PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a) Member State of notification: The Netherlands

(b) Notification number: B/NL/19/005

(c) Date of acknowledgement of notification: 28/06/2019

(d) Title of the project

A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Triplet Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3)

Proposed period of release

1 December 2019 to 31 December 2040

2. Notifier

Name of institution or company:

The Sponsor of Study bb2121-MM-003 is Celgene Corporation. Bluebird bio Inc. with its wholly owned subsidiary bluebird bio France is collaborating with Celgene Corporation for the development of the product bb2121 and supplies the lentiviral vector for bb2121.

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid (.)

RNA virus (.)

DNA virus (.)

bacterium (.)

fungus (.)

animal

- mammals (X)
- insect (.)
- fish (.)

- other animal (.) specify phylum, class

other, specify (kingdom, phylum and class)

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

The GMO, referred to as bb2121, is an autologous *Homo Sapiens* T lymphocyte population transduced with the anti-BCMA02 CAR lentiviral vector (LVV), which encodes a chimeric antigen receptor (CAR) targeting the human B cell maturation antigen (BCMA).

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

The inserted CAR transgene is stably integrated into the genome of the patient's T cells. The LVV encodes only genes necessary for the expression of the chimeric antigen receptor, 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): FR, DE, ES, BE, IT, UK, NL, NO, SE

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

Yes (X) No ()

If yes:

- Member State of notification : FR
- Notification number: DUO#4004
- Member State of notification : ES
- Notification number: B/ES/17/18
- Member State of notification : DE
- Notification number: Study BB2121-MM-001, EudraCT 2017-002245-29
- Member State of notification : IT
- Notification number: BG/IC/Op2/18/001 and BO/IC/Imp2/18/002
- Member State of notification : BE
- Notification number: SBB 219 2017/0768

Please use the following country codes:

Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

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

Yes (X) No ()

If yes:

- Member State of notification : United States, Canada
- Notification number: NIH protocol # 1507-1443

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

No environmental impact is expected from the administration of bb2121 drug product to subjects in clinical trial bb2121-MM-003. bb2121 drug product 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 shedding is 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

1. Recipient or parental organism characterization:

The following information is provided for the patient as the parental organism.

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

(select one only)

viroid (.)

RNA virus (.)

DNA virus (.)

bacterium (.)

fungus (.)

animal

- mammals (X)
- insect (.)
- fish (.)
- other animal (.)

(specify phylum, class)

other, specify

2. Name

The following information is provided for the patient as the parental organism.

(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

3. Geographical distribution of the organism

The following information is provided for the patient as the parental 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 points not applicable for 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 to human cells

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

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

4. Natural habitat of the organism

The following information is provided for the patient as the parental 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	(.)
in association with animals	(.)

other, specify:

Not applicable to human cells

(b) If the organism is an animal: natural habitat or usual agroecosystem:

Not applicable. bb2121 is a human T cell population intended for autologous use. The starting PBMC population was obtained by apheresis from the subject, followed by bb2121 manufacture and infusion to the same subject.

5. (a) Detection techniques

Quantitative PCR and common techniques of blood cell analysis (e.g. flow cytometry)

(b) Identification techniques

Quantitative PCR and 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)

The recipient organism is *Homo sapiens*

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 (.)

The recipient organism is *Homo sapiens.*

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 multiple myeloma patients. 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.

8. Information concerning reproduction

Not applicable for human T lymphocyte population.

(a) Generation time in natural ecosystems:

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

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

(d) Factors affecting reproduction:

9. Survivability

The following information is provided for the patient as the parental organism.

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

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

Not applicable for human cells

(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 in the general environment, the T cells will not survive.

10. (a) Ways of dissemination

Human T cells can only be transmitted between individuals through injection. There are no mechanisms of dissemination outside the human body, therefore, no dissemination in the environment is expected.

(c) Factors affecting dissemination

In any human recipients other than the autologous patient, an immune cell-mediated response will rapidly eliminate the disseminated blood cells.

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)

None.

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-BCMA02 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

The goal of the genetic modification is to add one or more copies of the gene for a chimeric antigen receptor specific to BCMA (CAR; the "therapeutic gene") to the autologous T cells by transduction. In vivo the transduced cells will express the therapeutic gene and become capable of recognising and responding to BCMA on the surface of B cells. BCMA is consistently expressed on plasma cells and myeloma cells from multiple myeloma patients. The presence of T cells capable of recognizing BCMA-expressing B cells is expected to result in reduction in the tumor load and improvements in the overall survival of treated patients, as a result of T cell activation.

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

Anti-BCMA02 CAR lentiviral vector (LVV) is a replication defective, self-inactivating (SIN), recombinant human immunodeficiency virus type 1 (HIV 1) based LVV, encoding a CAR specific for BCMA

(c) Host range of the vector

Lentiviral vectors of this type are capable of transducing animal and insect cells. However, it is important to emphasize that the Anti-BCMA02 CAR lentiviral vector is not replication competent and does not encode any pathogenic genes

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

Yes (X) No (.)

antibiotic resistance (.)

other, specify : The therapeutic gene product (anti-BCMA T cell receptor) is identified by flow cytometry, and lentiviral vector back-bone sequences are identified and quantified by qPCR.

Indication of which antibiotic resistance gene is inserted: None. No antibiotic resistance genes are present in the Anti-BCMA02 CAR lentiviral vector.

(e) Constituent fragments of the vector

The therapeutic anti-BCMA02 CAR gene product is a chimeric receptor, a multi-domain protein consisting of the extracellular antigen recognition domain (V_L and V_H), the CD8α hinge domain, a transmembrane domain (CD8 TM), and the intracellular CD137 co-stimulatory (4-1BB) and CD3zeta chain signaling domains. It is composed of an anti-BCMA02 single chain variable fragment (scFv) operably linked to T cell signaling domains by a CD8α transmembrane and truncated hinge region. The scFv was constructed by connecting the heavy and light variable fragments from an anti-BCMA antibody clone fused with a short flexible linker sequence. The T cell signaling domains include endodomains from CD3ζ, a component of the T cell receptor complex, and CD137 (4-1BB). The anti-BCMA02 CAR gene is under the transcriptional control of the myeloproliferative sarcoma virus enhancer, negative control region deleted, dl587rev primer-binding site substituted (MND) promoter. An amino terminus CD8α signal peptide shuttles the anti-BCMA02 CAR to the surface of an engineered T cell. T cells engineered with the anti-BCMA02 CAR molecule gain recognition and cytolytic function to cells expressing BCMA including multiple myeloma and some lymphoma tumors.

A schematic of the anti-BCMA CAR is shown below.

Anti-BCMA Chimeric Antigen Receptor

Abbrev.: V_L, light chain variable domain; V_H, heavy chain variable domain; TM, transmembrane

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

(i) transformation (.)

(ii) electroporation (.)

(iii) macroinjection (.)

(iv) microinjection (.)

(v) infection (.)

(vi) other, specify Transduction

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

(i) transformation (.)

(ii) microinjection (.)

(iii) microencapsulation (.)

(iv) macroinjection (.)

(v) other, specify (.)

6. Composition of the insert

(a) Composition of the insert

This is summarized under 6(c), below.

(b) Source of each constituent part of the insert

This is summarized under 6(c), below.

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

The following table provides the composition of the insert, the source of each key constituent part and its function. The insert also includes synthetic non-functional linker sequences to ensure functionality of the insert.

No functional HIV genes are encoded in the anti-BCMA02 CAR (bb2121) drug product insert. The insert encodes sequences necessary for the expression and production of the therapeutic CAR gene. The HIV sequences that are retained are necessary for the packaging and delivery of the insert. The insert has no replication function and does not encode any pathogenic genes. Additional sequences are derived from human genes encoding components of the T cell receptor. Anti- BCMA02 CAR lentiviral vector and bb2121 drug product are both tested to ensure the absence of replication competent lentiviral vector.

Insert Component	Source	Function
HIV-1 Repeat, unique 5'site PBS and Ψ packaging sequences	pNL4-3; GenBank Reference Accession #M19921.2 (Maldarelli et al., 1991)	Required for insertion of provirus DNA into the chromosome
HIV-1 gag region	pNL4-3 GenBank Reference Accession #M19921.2 (Maldarelli et al., 1991)	Secondary structures required for vector packaging.
HIV-1 Central Polypurine Tract (cPPT)	pNL4-3 GenBank Reference Accession #M19921.2 (Maldarelli et al., 1991)	Required for reverse transcription
HIV-1 env region Rev Response Element (RRE)	PgTAT-CMV GenBank Reference Accession #M14100.1 (Malim et al, 1988)	Binding site for Rev, for efficient packaging of the vector RNA
MND promoter	pccl-c-MNDU3c-x2 (Challita et al., 1995)	Promoter drives T cell-specific expression
Anti-BCMA02 scFv (VL-linker-VH)	Synthetic	Therapeutic gene
CD8a hinge and Transmembrane region	GenBank Reference Accession # NM_001768 (Milone et al., 2009)	Ensures correct T cell receptor conformation
CD137 (4-1BB) signaling domain	GenBank Reference Accession # NM_001561 (Milone et al., 2009)	Ensure correct T cell receptor function
CD3-ζ signaling domain	GenBank Reference Accession # NM_000734 (Milone et al., 2009)	Ensure correct T cell receptor function
HIV-1 unique 3' region and repeat region.	pNL4-3; GenBank Reference Accession #M19921.2 (Maldarelli et al., 1991)	Required for insertion of provirus DNA into the chromosome

References are as follows:

Challita, P.M., Skelton, D., el-Khoueiry, A., Yu, X.J., Weinberg, K., and Kohn, D.B. (1995). Multiple modifications in cis elements of the long terminal repeat of retroviral vectors lead to increased expression and decreased DNA methylation in embryonic carcinoma cells. J Virol 69, 748-755.

Maldarelli, F., Martin, M.A., and Strebel, K. (1991). Identification of posttranscriptionally active inhibitory sequences in human immunodeficiency virus type 1 RNA: novel level of gene regulation. J Virol 65, 5732-5743.

Malim, M.H., Hauber, J., Fenrick, R., and Cullen, B.R. (1988). Immunodeficiency virus rev trans-activator modulates the expression of the viral regulatory genes. Nature 335, 181-183.

Milone, M.C., Fish, J.D., Carpenito, C., Carroll, R.G., Binder, G.K., Teachey, D., Samanta, M., Lakhal, M., Gloss, B., Danet-Desnoyers, G., et al. (2009). Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. Mol Ther 17, 1453-1464.

(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

This section is not applicable.

The donor, Anti-BCMA02 CAR lentiviral vector, is an artificial organism. This vector uses the murine leukemia virus-derived MND promoter to drive expression of the chimeric receptor, a multi-domain protein consisting of the extracellular antigen recognition domain (VL and VH), the CD8α hinge domain, a transmembrane domain (CD8 TM), and the intracellular CD137 co-stimulatory (4-1BB) and CD3zeta chain signaling domains. The Anti-BCMA02 CAR lentiviral vector does not encode for any HIV proteins; the only HIV derived sequences in the transcript are the repeat regions that have been made self-inactivating by deleting promoter/enhancer sequences, and attenuated regions of the proteins and element that aid in the production, packaging, or transfer of the transcript containing the therapeutic gene. Additional sequences are derived from human genes encoding components of the T cell receptor.

(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 …

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:

(a) 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):

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

Group 2

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

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

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?

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

Specify

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?

Yes (.) No (X) Unknown (.)

Specify

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

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

Specify

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

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

Specify

2. Genetic stability of the genetically modified organism

In bb2121, the inserted CAR transgene is stably integrated into the genome of the patient's T cells. The inserted CAR transgene encodes only genes necessary for the expression of the chimeric antigen receptor, and lacks the required genes for HIV replication or pathogenicity. In addition, the inserted CAR transgene does not have the capacity for replication and mobilisation.

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

Yes (.) No (X) Unknown (.)

(a) to which of the following organisms?

humans (.)

animals (.)

plants (.)

other (.)

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

4. Description of identification and detection methods

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

Cells transduced with Anti-BCMA02 CAR lentiviral vector (i.e. bb2121 drug product) are not released into the environment, and are not stable under uncontrolled environmental conditions. They are infused into the subject from whom the autologous cells were originally obtained, and are detected using PCR specific to the integrated LVV sequences, or flow cytometry with a labelled antibody specific to the anti-BCMA CAR.

(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 therapeutic gene product (the CAR).

F. Information relating to the release

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

The bb2121 drug product (transduced T cells) is not released into the environment. It will be administered intravenously into subjects enrolled in bb2121 studies for the treatment of multiple myeloma, under highly controlled conditions for cell transplant at the clinical study site. The transduced cells may migrate to the bone marrow or may remain in the peripheral circulatory system post-infusion.

The bb2121 drug product begins with the isolation of peripheral blood mononuclear cells (PBMCs) at a cGMP manufacturing facility in the EU from the patient's leukapheresis collection which is performed at the clinical study site. The isolated PBMCs are transported to a cGMP manufacturing facility in the US, where they are transduced with Anti-BCMA02 CAR lentiviral vector to produce the final bb2121 drug product. Each lot of bb2121 drug product is tested to ensure identity and purity prior to release. The bb2121 drug product is then released and transported back to the clinical site under controlled conditions, where it is stored prior to infusion.

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

Yes (.) No (X)

If yes, specify

3. Information concerning the release and the surrounding area

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

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

(b) Size of the site (m^2): The entire Erasmus MC covers thousands of m2

The patients will be treated in a hospital room.

(i) actual release site (m^2): hospital room of 15 to 20 m2

(ii) wider release site (m^2): not applicable

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

Not applicable

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

Not applicable

4. Method and amount of release

(a) Quantities of GMOs to be released:

It is planned that up to 450 million T cells containing the gene for the anti-BCMA chimeric antigen receptor will be administered intravenously to each patient as a single dose. Approximately 254 patients will be treated with bb2121 in this study.

(b) Duration of the operation:

Only during infusion (1 hour) of the patient 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 bb2121 drug product containing T cells transduced with Anti-BCMA02 CAR lentiviral vector is administered intravenously into the subject under standard controlled conditions for cell transplant at the clinical site. bb2121 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. bb2121 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 bb2121 drug product will be carried out under the appropriate biohazard containment level. Prior to and during administration the GMO is contained; there will be no activities where third parties including medical personnel can come into direct contact with it. The administration of bb2121 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. bb2121 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 bb2121 (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 institution's 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 GMP facility. Contaminated waste and materials will be incinerated.

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 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.)

Not applicable.

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 bb2121. No bb2121 was released into the environment.

bb2121 is currently being investigated in 5 ongoing clinical studies, CRB-401, BB2121-MM-001, BB2121-MM-002, BB2121-MM-003, LTF-305 and GC-LTFU-001. After completion of, or discontinuation from studies, CRB-401, BB2121-MM-001, BB2121-MM-002 or BB212-MM-003, bb2121-infused subjects are asked to enroll into studies LTF-305 or GC-LTFU-001, where subjects are followed for up to 15 years post infusion. Initial analyses of bb2121 safety and efficacy in the CRB-401 study have been published (Raje, 2018).

Reference:
Raje N, Berdeja J, Lin Y, Munshi N, Siegel D, Liedtke M, et al. bb2121 Anti-BCMA CAR T Cell Therapy in Patients With Relapsed/Refractory Multiple Myeloma: Updated Results From a Multicenter Phase I Study. Oral Presented at: 2018 Annual Meeting of the American Society of Clinical Oncology (ASCO): 2018;Chicago, IL, USA. Abstract No. 8007

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 that comprise bb2121 are not released into the environment.

1. Name of target organism (if applicable)

(i)	order and/or higher taxon (for animals)	Homo sapiens
(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)

bb2121 drug product contains autologous T cells transduced with the Anti-BCMA02 CAR lentiviral vector encoding a chimeric anti-BCMA T cell receptor gene. Upon infusion to the patient, the cells may migrate to the bone marrow or remain in circulation. It is expected that bb2121 will have a

therapeutic effect in patients with multiple myeloma expressing B cell maturation antigen (BCMA). Transduced cells are not viable in the environments outside of the subject

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

Possible interaction with other foreign organisms as HIV present in the patients is extremely low as no HIV+ patients are exposed to bb2121. Subjects are screened prior to acceptance into the current bb2121 clinical study. No bb2121 product is made from HIV positive 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 shedding 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 bb2121 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 (.)

Give details

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

There is no possibility to disseminate bb2121 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.

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

None. 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 bb2121 drug product is made with a replication incompetent vector that stably inserts the proviral DNA encoding the chimeric antigen receptor into the genome of the autologous T cells. The anti-BCMA02 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 shedded 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 exposed to bb2121

Subjects are screened prior to acceptance into the current bb2121 clinical study. No bb2121 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 bb2121 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 bb2121 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 stimulated natural environments (e.g. microcosms, etc.):

Not applicable.

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 cytometric methods for identification and quantification of the therapeutic cell type, with a labelled antibody specific to the anti-BCMA CAR .

2. Methods for monitoring ecosystem effects

Not applicable. The bb2121 drug product is not released into the environment.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms

Not applicable. The bb2121 drug product is not released into the environment.
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 bb2121 drug product is not released into the environment.

Moreover, the bb2121 drug product (autologous CAR T cells) is not capable of surviving in the environment.

5. Duration of the monitoring

All subjects who receive bb2121 will be monitored until progressive disease or withdrawal of consent after which they will then have a 28-day safety follow-up visit. Then subjects will be followed in the Survival Follow-up for delayed toxicities related to bb2121, viral vector safety, disease status, survival status, subsequent anti-myeloma therapies including subsequent date of progression and the occurrence of second primary malignancies (SPMs), every 3 months until the end of trial (5 years after the last subject has been randomized). 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

The frequency of monitoring is at baseline, during the first month on Days 1-15, 18, 22, 25, monthly thereafter until 24 months post infusion and then every three months for subjects that have not progressed and until progression (posttreatment follow-up period) and every three months for subjects that have progressed (survival follow-up)

I. Information on post-release and waste treatment

1. Post-release treatment of the site

The bb2121 drug product (transduced T cells) is not released in the environment. It is administered intravenously into the subject under standard controlled conditions for cell transplant at the clinical site.

All clinical waste is destroyed according to hospital bio-hazard disposal procedures.

All manufacturing waste is destroyed according to the manufacturing facility bio-hazard disposal procedures. bb2121 drug product and Anti-BCMA02 CAR lentiviral vector are manufactured outside the EU.

2. Post-release treatment of the GMOs

The bb2121 drug product is not released into the environment. bb2121 is infused into the patient as a one-time therapeutic treatment.

3. (a) Type and amount of waste generated

The waste generated following treatment of patients with bb2121 drug product is minimal and consists mainly of residual cells remaining in the infusion bag.

All waste is destroyed according to hospital or manufacturing facility bio-hazard disposal procedures after appropriate disinfection.

(b) Treatment of waste

All waste is destroyed according to hospital or manufacturing facility bio-hazard disposal procedures.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

bb2121 (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. The Anti-BCMA02 CAR lentiviral vector is used to transduce ex vivo the autologous T cells in the controlled and insulated manufacturing laboratory setting. 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 bb2121 (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

No plant, animal or soil will be in the manufacturing facility or the transplant unit where bb2121 is administered to the subject.

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

The bb2121 drug product (transduced cells) and the Anti-BCMA02 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-BCMA02 CAR lentiviral vector 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.