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

Application for authorization to use the genetically modified liso-cel (also known as BMS-986387 and JCAR017) in Norway

(a) Member State of notification Norway
(b) Notification number
(c) Date of acknowledgement of notification
(d) Title of the project
A Global Randomized Multicenter Phase 3 Trial to Compare the Efficacy and Safety of Lisocabtagene Maraleucel (JCAR017/BMS-986387) to Standard of Care in Adults with Relapsed or Refractory Follicular Lymphoma (TRANSFORM FL)

(e) Proposed period of release From June 2024 (tentative) until January 2032

2. Notifier

Name of institution or company:
The sponsor of the study is Celgene Corporation, 86 Morris Avenue, Summit, New Jersey 07901, United States of America (USA). The notifier/applicant is Bristol-Myers Squibb AB, Sweden

3. GMO characterization

(a) Indicate whether the GMO is a:

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

other, specify (kingdom, phylum and class)

(b) Identity of the GMO (genus and species)
The GMO JCAR017 (also known as liso-cel) is comprised of autologous *Homo sapiens* T cells transduced with a lentiviral vector (LVV) which encodes an anti-CD19 Chimeric Antigen Receptor (CAR) directed against CD19-expressing cancer cells. JCAR017 is a second-generation CAR T cell construct comprised of autologous CD4+ and CD8+ T cells expressing a CD19-specific CAR consisting of a single chain variable fragment (scFv) binding domain sequence isolated from a murine CD19-specific hybridoma cell line (FMC63), fused in sequence to the IgG4 hinge, the CD28 transmembrane, the 4-1BB and CD3ζ (zeta) chain signaling domains. A non-functional truncated epidermal growth factor receptor (EGFRt) is also co-expressed with the CD19-specific CAR *via* a self-cleaving peptide.

(c) Genetic stability – according to Annex IIIa, II, A(10)
The sequences encoding the CD19 targeting CAR and the EGFRt are introduced to the T cells via *ex vivo* transduction with a third-generation replication incompetent self-inactivating (SIN) 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. The LVV is designed so it encodes only genes necessary for the expression of the CAR and EGFRt and lacks the required genes for HIV replication or pathogenicity.

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, CZ, DE, DK, ES, FI, FR, IT, NL, PL, RO 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: **AT**
- Notification number: BMASGK-76110/0015-IX/B/16C/2018; 2020-0.607.477

- Member State of notification: **BE**
- Notification number: LNE/AMV/HB/PB/CL/vr AMV/SBB219.2018/0102R (previously referenced as AMV/06081998/SBB219.1998/0433); LNE/AMV/HB/PB/CL/vr AMV/SBB219.2018/0460R

- Member State of notification: **FI**
- Notification number: 10/M/18

- Member State of notification: **FR**
- Notification number: TG 3754; TG 3788; TG 6500; 4925; 4916B; 4928; 4927; 5024; 5025; 5026; 7293; 7326; 7292

- Member State of notification: **DE**

- Notification number: B/DE/18/PEI3370; B/DE/18/PEI3397; B/DE/18/PEI3428; B/DE/20/PEI4034

- Member State of notification: **IT**
- Notification number: MI/IC/Op2/18/004; TO/IC/Op2/18/001; RM/IC/Op2/18/002; IM/IC/Imp2/18/002; TO/IC/Op2/18/002; RM/IC/Imp2/18/002; MB/IC/Op2/18/002; BG/IC/Op2/20/001

- Member State of notification: **NL**
- Notification number: IM-MV 19-019_000.ob.1 (B/NL/17/005); IM-MV 19-019_000 (B/NL/17/005-2); IM-MV 18-010_006.bes.1 (B/NL/18/010)

- Member State of notification: **ES**
- Notification number: B/ES/17/12; B/ES/18/08; B/ES/18/09; B/ES/20/06

- Member State of notification: **SE**
- Notification number: Eu-No. 2018-000929-32, Ref. No. 5.1-2018-43598; B/SE/19/2019-004081-18

**Please use the following country codes:**
*Austria AT; Belgium BE; Finland FI, France FR; Germany DE; Italy IT; Netherlands NL; Spain ES; 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

- Member State of notification Canada
- Notification number Substances Notification (NSN) No. 20367 (JCAR017)

- Member State of notification Japan
- Notification number Not applicable

- Member State of notification Switzerland
- Notification number New Swissmedic ref.: 701068 (old Swissmedic ref.: 2018GT2003) - CEC BE ref.: 2018-00628; New Swissmedic Ref. / Case number: 701132 (old Swissmedic ref. 2019GT3002) - KEK-BE BASEC-ID: 2019-00499.

- Member State of notification UK
- Notification number 14758/0286/001-0001; 14758/0287/001-0001; 14758/0306/001-0001

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

No environmental impact is expected from the administration of JCAR017 drug product to participants in this clinical trial. JCAR017 drug product will be supplied to the clinical site for infusion into the patient *via* intravenous route. Thus, an environmental impact is not expected as the release of the transduced autologous T cells is limited to patient administration in a hospital setting and will not reach the environment at large. There are no mechanisms of dispersal outside the human body. Transduced cells are not viable in the environments outside of the patient. Viral persistence and replication in the environment are not possible due the use of a replication incompetent LVV.

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

The following information is provided for the human T lymphocytes as the recipient or parental organisms.

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) Autologous T lymphocytes (human)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class)

other, specify

2. Name
(i) order and/or higher taxon (for animals): Primates
(ii) genus: *Homo*
(iii) species: *H. sapiens*
(iv) subspecies: Not applicable
(v) strain: Not applicable
(vi) pathovar (biotype, ecotype, race, etc.) : Not applicable
(vii) common name: Human T lymphocytes, T cells

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 human cells

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 (.) not applicable for human cells

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

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

4. Natural habitat of the organism

(a) If the organism is a microorganism

| | |
|---|---|
| water | (.) |
| soil, free-living | (.) |
| soil in association with plant-root systems | (.) |
| in association with plant leaf/stem systems | (.) |
| other, specify | - not applicable to human cells |

(b) If the organism is an animal: natural habitat or usual agroecosystem:
Not applicable. JCAR017 is a human T cell population intended for autologous use. The starting peripheral blood mononuclear cell population was obtained by apheresis from the patient, followed by JCAR017 manufacture and infusion into the same patient.

5. (a) Detection techniques
Common techniques of blood cell analysis (e.g., flow cytometry)

(b) Identification technique
Common techniques of blood cell analysis (e.g., flow cytometry)

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

Yes (.) No (X) Human T cells are not classified under existing Community rules.

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

The GMO is derived from autologous T cells isolated from the peripheral blood of patients with Relapsed or Refractory (R/R) Follicular Lymphoma (FL). The T cells cannot survive outside of the patient. The cells are not pathogenic and cannot persist or replicate in the environment or in other organisms.

Patients are tested for HIV, HBV and HCV during screening (prior to leukapheresis) and excluded from the clinical trial if tested positive for or have an history of HIV infection, or if the results of the tests support an active HBV and HCV infection (Note: Participants with a negative hepatitis B polymerase chain reaction assay or a negative hepatitis C virus RNA assay for viral load quantification for hepatitis B or C are permitted). Participants positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody with a negative viral load are eligible and should be considered for prophylactic antiviral therapy. In addition, participants with uncontrolled infections, despite appropriate antimicrobials or other infection-directed treatments, are excluded from the study.

Autologous leukapheresis source material is controlled for viral adventitious agents as per country specific guidance. The testing for adventitious agents (including HIV, HBV and HCV) is performed on blood samples within 30 days prior the leukapheresis procedure or according to local regulations. Sponsor will process cells except in cases where the patient fails clinical trial eligibility criteria as detailed in the clinical protocol.

8. Information concerning reproduction

Not applicable for genetically modified human T lymphocytes in the recipient.

(a) Generation time in natural ecosystems:
This information is not applicable for genetically modified human T lymphocytes in the recipient.

(b) Generation time in the ecosystem where the release will take place:
This information is not applicable for genetically modified human T lymphocytes in the recipient.

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

(d) Factors affecting reproduction:
This information is not applicable for genetically modified human T lymphocytes in the recipient.

9. Survivability

Not applicable. Human T lymphocytes cannot survive in the environment.

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

Not applicable.

| | | |
|---|---|---|
| (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, such as special media, temperature and $CO_2$, 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. There are no mechanisms of dissemination outside the human body; therefore, no dissemination in the environment is expected.

(b) Factors affecting dissemination
Should the human T cells be infused or injected into an immune-competent individual other than the donor (autologous patient), 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)

Reference is made to notification numbers provided in answer to question A.5 of this form.

## C. Information relating to the genetic modification

The information provided in this section relates to the autologous T cells that are genetically modified by transduction with the Anti-CD19 CAR lentiviral vector.

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

*Ex vivo* lentiviral transduction of autologous CD4+ and CD8+ T cells leads to the integration of the transgene into the host genome, resulting in the expression of anti CD19-specific CAR and EGFRt on the surface of T cells. The anti-CD19-specific CAR consists 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 are expected to target CD19, a specific protein commonly found on cancerous malignant cells and to lyse those CD19-expressing cells. The co-expressed non-functional EGFRt cell surface protein could serve as an identification of transduced 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 v20006 vector is a third-generation replication incompetent self-inactivating (SIN) lentiviral vector derived from human immunodeficiency virus type 1 (HIV-1) and pseudotyped with the glycoprotein G of the vesicular stomatitis virus (VSV-G). It encodes a CAR specific for CD19 antigen, as well as a non-functional truncated EGFR.

(c) Host range of the vector

The v20006 vector is amphotropic and has a wide host range that can infect more than one species or cell culture line. However, it is important to emphasize that the lentiviral vector is not replication competent and does not encode any pathogenic genes. Also, the transduced cell suspension infused in the patient does not contain neither residual infectious lentiviral vector particles nor replication-competent virus particles.

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

Yes (X) No (.)

antibiotic resistance (.)

other, specify

The lentiviral back-bone sequences are detected and quantified by qPCR detecting woodchuck hepatitis virus post-transcriptional regulatory element (WPRE) as a marker for vector integration and albumin gene as an endogenous control. A DNA standard curve is used to quantify the amount of vector amplified, and the number of vector integrations per genome is calculated. Albumin is used as a housekeeping gene to determine the number of genomes present in the sample.

The number of vector integrations per genome and percent CD3+CAR+ cells in the test sample (obtained from flow cytometry immunophenotyping method using anti-CD19 CAR anti-idiotype antibody) are used to calculate and report the average number of vector integrations (copies) per CD3+CAR+ cell.

Indication of which antibiotic resistance gene is inserted: –
Not applicable. No antibiotic resistance genes are present in the anti-CD19 CAR lentiviral vector.

(e) Constituent fragments of the vector

The components of the LVV particle required for full infectivity include nucleic acid (RNA), structural vector proteins, enzymes and a lipid envelope, which is derived from the producer cells during budding and pseudotyped with glycoprotein G of the vesicular stomatitis virus (VSV-G). All structural proteins and enzymes are derived from the vector polyprotein Gag-Pol, which is cleaved by the protease enzyme during particle maturation. The matrix protein forms the spherical shell of the LV particle, while the capsid protein forms an inner shell containing vector ribonucleic acid (RNA) associated with the nucleocapsid protein. This inner capsid shell also contains the reverse transcriptase and integrase enzymes.

The linear, single- stranded RNA genome for the v20006 lentiviral vector encodes genes for the JCAR017 chimeric antigen receptor (CAR) as well as the truncated non-functional EGFRt downstream of the same promoter and does not encode any viral gene. The promoter that drives the expression of the transgene is a hybrid promoter consisting of elongation factor 1 (EF1) α (alpha) eukaryotic promoter and the Human T-cell leukemia virus type (HTLV)-1 R element (EF1α (alpha)/HTLV-1R promoter). The HTLV-1 R element serves as an intron/enhancer for the EF1α (alpha) promoter.

The other inserted proviral sequences are derived from HIV-1. These sequences comprise the LTR regions that have been made self-inactivating by deleting promoter/enhancer sequences, and attenuated regions of the proteins and elements that aid in the production, packaging, or transfer of the transcript containing the therapeutic gene. The LVV does not encode for any HIV proteins.

More precisely, the anti-CD19 CAR LVV RNA encodes several viral elements, including Long Terminal Repeats (LTRs) that direct reverse transcription and integration of the proviral form, a Rev responsive element that allows a Rev-mediated increase in stability of the viral RNA, and a central polypurine tract that is required for efficient reverse transcription. The 3' LTR was modified to delete the promoter/enhancer in the U3 region and confers SIN properties to the integrated proviral form. The SIN modification deletes 400 bp, including the TATA box and binding sites for transcription factors Sp1 and NF-κB, and is transferred to the 5′ LTR during reverse transcription. Thus, the LTRs in the integrated proviral form are transcriptionally inactive and greatly impaired for synthesis of full-length viral RNA in transduced T cells. SIN LTRs also reduce the potential for affecting transcription of cellular coding regions adjacent to the viral integration site. In addition, the translational start codon present in the gag gene fragment that is part of the Psi packaging signal has been mutated to a translational stop codon, preventing the production of any Gag protein. Additionally, a Woodchuck hepatitis virus (WHP) Posttranscriptional Regulatory Element (WPRE) derived mutant regulatory element is present to enhance viral RNA stability.

The vector is replication-defective and self-inactivating. No new viral particles can be assembled and shredded from the final host cell due to the absence, in the provirus, of all the accessory proteins that confers infectivity and replicative potential to the lentivirus.

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

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

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

Not applicable.

| | | |
|---|---|---|
| (i) | transformation | (.) |
| (ii) | microinjection | (.) |
| (iii) | microencapsulation | (.) |
| (iv) | macroinjection | (.) |
| (v) | other, specify | (.) |

6. Composition of the insert

(a) Composition of the insert

The insert encodes sequences necessary for the expression and production of the therapeutic CAR and the EGFRt.

The transgene encodes the CD19-specific CAR, comprised of an N-terminal leader peptide of the human GM-CSF 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. The CD19-specific CAR fragment is linked to EGFRt with a self-cleaving T2A linker peptide.

EGFRt, is a truncated non-functional human epidermal growth factor receptor type I transmembrane polypeptide. Domains I and II, as well as the cytoplasmic tail of EGFR have been deleted resulting in the truncated form, EGFRt, which contains only domains III, IV and the trans-membrane domain (Wang et al, 2011). This truncation is such that EGFRt retains the anti- EGFR binding site within domain III, allowing for selection and detection. Deletion of domains I and II prevents binding to its natural ligands Epidermal Growth Factor (EGF) and Transforming Growth Factor alpha (TGFα). Deletion of the cytoplasmic tail renders EGFRt void of signaling activity.

The description of the transgene, including the origin and function of each component, is provided below:

**Insert Component:** N-terminal leader peptide of the human GM-CSF receptor alpha chain signal sequence
**Source:** Human
**Function:** Directs surface expression of the CAR

**Insert Component:** Anti-CD19 scFv
**Source:** Mouse and Synthetic (derived from the IgG1 murine monoclonal antibody FMC63)
**Function:** CD19-specific antigen receptor

**Insert Component:** IgG4 hinge
**Source:** Human
**Function:** Provides sufficient spacing to the scFv from the cell membrane

**Insert Component:** CD28 transmembrane region
**Source:** Human
**Function:** Trans-membrane domain for anchoring to the cell membrane

**Insert Component:** 4-1BB costimulatory element
**Source:** Human
**Function:** Cytoplasmic domain for T cell co-stimulation

**Insert Component:** Cytoplasmic tail of CD3zeta

**Source:** Human
**Function:** Cytoplasmic domain for T cell activation

**Insert Component:** T2A Linker peptide
**Source:** Thosea Asigna Virus
**Function:** Self-cleaving linker polypeptide for separating CAR from EGFRt post translationally

**Insert Component:** N-terminal leader peptide of the human GM-CSF receptor alpha chain signal sequence
**Source:** Human
**Function:** Directs surface expression of EGFRt

**Insert Component:** EGFRt transmembrane polypeptide
**Source:** Human
**Function:** Truncated non-functional cell surface protein for identification of transduced cells

(b) Source of each constituent part of the insert
See response to 6 (a).

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

(d) Location of the insert in the host organism

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

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

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

1. Indicate whether it is a:

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

other, specify

2. Complete name

The insert sequences and their origin are listed in Section C.6.(a).

Transgene sequences (anti-CD19 and EGFRt) are human-derived except for the linker peptide (24 amino acids), which is derived from the Thosea Asigna virus and the Anti-CD19 scFv derived from the IgG1 murine monoclonal antibody FMC63.

| | | |
|---|---|---|
| (i) | order and/or higher taxon (for animals) | … |
| (ii) | family name for plants | … |
| (iii) | genus | Homo, Thosea, Mus |
| (iv) | species | Homo sapiens, Thosea Asigna, Mus musculus |
| | | … |
| (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 (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 (X) No ()
If yes, specify
Sequences of the transgene are human-derived except for the linker peptide (24 amino acids) derived from the Thosea Asigna virus, which is classified as Risk group 1. Human and mouse are not classified under the existing Community rules.

5. Do the donor and recipient organism exchange genetic material naturally?

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

## E. Information relating to the genetically modified organism (REG-CMC)

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 third-generation 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. The inserted CAR transgene only carries genes for expression of CD-19-specific CAR and EGFRt. It lacks genes required for HIV replication or pathogenicity.

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 (.)

Not applicable.

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)

The GMO is neither pathogenic nor harmful. No safety issues have been reported during the nonclinical and clinical development of JCAR017.

Moreover, v20006 used to transduce the autologous T lymphocytes, is a replication-incompetent self-inactivating lentiviral vector. It is not capable of replicating in human cells and therefore can't form progeny virions that would result in the spread of a replicating virus or recombination with other retroviruses.
The v20006 lentiviral 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 three separate helper 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), and the *rev* gene on a third plasmid (derived from HIV-1). The transgene is encoded on a transfer plasmid (derived from HIV-1 but self-inactivating due to a deletion in the 3'LTR). All sequences are provided *in trans* via transfection of plasmids into the HEK-293T cell line which only allows for 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 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).

The GMO is derived from autologous T cells isolated from the peripheral blood of patients with R/R folicular lymphoma. Based on the conditions and wash steps of the manufacturing process, it is expected that no residual infectious lentiviral vector particles will be present in the drug product JCAR017.

Finally, the T cells cannot survive outside of the patient. The cells are not pathogenic and cannot persist or replicate in the environment or other organisms. Patients are tested for HIV during screening and excluded from the clinical trial if tested positive, thus eliminating risk of recombination with any LVV that could potentially remain in the drug product.

4. Description of identification and detection methods

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

Cells transduced with anti-CD19 CAR lentiviral vector (i.e. JCAR017 drug product) are not released into the environment and are not stable under uncontrolled environmental conditions. Following administration of the product, patients are monitored for persistence of JCAR017 using qPCR specific to the integrated LVV sequences.

(b) Techniques used to identify the GMO

Quantitative PCR is used to measure the integrated vector sequences and detect the presence of transduced T cells. Flow cytometry is used to confirm expression and identify cells expressing the CD19-specific CAR.

## F. Information relating to the release

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

The final GMO (autologous product) 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 compare the efficacy and safety of JCAR017 to standard of care in adults with relapsed or refractory follicular lymphoma.

JCAR017 treatment is not expected to have any significant environmental effects.
Note that the anti-CD19 CAR lentiviral vector is used only to transduce *ex vivo* the autologous T cells in a controlled and insulated GMP manufacturing site based outside the EU.

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):

Department of Oncology, Oslo University Hospital, Radiumhospitalet,
Postal address: P.O. box 4953 Nydalen, 0424 Oslo, Norway
Street address: Ullernchausseen 70, 0310 Oslo, Norway

(b) Size of the site ($m^2$):

(i) actual release site ($m^2$):

Administration of JCAR017 will take place in a clinical setting, in a hospital room.

(ii) wider release site ($m^2$):

Administration of JCAR017 will take place in a clinical setting.

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

Not applicable since the release will take place during a clinical study in investigational sites.

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO

Not applicable since the release will take place during a clinical study in investigational sites.

4. Method and amount of release

(a) Quantities of GMOs to be released:
The GMO is not intended to be released into the environment. JCAR017 will be infused intravenously once per patient at a target total dose of $100 \times 10^6$ CAR-positive viable T cells (CAR+ viable T cells), 2 to 7 days after completion of lymphodepleting (LD) chemotherapy. Each JCAR017 dose includes CD4+ CAR+ T cells and CD8+ CAR+ T cells.

(b) Duration of the operation:
For the administration of JCAR017, the product is expected to be thawed and the labelled dose volume administered into the participant within 2 hours after removal from shipping container or liquid nitrogen (LN2) freezer (if storing product on-site).

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

The JCAR017 drug product containing T cells transduced with anti-CD19 CAR lentiviral vector is administered intravenously into the subject under standard controlled conditions for cell transplant at the clinical site. JCAR017 will be shipped to the clinical site in a validated shipping container prior to the scheduled administration to the patient. Storage of the product in the liquid nitrogen tanks of site is optional, according to country-specific requirements.

Any manipulations of the JCAR017 finished drug product will be carried out under the appropriate biohazard containment level and in accordance with local laws/regulations. Celgene has assigned Biosafety Level 2 (BSL2) to JCAR017. Per Table 1 of the "Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified by means of retro/lentiviral vector" guidance, it can be downgraded and handled as BSL1 for activities downstream of manufacturing (*i.e., after transduction).* Sponsor has mitigated the risk of RCL formation through intentional design of lentiviral vector properties (lack of sequence homology between provirus and WT-HIV 1/2 and HTLV 1/2 minimizing homologous recombination as a mechanism for RCL generation), manufacturing process conditions (separation of viral genes across multiple plasmids during viral production), and analytical control (demonstrated absence of HIV/HTLV/RCL from viral vectors and demonstrated absence of RCL from drug product). Resultingly, the negligible risk of RCL occurrence defined by the

guidance is met. In context of the conditions outlined in Table 1 under "absence of replication competent virus in the GM cells", we confirm cells from HIV positive patients/donors are excluded *via* clinical trial protocol exclusion criteria; however, HTLV positive patients/donors are not excluded from JCAR017 manufacturing. As described above, there is negligible risk of RCL generation in regard to HTLV co-infection. According to this rationale, handling of JCAR017 within BSL-1 conditions for activities downstream of product manufacturing is justifiable per the general scope of the guidance document.

Prior to and during administration the GMO is contained in dedicated closed containers; there will be no activities where third parties including medical personnel can come into direct contact with it. The administration of JCAR017 will be performed at specialized medical centers equipped for the safe administration of biological or cellular products, and by experienced health care professionals, appropriately trained in hygiene procedures and standards regarding safety and infectious materials handling. JCAR017 contains autologous human T cells and therefore, healthcare professionals should employ universal precautions for the prevention of transmission of blood-borne infections. Any partially used or unused JCAR017 (material remaining in the vials), the vials, the absorbent barrier pads, any supplies used in the preparation and administration process, including the IV administration set, must be disposed of in accordance with the institution's biohazard disposal policy for tissues with bloodborne pathogens or potentially infectious patient material. Used syringes and protective equipment will be collected in a sealable bag and placed in a dedicated and properly labelled container, which will then be delivered to the waste room of the appropriate facility. The disposal of all contaminated material will be performed according to the biohazard disposal procedures in place at the participating sites.

Other than standard cleaning and sanitation of the clinic room and the disposal of product waste and contaminated materials, no particular treatment of the site is necessary. 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.

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

JCAR017 will be administered in a clinical 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.

There are no applicable relevant data regarding potential environmental impacts from previous releases carried out with JCAR017. JCAR017 cannot persist in the environment.

## G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

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

1. Name of target organism (if applicable)

| | | |
|---|---|---|
| (i) | order and/or higher taxon (for animals) | *Homo sapiens* (Primates) |
| (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. Transduced cells are not viable in the environments outside of the subject.

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

None expected. Possible interaction with other organisms, such as HIV (and that could lead to *in vivo* recombination leading to formation of RCL), in patients is extremely low as no HIV+ patients are exposed to JCAR017. Study participants are screened prior to acceptance into the current JCAR017 clinical study. No JCAR017 product is made from HIV+ subjects, therefore eliminating the possibility of recombination of the LVV with HIV. The transduced cells are not viable outside of the body of the treated subjects. Viral persistence or recombination into the environment is not possible due the use of a replication incompetent LVV. The administration of the GMO product to immunocompetent people leads to rejection of the GMO cells. In summary, no interactions are expected between JCAR017 and 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 (.)

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

There is no possibility to disseminate JCAR017 from the clinical study site to any other ecosystem. All clinical waste is destroyed according to hospital's procedures for the disposal of bio-hazardous waste. Refer to the Product Administration Manual for disposal and destruction of any unused JCAR017 and materials that have come into contact with the drug product provided by the Sponsor.

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

There are no non-target organisms which may be unintentionally significantly harmed by the release of the GMO. This section is not applicable.

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

7. Likelihood of genetic exchange *in vivo*

(a) from the GMO to other organisms in the release ecosystem:

The JCAR017 drug product is made with a replication incompetent vector that stably inserts the proviral DNA encoding the CAR into the genome of the autologous T cells. The anti-CD19 CAR transgene is not capable of mobilization or amplification. Therefore, gene transfer to unintended organisms is not anticipated and is extremely low for the following reasons:

1. Potential risks to the treated subject include the theoretical risk of generation of a replication competent lentivirus (RCL). However, it is important to note that all viral genes responsible for HIV pathogenicity and replication have been removed from the proviral sequence, and replaced with a human therapeutic gene, thereby making the risk of RCL negligible. No new viral particles can be assembled and shed from the final host cell due to the absence in this proviral form of all the accessory proteins that confers infectivity and replicative potential to the lentivirus.
2. No HIV+ patients are exposed to JCAR017.

   Subjects are screened prior to acceptance into the current clinical study. HIV positive subjects are excluded from participating in the study: no JCAR017 product is made from HIV positive subjects, therefore eliminating the possibility of recombination of the inserted proviral sequences with HIV.

(b) from other organisms to the GMO:

The JCAR017 drug product will exist as differentiated T cells in the patient. While it is always possible that human subjects are infected with other organisms, there is no added risk to the subject as the GMO does not encode any viral or pathogenic genes.

(c) likely consequences of gene transfer:
Once JCAR017 drug product is created, no further gene transfer is anticipated.

8. Give references to relevant results (if available) from studies of the behavior and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g., microcosms, etc.):

Not applicable. No studies of the behavior 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)

Not applicable.

## H. Information relating to monitoring

1. Methods for monitoring the GMOs

Upon infusion into the subject, CAR-positive T cells will be detected using PCR-based method to quantify CAR transgene.

As JCAR017 is administered as a single course of treatment, subjects are followed on study for up to 5 years after the randomization for safety and efficacy evaluations. In addition, 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 JCAR017 infusion under the clinical protocol of the long-term follow-up study (GC-LTFU-001).

In the long term follow up, subjects will undergo a routine, as defined per protocol, physical examination and medical history, including concomitant medications and adverse events (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, or new infections. 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. JCAR017 drug product is not released into the environment. Moreover, drug product (autologous CAR T cells) is not capable of surviving in the environment.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
Not applicable. The JCAR017 drug product is not released into the environment. No genetic material is expected to be donated to another organism other than the patient for whom the product has been specifically manufactured. Should such transfer occur, PCR described in section E.4. could be used to detect and identify the GMO. Moreover, the administration of the GMO product to immunocompetent human subject who is not the autologous patient leads to an immune-mediated rejection of the GMO cells.

4. Size of the monitoring area ($m^2$)

Not applicable. The JCAR017 drug product is not released into the environment. Moreover, the JCAR017 drug product (autologous CAR T cells) is not capable of surviving in the environment.

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
The Sponsor 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. Type and amount of waste is also documented on a Product Disposal/Destruction Form and filed in the Investigational Site File (ISF) and in the subject's study records.

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. JCAR017 (drug product) is not viable in the environment outside of the body of the treated patient. It is not possible for the drug product to spread into the environment.
Note that the anti-CD19 CAR lentiviral vector is used only to transduce *ex vivo* the autologous T cells in the controlled and insulated GMP manufacturing based outside the EU; and it degrades rapidly in the environment.

2. Methods for removal of the GMO(s) of the areas potentially affected

In case of accidental spill of JCAR017 (drug product), decontamination is performed according to hospital spill procedures, such as wearing personal protective equipment, covering spill with absorbent, applying hospital approved disinfectant for appropriate contact time, and disposing of waste as biohazardous. The study team at site, which will be involved in the study drug product administration will be fully trained to the study requirements and to the hospital's procedures.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread

According to local hospital's procedures, it is anticipated that no plant, animal or soil will be in the hospital room where JCAR017 is administered to the subject.

4. Plans for protecting human health and the environment in the event of an undesirable effect

The JCAR017 drug product (transduced cells) and the anti-CD19 CAR lentiviral vector do not encode any pathogenic gene. The transduced cells are not viable outside of the body of the treated subjects. The anti-CD19 CAR lentiviral vector used to manufacture JCAR017 degrades rapidly in the environment. The administration of the GMO product to immunocompetent people leads to rejection of the GMO cells. Therefore, no undesirable effects are expected.