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

Application for authorization to use the genetically modified BMS-986393 (also known as CC-95266) in Norway:

1. Details of notification

(a) Member State of notification Norway
(b) Notification number
(c) Date of acknowledgement of notification
(d) Title of the project
A Phase 3, Randomized, Open-Label, Multicenter Study to Compare the Efficacy and Safety of BMS-986393, a GPRC5D-directed CAR-T Cell Therapy, Versus Standard Regimens in Adult Participants with Relapsed or Refractory and Lenalidomide-refractory Multiple Myeloma
(Trial number CA088-1007)

(e) Proposed period of release From February 2025 until July 2032

2. Notifier

Name of institution or company:
The sponsor of the study is Celgene Corporation, Route 206 and Province Line Road Princeton, NJ USA 08543 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 BMS-986393 (also known as CC-95266) consists of autologous *Homo sapiens* T cells transduced with a lentiviral vector (LVV) which encodes a chimeric antigen receptor (CAR) specific for G protein-coupled receptor class C, group 5, member D (GPRC5D), and directed against GPRC5D-expressing cells. BMS-986393 is a second-generation CAR-T cell construct comprised of autologous CD3+ T cells expressing a GPRC5D-specific CAR consisting of a fully human derived single chain variable fragment (scFv) binding domain sequence, fused in sequence to the human IgG4 hinge, the human CD28 transmembrane region, the human 4-1BB and CD3ζ (zeta) chain signaling domains.

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

The sequences encoding the GPRC5D targeting CAR are introduced to the T cells by *ex vivo* transduction with a third-generation replication-incompetent self-inactivating (SIN) lentiviral vector. 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 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; GR; HU; IT; NL; PL; PT; RO; SE

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

Yes () No (X)

If yes:

- Member State of notification: **XX**
- Notification number:

Please use the following country codes:
Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; Greece GR; Romania RO; Poland PO; Italy IT; Czech Republic CZ; Netherlands NL; Norway NO; Portugal PT; Sweden SE , Hungary HU

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 US: INDs 026033 and 029333;

- Member State of notification — Canada
- Notification number — Substances Notification (NSN) No. 21715

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

No environmental impact is expected from the administration of BMS-986393 drug product to subjects in this clinical trial. BMS-986393 drug product will be supplied to the clinical site for intravenous infusion into the patient. 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 environment outside of the patient. Viral vector persistence and replication in the environment are highly unlikely due to the use of a replication incompetent LVV.

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

The information provided in this section relates to the human T lymphocytes as the recipient and parental organism.

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 (.), 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 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

(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. BMS-986393 is a human T cell population intended for autologous use. It is manufactured from autologous leukapheresis, followed by BMS-986393 manufacture and infusion into the same patient.

5. (a) Detection techniques

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

(b) Identification techniques

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 and/or Refractory Multiple Myeloma (R/R MM). 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. The hazard is similar to that of human blood and/or tissue which may contain bloodborne pathogens.
Patients will be tested for HIV, HBV and HCV prior to leukapheresis and excluded from the clinical study if tested positive.
Autologous blood leukapheresis source material is controlled for viral adventitious agents as per country specific guidance.

8. Information concerning reproduction

Not applicable for human T-lymphocytes

(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

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

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

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

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

The information provided in this section relates to the autologous T cells that are genetically modified by transduction with the anti-GPRC5D 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 purified autologous CD3+ T cells leads to the integration of the transgene into the host genome, resulting in the expression of anti GPRC5D-specific CAR on the surface of T cells. The anti-GPRC5D-specific CAR consists of a fully human derived scFv binding domain fused to the human IgG4 hinge, the human CD28 transmembrane, and the human 4-1BB and CD3ζ chain signaling domains. BMS-986393 CAR T cells are expected to recognize and kill GPRC5D-expressing 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 v20054 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 GPRC5D antigen.

(c) Host range of the vector

The v20054 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 is not expected to contain either residual infectious lentiviral vector particles or 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-GPRC5D 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-GPRC5D 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 production 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 LVV 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 v20054 lentiviral vector encodes gene for the anti-GPRC5D CAR 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.

Other inserted non-coding 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 any HIV proteins.

More precisely, the anti-GPRC5D 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. 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 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 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 shed from the final host cell due to the absence, in the provirus, of all the accessory proteins that confer 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 transgene.

The composition and 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-GPRC5D scFv
Source: Human and Synthetic
Function: GPRC5D-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

(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).

(f) Location of the insert in the host organism

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

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

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

1. Indicate whether it is a:

viroid (.)
RNA virus (.)
DNA virus (.)
bacterium (.)
fungus (.)

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

other, specify

2. Complete name

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

Transgene sequences (anti-GPRC5D CAR) are all human-derived.

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	Homo
(iv)	species	Homo sapiens
(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 (.) No (X)

If yes, specify

Sequences of the transgene are human-derived. Human is 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

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 GPRC5D targeting CAR are introduced to the T cells by 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 the gene for expression of GPRC5D-specific CAR. 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?
Not applicable

humans (.)
animals (.)
plants (.)
other (.)

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

The GMO is neither pathogenic nor harmful. No safety issues have been reported during the nonclinical and clinical development of BMS-986393.

Moreover, the v20054 vector 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 cannot form progeny virions that would result in the spread of a replicating virus or recombination with other retroviruses.
The v20054 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 (derived from HIV-1) on another plasmid, and the *rev* gene (derived from HIV-1) on a third plasmid. The transgene is encoded on a transfer plasmid (derived from HIV-1 but self-inactivating due to a deletion in the 3'LTR). Additionally, a supplemental plasmid is added which encodes a modified U1 pre-snRNA which can increase lentiviral vector titer. All sequences are provided *in trans* by transfection of plasmids into the HEK293T 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 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 Relapsed and/or Refractory Multiple Myeloma (R/R MM). 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 BMS-986393.

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-GPRC5D CAR lentiviral vector (i.e., BMS-986393 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 BMS-986393 using ddPCR specific to the integrated LVV sequences.

(b) Techniques used to identify the GMO

ddPCR is used to measure the integrated vector sequences and detect the presence of transduced T cells.

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 targeting GPRC5D-expressing cells, including the malignant cells. Upon binding to GPRC5D-expressing cells, BMS-986393 is designed to activate, proliferate, secrete pro-inflammatory cytokines, and selectively kill GPRC5D-expressing target cells. The purpose of the release is to conduct a Phase 3, randomized, open-label, multicenter study to compare the efficacy and safety of BMS-986393, versus standard regimens in adult participants with Relapsed or Refractory and Lenalidomide-refractory Multiple Myeloma. The BMS-986393 drug product will not be released into the environment. No significant environmental effects are expected.

Note that the anti-GPRC5D CAR lentiviral vector is used only to transduce *ex vivo* the autologous T cells in a controlled GMP manufacturing facility.

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):

Oslo University Hospital, Rikshospitalet, Department of Hematology,
Sognsvannsveien 20, 0372 Oslo, Norway

(b) Size of the site (m^2):
(i) actual release site (m^2):

Administration of BMS-986393 will take place in a clinical setting, in a hospital room.

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

Administration of BMS-986393will 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. BMS-986393 will be infused once per patient at a target dose of 150 x 10^6 CAR-positive viable T cells (CAR+ T cells).

(b) Duration of the operation:

The entire operation, from the start of thaw (removal from LN2 storage) to the completion of BMS-986393 administration, must be completed within 2 hours.

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

The GMO is administered iv into the patient under standard controlled conditions for cell transplant at the site. BMS-986393 will be shipped to the site in a validated shipping container prior to the scheduled administration. BMS-986393 will be thawed on site in a hospital infusion area. In-house transport of the GMO, residual GMO and samples of study patients is done in a disinfectable, appropriately labelled, leakproof, unbreakable container. The site staff will be trained in handling, administration, thawing, and GMO accountability procedures. Any manipulations of the GMO will be done under the appropriate biohazard containment level. The Sponsor has assigned Biosafety Level 1 (BSL1) to BMS-986393 according to the risk

assessment of the product, it's meeting the conditions listed in 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". As described in this document, human GMOs modified by lentiviral vectors can't proliferate in the environment. For BMS-986393, the risk of the formation of replication competent virus or the presence of infectious viral vector particles in the finished product is negligible. 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 RCL from viral vectors). Additionally, the first 40 clinical lots of the BMS-986393, out of a total of 142 lots manufactured through July 2024, have been tested for RCL, and all results have been negative. As a result, the negligible risk of RCL occurrence defined by the guidance is met. As per the conditions from Table 1 of the document, cells from HIV positive patients/donors are excluded via clinical trial protocol exclusion criteria; however, HTLV positive patients/donors are not excluded from manufacturing. As described above, there is negligible risk of RCL generation in regard to HTLV co-infection. Therefore, handling within BSL1 conditions for activities downstream of product manufacturing is justifiable per the guidance.

Prior to and during administration, the GMO is contained in closed containers; there will be no activities where third parties or medical staff can come into direct contact with it. The administration of GMO will be done at medical centres equipped for the safe administration of biological or cellular products, by experienced staff, appropriately trained in hygiene procedures and standards for safety and infectious materials handling. BMS-986393 contains autologous human T cells therefore, site staff should apply universal precautions for the prevention of transmission of blood-borne infections. During sampling, decontamination of potentially contaminated surfaces and areas, decontamination and disposal of waste and potential leftovers, the medical staff will wear appropriate gowning. All partially used or unused GMO, the bags, the absorbent barrier pads, any supplies used in the preparation and administration process, must be disposed of in accordance with the site 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, to be delivered to the waste room of the site.

Other than standard cleaning and sanitation of the hospital room and the disposal of GMO 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.

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

BMS-986393 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 BMS-986393 is ongoing. There are no applicable relevant data regarding potential environmental impacts from previous releases carried out with BMS-986393. BMS-986393 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)

BMS-986393 CAR T cells are used in the treatment of patients with Relapsed and/or Refractory Multiple Myeloma (R/R MM). When injected into the patient BMS-986393 cells effectively recognize and target GPRC5D-expressing cells. Upon binding to GPRC5D-expressing cells BMS-986393 is designed to activate, proliferate, secrete pro-inflammatory cytokines, and selectively kill GPRC5D-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 BMS-986393. Subjects are screened prior to acceptance into the current BMS-986393clinical study. No BMS-986393 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. In summary, no interactions are expected between BMS-986393 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 BMS-986393 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

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 BMS-986393 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-GPRC5D 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 BMS-986393. Subjects are screened prior to acceptance into the planned clinical study. HIV positive subjects are excluded from participating in the study. No BMS-986393 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 BMS-986393 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 BMS-986393 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. 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 a PCR-based method to quantify CAR transgene.

2. Methods for monitoring ecosystem effects

Not applicable. BMS-986393 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 BMS-986393 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 BMS-986393 drug product is not released into the environment. Moreover, the BMS-986393 drug product (autologous CAR T cells) is not capable of surviving in the environment.

5. Duration of the monitoring

All subjects who receive BMS-986393 will be followed for safety and efficacy for up to 5 years after the last subject was randomized. Upon either prematurely discontinuing from or completing the study, all subjects who receive BMS-986393 will continue to be monitored for delayed toxicities related to BMS-986393, viral vector safety, disease status, survival status, and subsequent multiple myeloma therapies under a separate long-term follow-up (LTFU) protocol GC-LTFU-001 for up to 15 years after the BMS-986393-infusion.

6. Frequency of the monitoring

All Adverse Events (AEs), AEs of special interest (AESI), and Serious Adverse Events (SAEs) must be collected from the time of signing the informed consent form, including those thought to be associated with protocol-specified procedures, and until 6 months after BMS-986393 infusion. From Month 7 after BMS-986393 infusion and until the start of subsequent anti-myeloma therapy or end of study (EOS), whichever occurs first, all AEs related to study treatment and all SAEs and AESI regardless of relationship to study treatment must be collected. From the start of subsequent anti-myeloma therapy and until EOS, all AEs, AESI, and SAEs that are related to study treatment and Grade 5 AEs (fatal) regardless of relationship to study treatment must be collected.

For all subjects who receive BMS-986393, monitoring of the GMO by ddPCR will be performed at Day (D)1 (prior to infusion), D8 (+/- 1 day), D11 (+/- 1 day), D15 (+/- 2 days), month 2 day 1 (M2D1) (+/- 3 days), and M7D1 (+/- 3 days) after the BMS-986393 infusion. From month 7 after infusion, the GMO monitoring will be performed every 6 months until EOS. After either prematurely discontinuing from or completing the study, GMO monitoring will continue per the LTFU protocol (GC-LTFU-001). Additional monitoring will be performed at the time of new malignancy.

I. Information on post-release and waste treatment

1. Post-release treatment of the site

The Sponsor will provide a BMS-986393 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 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 BMS-986393 including product container(s), IV administration sets, and any supplies used in the preparation that have been in contact with BMS-986393. 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 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 are in place at hospitals and research institutions for the treatment of medical waste which may contain bloodborne pathogens. BMS-986393 (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-GPRC5D CAR lentiviral vector is used only to transduce the autologous T cells *ex vivo* in a controlled and insulated GMP manufacturing site; 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 BMS-986393 (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 transplant unit where BMS-986393 is administered to the subject.

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

The BMS-986393 drug product (transduced cells) and the anti-GPRC5D 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 BMS-986393 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.