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/16/09
(c) Date of acknowledgement of notification: 08-Sep-2016
(d) Title of the project
Study of JCAR015 in clinical trials with patients with B cell malignancies
(e) Proposed period of release: From 01/12/2016 until 31/12/2020

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)
Autologous CD3+ T cells expressing a CD19-specific CAR comprised of an extracellular scFv binding domain derived from a murine CD19-specific hybridoma cell line (SJ25C1), CD28 transmembrane and cytoplasmic domain, and CD3ζ signaling domain.

(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 gammaretrovirus 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) DE, GB, BE, IT, FR

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 JCAR015 is very low. The release of JCAR015 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 retroviral vector, which needs no special precautions for disposal of contaminated clinical waste.

Excretion of vector used to manufacture JCAR015 ("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
JCAR015 cell product consists of autologous CD3+ T cells that are genetically modified to express the 1928z CD19-specific CAR under the control of the Moloney Murine Leukemia Virus (Mo-MuLV) long terminal repeat (LTR). The CAR consists of a CD19-specific scFv, derived from the murine monoclonal antibody SJ25C1, fused to the transmembrane and cytoplasmic signaling domains of CD28 and the cytoplasmic signaling domain of the CD3ζ chain. JCAR015 CAR T cells target CD19+ B-cell malignancies and are effectively redirected toward recognition and lysis of CD19-expressing target cells including leukemia 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 SFG-1928z retroviral vector is a replication incompetent gammaretroviral vector.

(c) Host range of the vector
The SFG-1928z viral vector is pseudotyped with the gibbon ape leukemia virus (GALV) envelope, which targets a ubiquitously expressed receptor that is a type III inorganic phosphate transporter known as Pit-1 (also known as SLC20A1, or GLVR1). Therefore, the SFG-1928z viral vector is expected to have tropism to human and animal cells.

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype
Yes (X) No (.)

antibiotic resistance (.)
other, specify Transduced cells can be identified by the detection of CAR expression (ie the expression of the transgene inserted via the vector) using flow cytometry.

Indication of which antibiotic resistance gene is inserted

(e) Constituent fragments of the vector
The CAR consists of the CD8α leader, followed by the single chain variable fragment (scFv) which consists of heavy (V_H) and light (V_L) chain variable regions linked by a $(Gly_4Ser)_3$ repeat linker, followed by the CD28 extracellular (rod), transmembrane (TM) and intracellular (endo) domains, followed by the intracellular domain of CD3ζ. The CAR sits within a gammaretroviral vector flanked by 5' and 3' long terminal repeats (LTR). Upstream of the CAR exists the packaging signal (Ψ) which is flanked by splice donor (SD) and splice acceptor (SA) sites.

(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 CAR consists of the CD8α leader, followed by the single chain variable fragment (scFv) which consists of heavy (V_H) and light (V_L) chain variable regions linked by a $(Gly_4Ser)_3$ repeat linker, followed by the CD28 extracellular (rod), transmembrane (TM) and intracellular (endo) domains, followed by the intracellular domain of CD3ζ. The CAR sits within a gammaretroviral vector flanked by 5' and 3' long terminal repeats (LTR). Upstream of the CAR exists the packaging signal (Ψ) which is flanked by splice donor (SD) and splice acceptor (SA) sites

(b) Source of each constituent part of the insert

Name	Source	Intended Function
5' LTR	Moloney murine	5' long terminal repeat of

	leukemia virus	retroviral vector, also serves as the promoter for the transgene.
SD	Moloney murine leukemia virus	Splice donor site.
Packaging signal extended	Moloney murine leukemia virus	Site for packaging vector genomes into vector capsid.
SA	Moloney murine leukemia virus	Splice acceptor site.
CD8α leader	*Homo sapiens*	Leader peptide for transport to the cell surface via the endoplasmic reticulum.
scFv	mouse hybridoma SJ25C1 cDNA	CD19 specific antigen receptor.
CD28 rod, TM, endo	*Homo sapiens*	Rod serves as the spacer. TM is the trans-membrane domain. The endo domain works as T cell co-stimulation.
CD3ζ cytoplasmic domain	*Homo sapiens*	T cell activation.
3' LTR	Moloney murine leukemia virus	3' long terminal repeat of retroviral vector, also contains the polyadenylation signal for the transgene RNA.

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

(d) Location of the insert in the host organism

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

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No (X)
If yes, specify

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

viroid (.)
RNA virus (.)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (X)

- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class)

other, specify

2. Complete name

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	
(iv)	species	Mus musculus and Homo sapiens
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	Mouse and 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 (.) 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 gammaretrovirus. 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 SFG-1928z viral vector is a split genome replication incompetent 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 SFG-1928z viral vector is rendered replication incompetent because a majority of the *gag*, *pol* and *env* sequences are deleted. A partial region of *gag* remains in order to keep the packaging sequence and allow

packaging of RNA into virions; however, the partial *gag* sequence contains a stop codon to prevent any translation. A partial region of *pol* remains in order to retain a splice acceptor site. Only the last nucleotides of *env* remain as part of the 3' LTR junction. The CAR transgenes inserted in the vector do not encode pathogenic or toxic factors, nor factors that would provide antibiotic resistance or other dangerous factors. The transgenes encode factors that function to provide for T cell activation, T cell stimulation, and a CD19 specific antigen receptor.

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 JCAR015 using qPCR.

(b) Techniques used to identify the GMO
The techniques used to identify JCAR015 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 recongnizing and lysing leukemic cells.

The purpose of the release is to conduct a multi-center clinical trial to determine the safety, feasibility and efficacy of JCAR015 in adult subjects with B-cell acute lymphoblastic leukaemia.

Acute lymphoblastic leukemia (also called ALL) is an aggressive type of leukemia characterized by the presence of too many white blood cells (lymphoblasts) in the bone marrow and blood. It can spread to the lymph nodes, spleen, liver, central nervous system (CNS), and other organs. Without treatment, ALL usually progresses quickly. Patients with leukemia that fails to respond to initial treatment (refractory disease) or whose leukemia returns after initial treatment (relapse) have dismal outcomes. Those patients who are able to undergo a bone marrow transplant have a 5-year survival rate of 25% and those who cannot undergo transplant have a 5-year survival rate of less than 5%.

Chimeric antigen receptor (CAR) T cells are a new therapeutic approach to patients with ALL. Early clinical data shows this therapy to be highly effective at putting both adult and pediatric patients with relapsed or refractory leukemia into a disease-free state (remission).

JCAR015 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):
The JCAR015 clinical trials will take place at hospital and research centers in the Community.

(b) Size of the site (m^2):
(i) actual release site (m^2):
(ii) wider release site (m^2):
Administration of JCAR015 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:
JCAR015 will be administered as two intravenous (IV) infusions, administered 14 to 28 days apart. The first infusion (Dose #1) will be administered at a target dose of 1×10^6 JCAR015 cells/kg. The second infusion (Dose #2) will be administered at a target dose of 3×10^6 JCAR015 cells/kg.

(b) Duration of the operation:
Administration of JCAR015 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 JCAR015 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.)
JCAR015 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.
A number of clinical trials with JCAR015 are in progress or have been completed in the United States. The potential environmental and human health impacts from the release of JCAR015 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)

   JCAR015 CAR T cells are used in the treatment of patients with B-cell malignancies. When injected into the patient JCAR015 cells effectively recognize and target CD19+ B-cells (including the malignant B-cells),and upon binding, induce the lysis of CD19-expressing target cells including leukemia 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 JCAR015 is administered as a single course of treatment, subjects are followed on study for 2 years after the final JCAR015 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 JCAR015 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, JCAR015 vector persistence, and RCR.

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 JCAR015 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 cryobags) and materials used for the administration of JCAR015, including cryobags, IV administration sets, and any supplies used in the preparation that have been in contact with JCAR015.

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