Administration Manual per the institution's biohazard disposal

safety measures in place for bloodborne pathogens or potentially infectious patient material. This destruction will be clearly documented and kept available in the records. These procedures and containment measure will ensure safe handling and prevention of any release into the environment.

2. Post-release treatment of the GMOs
No post-release treatment of the GMO applies, other than the disposal of product waste and contaminated materials as described under I.1. Human T cells require complex solutions, environmental, and physical controls in order to survive outside the human body. Without these controls in the general environment the T cells will not survive.

3. (a) Type and amount of waste generated
Any partially unused product (remaining in the product container(s)) and materials used for the administration of JCAR017, including product container(s), IV administration sets, and any supplies used in the preparation that have been in contact with JCAR017.

3. (b) Treatment of waste
Any product waste and potentially contaminated materials after administration must be disposed as outlined in the Product Administration Manual per the institution's biohazard disposal safety measures in place for bloodborne pathogens or potentially infectious patient material. This destruction will be clearly documented and kept available in the records.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
Standard policies and procedures in place at hospitals and research institutions for the treatment of medical waste which may contain bloodborne pathogens.

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
Not applicable