SNIF: GMOB-2023-17598

Domain:
GMO

Authorisation type:
Deliberate release of GMO or a combination of GMOs for any other purpose than for placing on the market

Application type:
Summary notification for the release of genetically modified higher organisms other than higher plants in line with Decision 2002/813/EC Annex, Part 1.

Recipient Member State:
Spain

Competent Authority:
Interministerial Council of GMO

Notification number:
B/ES/23/17

Acknowledgement date:
2023-07-11

A- General information

Details of notification

Details of notification
Application for authorization to use the genetically modified modified NEX-T CD19 CAR T cells (also known as CC-97540 and BMS-986353) in a clinical trial
Member State of notification
Spain
Title of the project
A Phase 1, Multicenter, Open-Label Study Of CC-97540 (BMS 986353), CD19-Targeted NEX-T Chimeric Antigen Receptor (CAR) T Cells, in Participants with Severe, Refractory Systemic Lupus Erythematosus (SLE), trial number CA061-1001
Proposed period of release
Starting date
2023-10-01
Finishing date
2027-04-30

Notifier

Name of institute or company
Celgene Corporation
Email
Not provided
Phone number
Not provided
Website
Not provided
Address
86 Morris Avenue, Summit, New Jersey
Post code
07901
Country
United States

GMO characterisation

(a) Indicate whether the GMO is a:

Viroid
No
RNA virus
No
DNA virus
No
Bacterium
No
Fungus
No

Animal
Yes

Select from following options:

Mammal
Yes
Insect
No
Fish
No
Other animal
No
Other
No

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

The GMO CC-97540 (also known as BMS-986353) consists 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 cells. CC-97540 is a second-generation CAR T cell construct comprised of autologous CD3+ 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 CD3 (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, these sequences will be present as a stable, integral part of the host DNA in transduced T 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.

Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

Yes
Country
Germany
France
Italy
Belgium

Has the same GMO been notified for release elsewhere in the Community by the same notifier?

No

Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

Yes
Country
US
Insert the notification number(s) (if exist)
IND 019292 and IND 029373
Country
CA
Insert the notification number(s) (if exist)
NSN 20512

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

No environmental impact is expected from the administration of CC-97540 drug product to subjects in this clinical trial. CC-97540 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 vector 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 organisms from which the GMO is derived

1. Recipient or parental organism characterisation

Indicate whether the recipient or parental organism is a:

Viroid
No
RNA virus
No
DNA virus
No
Bacterium
No
Fungus
No
Animal
Yes

Select from following options:

Mammal
Yes
Insect
No
Fish
No
Other animal
No
Other
No

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

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
yes
(b) Indigenous to, or otherwise established in, other EC countries:
no
(c) Is it frequently used in the country where the notification is made?
No
(d) Is it frequently kept in the country where the notification is made?
No

4. Natural habitat of the organism

(a) Is the organism a microorganism ?
No
Specify
(b) Is the organism an animal?
No

5(a) Detection Techniques

Detection Techniques
Common techniques of blood cell analysis (e.g. flow cytometry)

5(b) Identification Techniques

Identification Techniques
Common techniques of blood cell analysis (e.g. flow cytometry)

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

No

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

no

8. Information concerning reproduction

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

9. Survivability

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

(i) endospores
No
(ii) cysts
No
(iii) sclerotia
No
(iv) asexual spores (fungi)
No
(v) sexual spores (fungi)
No
(vi) eggs
No
(vii) pupae
No
(viii) larvae
No
Other
Yes
Specify
This information is not applicable for genetically modified human T lymphocytes in the recipient
(b) Relevant factors affecting survivability
Human T cells require complex solutions, environmental, and physical controls, such as special media, temperature and CO2, 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.
10(b) Factors affecting dissemination
Should the human T cells be infused or injected into an individual other than the donor (autologous patient), it is expected that the recipients 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)

This specific genetic modification of the recipient or parental organism has never been notified for release in the country where the notification is made.

C. Information relating to the genetic modification

1. Type of the genetic modification

Insertion of genetic material
Yes
Deletion of genetic material
No
Base substitution
No
Cell fusion
No
Other
No

2. Intended outcome of the genetic modification

Ex vivo lentiviral transduction of purified autologous CD3+ 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 a scFv binding domain derived from the FMC63 murine CD19-specific mAb fused to the IgG4 hinge, the CD28 transmembrane, and the 4-1BB and CD3 chain signaling domains. CC-97540 CAR T cells are expected to recognize and lyse 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
3(b) If yes, is the vector wholly or partially present in the modified organism?
Yes

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

Plasmid
No
Bacteriophage
No
Virus
Yes
Cosmid
No
Transposable element
No
Other
No
(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

Antibiotic resistance

No

Other

Yes

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.

(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 of the v20006 lentiviral vector encodes genes for the anti-CD19 CAR as well as 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) (alpha) eukaryotic promoter and the Human T-cell leukemia virus type (HTLV)-1 R element (EF1 (alpha)/HTLV-1R promoter). The HTLV-1 R element serves as an intron/enhancer for the EF1 (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-B, 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
No
(ii) electroporation
No
(iii) macroinjection
No
(iv) microinjection
No
(v) infection
No
Other
Yes
Specify
Transduction

6. Composition of the insert

(a) Composition of the insert

The insert encodes sequences necessary for the expression and production of the therapeutic CAR transgene. The transgene encodes an N-terminal leader 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, a self-cleaving linker peptide, and EGFRt, a truncated non-functional human epidermal growth factor receptor type I transmembrane polypeptide. The description of transgene elements, including the origin and function of each component, is provided below: Insert Component: N-terminal leader signal sequence Source: Human Function: Directs surface expression of 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: Linker peptide Source: Thosea Asigna Virus Function: Self-cleaving linker polypeptide for separating CAR from EGFRt post translationally Insert Component: N-terminal leader 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 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
No
Integrated in the chromosome
Yes
Other
No

(e) Does the insert contain parts whose product or function are not known?

No

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

1. Indicate whether it is a:

Viroid
No
RNA virus
Yes
DNA virus
No
Bacterium
No
Fungus
No
Animal
Yes

Select from following options:

Mammal
Yes
Insect
No
Fish
No
Other animal
No
Other
No

2. Complete name

(i) Order and/or higher taxon (for animals)
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.
(ii) Family name (for plants)
Not applicable
(iii) Genus
Homo, Thosea, Mus
(iv) Species
Homo sapiens, Thosea Asigna, Mus musculus
(v) Subspecies
Not applicable
(vi) Strain
Not applicable
(vii) Cultivar/Breeding line
Not applicable
(viii) Pathovar
Not applicable

(ix) Common name
Not applicable

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

no
(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism?
no
Give the relevant information specified under Annex III A, point II, (A)(11)(d) of Directive 2001/18/EC
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 related to exposure to biological agents at work?

Yes
If yes, specify the following:
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?

no

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?
no
Specify
(b) Is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
no
Specify
(c) Is the GMO in any way different from the recipient as far as dissemination is concerned?
no
Specify
(d) Is the GMO in any way different from the recipient as far as pathogenicity is concerned?
no
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 CD19-specific CAR and EGFRt. It lacks genes required for HIV replication or pathogenicity.

3. Is the GMO significantly pathogenic or harmfull in any way (including its extracellular products), either living or dead?

no
(b) Give the relevant information 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 development of CC-97540. 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 cant 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 3LTR). 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 formation of replication competent lentivirus (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 from the LTR is significantly reduced due to the 3LTR 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 systemic lupus erythematosus (SLE) patients. 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 CC-97540. 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 and HTLV 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. CC-97540 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 CC-97540 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 CD-19-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) will be infused to a patient enrolled in a clinical trial with the aim of recognizing and lysing CD19+ B-cells (including the autoreactive B cells and plasmablasts). The purpose of the release is to conduct a Phase 1, Multicenter, Open-Label Study Of CC-97540 CD19-Targeted NEX-T Chimeric Antigen Receptor (CAR) T Cells, in Participants with Severe, Refractory Systemic Lupus Erythematosus (SLE). The CC-97540 drug product will not be released into the environment. No significant environment effects are expected. 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?

No

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):

Hospital Universitario Marqus de Valdecilla. Av. de Valdecilla, 25, 39008 Santander, Cantabria. Hospital Universitari Vall dHebron. Passeig de la Vall dHebron, 119-129, 08035 Barcelona

(b) Size of the site (m2)

(i) actual release site (m2)
Administration of CC-97540 will take place in a clinical setting, in a hospital room.
(ii) wider release area (m2)
Administration of CC-97540 will take place in a clinical setting, in a hospital room.

(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. CC-97540 will be infused once per patient at a target dose range of 10 to 25 x 106 CAR-positive viable T cells (CAR+ T cells).

(b) Duration of the operation:

The duration of the operation is 1 hour, which is the time it takes to infuse the patient with the drug product during the clinical trial.

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

The CC-97540 drug product containing T cells transduced with the anti-CD19 CAR LVV is administered intravenously into the subject under standard controlled conditions for cell transplant at the clinical site. CC-97540 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. CC-97540 will be thawed on site and administered to the patient via intravenous infusion in a hospital infusion area. The appropriate clinical site personnel will be trained in handling and administration, thawing and product accountability procedures. Any manipulations of the CC-97540 drug product will be carried out under the appropriate biohazard containment level. The Sponsor has assigned Biosafety Level 1 (BSL1) to CC-97540, since according to the risk assessment of the product, it is meeting the conditions listed in Table 1 of the document entitled 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 to which the competent authorities of many member states, including Spain, Germany, France, Italy and Belgium have endorsed. As described in this document, human cells genetically modified by lentiviral vectors cannot proliferate in the environment. Additionally, for CC-97540, the risk of the formation of replication competent virus or the presence of infectious viral vector particles in the finished product is negligible. Based on these points and in consideration of the aforementioned document, it is reasonable to downgrade CC-97540 finished drug product to BSL1 for activities downstream of manufacturing (i.e., after transduction). Prior to and during administration to the patient, 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 CC-97540 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. CC-97540 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 CC-97540 (material remaining in the bags), the bags, 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 institutions biohazard disposal policy for tissues with bloodborne pathogens or potentially infectious patient material. Used transfusion bags 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 hospital 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 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.)

CC-97540 will be administered in patient in a hospital 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 CC-97540 is ongoing. There are no applicable relevant data regarding potential impacts from previous releases carried out with CC-97540. CC-97540 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

1. Name of target organisms (if applicable)

Applicable?
Yes
(i) Order and/or higher taxon (for animals)
Homo sapiens (Primates)
(ii) Family name (for plants)
This section is not applicable. The target organism is the autologous patient recipient. The transduced autologous T cells are not released into the environment
(iii) Genus
This section is not applicable. The target organism is the autologous patient recipient. The transduced autologous T cells are not released into the environment
(iv) Species
This section is not applicable. The target organism is the autologous patient recipient. The transduced autologous T cells are not released into the environment
(v) Subspecies
This section is not applicable. The target organism is the autologous patient recipient. The transduced autologous T cells are not released into the environment
(vi) Strain
This section is not applicable. The target organism is the autologous patient recipient. The transduced autologous T cells are not released into the environment
(vii) Cultivar/Breeding line
This section is not applicable. The target organism is the autologous patient recipient. The transduced autologous T cells are not released into the environment
(viii) Pathovar
This section is not applicable. The target organism is the autologous patient recipient. The transduced autologous T cells are not released into the environment
(ix) Common name
This section is not applicable. The target organism is the autologous patient recipient. The transduced autologous T cells are not released into the environment

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

Applicable?
Yes
Specify
CC-97540 CAR T cells are used in the treatment of patients with systemic lupus erythematosus (SLE). When injected into the patient CC-97540 cells effectively recognize and target CD19+ B-cells (including the autoreactive B cells and plasmablasts), 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 or HTLV (and that could lead to in vivo recombination leading to formation of RCL), in patients is extremely low as no HIV+ or HTLV+ patients are exposed to CC-97540. Subjects are screened prior to acceptance into the current CC-97540 clinical study. No CC-97540 product is made from HIV+ or HTLV+ subjects, therefore eliminating the possibility of recombination of the LVV with HIV or HTLV. 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. In summary, no interactions are expected between CC-97540 and other organisms in the environment.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?

no

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 CC-97540 from the clinical study site to any other ecosystem. All clinical waste is destroyed according to hospitals procedures for the disposal of bio-hazardous waste.

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)
There are no non-target organisms which may be unintentionally significantly harmed by the release of the GMO. This section is not applicable
(ii) Family name (for plants)
There are no non-target organisms which may be unintentionally significantly harmed by the release of the GMO. This section is not applicable
(iii) Genus
There are no non-target organisms which may be unintentionally significantly harmed by the release of the GMO. This section is not applicable
(iv) Species
There are no non-target organisms which may be unintentionally significantly harmed by the release of the GMO. This section is not applicable
(v) Subspecies
There are no non-target organisms which may be unintentionally significantly harmed by the release of the GMO. This section is not applicable
(vi) Strain
There are no non-target organisms which may be unintentionally significantly harmed by the release of the GMO. This section is not applicable
(vii) Cultivar/Breeding line
There are no non-target organisms which may be unintentionally significantly harmed by the release of the GMO. This section is not applicable
(viii) Pathovar
There are no non-target organisms which may be unintentionally significantly harmed by the release of the GMO. This section is not applicable

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

7. Likelihood of genetic exchange in vivo

(a) from the GO to other organisms in the release ecosystem:
The CC-97540 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+ or HTLV+ patients are exposed to CC-97540. Subjects are screened prior to acceptance into the planned clinical study. HIV positive and HTLV positive subjects are excluded from participating in the study. No CC-97540 product is made from HIV or HTLV positive subjects, therefore eliminating the possibility of recombination of the inserted proviral sequences with HIV or HTLV.
(b) from other organisms to the GMO:
The CC-97540 drug product will exist as differentiated T cells in the subject. 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 CC-97540 drug product is created, no further gene transfer is anticipated.

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in simulated 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

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 and cytometry-based methods to quantify CAR transgene.
2. Methods for monitoring ecosystem effects
Not applicable. CC-97540 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 CC-97540 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 (m2)
Not applicable. The CC-97540 drug product is not released into the environment. Moreover, the CC-97540 drug product (autologous CAR T cells) is not capable of surviving in the environment.
5. Duration of the monitoring
All subjects who receive CC-97540 will be monitored up to completion of the study, lost to follow-up or withdrawal of consent for delayed toxicities related to CC-97540, viral vector safety, disease status, survival status, subsequent lupus therapies, etc., every 4 weeks to 3 months until the end of trial (2 years after the last subject received CC-97540). Thereafter subjects will be asked to enroll in a separate long-term follow-up protocol GC LTFU 001 for a total of 15 years post last drug product infusion.
6. Frequency of the monitoring
All Adverse Events (AEs) and Serious Adverse Events (SAEs) will be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and until 3 months following CC-97540 infusion. After 3 months following CC-97540 infusion until end of study, only the following AEs will be collected: All AEs and SAEs suspected related to CC-97540 or study procedures All new malignancies regardless of relationship to CC-97540 Monitoring of the GMO by qPCR will be performed at Day 1, 4, 8, 11,15, 18, 22, 29, 57, 85, 169, 253, 365, 547, 729, and at the time of a flare during the first two years following infusion. After the D729 visit subjects will be asked to enroll on a long-term follow-up study on which qPCR testing will be performed every 6 months through year 5 and then annually up to year 15 as long as the transgene remains detectable. Monitoring of the GMO by flow cytometry will be performed at Day 1, Day 4, 8, 11, 15, 18, 22, 25, and 29.

I. Information on post release and waste treatment

I. Information on post release and waste treatment

1. Post-release treatment of the site
The Sponsor will provide a CC-97540 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 institutions 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 measures 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 CC-97540 including product container(s), IV administration sets, and any supplies used in the preparation that have been in contact with CC-97540. Type and amount of waste is also documented on a Product Disposal/Destruction Form and filed in the Investigational Site File (ISF).

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 institutions 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

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 are in place at hospitals and research institutions for the treatment of medical waste which may contain bloodborne pathogens. CC-97540 (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 a controlled and insulated GMP manufacturing site based outside the EU; and it degrades rapidly in the environment.

2. Methods for removal of the GMOs of the areas potentially affected

In case of accidental spill of CC-97540 (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 hospitals procedures.

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

No plant, animal or soil will be in the transplant unit where CC-97540 is administered to the subject.

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

The CC-97540 drug product (transduced cells) and the anti-CD19 CAR lentiviral vector do not encode any pathogenic genes. The transduced cells are not viable outside of the body of the treated subjects. The lentiviral vector used to manufacture CC-97540 degrades rapidly in the environment. The administration of the GMO to immunocompetent people leads to rejection of the cells. Therefore, no undesirable effects are expected.