RESEARCH AND DEVELOPMENT

IDECABTAGENE VICLEUCEL (ABECMA®)

RISK MANAGEMENT PLAN

Version Number: 5.1

Data-lock Point for this RMP: 25-Mar-2025

Date of final sign off: 07-Nov-2025

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LIST OF ABBREVIATIONS

Term	Definition
ADA	Antidrug antibodies
ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
AMT	antimyeloma therapy
ASCT	autologous stem cell transplant
ASR	age-standardised incidence rates
ATC	Anatomical Therapeutic Chemical Classification
BCMA	B cell maturation antigen
CAR	chimeric antigen receptor
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CNS	central nervous system
CrCl	creatinine clearance
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
DLP	data-lock point
DMSO	dimethyl sulfoxide
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic Common Technical Document
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
E+R	evaluation plus reporting
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
EURD	European Union Reference Date
GM	genetically modified
GMCT	Gene Modified Cell Therapy
GVHD	graft versus host disease

Term	Definition
GVP	Good Pharmacovigilance Practices
HBV	hepatitis B virus
HC	high confidence
HCP	healthcare professional
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	haemophagocytic lymphohistiocytosis
HRQoL	health-related quality of life
HSCT	haematopoietic stem cell transplantation
IBD	international birth date
ICANS	immune effector cell-associated neurotoxicity syndrome
Ig	Immunoglobulin
IL	interleukin
IND	Investigational New Drug
INN	International Nonproprietary Name
IS	insertion site
LDC	lymphodepleting chemotherapy
LTFU	long-term follow-up
LVV	lentiviral vector
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MAS	macrophage activation syndrome
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MOA	mechanism of action
MRD	minimal residual disease
NGS	next generation sequencing
NMSC	Non-melanoma skin cancer
OOS	out of specification
OS	overall survival
PASS	postauthorisation safety study
PEPA	Pre-Existing Product Access
PFS	progression-free survival

Term	Definition
PI	proteasome inhibitor
PK	pharmacokinetics
PL	package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	preferred term
QPPV	Qualified Person for Pharmacovigilance
RCL	replication competent lentivirus
RCR	replication competent retrovirus
RMP	Risk Management Plan
RRMM	relapsed and refractory multiple myeloma
SAE	serious adverse event
SEER	Surveillance, Epidemiology and End Results
sHLH	Secondary haemophagocytic lymphohistiocytosis
SIN	Self-inactivating
SMN	second malignant neoplasm
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA queries
T-LGL	T-cell large granular lymphocytosis
TLS	tumour lysis syndrome
ULN	upper limit of normal
US	United States of America
VCN	vector copy number
WT	wild type

EU RMP FOR IDECABTAGENE VICLEUCEL

RMP version to be assessed as part of this application:

Version Number: 5.1

Data-lock Point for this RMP: 25-Mar-2025

Date of Final Sign-off: 07-Nov-2025

Rationale for submitting an updated RMP:

- Updated the timing of the monitoring requirements in the patient educational program (from 4 weeks to 2 weeks)
- Updated the milestones due dates for Transgene assay service to align with the EC decision date
- Updated EU QPPV Contact Person

Summary of Significant Changes in this RMPs

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	NA	V3.2 / 19-Mar-2024
SII Non-clinical part of the safety specification	NA	V1.0 / 29-Jul-2021
SIII Clinical trial exposure	NA	V3.2 / 19-Mar-2024
SIV Populations not studied in clinical trials	NA	V4.1 / 06-Jan-2025
SV Post-authorization experience	Update of Section 2.5 Post-authorization Experience	V5.1 / pending
SVI Additional EU requirements for the safety specification	NA	V1.0 / 29-Jul-2021
SVII Identified and potential risks	Updated the timing of the monitoring requirements in the patient educational program.	V5.1 / pending
SVIII Summary of the safety concerns	NA	V4.1 / 06-Jan-2025
Part III Pharmacovigilance Plan	Updated the milestones due dates for Transgene assay service.	V5.1 / pending
Part IV Plan for post-authorization efficacy studies	NA	V2.1 / 24-Jun-2022
Part V Risk Minimisation Measures	Updated the timing of the monitoring requirements in the patient educational program.	V5.1 / pending
Part VI Summary of the Risk Management Plan	NA	V4.1 / 06-Jan-2025

Summary of Significant Changes in this RMPs

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Updated the milestones due dates for Transgene assay service.	V5.1 / pending
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	NA	V4.1 / 06-Jan-2025
ANNEX 4 Specific adverse drug reaction follow-up forms	NA	V4.1 / 06-Jan-2025
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	NA	V3.2 / 19-Mar-2024
ANNEX 6 Details of proposed additional risk minimisation activities	Updated the timing of the monitoring requirements in the patient educational program.	V5.1 / pending
ANNEX 7 Other supporting data	NA	V1.0 / 29-Jul-2021
ANNEX 8 Summary of changes to the risk management plan over time	Updated to include V5.1	V5.1 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP:

Version number: 4.1

Approved with procedure: EMEA/H/C/004662/IB/0056

Date of approval: 06-Jan-2025

EU RMP Contact Person: PharmD. Roberta Di Menno Di Bucchianico, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Idecabtagene vicleucel (ide-cel)[a]
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic cell and gene therapy (L01XL07)
Marketing Authorisation Holder	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Abecma
Marketing authorization procedure	Centralised
Brief description of the product	Ide-cel is a GM autologous cell-based product containing T cells transduced *ex-vivo* using a replication incompetent LVV expressing a CAR. The CAR construct includes an anti-BCMA scFv-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T cell activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of ide-cel results in CAR-positive T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.
Hyperlink to the Product Information	Refer to eCTD sequence number 0121
Indication(s) in the EEA	**Current:** Treatment of adult patients with relapsed and refractory MM who have received at least two prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. **Proposed:** None.
Dosage in the EEA	**Current:** The target dose is 420×10^6 CAR-positive viable T cells within a range of 260 to 500×10^6 CAR-positive viable T cells. **Proposed:** None
Pharmaceutical form (s) and strength(s)	**Current:** A single dose for infusion containing a dispersion of CAR-positive viable T cells in one or more infusion bags. **Proposed:** None
Is/will the product be subject to additional monitoring in the EU?	Yes

[a] "Idecabtagene vicleucel (ide-cel, bb2121)" will be referred to throughout this RMP as ide-cel, except where "BB2121" is used in clinical study protocol titles.

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

Table 2.1-1: Epidemiologic Characteristics of Patients with Multiple Myeloma

Multiple Myeloma	
Incidence	• MM accounts for approximately 14% to 19% of incident haematologic malignancies.[1,2] • Crude and ASR (world) of incident MM in the population of the EU-27 states are 8.0 and 3.2 per 100,000 persons per year, respectively, based upon estimates obtained from GLOBOCAN 2020 data.[1]
Prevalence	• The prevalence of MM varies from country to country in the EU. Overall, the prevalence of MM in the EU-27 states is estimated to range from 3.68 to 4.88 per 10,000 persons (data on file). In Europe, 50,918 new cases of MM and 32,495 deaths due to MM were estimated in 2020.[1] • The 1-year, 3-year, and 5-year prevalence proportions of MM (for ages 15 years and older) in the EU-27 countries were approximately 7.5 per 100,000 persons, 18.6 per 100,000 persons, and 25.7 per 100,000 persons, respectively.[1] • Gains in survivorship associated with new therapies will increase the prevalence of MM.
Demographics of the population: age, gender, racial and/or ethnic origin	• In Europe, the median age at onset of MM is 72 years.[3] • ASR (world) of incident MM (per 100,000 persons per year) among males and females in Europe rise with increasing age intervals: 0.0 (ages 0 to 14 years), 0.1 (ages 15 to 39 years), 2.7 (ages 40 to 54 years), 12.3 (ages 55 to 69 years), 26.9 (ages 70 and older).[1] • The ASR (world) of incident MM (per 100,000) in men in the EU-27 countries is 4.0, based upon the diagnosis of MM in approximately 20,000 men. In 2020, MM accounted for 1.4% of all incident malignancies (excluding NMSC) in men.[1] • The ASR (world) of incident MM (per 100,000) in women in the EU-27 countries is 2.5, based upon the diagnosis of MM in approximately 15,700 women. In 2020, MM accounted for 1.3% of all incident malignancies (excluding NMSC) in women.[1] • Analysing 18,824 MM registrations with ethnicity obtained by linkage to the English Hospital Episodes Statistics Database, [4] reported markedly higher incidence rates of MM in Black African men (ASR 8.6 per 100,000) and Black Caribbean men (8.3 per 100,000) relative to White men (3.7 per 100,000). Similar results were obtained when MM incidence rates in Black African women (5.8 per 100,000) and Black Caribbean women (5.7 per 100,000) were compared to White women (2.4 per 100,000). This pattern is similar to that reported in the US, where 5-year age-adjusted incidence rates of MM are markedly higher in non-Hispanic Black men compared to non-Hispanic White men (17.0 versus 8.1 per 100,000) and in non-Hispanic Black women compared to non-Hispanic White women (12.9 versus 5.0 per 100,000, respectively), based on 2019 SEER cancer registry data.[5]
Risk factors for the disease	Age is the most important risk factor for MM, although race and gender are also important. While strong familial clustering of MM suggests that underlying genetic factors are important, findings from studies of lifestyle, dietary, occupational and environmental risk factors have been inconsistent.[6,7]
Main treatment options	***Newly Diagnosed MM*** For fit NDMM patients, aged < 70 years in good clinical condition, the 2021 EHA-ESMO clinical practice guidelines recommend several options of induction therapy followed by high-dose melphalan (HDM) conditioning chemotherapy with ASCT

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Multiple Myeloma	
	and lenalidomide maintenance. The induction regimen of bortezomib/ lenalidomide/dexamethasone (VRd) is likely to offer the best risk-benefit profile to-date among triplets based on bortezomib [II, B]; however, VRd lacks direct comparisons with bortezomib/thalidomide/dexamethasone (VTD) or DaraVTD and is not licensed by the EMA. The four-drug combination DaraVTD is more efficacious than VTD [I, A] and is the new standard of care. If this is not available, VTD [I, A] or bortezomib/cyclophosphamide/dexamethasone (VCD) [II, B] may be used. HDM (200 mg/m^2) [I, A] is the standard conditioning regimen before ASCT [I, A]. Maintenance with lenalidomide is considered the standard of care for all MM patients post-ASCT [I, A]. For those not suitable for ASCT, there are 3 new standards of care: VRd; Dara/bortezomib/melphalan/prednisone (DaraVMP); and DaraRd. When DaraRd and DaraVMP are not available, VRd is the preferred option in fit patients; Rd and VMP may be considered for patients who cannot receive the previous regimens.[8] ***Relapsed and Refractory MM*** • There is no consensus among guidelines regarding the optimal treatment for patients with RRMM.[9] • Many factors influence the choice of therapy in the RRMM setting, including age; performance status; comorbidities; the type, efficacy and tolerance of the prior AMT; the number of prior treatment lines; the available remaining treatment options; the interval since the last therapy; and the type of relapse (clinical versus biochemical).[1,10] • Current recommended treatment options for RRMM are described in the 2021 EHA-ESMO clinical practice guidelines and are briefly summarized in the 2 bullets below.[8] • For patients who have received 1 prior line of therapy, the 2021 EHA-ESMO guidelines recommend the following: – Second-line ASCT is an option for patients who received front-line therapy that included an ASCT followed by lenalidomide maintenance and had an initial remission duration of ≥ 36 months (panel consensus). – Patients who had received a bortezomib-based therapy upfront without lenalidomide or Dara should receive an Rd-based regimen, ie, KRd, DaraRd, IRd or EloRd [I, A]. DaraRd provides the best PFS for these patients, while only KRd and EloRd showed an OS benefit over Rd to date. – Patients who are refractory to lenalidomide upfront could receive either PomVD, DaraKd, IsaKd, or DaraVd [I, A]. Of the approved treatments for second-line therapy in lenalidomide-refractory patients, PomVd has the best PFS results. DaraKd has the best *reported* PFS to date in lenalidomide-refractory patients, but DaraKd was awaiting EMA approval at the time the 2021 EHA-ESMO clinical practice guidelines were released/published. Similarly, IsaKd and SVd, which are also suitable for this setting [I, A], were not yet approved by the EMA. – VenVd is an option for patients with t(11;14) who have failed lenalidomide and are sensitive to PIs [I, A], if available. • For patients who have received 2 or more prior lines of therapy, the 2021 EHA-ESMO guidelines recommend the following: – For patients who have been exposed or are refractory to both bortezomib and lenalidomide, DaraKd [I, A], IsaPd [I, A], IsaKd [I, A], and EloPd [II, B] are recommended. – Patients with t(11;14), who are refractory to lenalidomide and are PI-sensitive may be treated with VenVd [I, A], if available.

Table 2.1-1: Epidemiologic Characteristics of Patients with Multiple Myeloma

Multiple Myeloma	
	– For triple-class refractory patients, Sd or belantamab mafodotin monotherapy is recommended [II, B], if available. • Daratumumab, a CD38-directed cytolytic human monoclonal antibody, is approved in RRMM in the EU – in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed MM who are ineligible for ASCT – in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed MM who are eligible for ASCT – in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with MMwho have received at least one prior therapy; and – as monotherapy for the treatment of adult patients with RRMM, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. – The progressive incorporation of daratumumab-based therapy in frontline and early line relapse is leading to a new subset of patients exposed to all 3 AMT classes and for whom survival outcomes are especially poor.[11,12,13] There is no standard of care for subjects who have relapsed after prior exposure to daratumumab. • Teclistamab, a BCMA- and CD3-directed humanised bispecific antibody, is approved in the EU as monotherapy for the treatment of adult patients with RRMM, who have received at least 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.[14] • Melphalan flufenamide is approved in the EU in combination with dexamethasone, for the treatment of adult patients with MM who have received at least 3 prior lines of therapies, whose disease is refractory to at least 1 PI, 1 immunomodulatory agent, and 1 anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy.[15] • Ciltacabtagene autoleucel, a BCMA-directed genetically modified autologous T cell immunotherapy, is approved in the EU for the treatment of adult patients with RRMM, who have received at least 3 prior therapies, including an immunomodulatory agent, a PI and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.[16] • Other drugs or classes of drugs such as histone-deacetylase inhibitors, monoclonal antibodies, antibody-drug conjugates and novel small molecules are under clinical development.
Mortality and morbidity (natural history)	• The course of MM is characterised by a period of disease control after initial therapy followed by progression, typically with subsequently shorter periods of response and relapse with each successive therapy.[1,17] With each relapse and each subsequent line of AMTs, tumours typically recur more aggressively, leading to shorter response duration and ultimately, refractory MM, which is associated with shortened survival times.[18,19,20] Furthermore, each line of therapy is associated with an increased risk of comorbidities, including treatment and disease related complications.[21,22] Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures.[23] • Crude and age-standardised (world) mortality rates of MM in the EU-27 population were estimated to be approximately 5.2 and 1.7 per 100,000,

Table 2.1-1: Epidemiologic Characteristics of Patients with Multiple Myeloma

Multiple Myeloma	
	respectively, based upon GLOBOCAN 2020 data. Within the EU-27 population, 23,275 men and women died with MM in 2020. The cumulative mortality risk of MM is 0.59% in Europe and 0.39% worldwide.[1] • According to GLOBOCAN 2020 data, MM accounts for 1.7% of all deaths among persons with invasive malignancy in the European population.[1] • Between 1989 and 2009, 1206 patients with MM were identified through the Modena Cancer Registry,[24] corresponding to periods of conventional therapy (1988 to 1996), high dose melphalan and ASCT (1997 to 2005) and novel agents (2006 to 2009). Relative survival and OS improved over the years, with little change noted for patients aged ≥ 75 years. The survival of MM patients aged < 65 years and, in particular, 65 to 74 years improved over time, especially after 2006. • In a retrospective analysis of MM patients who received HSCT, median OS was 79.5 months in those < 60 years of age and 63.4 months in those ≥ 60 years of age.[25]
Important co-morbidities	• Renal impairment[26,27,28] • Peripheral neuropathy[29,30,31] • Thromboembolic events[32,33,34,35] • Anaemia, leukopenia and infection[26,36] • Secondary malignancies[37,38,39,40,41,42] • GVHD[43,44] • Bone diseases[45,46,47] • Gastrointestinal haemorrhage[48,49]

2.2 Nonclinical Part of the Safety Specification

Full details of the nonclinical safety data for ide-cel are presented in the Nonclinical Overview (MAA, Procedure EMEA/H/C/0004662, Module 2, Section 2.4 Nonclinical Overview).

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
Toxicity Studies **Single and Repeat-dose Toxicity** • No single-dose toxicity studies were conducted with ide-cel; traditional animal studies employing common toxicology study designs are not appropriate for ide-cel since autologous human T cells do not graft in immunocompetent animals. The only in vivo nonclinical studies conducted with ide-cel were intravenous single-dose pharmacology studies to evaluate the activity and dose-response relationship of ide-cel. The two models used in pharmacology studies were subcutaneous MM RPMI-8226 and systemic Burkitt Lymphoma Daudi tumour cell line xenografts in NSG mice.	Preclinical models for testing CAR T cells are currently limited to the xenotransplantation of human CAR T cells into immunocompromised murine models. It should be noted these experimental systems are limited in their ability to fully model on-target/off-tumour toxicity observed in Phase 1 clinical studies, such as CRS and neurologic toxicity. Alternative animal models (eg, immune-competent rodents, dog, monkey) are not available at this time.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
• No repeat-dose toxicity studies of ide-cel were conducted as ide-cel will be administered to patients as a single dose (infusion).	
Reproductive and Developmental Toxicity • In the absence of a relevant animal model for assessing the safety of ide-cel, no reproductive or developmental toxicity studies were conducted with ide-cel.	In clinical studies, ide-cel was administered after immunosuppressive preconditioning with lymphodepletion agents, which affects reproductive outcomes.
Nephrotoxicity • No separate studies were performed to investigate nephrotoxicity	Not applicable
Hepatotoxicity • No separate studies were performed to investigate hepatotoxicity.	Not applicable
Genotoxicity • Ide-cel is an autologous human cellular product, therefore, standard genotoxicity studies (eg, Ames assay, clastogenicity assessments) were not conducted. However, vector insertion site analysis was conducted to assess the potential risk for insertional mutagenesis. Twenty clinical ide- cel drug product lots, representative of the range of clinical manufacturing experience, were analysed; the LVV insertion preference was consistent with WT HIV and other LVV described in the literature. • HC-IS showed statistically significant correlation with VCN (copies/diploid genome and copies/CAR+ T cell). HC-IS was determined by filtering uniquely mapped genomic sequences with removal of identical IS between samples. • The insertion profile of anti-BCMA LVV demonstrated preference for the coding regions of expressed genes versus regulatory elements which decreases the likelihood of insertions that disrupt gene regulation and therefore the probability of oncogenesis via malignant transformation. • The vector exists as a single proviral sequence in 99.7% of vector containing reads which indicate that the majority of vector genomes present are not in concatemeric orientation. • Across all samples, the top 10 HC-IS identified were < 0.35% of the total number of unique IS per sample and the ten most prominent vector IS showed no repetition in individual amplicons which is an indicator for a highly polyclonal vector insertion, without any dominant recurring vector IS. • A highly polyclonal vector integration profile was observed across all samples which supports the conclusion that no clonal selection due to vector insertional oncogenesis was observed during ex vivo T cell expansion in the ide-cel manufacturing process. • All chosen genomic features tested (density of genes, CpG dinucleotides, DNaseI hypersensitivity sites, average GC base content) increased significantly with HC-IS density which was as expected based on what is known about WT HIV.	The insertion site analysis of ide-cel drug product lots demonstrated no unique indications of oncogenicity of the manufacturing process.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
• The highest frequency of HC-IS with a 100 kb window of transcription start site of an oncogene was found to be 0.031% which is a low frequency, and thus a worst case per sample, and suggests that there is no specificity of vector integration relative to the transcription start site of oncogenes.	
Carcinogenicity • Ide-cel is an autologous human cellular product which limits the utility of standard nonclinical rodent models for informing carcinogenicity risk. • The potential for transformation of transduced human T cells was assessed, but no standard rodent carcinogenicity studies were conducted. • There was no expansion detected in cultures without IL-2. There were no demonstrative changes in CAR T cell phenotypes, in CD4:CD8 ratio, or substantial decreases in clonal diversity under any condition tested.	The results of this IL-2-independent growth study suggest that there is no indication of tumorigenic transformation of T cells following transduction in the ide-cel manufacturing process.
Immunotoxicity • No immunotoxicity studies were conducted as studies using nonclinical species with intact immune systems are not feasible due to lack of tolerability.	Not applicable
General Safety Pharmacology	
Cardiovascular • Standard safety pharmacology studies with ide-cel were not conducted.	Not applicable
Nervous system • Standard safety pharmacology studies with ide-cel were not conducted.	Not applicable
Respiratory • Standard safety pharmacology studies with ide-cel were not conducted	Not applicable
Mechanisms for Drug Interactions No PK drug interaction studies of ide-cel were conducted because ide-cel is an autologous human cell-based product. Ide-cel is not metabolised and presumed to not induce or inhibit cytochrome P450 enzymes. Ide-cel would not affect the metabolism or PK of other drugs.	Not applicable
Other Toxicity-related Information or Data Not applicable	Not applicable

2.3 Clinical Trial Exposure

2.3.1 Clinical Study Information

Table 2.3.1-1: Ide-cel Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number	Study Title/Design	Number Treated Subjects[a]
Study CRB-401	An open-label, nonrandomised, 2-part, multicentre, first-in-human, Phase 1 study in subjects with relapsed or refractory MM	56
BB2121-MM-001 (Study MM-001)	An open-label, single-arm, multicentre, multinational, Phase 2 study to evaluate the efficacy and safety of ide-cel in subjects with RRMM who have received at least 3 prior regimens including an immunomodulatory agent, a PI, and an anti-CD38 antibody, and who are refractory to their last prior treatment regimen	128
BB2121-MM-003 (Study MM-003)	A global, open-label Phase 3, multicentre, randomised, controlled study of ide-cel versus standard regimens in subjects with RRMM who have received 2 to 4 prior regimens, including an IMiD, a PI, and daratumumab and are refractory to their last prior treatment regimen	225

[a] Data cut-off date: Studies CRB-401 and MM-00-1: 07-Apr-2020; Study MM-003: 18-Apr-2022.

2.3.2 Clinical Trial Exposure

The overall safety analysis includes pooled data for 409 subjects exposed to ide-cel across the 3 clinical trials to support the use of ide-cel in the treatment of adult patients with RRMM.

Ide-cel is provided as a single dose for infusion containing a dispersion of CAR+ viable T cells in one or more infusion bags.

In Studies CRB-401, MM-001, and MM-003, the protocol allowed dose range was 150 to 450 × 10^6 CAR+ T cells, with a maximum dose of 540 × 10^6 CAR+ T cells (upper limit of 450 × 10^6 CAR+ T cells plus 20%). The target dose levels used in the clinical studies are based on the total number of CAR+ T cells.

Administration of ide-cel was preceded by LDC with fludarabine (30 mg/m^2) plus cyclophosphamide (300 mg/m^2) for 3 days to increase the expansion, persistence, and anti-tumour activity of the CAR+ T cells.

In the pooled analysis, 409 subjects received an infusion of ide-cel, with a median (min, max) of actual infused dose of 442.1 (range: 140.8, 529.0) × 10^6 CAR+ T cell. No subject received an actual dose > 540 × 10^6 CAR+ T cells (Table 2.3.2-2). The majority of subjects had at least 12 months of follow-up (Table 2.3.2-1).

Distribution among age, sex and racial or ethnic groups is provided in Table 2.3.2-3 and Table 2.3.2-4.

Table 2.3.2-1: Follow-up Duration in Subjects with Multiple Myeloma (Pooled Analysis)

Duration of Follow-up using Cut-off Date[a]	Persons (n, %) N = 409
< 1 month	1 (0.2)
1 to < 3 months	0
3 to < 6 months	1 (0.2)
6 to < 9 months	13 (3.2)
9 to < 12 months	39 (9.5)
12 to < 15 months	32 (7.8)
15 to < 18 months	85 (20.8)
18 to < 24 months	121 (29.6)
≥ 24 months	117 (28.6)

[a] (Cut-off date - ide-cel infusion date + 1)/30.4375

Table 2.3.2-2: Dose Administration in Subjects with Multiple Myeloma (Pooled Analysis)

Actual CAR+T Cells Infused (10_6 cells)	Persons (n, %) N = 409
< 150	6 (1.5)
150 to < 180	17 (4.2)
180 to < 240	3 (0.7)
240 to < 360	73 (17.8)
360 to ≤ 540	310 (75.8)
360 to ≤ 450	128 (31.3)
> 450 to ≤ 500	148 (36.2)
> 500 to ≤ 540	34 (8.3)
> 540	0

Table 2.3.2-3: Exposure by Age Group and Sex in Subjects with Multiple Myeloma (Pooled Analysis)

Age Group (years)	Persons (n, %) N = 409
< 65	246 (60.1)
65 to 74	146 (35.7)
≥ 75	17 (4.2)
Sex	**Persons (n, %) N = 409**
Male	253 (61.9)

Table 2.3.2-3: Exposure by Age Group and Sex in Subjects with Multiple Myeloma (Pooled Analysis)

Age Group (years)	Persons (n, %) N = 409
Female	156 (38.1)

Table 2.3.2-4: Exposure by Ethnic or Racial Origin in Subjects with Multiple Myeloma (Pooled Analysis)

Ethnic Origin	Persons (n, %) N = 409
American Indian or Alaska Native	1 (0.2)
Asian	10 (2.4)
Black or African American	27 (6.6)
White	308 (75.3)
Other	8 (2.0)
Unknown	55 (13.4)

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Age < 18 years	MM does not occur in paediatric populations. Studies were only conducted in adult subjects and no dose has been established for subjects < 18 years of age.	No	MM does not occur in paediatric populations.
Inadequate hepatic function defined by aspartate aminotransferase and/or alanine aminotransferase > 2.5 × ULN and total bilirubin > 1.5 × ULN (unless due to Gilbert's syndrome and direct bilirubin is ≤ 1.5 × ULN)	CRS can be associated with hepatic toxicity which may predispose to severe AEs in subjects with pre-existing inadequate hepatic function.	No	• There are no clinical study data available on experience with ide-cel in subjects with inadequate hepatic function as stated in Section 5.2 of the SmPC. • Section 4.4 of the SmPC describes risk of adverse reactions in patients with underlying concomitant diseases including reduced hepatic function.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Renal impairment by CrCl < 45 mL/min (< 30 mL/min to be eligible to start LDC)	Confounds study interpretation by inability to give adequate lymphodepletion. Fludarabine dosing is contraindicated in subjects with CrCl < 30 mL/min	No	• There is limited clinical experience with ide-cel in subjects with severe renal impairment. • There is no unique toxicity of ide-cel in subjects with renal impairment; however, they are not able to receive complete LDC consisting of both cyclophosphamide and fludarabine.
History of positive HIV	Theoretical risk of recombination of WT HIV and ide-cel LVV.	No	• There is no clinical experience in subjects with active HIV as described in Section 4.2 of the SmPC. Screening for HBV, active HIV and active HCV must be performed before collection of cells for manufacturing. Leukapheresis material from patients with active HIV or active HCV will not be accepted for Abecma manufacturing (see Section 4.4 of the SmPC). • There is no known risk of toxicity in subjects with a history of HIV. Theoretical risk of recombinant replication competent lentivirus has not been observed across broad clinical experience.
Subjects with a malignancy in addition to myeloma.[a]	Confounds study data interpretation of secondary malignancies after ide-cel	No	• There is no known safety risk in subjects with a prior history of malignancies in addition to myeloma. • Secondary malignancy of T-cell origin is considered an important identified risk and Secondary malignancies (except secondary malignancy of T-cell origin) is considered an important potential risk and Section 4.4 of the SmPC clearly states that patients may develop secondary malignancies
Subjects with a history of class III or IV congestive heart failure or severe non-ischemic cardiomyopathy, unstable or poorly controlled angina, myocardial	CRS can be associated with cardiac toxicity which may exacerbate pre-existing poor cardiac function.	No	• There are no data available on experience with ide-cel in subjects with reduced cardiac function. • Section 4.4 of the SmPC describes risk of adverse reactions in patients with underlying

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
infarction, or ventricular arrhythmia within the previous 6 months prior to starting study treatment.			concomitant diseases including reduced cardiac function. • Section 4.4 of the SmPC clearly states that ide- cel infusion should be delayed in cases of unresolved serious adverse reactions including cardiac events.
Inadequate pulmonary function as defined as oxygen saturation < 92% on room air.	CRS can be associated with pulmonary toxicity which may exacerbate pre-existing poor pulmonary function.	No	• There are no data available on experience with ide-cel in subjects with inadequate pulmonary function. • Section 4.4 of the SmPC describes risk of adverse reactions in patients with underlying concomitant diseases including reduced pulmonary function.
History or presence of clinically relevant CNS pathology	Patients with pre-existing CNS pathology may be at higher risk of neurologic toxicity.	No	• There are no data available on experience with ide-cel in subjects with clinically relevant CNS disorders. • Section 4.4 of the SmPC describes risk of adverse reactions in patients with underlying concomitant diseases including CNS disorders.
Pregnant or lactating females	Pregnant or lactating females excluded from clinical studies based on potential risk to foetus or breastfeeding new born.	Yes	Included as missing information.
Active HBV or HCV infection[b]	Immunosuppression after ide-cel could lead to reactivation of latent HBV or HCV infections.	No	• A total of 15 subjects with a history of HBV or HCV infection were treated with ide-cel across all doses in MM-001 and CRB-401 studies. • Section 4.4 of the SmPC describes the risk of viral reactivation. • Screening for HBV, active HCV and active HIV must be performed before collection of cells for manufacturing. Leukapheresis material from patients with active HIV or active HCV infection will not be accepted for Abecma

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			manufacturing (see Section 4.4 of the SmPC).
Subject with known hypersensitivity to any component of ide-cel product, cyclophosphamide, fludarabine or tocilizumab.	Subjects with hypersensitivity are at higher risk of AEs.	No	Section 4.3 of the SmPC includes hypersensitivity as a contraindication.
Subjects with solitary plasmacytomas or non-secretory myeloma without other evidence of measurable disease.	Potential to confound study results by inability to assess tumour response after ide-cel.	No	There is no expectation of an increased safety risk in these subjects, and they are likely to benefit from ide-cel. No subjects with solitary plasmacytoma or non-secretory myeloma without evidence of measurable disease were included in MM-001, CRB-401 or MM-003. These subjects were assessed for response according to International Myeloma Working Group guidelines.
Previous history of an allogeneic HSCT or prior treatment with any gene therapy-based therapeutic for cancer or investigational cellular therapy for cancer.	Theoretical risk considered not important of GVHD after ide-cel therapy.	No	Risk of GVHD is theoretical and has not been observed.
International normalised ratio or partial thromboplastin time > 1.5 × ULN, or history of Grade ≥ 2 haemorrhage within 30 days, or subject required ongoing treatment with chronic, therapeutic dosing of anti-coagulants (eg, warfarin, low molecular weight heparin, or Factor Xa inhibitors).	Severe CRS or neurologic toxicity can be associated with increased bleeding risk. Those subjects with baseline abnormal coagulation parameters or on therapeutic doses of anti-coagulants may be at increased risk, including subjects with thrombocytopenia.	No	• The PL lists risk of bleeding. • There is clinical experience with subjects treated with therapeutic doses of anti-coagulants after ide-cel infusion. These subjects can benefit from ide-cel.

[a] Unless the subject has been free of the disease for ≥ 5 years (3 years in MM-001) with the exception of the following non-invasive malignancies: basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the breast, incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis clinical staging system), or prostate cancer that can be treated with curative intent.

[b] For exclusion criteria of Active HBV or HCV infection and Subjects with solitary plasmacytomas or non-secretory myeloma without other evidence of measurable disease, data are presented for the full treated population. For the

remaining exclusion criteria, are presented for 184 subjects who received ide-cel across the target dose of 150 to 450 × 10^6 CAR+ T cells and safety population from MM-003 (n = 225).

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure (Table 2.4.2-1).

Table 2.4.2-1: Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare or very rare	Subject numbers may not be sufficient to capture all rare (≥ 1/10,000 to < 1/1000) or very rare (< 1/10,000) ADRs. The total RRMM population exposed to ide-cel in the pooled analysis was 409 subjects.	With 409 subjects exposed to ide-cel in RRMM studies, at least 1 AE would be observed with a 95% probability of the true incidence being 0.73%.
Due to prolonged exposure	Ide-cel is a single infusion that may persist in the blood up to 1 year after infusion. Of 409 subjects treated with ide-cel in the pooled analysis, 117 (28.6%) subjects have equal to or greater than 24 months of follow-up.	Late safety events could occur after a single infusion of ide-cel. LTFU studies are proposed as pharmacovigilance measures to continue characterising the cumulative safety profile.
Due to cumulative effects which have a long latency	Ide-cel is a single infusion and cumulative exposure is not applicable; however, ide-cel may persist in the blood up to 1 year after infusion.	Late safety events could occur after a single infusion of ide-cel. Long-term follow-up studies are proposed as pharmacovigilance measures to continue characterising the cumulative safety profile.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

To ensure subject safety, specific populations of subject were excluded from the pivotal and supportive studies. Thus, experience in these populations is limited (Table 2.4.3-1).

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Studies MM-001, CRB-401, and MM-003 contained criteria for adequate hepatic function (aspartate aminotransferase and/or alanine

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	aminotransferase ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN (unless due to Gilbert's syndrome and direct bilirubin is ≤ 1.5 × ULN).
Patients with renal impairment	Studies MM-001, CRB-401, and MM-003 contained criteria for adequate renal function (CrCl ≥ 30 mL/min). The majority of subjects (86.7%; 355/409) had CrCl ≥ 60 mL/min at baseline.
Patients with cardiovascular impairment	Studies MM-001, CRB-401, and MM-003 excluded subjects with severe cardiac impairment (left ventricular ejection fraction < 45%).
Immunocompromised patients	The target population were immunocompromised.
Patients with a disease severity different from inclusion criteria in clinical trials	Subjects enrolled in Studies MM-001, CRB-401, and MM-003 were heavily pretreated with a median prior antimyeloma regimens of 4.0 as well as a higher percentage refractory to standard myeloma treatments. Almost all subjects had an ECOG performance score of 0 (43.3%) or 1 (54.8%) at baseline. 38.4% of the subjects were defined as having high tumour burden (≥ 50% bone marrow CD138+ plasma cells) and 30.6% had extramedullary plasmacytoma. 60.4% of subjects were assessed as having a revised International Staging System Stage II disease; 14.7% had revised International Staging System Stage III disease. 35.5% of subjects had at least 1 high-risk cytogenetic abnormality (defined as del[17p], t[4;14], or t[14;16]).
Population with relevant different ethnic origin	Subjects across various ethnic backgrounds were enrolled in Studies MM-001, CRB-401, and MM-003. The majority of subjects were White (75.3%), with 6.6% reported to be Black or African American, 2.4% reported to be Asian, 0.2% reported to be American Indian or Alaska Native, 2.0% reported to be 'other', and the ethnic origin of the remaining subjects (13.4%) was reported as unknown.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.

2.5 Post-Authorization Experience

Abecma (idecabtagene vicleucel [ide-cel], BMS-986395) has been approved in 35 countries for the treatment of RRMM in adult patients.[50]

2.5.1 Method Used to Calculate Exposure

The estimated value for cumulative commercial patient exposure represents the estimated number of unique patients exposed to ide-cel from the IBD of 26-Mar-2021 through the DLP of 25-Mar-2025.[50]

The estimate of patient exposures from commercial experience is based on controlled manufacturing and shipment reporting provided to BMS. The estimate was obtained by querying the resulting database for infusions of commercial ide-cel (Abecma) to treatment sites with dates on or before 25-Mar-2025.[50]

2.5.2 Exposure

Estimated cumulative commercial exposure to ide-cel or nonconforming/OOS product through 25-Mar-2025 is approximately 4744 patients, including 1650 EU patients. French patients received ide-cel as part of a temporary authorization for use granted on 29-Apr-2021 by the French National Agency for Medicines and Health Products Safety (ANSM).

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Ide-cel has not been systematically studied in humans for its potential for abuse, tolerance or physical dependence. Based on its pharmacological properties, there is no anticipated risk of abuse or misuse for illegal purposes. Ide-cel is an intra-patient product manufactured from individual patient T cells and distributed via a controlled access programme.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP are summarised in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	Cytokine release syndrome
	Neurologic toxicity
	Cytopenias
	Hypogammaglobulinaemia
	Infections
Important potential risks	Secondary malignancies
	Tumour lysis syndrome
	Aggravation of GVHD
	Generation of replication competent lentivirus
	Immunogenicity
Missing information	Impact on pregnancy and lactation
	Long-term safety
	Safety in elderly patients (≥ 75 years)

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reasons for not including a risk as identified or potential in the list of safety concerns in the RMP are provided in Table 2.7.1.1-1:

Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk	Justification
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	
Transmission of infectious agents via product.	There have been no reported cases of infectious agent transmission via ide-cel in the 2 Studies (MM-001 and CRB-401).
Decreased viability of the product due to inappropriate preparation of infusion.	There have been no reported cases of decrease in viability of ide-cel due to inappropriate product handling in the 2 Studies (MM-001 and CRB-401).
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised)	
Hypersensitivity Reactions - Allergic reactions that may include anaphylaxis may occur with the infusion of ide-cel. These reactions may be due to DMSO or the materials used in the ide-cel manufacturing	No hypersensitivity reactions have been reported during the ide-cel clinical study programme. The concentration of DMSO or the materials used in the ide-cel manufacturing process is very low. Therefore, hypersensitivity reactions are considered a low risk based on experience to date.
Known risks that do not impact the risk-benefit profile	
Hepatitis B or C Reactivation – Depletion of plasma cells which is an expected on-target toxicity increases the risk for viral reactivation among patients with prior viral infections such as Hepatitis B or C	The SmPC states that screening for HBV, active HIV and active HCV must be performed before collection of cells for manufacturing. Leukapheresis material from patients with active HIV or active HCV will not be accepted for Abecma manufacturing (see Section 4.4 of the SmPC).

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Cytokine release syndrome	Can have mild to severe to life-threatening or fatal impact. Severe and life-threatening symptoms of CRS include cardiac toxicity, respiratory distress, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation.[51] Cytokine release syndrome may be an immune trigger, leading to macrophage activation syndrome, a potentially life-threatening condition.
Neurologic toxicity	Neurologic toxicity can have mild to severe to life-threatening or fatal impact if not treated.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Cytopenias	Prolonged cytopenias are an important aspect of ide-cel benefit-risk and management, but the great majority of patients treated can be managed with conventional supportive care that is well established for patients treated with either stem cell transplant or cellular therapies.
Hypogammaglobulinaemia	Hypogammaglobulinaemia makes patients susceptible to potentially life-threatening infections, which can be managed through adequate treatment.
Infections	Infections may have mild to severe to life-threatening or fatal impact in this patient population. Risks from infections can be mitigated by antimicrobial prophylaxis and prompt evaluation and treatment.
Important potential risks	
Secondary malignancies	Secondary malignancy (including secondary malignancies due to insertional mutagenesis) is a potentially serious and life-threatening illness that will require medical intervention.
Tumour lysis syndrome	Tumour lysis syndrome can cause life-threatening complications including death if not appropriately and immediately treated.
Aggravation of GVHD	There is a theoretical risk of aggravation of pre-existing GVHD in patients with donor chimerism from a prior allogeneic HSCT post ide-cel infusion due to the milieu provided by robust activation of ide-cel CAR T cells.
Generation of replication competent lentivirus	The presence of RCL has not been detected in the drug product or the LVV, or in the blood of subjects in clinical Studies MM-001 and CRB-401. Therefore, the risk of RCL with ide-cel treatment remains theoretical.
Immunogenicity	Ide-cel has the potential to induce an immune response against foreign epitopes like the non-human or partially human sequences in the CAR construct or against impurities from the manufacturing process like residual viral proteins or other non-human origin proteins. This immune response could potentially cause allergic reactions such as anaphylaxis that require medical intervention. In addition, an immune response against ide-cel could theoretically reduce ide-cel efficacy by effector cell neutralisation or by promotion of more rapid clearance from circulation. Cases of immunogenicity have been reported in clinical trials. Antibodies due to immune response can reduce efficacy by effector cell neutralisation or by promotion of more rapid cell clearance from circulation or can cause safety issues like anaphylaxis, CRS, infusion reactions etc. that may require medical intervention.
Missing Information	
Impact on pregnancy and lactation	The theoretical risk for germline integration cannot be excluded; however, the absence of detectable replication competent virus in drug product or in treated subjects suggests a negligible risk. It is not known whether ide-cel has the potential to be transferred to the foetus/child via the placenta/breastmilk that could cause toxicity. Clinical studies have excluded pregnant and lactating female patients; both male and female

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
	patients of childbearing potential were required to use an effective method of contraception during treatment because of the known teratogenicity of LDC. Pregnancy status for females of childbearing potential should be verified prior to treatment with ide-cel.
Long-term safety	The LTFU safety study protocol (GC-LTFU-001) follows patients for up to 15 years and will provide information on any potential delayed new safety signals.
Safety in elderly patients (≥ 75 years)	To date, there is limited information available to determine the safety of ide-cel in patients ≥ 75 years old. In the clinical study programme, there were only 5 subjects ≥ 75 years of age in the ide-cel treated population (1 subject had a target dose of 150×10^6 CAR+ T cells, 1 subject had a target dose of 300×10^6 CAR+ T cells, and 3 subjects had a target dose of 450×10^6 CAR+ T cells) with no Grade ≥ 3 events of CRS or neurologic toxicity.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new or reclassification of safety concerns with the submission of the updated RMP.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

2.7.3.1 Presentation of Important Identified and Important Potential Risks

The important identified and potential risks as well as missing information are listed below.

Important Identified Risks

- Cytokine release syndrome (Table 2.7.3.1-1)
- Neurologic toxicity including ICANS (Table 2.7.3.1-2)
- Cytopenias (Table 2.7.3.1-3)
- Hypogammaglobulinaemia (Table 2.7.3.1-4)
- Infections (Table 2.7.3.1-5)
- Secondary malignancy of T-cell origin (Table 2.7.3.1-6)

Important Potential Risks

- Secondary malignancies (except secondary malignancy of T-cell origin) (Table 2.7.3.1-7)
- Tumour Lysis Syndrome (Table 2.7.3.1-8)
- Aggravation of graft versus host disease (Table 2.7.3.1-9)
- Generation of replication competent lentivirus (Table 2.7.3.1-10)
- Immunogenicity (Table 2.7.3.1-11)

Missing Information

- Impact on pregnancy and lactation (Table 2.7.3.2-1)
- Long-term safety (Table 2.7.3.2-2)
- Safety in elderly patients ≥ 75 years (Table 2.7.3.2-3)

Table 2.7.3.1-1: Important Identified Risk: Cytokine Release Syndrome

Important Identified Risk: Cytokine Release Syndrome

Potential mechanisms

CRS is a non–antigen-specific toxicity that occurs as a result of high-level immune activation resulting in elevated inflammatory cytokines. CRS clinically manifests when large numbers of lymphocytes (eg, B-cells, T cells, and/or natural killer cells) and/or myeloid cells (eg, macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines.[51] Higher disease burden and higher baseline levels of inflammatory cytokines are associated with higher incidence of CRS.[52,53,54]

MAS may be part of the continuum of dysregulated inflammatory responses including cytokine release, lymphohistiocytic tissue infiltration, and multiorgan dysfunction. CRS may be an immune trigger, leading to MAS.

Evidence source and strength of evidence

In the pooled analysis (n = 409), 346 (84.6%) subjects who received ide-cel had ≥ 1 CRS event. CRS has likewise been reported with CD19 directed CAR T providing further evidence of a class risk.

MAS (PT of HLH) was reported for 9 (2.2%) subjects in the pooled analysis: 2 (0.5%) subjects had a maximum severity of Grade 2, 2 (0.5%) had a maximum severity of Grade 3, and 5 (1.2%) had a maximum severity of Grade 4.

CRS is considered an important identified risk due to its frequency and the potential for serious outcomes, including death, if untreated. Thus, further evaluation of frequency, severity, seriousness and outcome of this risk in the postmarketing period is warranted. MAS and HLH are potentially life-threatening.[55] CRS has been reported in a few cases to be associated with findings of MAS/HLH, and the physiology of the syndromes may overlap.

Characterization of risk

Frequency with 95% CI

In the pooled analysis, 346 subjects (84.6%; 95% CI: 80.7, 88.0) experienced at least 1 AE of CRS; 9 subjects (2.2%; 95% CI: 1.0, 4.1) experienced at least 1 AE of MAS.

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
CRS			
Subjects ≥ 1 SAE, n (%)	32 (17.4)	10 (4.4)	42 (10.3)
Subjects ≥ 1 AE, n (%)	149 (81.0)	197 (87.6)	346 (84.6)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	81.0 (74.6, 86.4)	87.6 (82.5, 91.6)	84.6 (80.7, 88.0)
MAS			
Subjects ≥ 1 SAE, n (%)	2 (1.1)	5 (2.2)	7 (1.7)
Subjects ≥ 1 AE, n (%)	4 (2.2)	5 (2.2)	9 (2.2)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	2.2 (0.6, 5.5)	2.2 (0.7, 5.1)	2.2 (1.0, 4.1)

Seriousness/Outcomes

Serious events of CRS were experienced by 42 ide-cel treated subjects in the pooled analysis (all PT: CRS). Serious events of MAS were experienced by 7 ide-cel treated subjects (all PT: HLH).

Table 2.7.3.1-1: Important Identified Risk: Cytokine Release Syndrome

Important Identified Risk: Cytokine Release Syndrome

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
CRS, n (%)	32 (17.4)	10 (4.4)	42 (10.3)
Recovered/Resolved	31 (16.8)	6 (2.7)	37 (9.0)
Recovered/Resolved with Sequelae	0	1 (0.4)	1 (0.2)
Not Recovered/Not Resolved	0	1 (0.4)	1 (0.2)
Fatal	1 (0.5)	2 (0.9)	3 (0.7)
MAS, n (%)	2 (1.1)	5 (2.2)	7 (1.7)
Recovered/Resolved	1 (0.5)	3 (1.3)	4 (1.0)
Recovered/Resolved with Sequelae	0	1 (0.4)	1 (0.2)
Not Recovered/Not Resolved	1 (0.5)	1 (0.4)	2 (0.5)

Severity and Nature of Risk

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
CRS			
All AEs, n (%)	149 (81.0)	197 (87.6)	346 (84.6)
Grade 3 or 4 AE, n (%)	10 (5.4)	10 (4.4)	20 (4.9)
Grade 5 AE, n (%)	1 (0.5)	2 (0.9)	3 (0.7)
MAS			
All AEs, n (%)	4 (2.2)	5 (2.2)	9 (2.2)
Grade 3 or 4 AE, n (%)	2 (1.1)	5 (2.2)	7 (1.7)
Grade 5 AE, n (%)	0	0	0

Risk factors and risk groups

In the pooled analysis, 346 (84.6%) subjects who received ide-cel had ≥ 1 CRS event.

An exploratory analysis of baseline predictors for CRS in Study MM-003 showed no correlation of baseline soluble BCMA, body weight, or dose with CRS requiring tocilizumab or CRS requiring steroids. However, higher odds ratio of CRS (Gr3+) was associated with higher level of baseline soluble BCMA and with lower body weight.

Macrophage activation syndrome is usually associated with more severe forms of CRS.

Preventability

Detailed guidance on the identification, grading, and management of CRS is included in the label to prevent severe CRS-related toxicities. CRS management guidance on the use of tocilizumab and corticosteroids for the management of CRS is included in Table 1 (CRS Grading and Management Guidance) of the SmPC. Education of HCPs enables detection and management of CRS at an early stage that can mitigate serious outcomes.

MAS/HLH should be suspected in clinical presentations with fever, cytopenias and hyperinflammatory markers. Early diagnosis and treatment of MAS are important to prevent progression and organ failure. MAS is a potentially life-threatening condition, and patients should be closely monitored for evidence of MAS. Treatment of MAS should be administered per local guidelines.

Table 2.7.3.1-1: Important Identified Risk: Cytokine Release Syndrome

Important Identified Risk: Cytokine Release Syndrome	
Impact on the risk-benefit balance of the product	Can have mild to severe to life-threatening or fatal impact. Severe and life-threatening symptoms of CRS include cardiac toxicity, respiratory distress, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation.[56] MAS is a potentially life-threatening condition.
Public health impact	CRS occurs mainly after bispecific T cell engaging and CAR T cell therapy, with a quite variable incidence, ranging from 2% to 94%, reflecting different prophylactic approaches, variable doses, underreporting and variable CRS definitions. Isolated cases of CRS have been related to HSCT, and even conventional chemotherapy and radiotherapy.[57] Grade 1 CRS can be managed with symptomatic treatment on the hospitalisation ward. In patients with Grade 2 CRS, hypotension requires prompt treatment with intravenous fluid boluses. If hypotension is refractory to fluid boluses, transferring the patient to the intensive care unit should be considered, with anti-IL6 therapy and low dose vasopressors. Severe CRS, involving Grades 3 and 4, or persistent Grade 2 despite two doses of anti-IL6 therapy, should be treated with corticosteroids.[57] CRS generally occurs within days after CAR T cell infusion. While identification of factors predictive of severe CRS continues to evolve, one mainstay of CRS treatment is to deploy anti-cytokine therapy early in the CRS course to prevent progression into severe life-threatening higher-grade CRS.[58] Severe CRS may require intensive care unit management, including treatment with tocilizumab, an antibody against the IL6 receptor; steroids; vasopressors; anti-epileptics; antipyretics; and/or mechanical ventilation. Administration of lower dose corticosteroids and/or tocilizumab has reportedly decreased severe CRS symptoms without reducing blood levels of CAR T cells.[59] HLH is a hyperinflammatory syndrome, it is termed MAS when associated with rheumatic disease (where it is best characterised in systemic juvenile idiopathic arthritis) and sHLH when associated with other triggers including malignancy and infection. Secondary HLH can also occur as the consequence of malignancy, either at presentation or relapse, during treatment of the malignancy (HLH during chemotherapy) or after bone marrow transplantation. The most common malignancies causing sHLH are haematological malignancies, including T cell, NK-cell leukaemias or lymphomas, diffuse large B cell lymphoma and Hodgkin lymphoma.[60] MAS is more commonly observed in rheumatic diseases such as systemic juvenile idiopathic arthritis, Kawasaki disease, systemic lupus erythromatosus, Still's disease, juvenile dermato-myositis and Becket's disease. MAS is more frequently observed in children, but increased prevalence is also present in adults nowadays.[61] The estimated prevalence of MAS in systemic juvenile idiopathic arthritis was ~10%, and it increased up to 40% in subclinical MAS. The prevalence of MAS in systemic lupus erythromatosus varied from 0.9% to 4.6% and it increased up to 9.4% in those subjects with a hepatic dysfunction.[62] Morbidity and mortality of sHLH and MAS are high, and early identification is important to enable early and aggressive treatment with combination immunosuppression and treatment of cotriggers to achieve remission.[60]
MedDRA Terms	MedDRA PTs of cytokine release syndrome and haemophagocytic lymphohistiocytosis

Table 2.7.3.1-2: Important Identified Risk: Neurologic Toxicity including ICANS

Important Identified Risk: Neurologic Toxicity including ICANS	
Potential mechanisms	The causative pathophysiology of these neurologic side effects is unknown. Neurologic toxicity including ICANS, is often associated with CRS, and Bonifant et al[63] suggest it is plausible that elevated cytokine levels are partly responsible for the neurologic sequelae. However, they also state that direct CAR T cell toxicity on the CNS is possible but has not been demonstrated. Elevated levels of IL-6 have been implicated;[51] however, neurologic symptoms have been observed in subjects for whom IL-6 is not the primary elevated cytokine and in whom no CRS occurs. Subjects with severe neurologic toxicity demonstrated evidence of endothelium activation blood brain barrier permeability.[64]
Evidence source and strength of evidence	Neurologic toxicity including ICANS, is considered an important identified risk due to its seriousness and its potential for associated disability, including death, if left untreated. In addition to CRS, neurologic toxicity is an expected acute AE associated with CAR T cell therapy.[55] The diagnosis is based on clinical signs and symptoms in the absence of definitive diagnostic tests. Neurologic toxicity is primarily managed with supportive care for low grade toxicity, and corticosteroids are frequently used for more severe neurologic toxicity.[56] In order to enable a side-by-side comparison and pooling of data across Studies MM-001, CRB-401, and MM-003 a Neurologic Toxicity-Focused AEs search approach was required that included selected PTs of neurologic toxicity events as determined by the MAH with consideration of biological/pharmacological plausibility for a drug-event relationship, known neurologic toxicities reported with this class of drug and consistent with published guidelines for CAR T cell-associated encephalopathy,[56] and clinical judgement. In the pooled analysis, 153 (37.4%) subjects who received ide-cel had ≥ 1 Neurologic Toxicity – Focused AE on or after ide-cel infusion. Neurologic Toxicity – Focused AEs reported for ≥ 5% of subjects were confusional state (11.0%), insomnia (10.3%), tremor (5.6%), and somnolence (5.6%).

Table 2.7.3.1-2: Important Identified Risk: Neurologic Toxicity including ICANS

Important Identified Risk: Neurologic Toxicity including ICANS

Characterization of risk

Frequency with 95% CI

In the pooled analysis, 153 subjects (37.4%; 95% CI: 32.7, 42.3) experienced at least 1 AE of Neurologic Toxicity - Focused.

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Subjects ≥ 1 SAE, n (%)	12 (6.5)	14 (6.2)	26 (6.4)
Subjects ≥ 1 AE, n (%)	78 (42.4)	75 (33.3)	153 (37.4)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	42.4 (35.2, 49.9)	33.3 (27.2, 39.9)	37.4 (32.7, 42.3)

Seriousness/Outcomes

Serious events of Neurologic Toxicity - Focused were experienced by 26 (6.4%) ide-cel treated subjects in the pooled analysis. The PTs reported in > 5 subjects were confusional state (10 subjects) and encephalopathy (6 subjects).

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
NT - Focused, n (%)	12 (6.5)	14 (6.2)	26 (6.4)
Recovered/Resolved	10 (5.4)	8 (3.6)	18 (4.4)
Recovered/Resolved with Sequelae	1 (0.5)	1 (0.4)	2 (0.5)
Not Recovered/Not Resolved	0	5 (2.2)	5 (1.2)
Fatal	1 (0.5)	0	1 (0.2)

Severity and Nature of Risk

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
All NT - Focused AEs	78 (42.4)	75 (33.3)	153 (37.4)
Grade 3 or 4 AE	10 (5.4)	12 (5.3)	22 (5.4)
Grade 5 AE	1 (0.5)	0	1 (0.2)

Risk factors and risk groups

In the pooled analysis, 153 (37.4%) subjects who received ide-cel had ≥ 1 Neurologic Toxicity – Focused AE on or after ide-cel infusion. Neurologic Toxicity - Focused AEs were reported for 32.3% of subjects in the pooled analysis within the first 8 weeks and for 8.6% of subjects > 8 weeks after ide-cel infusion.

In Study MM-001, there was no correlation of pre-infusion soluble biomarkers with investigator-identified neurotoxicity events, and no association of serum BCMA levels with any grade investigator-identified neurotoxicity events.

Preventability

Health care providers will be provided with the HCP Guide on management of neurologic toxicity including ICANS. This educational tool includes information on the appropriate patient monitoring following ide-cel infusion at the qualified clinical facility for signs and symptoms of neurologic toxicities. If neurologic toxicity is suspected, patients will be managed according to recommendations in Table 2 (Neurologic Toxicity including ICANS Grading and Management Guidance) of the SmPC.

Table 2.7.3.1-2: Important Identified Risk: Neurologic Toxicity including ICANS

Important Identified Risk: Neurologic Toxicity including ICANS	
	Therefore, detection and management at an early stage could mitigate seriousness of neurologic toxicity.
Impact on the risk-benefit balance of the product	Neurologic toxicity including ICANS, is considered an important identified risk due to its seriousness and its potential for serious outcomes including death, if left untreated.
Public health impact	There has been an increase in the incidence of a serious, potentially fatal neurotoxicity known as ICANS as the use of CAR T adoptive cell therapy has grown.. Symptoms vary from delirium, headache, aphasia, seizures, and cerebral oedema. In rare circumstances, it can be fatal. Most efforts in the management and treatment of ICANS have focused on symptom management, specifically to address cerebral oedema and seizures. While Grade 1 neurotoxicity may only require supportive care, ICANS can progress quickly and therefore requires close attention and may need rapid intervention. For patients with severe (Grade 3 to 4) neurotoxicity, monitoring in the intensive care unit is recommended.[65] In severe cases, neurologic symptoms may require admission to the intensive care unit for frequent monitoring, respiratory support, or intubation for airway protection. Most neurotoxicity is reversible, and reported complications include confusion, delirium, expressive aphasia, obtundation, myoclonus, seizure-like activity and seizures.[59,66,67,68,69]
MedDRA Terms	Neurologic Toxicity – Focused AEs included selected PTs of neurologic toxicity events as determined by the MAH with consideration of biological/pharmacological plausibility for a drug event relationship, known neurologic toxicities reported with this class of drug and consistent with published guidelines[56] for CAR T cell-associated encephalopathy, and clinical judgement.

Table 2.7.3.1-3: Important Identified Risk: Cytopenias

Important Identified Risk: Cytopenias	
Potential mechanisms	Cytopenias are common in patients with advanced MM[23] and in patients treated with CAR T cell therapy.[70,71] Contributing factors in patients with RRMM include progressive myeloma, prior AMTs, concomitant medications, LDC, and postinfusion toxicities (eg, CRS and infection).
Evidence source and strength of evidence	The AE category of Cytopenia – Overall and sub-category names refer to not only the individual PT, but also includes AE PTs relating to the defined medical condition/concept of neutropenia, thrombocytopenia, and anaemia. In the pooled analysis, 379 (92.7%) subjects who received ide-cel had ≥ 1 Cytopenia – Overall AE. The 3 most commonly reported events were neutropenia, anaemia, and thrombocytopenia. Cytopenias (eg, neutropenia, anaemia, and thrombocytopenia) were among the most frequently reported Grade 3 or 4 AEs, and most of these events were reported within the first 8 weeks after ide-cel infusion. As anaemia was considered less severe and more manageable compared with neutropenia and thrombocytopenia, this section focuses on neutropenia and thrombocytopenia. In the pooled analysis, Cytopenia – Neutropenia AEs were reported for 87.8% of subjects who received ide-cel. Cytopenia – Neutropenia AEs were reported for 86.8% of subjects within the first 8 weeks and for 37.2% of subjects > 8 weeks after ide-cel infusion.[72] 83.6% of subjects had ≥ 1 Grade 3 or 4 Cytopenia – Neutropenia AE. No subject had a Grade 5 Cytopenia – Neutropenia AE. The frequency of subjects with Grade 3 or 4 Cytopenia –

Table 2.7.3.1-3: Important Identified Risk: Cytopenias

Important Identified Risk: Cytopenias

Neutropenia AEs was 81.9% within the first 8 weeks and 25.6% > 8 weeks after ide-cel infusion.

In the pooled analysis, Cytopenia – Thrombocytopenia AEs were reported for 59.9% of subjects who received ide-cel. Cytopenia – Thrombocytopenia AEs were reported for 55.3% of subjects within the first 8 weeks and for 29.1% of subjects > 8 weeks after ide-cel infusion.[72]

Grade 3 or 4 Cytopenia – Thrombocytopenia AEs were reported for 47.7% of subjects, with Grade 4 events reported for 34.5% of subjects. No subject had a Grade 5 Cytopenia – Thrombocytopenia AE. The frequency of subjects with Grade 3 or 4 Cytopenia – Thrombocytopenia AEs was 42.5% within the first 8 weeks and 19.7% > 8 weeks after ide-cel infusion.[72]

Characterization of risk

Frequency with 95% CI

In the pooled analysis, 379 subjects (92.7%; 95% CI: 89.7, 95.0) experienced at least one AE of Cytopenia – Overall. 359 subjects (87.8%; 95% CI: 84.2, 90.8) experienced at least one event of Cytopenia – Neutropenia. 245 subjects (59.9%; 95% CI: 55.0, 64.7) experienced at least one event of Cytopenia – Thrombocytopenia. 5 subjects (1.2%; 95% CI: 0.4, 2.8) experienced at least one event of Cytopenia – Pancytopenia.

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Subjects with ≥ 1 SAE, n (%)			
Cytopenia – Overall	23 (12.5)	11 (4.9)	34 (8.3)
Neutropenia	19 (10.3)	11 (4.9)	30 (7.3)
Thrombocytopenia	7 (3.8)	0	7 (1.7)
Pancytopenia	1 (0.5)	0	1 (0.2)
Subjects with ≥ 1 AE, n (%)			
Cytopenia – Overall	176 (95.7)	203 (90.2)	379 (92.7)
Neutropenia	173 (94.0)	186 (82.7)	359 (87.8)
Thrombocytopenia	126 (68.5)	119 (52.9)	245 (59.9)
Pancytopenia	3 (1.6)	2 (0.9)	5 (1.2)
Incidence (%) of subjects with ≥ 1 AE (95% CI)			
Cytopenia – Overall	95.7 (91.6, 98.1)	90.2 (85.6, 93.8)	92.7 (89.7, 95.0)
Neutropenia	94.0 (89.6, 97.0)	82.7 (77.1, 87.4)	87.8 (84.2, 90.8)
Thrombocytopenia	68.5 (61.2, 75.1)	52.9 (46.1, 59.6)	59.9 (55.0, 64.7)
Pancytopenia	1.6 (0.3, 4.7)	0.9 (0.1, 3.2)	1.2 (0.4, 2.8)

Seriousness/Outcomes

Serious events of Cytopenia – Overall were experienced by 34 (8.3%) ide-cel treated subjects in the pooled analysis. The most commonly reported PTs were febrile neutropenia (17 subjects), neutropenia (13 subjects), and thrombocytopenia (7 subjects).

Serious events of Cytopenia – Neutropenia were experienced by 30 (7.3%) ide-cel treated subjects in the pooled analysis. The reported PTs were febrile neutropenia (17 subjects), neutropenia (13 subjects), and leukopenia (1 subject).

Serious events of Cytopenia – Thrombocytopenia were experienced by 7 ide-cel treated subjects in the pooled analysis (all PT thrombocytopenia).

A serious event of Cytopenia – Pancytopenia (PT pancytopenia) was experienced by 1 ide-cel treated subject in the pooled analysis.

Table 2.7.3.1-3: Important Identified Risk: Cytopenias

Important Identified Risk: Cytopenias

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Cytopenia – Overall, n (%)	23 (12.5)	11 (4.9)	34 (8.3)
Recovered/Resolved	18 (9.8)	10 (4.4)	28 (6.8)
Not Recovered/Not Resolved	5 (2.7)	1 (0.4)	6 (1.5)
Fatal	0	0	0
Neutropenia, n (%)	19 (10.3)	11 (4.9)	30 (7.3)
Recovered/Resolved	16 (8.7)	10 (4.4)	26 (6.4)
Not Recovered/Not Resolved	3 (1.6)	1 (0.4)	4 (1.0)
Thrombocytopenia, n (%)	7 (3.8)	0	7 (1.7)
Recovered/Resolved	6 (3.3)	0	6 (1.5)
Not Recovered/Not Resolved	1 (0.5)	0	1 (0.2)
Pancytopenia, n (%)	1 (0.5)	0	1 (0.2)
Not Recovered/Not Resolved	1 (0.5)	0	1 (0.2)

Severity and Nature of Risk

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Cytopenia – Overall			
All AEs	176 (95.7)	203 (90.2)	379 (92.7)
Grade 3 or 4 AE	175 (95.1)	197 (87.6)	372 (91.0)
Grade 5 AE	0	0	0
Neutropenia			
All AEs	173 (94.0)	186 (82.7)	359 (87.8)
Grade 3 or 4 AE	169 (91.8)	183 (81.3)	352 (86.1)
Grade 5 AE	0	0	0
Thrombocytopenia			
All AEs	126 (68.5)	119 (52.9)	245 (59.9)
Grade 3 or 4 AE	101 (54.9)	94 (41.8)	195 (47.7)
Grade 5 AE	0	0	0
Pancytopenia			
All AEs	3 (1.6)	2 (0.9)	5 (1.2)
Grade 3 or 4 AE	1 (0.5)	1 (0.4)	2 (0.5)

Table 2.7.3.1-3: Important Identified Risk: Cytopenias

Important Identified Risk: Cytopenias				
	Grade 5 AE	0	0	0
Risk factors and risk groups	Cytopenias are common in both advanced MM patients[23] and in patients treated with CAR T therapy.[70,71] Contributing factors in RRMM patients include progressive myeloma, prior AMTs, concomitant medications, LDC, and post-infusion toxicities, such as CRS and infection. In the pooled analysis, the frequency of subjects with Grade 3 or 4 Cytopenia – Overall was 90.5% within the first 8 weeks and 40.0% > 8 weeks after infusion.[72]			
Preventability	Patients may exhibit prolonged cytopenias following LDC and ide-cel infusion (SmPC Section 4.4). Blood counts should be monitored prior to and after ide-cel infusion. Cytopenias should be managed with myeloid growth factor and blood transfusion support according to local institutional guidelines.			
Impact on the risk-benefit balance of the product	Prolonged cytopenias are an important aspect of ide-cel benefit-risk and management, but the great majority of patients treated can be managed with conventional supportive care that is well established for patients treated with either stem cell transplant or cellular therapies.			
Public health impact	Various terminologies are used to define cytopenia and its severity. Pancytopenia refers to when all the three cell lines are affected. Bicytopenia refers to when 2 out of 3 cell lines are affected. Thrombocytopenia refers to low platelet count. The word leukopenia is often used interchangeably with neutropenia.[73] Cytopenias are common in patients with advanced MM[23] and in patients treated with CAR T cell therapy.[70,71]			
MedDRA Terms	See Annex 7 for a full list of terms			

Table 2.7.3.1-4: Important Identified Risk: Hypogammaglobulinaemia

Important Identified Risk: Hypogammaglobulinaemia	
Potential mechanisms	Hypogammaglobulinaemia is caused by prolonged B-cell depletion.
Evidence source and strength of evidence	Hypogammaglobulinaemia is considered an important identified risk due to the expected off-tumour, on-target toxicity of plasma cell aplasia from ide-cel which may result in some degree of hypogammaglobulinaemia and associated immunosuppression. Hypogammaglobulinaemia is a known risk factor for development of infections in MM patients. The expected duration of plasma cell aplasia is unknown, but may persist much longer than ide-cel CAR+ T cells remain in the body. Prolonged plasma cell aplasia is expected to result in hypogammaglobulinaemia which can also be observed as a manifestation of myeloma itself. Hypogammaglobulinaemia may increase the risk of bacterial and other infections including opportunistic infections and viral reactivation. Intravenous Ig replacement may be needed to maintain adequate IgG levels. The use of prophylactic antibiotics may also be necessary. In the pooled analysis, hypogammaglobulinaemia was reported in 14.4% of subjects treated with ide-cel.

Table 2.7.3.1-4: Important Identified Risk: Hypogammaglobulinaemia

Important Identified Risk: Hypogammaglobulinaemia

Characterization of risk

Frequency with 95% CI

In the pooled analysis, 59 subjects (14.4%; 95% CI: 11.2, 18.2) experienced at least 1 AE of hypogammaglobulinaemia.

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Subjects ≥ 1 SAE, n (%)	0	0	0
Subjects ≥ 1 AE, n (%)	39 (21.2)	20 (8.9)	59 (14.4)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	21.2 (15.5, 27.8)	8.9 (5.5, 13.4)	14.4 (11.2, 18.2)

Seriousness/Outcomes

No serious events of hypogammaglobulinaemia were experienced by ide-cel treated subjects in the pooled analysis.

Severity and Nature of Risk

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
All AEs	39 (21.2)	20 (8.9)	59 (14.4)
Grade 3 or 4 AE	1 (0.5)	2 (0.9)	3 (0.7)
Grade 5 AE	0	0	0

Risk factors and risk groups

The destruction of non-tumour BCMA+ plasma cells in healthy tissues, or "on-target/ off-tumour" toxicity, may result in some degree of hypogammaglobulinaemia and associated immunosuppression. Therefore, the MOA for ide-cel may play a role in subjects developing hypogammaglobulinaemia.

Preventability

Plasma cell aplasia and hypogammaglobulinaemia can occur in subjects receiving treatment with ide-cel (SmPC Section 4.4). Immunoglobulin levels should be monitored after treatment with ide-cel and managed per institutional guidelines including infection precautions, antibiotic or antiviral prophylaxis and Ig replacement.

Impact on the risk-benefit balance of the product

Hypogammaglobulinaemia makes subjects susceptible to potentially life-threatening infections and is therefore considered an important identified risk.

Public health impact

Hypogammaglobulinaemia can be secondary to malignancies that affect Ig production, such as chronic lymphocytic leukaemia, MM, B-cell lymphoma, primary amyloidosis, and monoclonal gammopathy of unknown significance. Immunodeficiency can also be secondary to treatment of the patient's underlying disease.

Some treatment-related hypogammaglobulinaemias are short lived, whereas others can be long term.[74] Symptomatic hypogammaglobulinaemia is defined as two or more non-neutropenic infections within 6 months of medication administration and requiring intravenous Ig treatment. Measuring pretreatment Ig levels (IgG, IgA, and IgM) and quantifying B cells in blood, in addition to systematic serial monitoring of these parameters following completion of therapy, is helpful to identify high-risk patients for developing symptomatic hypogammaglobulinaemia.[75]

MedDRA Terms

MedDRA PT of hypogammaglobulinaemia, blood immunoglobulin A decreased, blood immunoglobulin D decreased, blood immunoglobulin E decreased, blood

Table 2.7.3.1-4: Important Identified Risk: Hypogammaglobulinaemia

Important Identified Risk: Hypogammaglobulinaemia	
	immunoglobulin G decreased, blood immunoglobulin M decreased, immunoglobulins decreased, selective IgA immunodeficiency, selective IgG subclass deficiency, selective IgM immunodeficiency

Table 2.7.3.1-5: Important Identified Risk: Infections

Important Identified Risk: Infections	
Potential mechanisms	Infections are consistent with the known toxicities of the conditioning regimen of chemotherapy and effects from CAR T (eg, CRS, cytopenias, hypogammaglobulinaemia).
Evidence source and strength of evidence.	Infections are a major cause of morbidity in patients with MM with approximately 25% of patients presenting with recurrent infections and serious infections reported for > 75% of patient.[23] In the pooled analysis, 252 (61.6%) subjects who received ide-cel had Infections – Overall. The most frequently (≥ 5% of subjects) reported PTs were upper respiratory tract infection (14.9%), pneumonia (10.3%), and urinary tract infection (6.1%). Grade 3 or 4 Infections were reported for 22.0% of subjects, with 16.1% of subjects experiencing Grade 3 events. Infections represent an identified risk of treatment with ide-cel and may include bacterial, fungal, pneumocystis, viral reactivation and symptomatic viral infections (eg, cytomegalovirus, HBV, respiratory viruses and other viruses). Risk factors for infection include immune dysfunction from myeloma, LDC (ie, fludarabine and cyclophosphamide) associated lymphopenia and myelosuppression, and ide-cel treatment-associated toxicities. CRS may exacerbate and delay recovery from cytopenias, and treatment of CRS and neurotoxicity with corticosteroids may also increase infection risk. Plasma cell aplasia following ide-cel treatment is an expected on-target toxicity of BCMA-targeted CAR T cell therapies and may result in chronic hypogammaglobulinaemia. Infections including life-threatening and fatal have been reported after ide-cel including bronchopulmonary aspergillosis, pneumonia cytomegaloviral, pneumonia, fungal infection, and mucormycosis.
Characterization of risk	**Frequency with 95% CI** In the pooled analysis, 252 subjects (61.6%; 95% CI: 56.7, 66.4) experienced at least 1 AE of infection.

	MM-001 and CRB-401 (N = 184)	**MM-003 Arm A (N = 225)**	**Total (N = 409)**
Subjects ≥ 1 SAE, n (%)	50 (27.2)	46 (20.4)	96 (23.5)
Subjects ≥ 1 AE, n (%)	131 (71.2)	121 (53.8)	252 (61.6)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	71.2 (64.1, 77.6)	53.8 (47.0, 60.4)	61.6 (56.7, 66.4)

Table 2.7.3.1-5: Important Identified Risk: Infections

Important Identified Risk: Infections

Seriousness/Outcomes

Serious events of Infections - Overall were experienced by-96 (23.5%) ide-cel treated subjects. The PTs reported in > 2% of subjects were pneumonia (6.6%) and sepsis (2.7%).

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Infections, n (%)	50 (27.2)	46 (20.4)	96 (23.5)
Recovered/Resolved	40 (21.7)	29 (12.9)	69 (16.9)
Recovered/Resolved with Sequelae	3 (1.6)	0	3 (0.7)
Not Recovered/Not Resolved	2 (1.1)	7 (3.1)	9 (2.2)
Fatal	5 (2.7)	10 (4.4)	15 (3.7)

Severity and Nature of Risk

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
All AEs	131 (71.2)	121 (53.8)	252 (61.6)
Grade 3 or 4 AE	45 (24.5)	45 (20.0)	90 (22.0)
Grade 5 AE	5 (2.7)	10 (4.4)	15 (3.7)

Risk factors and risk groups	Risk factors for the development of infection include immunocompromised state resulting from neutropenia, lymphopenia, chemotherapy, immunosuppressive drugs, and hypogammaglobulinaemia. Cytokine release syndrome may exacerbate and delay recovery from cytopenias, and treatment of CRS and neurotoxicity with corticosteroids may increase infection risk.[76] Finally, plasma cell aplasia following ide-cel treatment is an expected on-target toxicity of BCMA targeted CAR T cell therapies and may result in chronic hypogammaglobulinaemia, which may further the risk of infection.
Preventability	Ide-cel should not be administered to patients with active infections or inflammatory disorders (SmPC Section 4.4). Severe infections, including life-threatening or fatal infections have occurred in patients after receiving ide-cel. Patients should be monitored for signs and symptoms of infection before and after ide-cel infusion and treated appropriately. Prophylactic, pre-emptive and/or therapeutic antimicrobials should be administered according to local guidelines. Healthcare professionals will be provided with information on the need to coordinate ide-cel thawing and its infusion. A high index of suspicion is warranted in the event of prolonged or recurrent cytopenias, especially in conjunction with hypogammaglobulinaemia, severe lymphopenia and/or recent use of corticosteroids.
Impact on the risk-benefit balance of the product	Infections are considered an important identified risk due to their potential for severe outcomes in this patient population, including death. Prescribers are

Table 2.7.3.1-5: Important Identified Risk: Infections

Important Identified Risk: Infections	
	encouraged to closely monitor patients for signs and symptoms of infection and consider use of prophylactic antiviral, antibacterial and antifungal therapies in accord with local practice standards. Thus, further evaluation of the frequency, severity, seriousness and outcome of postmarketing infections is planned for study in the ide-cel observational registry, the post-trial LTFU study and spontaneous AE reports.
Public health impact	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, and killing as many as one in four (and often more). Early recognition and resuscitation, including prompt infection control, treatment with empiric broad spectrum antibiotics and maintenance of hemodynamic stability, are cornerstones of the early-phase management of sepsis and septic shock.[77]
MedDRA Terms	MedDRA System Organ Class of infections and infestations

Table 2.7.3.1-6: Important Identified Risk: Secondary Malignancy of T-cell Origin

Important Identified Risk: Secondary Malignancy of T-cell Origin	
Potential mechanisms	A theoretical mechanism for secondary malignancy of T-cell origin is insertional oncogenesis following the use of lentiviral vectors in the manufacture gene of modified CAR T cell therapies. Potential mechanisms such as vector enhancer-mediated activation of down-stream gene expression, insertional gene inactivation, or gene activation by 3'end truncation, may disrupt gene expression due to vector integration within or near proto-oncogenic loci.[78] Based on the tumour samples received and tested from the studies summarized in this RMP, no secondary malignancy of T-cell origin due to insertional oncogenesis has been identified as of the data cutoff dates (07-Apr-2020 [CRB-401, MM-001] and 18-Apr-2022 [MM-003]).
Evidence source and strength of evidence	No insertional mutagenesis or malignancies from insertional oncogenesis have been reported or identified as of the cutoff date in the clinical study setting. In the pooled analysis, no secondary malignancies of T-cell origin have been reported after ide-cel infusion, including initial infusion and retreatment as of the data cutoff dates (07-Apr-2020 [CRB-401, MM-001] and 18-Apr-2022 [MM-003]). One case of secondary malignancy of T-cell origin was received for ide-cel from a study not summarized in this RMP (Study BB2121-MM-002) and was coded to the PT of large granular lymphocytosis (T-LGL).[50] The subject was diagnosed with Grade 3 T-LGL approximately 6 weeks after ide-cel infusion for RRMM. In this case, transgene testing and insertion site analysis indicated the level of CAR+ cells detected in circulation were within expected range relative to time from infusion, and highly polyclonal. No predominant clone was identified, suggesting no involvement from insertional oncogenesis. A causal relationship has not been found between ide-cel and T-cell malignancy. The product information for Abecma has been updated based on a class-warning regarding the occurrence of secondary malignancies of T-cell origin with CAR-T cell therapies and PRACs assessment that an at least reasonable possibility for a causal relationship for the class exists.

Table 2.7.3.1-6: Important Identified Risk: Secondary Malignancy of T-cell Origin

Important Identified Risk: Secondary Malignancy of T-cell Origin	
Characterization of risk	There were no subjects who experienced secondary malignancy of T-cell origin for ide-cel in clinical studies.
Risk factors and risk groups	The risk factors and risk groups described below for secondary hematologic malignancies that are not of T-cell origin (see Table 2.7.3.1-7) are likely also applicable to secondary T-cell malignancies. Much is unknown about the T-cell lymphomas after CAR T therapy in the cases received, including important patient characteristics such as age, prior therapies (including prior autologous or allogeneic stem cell transplantation), immune status, and other clinical features as well as the time from CAR-T infusion to the development of T cell lymphoma.[79] The clinical status of the patients in terms of immunosuppression, previous therapy, conditioning chemotherapy, and evidence of prior clonal hematopoiesis is also unknown. Related to the product, the vector copy number, integration site analysis and detection of the CAR transgene in the T cell lymphomas are all crucial information for analysis. These data are critical to determine any possible biological or causal relationship with CAR-T cells but can be difficult to obtain as measurements of CAR expression or integration are not commercially available as clinical diagnostic assays.[79]
Preventability	Patients treated with ide-cel may develop secondary malignancy of T-cell origin (SmPC Section 4.4) and should be monitored life-long for secondary malignancies. In the event that a secondary malignancy of T cell origin occurs, the company should be contacted to obtain instructions on the collection of patient samples for testing.
Impact on the risk-benefit balance of the product	Secondary malignancy of T-cell origin is a serious and potentially fatal illness that will require medical intervention and is an important identified risk.
Public health impact	Whether T-cell neoplasms after CAR-T cell therapy occur more often than expected is an unanswered question because of the disease- and treatment-related risk factors and the rarity of T-cell neoplasms.[80] The estimated incidence proportion of T-cell lymphomas in patients commercially exposed to CD19- or BCMA-CAR-T cell therapies at the end of 2023 ranged from 0.04% to 0.06% in the CIBMTR population followed in post-authorization studies (median follow up time: 13 months) and in the total exposed population, respectively.[79] This proportion seems to be even lower in patients with plasma cell neoplasm.[80]
MedDRA Terms	Selected HLGT of Lymphomas non-Hodgkin's T-cell; HLT of Leukaemias chronic T-cell and adhoc PTs of T-cell type acute leukaemia, Lymphoproliferative disorder and Lymphocytic leukaemia.

Table 2.7.3.1-7: Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell Origin)

Important Potential Risk Secondary Malignancies (except secondary malignancy of T-cell Origin)	
Potential mechanisms	No mechanism has been identified whereby ide-cel may cause non-T-cell malignancies.

Table 2.7.3.1-7: Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell Origin)

Important Potential Risk Secondary Malignancies (except secondary malignancy of T-cell Origin)

Evidence source and strength of evidence

In the pooled analysis, other secondary malignancies were reported for 31 (7.6%) subjects who received ide-cel. The most common secondary malignancies were basal cell carcinoma (8 [2.0%] subjects), MDS and squamous cell carcinoma (5 [1.2%] subjects each), and breast cancer and malignant melanoma (3 [0.7%] subjects each). Anal cancer, bladder cancer, Bowen's disease, leukemia, lung adenocarcinoma, metastases to CNS, rectal adenocarcinoma, renal cancer, and small intestine adenocarcinoma were reported for 1 (0.2%) subject each.

Characterization of risk

Frequency with 95% CI

In the pooled analysis, 31 subjects (7.6%, 95% CI: 5.2, 10.6) experienced at least one AE of Secondary Malignancies (except secondary malignancy of T-cell origin).

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Subjects ≥ 1 SAE, n (%)	16 (8.7)	15 (6.7)	31 (7.6)
Subjects ≥ 1 AE, n (%)	16 (8.7)	15 (6.7)	31 (7.6)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	8.7 (5.1, 13.7)	6.7 (3.8, 10.8	7.6 (5.2, 10.6)

Seriousness/Outcomes

All AEs of Secondary Malignancies (except secondary malignancy of T-cell origin) were considered Serious events.

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Secondary Malignancies, n (%)	16 (8.7)	15 (6.7)	31 (7.6)
Recovered/Resolved	9 (4.9)	9 (4.0)	18 (4.4)
Not Recovered/Not Resolved	6 (3.3)	4 (1.8)	10 (2.4)
Fatal	1 (0.5)	2 (0.9)	3 (0.7)

Severity and Nature of Risk

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
All AEs	16 (8.7)	15 (6.7)	31 (7.6)
Grade 3 or 4 AE	5 (2.7)	8 (3.6)	13 (3.2)
Grade 5 AE	1 (0.5)	2 (0.9)	3 (0.7)

Table 2.7.3.1-7: Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell Origin)

Important Potential Risk Secondary Malignancies (except secondary malignancy of T-cell Origin)	
Risk factors and risk groups	While none of the following may be exclusive, there may be several explanations why patients develop secondary malignancies: • Prior treatments for B-cell lymphoma (eg, alkylating agents, immunomodulatory drugs, autologous HCT, and/or other therapies), • Patient's exposure to lymphodepleting chemotherapy prior to CAR T-cell infusion, • Pre-existing mutations, • Hereditary. The occurrence of secondary malignancies (except secondary malignancy of T-cell origin) in cancer patients has increased as improvements in cancer therapies and cancer detection have led to larger number of long-term cancer survivors. Results of a population-based study of 19,791 patients with MM showed that a prior malignancy diagnosis was associated with a significantly increased risk of developing a subsequent malignancy.[81] Results of another large, population-based study (including 8740 patients with MM) showed that the risk of developing any secondary malignancy is 26% higher in patients with MM compared with the general population, with an 11-fold increased risk of developing acute myeloid leukaemia and MDS, and a 2-fold increased risk of developing nonmelanoma skin cancer.[40] In general, the risk of developing cancer is greater in older than in younger patients. In the pooled analysis, the median age of all subjects was 61.0 years. At present after surviving from a primary malignancy, 17% to 19% of patients develop SMN. This is due to three reasons: continued lifestyle, genetic susceptibility, and treatment modality. In the US National Cancer Institute's SEER programme, it was observed that proportion of SMNs was doubled in the last three decades (9% in 1975 through 1979 to 19% in 2005 through 2009). Interventions to reduce the risk of SMN can be considered during or following treatment for the first cancer. Lifestyle interventions after treatment such as quitting smoking, reduce alcohol consumption, regular exercise and weight loss may be effective in reducing the incidence of SMNs.[82]
Preventability	Patients treated with ide-cel may develop secondary malignancies (SmPC Section 4.4). They should be monitored life-long for secondary malignancies.
Impact on the risk-benefit balance of the product	Secondary malignancy is a serious and life-threatening illness that will require medical intervention and is an important potential risk.
Public health impact	After surviving from a primary malignancy, 17% to 19% of patients develop a SMN either as a random event, as a reflection of genetic susceptibility, or as a result of mutation induced by prior genotoxic exposures, including prior mutagenic chemotherapy.[82]
MedDRA Terms	Selected narrow scope of sub-SMQs Haematological malignant tumour, Haematological tumours of unspecified malignancy, Non-haematological malignant tumours and Non-haematological tumours of unspecified malignancy; excluding the HLGT Lymphomas non-Hodgkin's T-cell; HLT of Leukaemias chronic T-cell and PTs of plasma cell leukaemia, plasma cell leukaemia in remission, plasma cell myeloma, plasma cell myeloma in remission, plasma cell myeloma recurrent, plasma cell myeloma refractory, plasmacytoma, T-cell acute

Table 2.7.3.1-7: Important Potential Risk: Secondary Malignancies (except secondary malignancy of T-cell Origin)

Important Potential Risk Secondary Malignancies (except secondary malignancy of T-cell Origin)	
	leukaemia, lymphoproliferative disorder, lymphocytic leukaemia, and including the ad hoc HLT of myelodysplastic syndrome.

Table 2.7.3.1-8: Important Potential Risk: Tumour Lysis Syndrome

Important Potential Risk Tumour Lysis Syndrome	
Potential mechanisms	TLS is a consequence of cytokine release and subsequent cytotoxic killing of BCMA-expressing cells, following on target pharmacology activity.
Evidence source and strength of evidence	Because ide-cel has anti-neoplastic activity, complications of TLS may occur, therefore TLS is considered an important potential risk for ide-cel.
Characterization of risk	**Frequency with 95% CI** In the pooled analysis, 4 subjects (1.0%; 95% CI: 0.3, 2.5) had Grade 3 TLS. **Seriousness/Outcomes** 2 events of TLS were considered serious.
Risk factors and risk groups	Based on the MOA for this risk, patients with high disease burden are at increased risk of developing TLS.
Preventability	Subjects should be closely monitored for laboratory evidence of TLS (hyperuricaemia, hyperkalaemia, hyperphosphataemia, and hypocalcaemia) and subjects at high risk should receive prophylactic treatment as per standard clinical practice.
Impact on the risk-benefit balance of the product	TLS can cause life-threatening complications including death if not appropriately and immediately treated.
Public health impact	Clinical TLS is a predictor for worse overall morbidity and mortality in cancer patients but can be prevented. Thus, accurate prognostication is critical to appropriate management of patients at risk for TLS and incorporates both disease factors (tumour type and burden) and patient factors (baseline renal insufficiency or hyperuricaemia). Strategies to prevent TLS include hydration and allopurinol in low- and intermediate-risk patients and rasburicase in high-risk patients.[83] The complexity in managing TLS lies in making the diagnosis early enough that treatment can be initiated prior to end-organ damage.[84]
MedDRA Terms	MedDRA PT of tumour lysis syndrome

Table 2.7.3.1-9: Important Potential Risk: Aggravation of Graft Versus Host Disease

Important Potential Risk: Aggravation of Graft Versus Host Disease	
Potential mechanisms	GVHD can occur after allo-HSCT when immune cells from the donor attack the recipient patient host's tissues. In patients after allo-HSCT, donor cells in the ide-cel product could theoretically induce aggravation of GVHD.
Evidence source and strength of evidence	There is a theoretical risk of inducing or aggravating GVHD in patients with prior allo-HSCT.

Table 2.7.3.1-9: Important Potential Risk: Aggravation of Graft Versus Host Disease

Important Potential Risk: Aggravation of Graft Versus Host Disease	
Characterization of risk	**Frequency with 95% CI** No events of GVHD have been reported in the clinical study programme. **Seriousness/Outcomes** No events of GVHD have been reported in the clinical study programme. **Severity and Nature of Risk** No events of GVHD have been reported in the clinical study programme.
Risk factors and risk groups	Patients with active GVHD from prior HSCT.
Preventability	If there are no apparent treatment alternatives, the infusion of ide-cel should be delayed in patients with active GVHD pending a careful benefit/risk assessment performed by the treating prescriber. There is no experience treating such patients to date and ide-cel is not recommended in this setting.
Impact on the risk-benefit balance of the product	The risk of GVHD in patients treated with CAR T cells who have received prior allo-HSCT has not been determined. However, it is biologically plausible that the infusion and expansion of allogenic CAR T cells could aggravate GVHD.
Public health impact	Graft-versus-host disease is an adverse immunologic phenomenon observed in many patients after allo-HSCT. The incidence of GVHD is as high as 40% to 60% of patients receiving HSCT, depending on the type of transplant, patient characteristics, and GVHD prophylaxis regimen.[85] However, <1% of patients with MM undergo allo-HSCT. GVHD is a complex disease with acute and chronic presentations, multiorgan involvement, multispecialty management with many different treatment options and mortality may approach 15%.[86]
MedDRA Terms	MedDRA PT: Graft versus host disease

Table 2.7.3.1-10: Important Potential Risk: Generation of Replication Competent Lentivirus

Important Potential Risk: Generation of Replication Competent Lentivirus	
Potential mechanisms	RCL is a theoretical outcome of a lentivector genome recombination event resulting in the non-replicating vector acquiring the capacity to replicate.
Evidence source and strength of evidence	Lentiviral vectors used to transduce host autologous T cells for ide-cel manufacture are engineered to be replication-incompetent and self-inactivating. There have been no reports of RCL generated during lentiviral vector manufacturing from ide-cel and there have been no ide-cel subjects who have shown evidence of RCL. RCL has not been detected in third-generation lentiviral vector products manufactured for clinical use suggesting that current vector design and vector product screening provide a high level of assurance regarding the absence of replicating virus.[87] The potential generation of RCL during manufacturing remains a theoretical possibility that cannot be entirely excluded and RCL has the potential to increase the possibility of ide-cel transgene mediated transformation. However, all available evidence suggests that the overall risk is very low.
Characterization of risk	**Frequency with 95% CI**

Table 2.7.3.1-10: Important Potential Risk: Generation of Replication Competent Lentivirus

Important Potential Risk: Generation of Replication Competent Lentivirus	
	No events of replication competent retrovirus test positive have been reported in the clinical study programme. **Seriousness/Outcomes** No events of replication competent retrovirus test positive have been reported in the clinical study programme. **Severity and Nature of Risk** No events of replication competent retrovirus test positive have been reported in the clinical study programme.
Risk factors and risk groups	No known risk factors or risk groups.
Preventability	Modern vectors have been improved to reduce the risk of RCL generation. A number of design features of the anti-B-cell-maturation antigen 02 (anti-BCMA02) CAR LVV are intended to minimise the likelihood of plasmid recombination and generation of RCL during the LVV manufacturing process. These include the segregation of viral genes across multiple plasmids during LVV production, which significantly decreases the likelihood of RCL development as multiple recombination events would need to occur across all 4 plasmids for an RCL to be generated. A lack of significant sequence homology across all 4 plasmids utilised for vector production also decreases the likelihood of recombination leading to RCL generation. In addition, the anti-BCMA02 LVV does not contain the necessary genomic and regulatory elements to interact with HIV to form a mobilised, replication competent LVV. All ide-cel drug product lots manufactured during clinical development have been confirmed to be negative for RCL. Additionally, there is no evidence of RCL development in any ide-cel treated subjects.
Impact on the risk-benefit balance of the product	Although RCL represents a potential risk to patients in terms of the generation of a vector-derived, replication competent immunosuppressive virus, advances in viral vector engineering and the design of the ide-cel construct minimise this risk and make the likelihood of the occurrence very low.
Public health impact	The potential public health impact of this finding is considered low since no RCL have been observed in ide-cel human experience to date. RCL has not been detected in third-generation lentiviral vector products manufactured for clinical use suggesting that current vector design and vector product screening provide a high level of assurance regarding the absence of replicating virus.[87]
MedDRA Terms	MedDRA PT: Replication competent retrovirus test positive.

Table 2.7.3.1-11: Important Potential Risk: Immunogenicity

Important Potential Risk: Immunogenicity	
Potential mechanisms	CAR T cell immunotherapy has the potential to induce host immune responses. Immunogenicity induction risk factors have been shown to be associated with the presence of non-human or partially human sequences in the CAR construct, and also with the presence of residual viral proteins or other non-human origin proteins utilised as part of the gene editing step of CAR T production.[88]

Table 2.7.3.1-11: Important Potential Risk: Immunogenicity

Important Potential Risk: Immunogenicity

Evidence source and strength of evidence

In the pooled analysis, 70 (17.1%) subjects who received ide-cel had ≥ 1 immunogenicity event. In the pooled analysis, rash was reported for 24 (5.9%) subjects and infusion related reaction was reported for 14 (3.4%) subjects.

In Study MM-001, of the 128 subjects who received ide-cel across the target dose levels of 150 to 450 × 106 CAR+ T cells, 5 (3.9%) were positive for ADAs prior to ide-cel infusion (ie, pre-positive), 122 (95.3%) were negative for ADAs prior to ide-cel infusion (ie, pre-negative), and 1 (0.8%) subject was missing data pre-infusion. The 5 subjects who were pre-positive were also positive for ADAs after ide-cel infusion (ie, post-positive). As of the Safety Update data cutoff date (16-Oct-2019), 62 (48.4%) of 128 subjects were negative for ADAs prior to ide-cel infusion and became positive for ADAs after ide-cel infusion (ie, pre-negative to post-positive).

In Study CRB-401, of the 56 subjects who received ide-cel across the target dose levels of 150 to 450 × 106 CAR+ T cells, 3 (5.4%) subjects were positive for ADAs prior to ide-cel infusion (ie, pre-positive), and 50 (89.3%) subjects were negative for ADA prior to ide-cel infusion (ie, pre-negative), and 3 (5.4%) subjects were missing pre-infusion data. As of the Safety Update data cutoff date (22-Jul-2019), 31 (55.4%) of 56 subjects were negative for ADAs prior to ide-cel infusion and became positive for ADAs after ide-cel infusion (ie, pre-negative to post-positive).

In Study MM-003, of the225 subjects who received ide-cel, the proportion of subjects with pre-existing ADAs was low and 2/5 subjects remained positive. The treatment emergent positive rate with 56.9% with an onset of antibody response in the majority of subjects starting at Month 4 and beyond.[89]

No immunogenicity adverse events specific to the development of ADA (PTs of antibody test abnormal, antibody test positive, inhibiting antibodies, inhibiting antibodies positive, neutralising antibodies, and neutralising antibodies positive) nor specifically attributed to ADA were identified, and there is no evidence that the presence of pre-existing or post-infusion ADA impact the cellular expansion or safety of ide-cel.

Characterization of risk

Frequency with 95% CI

In the pooled analysis, 70 subjects (17.1%; 95% CI: 13.6, 21.1) experienced at least one AE of immunogenicity.

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Subjects ≥ 1 SAE, n (%)	42 (22.8)	28 (12.4)	70 (17.1)
Subjects ≥ 1 AE, n (%)	3 (1.6)	0	3 (0.7)
Incidence (%) of subjects with ≥ 1 AE (95% CI)	22.8 (17.0, 29.6)	12.4 (8.4, 17.5)	17.1 (13.6, 21.1)

Seriousness/Outcomes

Serious events of immunogenicity were experienced by 3 subjects in the pooled analysis (PTs distributive shock, rash, and urticaria, each in 1 subject).

Table 2.7.3.1-11: Important Potential Risk: Immunogenicity

Important Potential Risk: Immunogenicity

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
Immunogenicity, n (%)	3 (1.6)	0	3 (0.7)
Recovered/Resolved	1 (0.5)	0	1 (0.2)
Recovered/Resolved with Sequelae	1 (0.5)	0	1 (0.2)
Not Recovered/Not Resolved	1 (0.5)	0	1 (0.2)

Severity and Nature of Risk

	MM-001 and CRB-401 (N = 184)	MM-003 Arm A (N = 225)	Total (N = 409)
All AEs	42 (22.8)	28 (12.4)	70 (17.1)
Grade 3 or 4 AE	4 (2.2)	0	4 (1.0)
Grade 5 AE	0	0	0

Risk factors and risk groups	No known risk factors or risk groups.
Preventability	The use of LDC with fludarabine and cyclophosphamide (potent immunosuppressive agents) prior to ide-cel administration substantially reduces the potential for a clinically significant anti-ide-cel response. In addition, ide-cel is administered as a single intravenous infusion, which avoids the greater immunogenicity associated with subcutaneous or intradermal prime boost immunisation regimens.
Impact on the risk-benefit balance of the product	Pre-existing and post treatment ADA were present in patients in Studies MM-001, CRB-401, and MM-003. There is no evidence that the presence of pre-existing or post-infusion ADA impact the cellular expansion, safety or effectiveness of ide-cel. Therefore, the overall impact of ADA on ide-cel's risk-benefit balance remains acceptable.
Public health impact	CAR T therapeutics can induce antibody and possibly cellular immune response to various components of the CAR neoantigen construct. Risk factors are primarily associated with the non-human or partially human nature of various components of the CAR T construct as well as the complexity of the CAR T production process requiring use of viral or other types of gene transfer procedures. In cases where immune responses have been observed, they were associated with a quick reduction in the CAR T count in vivo and a loss of efficacy. Strategies to reduce the theoretical immunogenicity risk of CAR T treatment include reduction of the viral protein content, humanisation of the CAR construct, LDC prior to CAR T cell administration, and intravenous CAR T administration.[88] The potential public health impact of this potential risk is considered low based on what has been observed in ide-cel human experience to date: ADA have not been clearly associated with reductions in ide-cel cells in vivo.
MedDRA Terms	See Annex 7 for full list of terms.

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information - Impact on Pregnancy and Lactation

Missing Information	Evidence Source
Population in need of further characterisation:	
Pregnant or lactating female subjects exposed to ide-cel.	There is no information available from the clinical study program to determine the safety of ide-cel in these subjects. No cases of pregnancy or lactation have been reported in subjects exposed to ide-cel.

Table 2.7.3.2-2: Missing Information - Long-term Safety

Missing Information	Evidence Source
Population in need of further characterisation:	
All clinical study patients treated with ide-cel need to be followed for up to 15 years in the LTFU study starting from the date of the last infusion of GM T cells, or until study withdrawal, or death, whichever occurs first. For patients treated in clinical practice, a noninterventional PASS of patients treated with ide-cel for MM in the postmarketing setting will be conducted.	To date, there is limited information available from the clinical study programme to determine long-term safety/delayed AEs for patients exposed to ide-cel. Persistent biological activity from gene modified T cells could have adverse effects upon normal cell function, placing subjects at risk for development of AEs, some of which may be delayed by months or years.

Table 2.7.3.2-3: Missing Information - Safety in Elderly Patients (≥ 75 Years)

Missing Information	Evidence Source
Population in need of further characterisation:	
Patients aged ≥ 75 years of age.	To date, there is limited information available to determine the safety of ide-cel in patients ≥ 75 years old. In the clinical study programme, there were only 17 subjects ≥ 75 years of age in the ide-cel treated population.

2.8 Summary of the Safety Concerns

Table 2.8-1: Summary of Safety Concerns

Important identified risks	Cytokine release syndrome
	Neurologic toxicity including ICANS
	Cytopenias
	Hypogammaglobulinaemia
	Infections
	Secondary malignancy of T-cell origin

Table 2.8-1: Summary of Safety Concerns

Important potential risks	Secondary malignancies (except secondary malignancy of T-cell origin)
	Tumour lysis syndrome
	Aggravation of GVHD
	Generation of replication competent lentivirus
	Immunogenicity
Missing information	Impact on pregnancy and lactation
	Long-term safety
	Safety in elderly patients (≥ 75 years)

3 PART III: PHARMACOVIGILANCE PLAN

3.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance activities in BMS as described in the BMS Pharmacovigilance System Master File and Drug Safety's Standard Operating Procedures are in accordance with "GVP in the European Union".

In addition to expedited reporting, BMS vigilantly undertakes follow-up on all ADRs, including serious ADRs that are provided to health authorities to ensure that all details of the case are captured for optimal clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the ADRs.

Emerging potential safety signals can be detected by periodic and if appropriate, cumulative, evaluation of the ADRs. The results will be compiled in the PSUR, in accordance with Guidelines on GVP in the EU/EEA.

In addition, data regarding AEs of special interest will be targeted for review and will be specifically discussed in the PSUR. These data will include all case reports collected during the specified period together with cumulative data.

Using the data obtained from this plan, the benefit-risk profile of ide-cel will be re-evaluated on a periodic basis via the PSUR. If necessary, the related sections of the RMP will be updated accordingly.

Follow-up questionnaires are included in Annex 4 for secondary malignancies, CRS, and neurotoxicity.

3.2 Additional Pharmacovigilance Activities

Ide-cel EU registry-based study (BB2121-MM-006):

A noninterventional PASS of patients treated with ide-cel for MM in the postmarketing setting (see Annex 3). This observational registry-based study is being conducted using existing independent registry data sources such as the EBMT and the CIBMTR (secondary use of data). The study is evaluating rates and severities of selected AEs of special interest, including secondary

malignancies. Pregnancy outcomes and all other AEs considered related to ide-cel treatment will also be collected.

Healthcare professionals are informed to spontaneously report ADRs, including secondary malignancies, directly to the MAH. All consenting patients who have been treated with at least one infusion of ide-cel in the postmarketing setting will enter the post approval registry-based study, which includes out of specification product. All subjects will be followed for up to 15 years after infusion of ide-cel. All safety and effectiveness assessments will be made according to the standard clinical practice of the treating physicians. The investigator will not be requested to undertake any assessment that they would not normally carry out in their clinical practice.

The EBMT and CIBMTR are the registry holders and are responsible for the data held within the respective registry. As part of the regulatory commitments, the MAH will receive a pseudonymised data file to support postmarketing ide-cel pharmacovigilance requirements (eg, PSUR). The standard schedule for PSUR submissions will be followed.

Long-term follow-up Study GC-LTFU-001:

LTFU of safety and efficacy for all paediatric and adult subjects exposed to a gene-modified T cell therapy in BMS sponsored, or BMS alliance partner-sponsored, clinical studies in accordance with Health Authorities' guidance for LTFU (up to 15 years) of subjects treated with gene therapy products.

The following safety endpoints are defined in the protocol for GC-LTFU-001:

- Incidence of delayed AEs suspected to be related to prior GM T cell therapy, including:
  - new malignancies (hematologic or solid)
- new neurologic disorders or exacerbation of a pre-existing neurologic disorder;
- new rheumatologic or autoimmune disorder or exacerbation of a prior rheumatologic or other autoimmune disorder;
- new hematologic disorder;
- other new clinical conditions considered related to the prior GM T cell therapy by the investigator;
- hospitalizations, regardless of relationship to prior treatment, including reasons and dates;
- persistence of GM T cells;
- analysis of vector integration sites;
- incidence of RCR.

A summary of ongoing and completed pharmacovigilance study protocols is provided in Annex 2.

Table 3.2-1: Post-Authorization Safety Studies Short Name Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)	Due Date(s)
Noninterventional, postauthorisation, registry-based study BB2121-MM-006	**Primary Objective** To characterise the incidence and severity of selected ADRs, as outlined in the SmPC, in patients treated with ide-cel in the postmarketing setting and to monitor for potential clinically important events that have not yet been identified as part of the ide- cel safety profile. **Secondary Objective** To assess survival in patients treated with ide-cel in the postmarketing setting.	Noninterventional postauthorisation registry-based study.	All consenting subjects treated with at least one infusion of ide-cel in the postmarketing setting will enter the post approval registry-based study, which includes out of specification product.	1. Date of Initial Registry Protocol Submission to EMA as part of MAA	30-Apr-2020
				2. Start of data collection	14-Feb-2022[a]
				3. Study progress updates	Per the PSUR cycle, according to the EURD list
				4. Safety reports	Per the PSUR cycle according to the EURD list. Additional reports every 3 months if a new safety concern is identified.Year 5, 10, and 15 or when last patient is out of the registry-based study.
				5. Interim reports	Q1 2042 Q1 2043
				6. Date of Study Completion	
				7. Date of Final Study Report Submission to EMA	

Table 3.2-1: Post-Authorization Safety Studies Short Name Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)	Due Date(s)
Long-term follow-up study GC-LTFU-001	**Primary Objectives:** • To assess the risk of delayed AEs following exposure to GM T cells. • To monitor for long-term persistence of GM T cells, including analysis of vector integration sites, as appropriate. • To monitor for generation of replication competent retroviruses.	Subjects enrolled in this LTFU study will have safety assessments, central and local laboratory evaluations, and complete patient-reported outcome questionnaires at scheduled intervals, as conducted in the parent treatment protocol for up to 15 years after the GM T cell infusion.	All paediatric and adult subjects exposed to a gene- modified T cell therapy in BMS sponsored, or BMS alliance partner-sponsored, clinical studies.	1. Start of data collection	Jul-2018 Patients to be followed up for up to 15 years.
				2. Safety data will be included in PSURs	Submitted in accordance with the EURD list.
				3. Interim Reports	(5 and 10 years from first subject first visit in GC-LTFU-001 [Jul 2018]): Q3 2023 and Q3 2028
				4. Anticipated last subject last visit	Q1 2037[b]
				5. Final database lock	Q2 2037
				6. Final report of completed GC-LTFU-001 follow-up of 4L+[c] multiple myeloma ide-cel treated subjects	Mar 2038

[a] Based on the EC decision and protocol approval timeline

[b] Ide-cel-treated 4L+ multiple myeloma subjects enrolled in the GC-LTFU-001 trial.

[c] 4L+ = Fourth line and beyond.

3.2.1 Transgene Assay Service for Testing of Secondary Malignancies with Insertion Site Analysis as Applicable

Third-generation, self-inactivating (SIN) lentiviral vectors are used in the manufacture of ide-cel. This modern vector system has significantly improved the safety profile with reduced risk of RCLs and insertional mutagenesis. The ide-cel drug product is highly purified for CD3+ cells, a population with an expected lower propensity for gene therapy-induced insertional mutagenesis based on both the natural history of WT HIV infection as well as on published long-term follow-up data from patients treated with CAR T cells.[90] The transduction pool in the ide-cel manufacturing process has high T cell purity so there is low risk of transducing non-T cells.

With respect to LVV, the MAH intends to continue to include RCL release testing requirement of all manufactured LVV lots prior to their use in the ide-cel drug product manufacturing processes. [redacted] Notwithstanding, RCL testing will continue to be performed on patients post-infusion as part of Study GC-LTFU-001 for ide-cel in the clinical settings. Up to the data cutoff dates, no RCL+ patients have been reported via Study GC-LTFU-001.

Additional pharmacovigilance activities include the following, as detailed below:

- Specific CRF and specific adverse reaction follow-up templates are employed to characterise the clinical features and risk factors for secondary malignancies.
- For subjects who develop a new secondary malignancy of suspected T cell origin, additional testing for vector sequence will be conducted. The MAH will include details of the methodology and the plans for additional testing for insertion site mapping if the testing for the presence of the vector sequence is detected.

The MAH proposes to present results of the transgene assay service in two ways. First, safety data will be included in PSURs in accordance with EMA/816292/2011 Guideline on GVP. Second, presentation of results in reports will be submitted as a standalone variation at 5, 10, and 15 years from date of EC Decision approving ide-cel.

3.2.1.1 Testing in the Post-marketing Setting

Transgene testing will be conducted for all reported secondary malignancies of suspected T-cell origin where a sample is available. The MAH has developed a non-interventional laboratory testing protocol (protocol CA082-085), which is designed to test archived diagnostic tumor tissue samples from qualifying secondary malignancies in patients who received a BMS manufactured gene-modified product (including Abecma) and are not actively participating in a clinical trial.

When a secondary malignancy is reported, the specific adverse reaction follow-up questionnaire (Annex 4) will be employed to characterise all new malignancy reports and will collect the same information as from the structured secondary malignancy CRF used in Study GC-LTFU-001. A pathology review of the diagnosis will be conducted to ensure appropriate tissue with confirmed active disease is requested for transgene testing to mitigate risk of false negative results.

The MAH will assist prescribers in coordinating transfer of tumour and blood samples from patients with secondary malignancies of suspected T cell origin for ide-cel transgene testing. The

MAH will provide contact details for HCPs for tumour sample testing via the national implemented educational programme and in the product label. A sample of the tumour with confirmed active disease involvement will be requested to test for the presence of ide-cel transgene. The most appropriate specimen for testing is the original diagnostic tumour sample previously collected and used for the diagnosis of the secondary malignancy. If the original diagnostic tumour sample is not available, a tumour sample collected after diagnosis and confirmed to have involvement with the secondary malignancy is acceptable. In the case of a secondary malignancy with bone marrow involvement, bone marrow aspirate is the preferred specimen over bone marrow biopsy for testing, if available. In addition to tumour samples, peripheral blood collected during the diagnosis of the secondary malignancy may also be requested for testing.

If ide-cel transgene levels are detected at qualifying levels in the tumour specimen, insertion site analysis will be performed to assess the clonality of the transduced cell population by identifying the frequency and location of insertion sites to ascertain if insertional mutagenesis is suspected in the development of the malignancy. If insertional mutagenesis is suspected, further testing may be conducted to investigate the involvement of the BMS Gene Modified Cell Therapy (GMCT) with the secondary malignancy.

Details for the types and amounts of tumour and blood samples acceptable for testing, and information about the tests that will be performed can be found in the Observational Protocol CA082085 Transgene Assay Service on clinicaltrials.gov website under the study NCT06357754.[91]

3.2.1.2 Testing in Study GC-LTFU-001

Patients enrolled in Study GC-LTFU-001 will be followed for up to 15 years after the last infusion of ide-cel, or until study withdrawal, lost to follow-up or death, whichever occurs first. Testing for ide-cel transgene will be conducted on all secondary malignancies reported as per protocol to the MAH where tissue is available. A structured secondary malignancy CRF is employed to characterise all new malignancy reports by dates of ide-cel treatment and new malignancy onset, time to onset, stage, history of prior malignancies, previous cancer therapies, prior radiotherapy, other relevant exposures, family history, and biopsy report. Treatments for the secondary malignancy and clinical outcomes will also be collected.

If a secondary malignancy is reported while a patient is enrolled on GC-LTFU-001, a sample of the neoplastic tissue used for the diagnosis of the secondary malignancy will be requested for testing. The neoplastic tissues submitted for testing will be evaluated for the presence of ide-cel transgene. If the transgene levels are detected at qualifying levels in the tumour specimen, insertion site analysis will be performed to assess the clonality of the CAR transduced cell population by identifying the frequency and location of insertion sites to ascertain if insertional mutagenesis is suspected. If insertional mutagenesis is suspected, further testing may be conducted to investigate the involvement of ide-cel with the secondary malignancy. When a secondary malignancy is reported, blood samples will also be requested for quantification of ide-cel transgene and presence of RCL in peripheral blood.

In addition to transgene testing for secondary malignancies, patients enrolled in Study GC-LTFU-001 are routinely monitored by safety assessments, clinical laboratory evaluations, as well as testing for persistence of vector sequence and RCL in peripheral blood at scheduled intervals as per protocol. [redacted] If clonal outgrowth is detected in the peripheral blood, patients will be closely monitored at more frequent intervals for clinical abnormalities or development of a secondary malignancy.

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Noninterventional, postauthorisation, registry-based study (BB2121-MM-006) / Ongoing	**Primary Objective** To characterise the incidence and severity of selected ADRs, as outlined in the SmPC, in patients treated with ide-cel in the postmarketing setting and to monitor for potential clinically important events that have not yet been identified as part of the ide-cel safety profile. **Secondary Objective** To assess survival in patients treated with ide-cel in the postmarketing setting.	Cytokine release syndrome Neurologic toxicity including ICANS Cytopenias Hypogammaglobulinaemia Infections Secondary malignancy of T-cell origin Secondary malignancies (except secondary malignancy of T-cell origin) Tumour lysis syndrome Aggravation of graft versus host disease[a] Impact on pregnancy and lactation Long-term safety	1. Date of Final Registry Protocol Submission to EMA	Date of Initial Registry Protocol Submission to EMA as part of MAA: 30-Apr-2020
			2. Start of data collection	14-Feb-2022[b]
			3. Study progress updates	Per the PSUR cycle, according to the EURD list
			4. Safety Reports	Per the PSUR cycle according to the EURD list. Additional reports every 3 months if a new safety concern is identified
			5. Interim Reports	Year 5, 10, and 15 or when last patient is out of the registry-based study
			6. Date of Study Completion	Q1 2042
			7. Date of Final Report Submission to EMA	Q1 2043
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 3 - Required additional pharmacovigilance activities				
Long-term follow-up study (GC-LTFU-001) / Ongoing	**Primary Objectives:** • To assess the risk of delayed AEs following exposure to GM T cells. • To monitor for long-term persistence of GM T cells, including analysis of vector integration sites, as appropriate. • To monitor for generation of replication competent retroviruses.	Long-term safety Secondary malignancy of T-cell origin Secondary malignancies (except secondary malignancy of T-cell origin) Long-term safety Secondary malignancy of T-cell origin Secondary malignancies (except secondary malignancy of T-cell origin) Generation of replication competent lentivirus Long-term safety	1. Patients to be followed up for up to 15 years 2. Start of data collection 3. Interim Reports (5 and 10 years from first subject first visit in GC-LTFU-001 [Jul 2018]) 4. Anticipated last subject last visit 5. Final database lock 6. Final report of completed GC-LTFU-001 follow-up of 4L+[c] multiple myeloma ide- cel treated subjects 7. Safety data will be included in PSURs	NA Jul-2018 Q3 2023 and Q3 2028 Q1 2037[d] Q2 2037 Mar-2038 Submitted in accordance with EURD list
Transgene assay service testing of secondary malignancies with insertion site analysis as applicable	Tumour tissue sample testing from patients that develop a secondary malignancy of T cell origin.	Secondary malignancy of T-cell origin	1. Safety data will be included in PSURs 2. Interim Reports	Submitted in accordance with the EURD list EC decision + 5 years (Q3 2026) EC decision + 10 years (Q3 2031) EC decision + 15 years (Q3 2036)

[a] Included under the category of Other AEs considered related to ide-cel treatment in Study BB2121-MM-006.

[b] Based on the EC decision and protocol approval timeline.

[d] 4L+ = Fourth line and beyond.

[e] Ide-cel-treated 4L+ multiple myeloma subjects enrolled in the GC-LTFU-001 trial.

4 PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

[redacted]

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Routine Risk Minimisation Measures

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Cytokine release syndrome	**Routine risk communication**: SmPC: Sections 4.2, 4.4, and 4.8. PL: Sections 2, 3, and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.2 Advice regarding monitoring for sign/symptoms of CRS Section 4.4 Detailed guidance on the identification, grading, and management of CRS and the monitoring and management of MAS PL Section 2 What you need to know before you are given ide-cel Section 4 Possible side effects Description of the signs of CRS, and guidance to tell doctor straight away if the patient gets any of these signs **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription
Neurologic toxicity including ICANS	**Routine risk communication**: SmPC: Sections 4.2, 4.4, 4.7, and 4.8 PL: Sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.2 Advice regarding monitoring for neurological events Section 4.4-Detailed guidance on the identification, grading, and management of neurologic toxicity PL Section 2 What you need to know before you are given ide-cel Section 4 Possible side effects Description of the signs of neurologic toxicity including ICANS, and guidance to tell doctor straight away if the patient gets any of these signs **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Legal Status: Ide-cel is subject to restricted medical prescription
Cytopenias	**Routine risk communication**: SmPC: Sections 4.4 and 4.8 PL: Sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4 Guidance on the monitoring and management of cytopenia PL Section 2 What you need to know before you are given ide-cel Section 4 Possible side effects Description of the signs of low red blood cells or platelets, and guidance to tell doctor straight away if the patient gets any of these signs **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription
Hypogammaglobulinaemia	**Routine risk communication**: SmPC: Sections 4.4, 4.6, and 4.8 PL: Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4 Guidance on the monitoring and management of hypogammaglobulinaemia Section 4.6-Assessment of Ig levels in new-borns of mothers treated with ide-cel should be considered **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription
Infections	**Routine risk communication**: SmPC: Sections 4.2, 4.4, and 4.8 PL: Sections 2, 3, and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4 Ide-cel should not be administered to patients with active infections or inflammatory disorders. Guidance on the monitoring and management of infections. PL

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Section 2 What you need to know before you are given ide-cel Section 4 Possible side effects Description of the signs of infection, and guidance if the patient shows any signs Section 3 How ide-cel is given Advice on preventing infection **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription
Secondary malignancy of T-cell origin	**Routine risk communication:** SmPC: Section 4.4 and 4.8 PL: None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC: Section 4.4 Guidance on the monitoring and what do in the event of secondary malignancy of T cell origin PL: Section 2 What you need to know before you are given ide-cel and Section 4 Possible side effects Description of the signs of secondary malignancy of T-cell origin and guidance to tell doctor straight away if the patient gets any of these signs. **Other routine risk minimisation measures beyond the Product Information:** Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription
Secondary malignancies (except secondary malignancy of T-cell origin)	**Routine risk communication**: SmPC: Section 4.4 PL: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC: Section 4.4 Guidance on monitoring for secondary malignancies PL: None **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Tumour lysis syndrome	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription
Aggravation of graft versus host disease	**Routine risk communication**: SmPC: Section 4.4 PL: Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4 Infusion should be delayed up to 7 days if a patient has active GVHD PL Section 2 **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription
Generation of replication competent lentivirus	Routine risk minimisation activities are not deemed necessary. The safety concern can be addressed by conducting active monitoring with routine pharmacovigilance and additional pharmacovigilance activity (Study GC-LTFU-001).
Immunogenicity	**Routine risk communication**: SmPC: Sections 4.2 and 4.8 PL: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.2 The patient should be pre-medicated with paracetamol and diphenhydramine or another H1-antihistamine PL Section 3 How ide-cel is given Statement that paracetamol and an antihistamine medicine will be given shortly before ide-cel treatment to reduce the risk of infusion reactions. **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Legal Status: Ide-cel is subject to restricted medical prescription
Impact on pregnancy and lactation	**Routine risk communication**: SmPC: Section 4.6 PL: Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.6 Ide-cel is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. PL Section 2 What you need to know before you are given ide-cel Advice on pregnancy and breastfeeding **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription
Long-term safety	**Routine risk communication**: SmPC: Annex II D PL: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription
Safety in elderly patients (≥ 75 years)	**Routine risk communication**: SmPC: Section 4.2 PL: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None **Other routine risk minimisation measures beyond the Product Information**: Ide-cel is administered by an HCP **Legal Status:** Ide-cel is subject to restricted medical prescription

5.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are provided in Table 5.2-1. Details of proposed additional risk minimisation activities are provided in Annex 6.

Table 5.2-1: Additional Risk Minimisation Measures

Additional Risk Minimisation **Controlled Distribution Programme**	**Objectives:** The MAH will ensure that hospitals and their associated centres that dispense ide-cel are qualified in accordance with the agreed controlled distribution programme by: • ensuring immediate on-site access to 1 dose of tocilizumab per patient prior to ide-cel infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on site; • HCPs involved in the treatment of a patient have completed the educational programme. **Rationale for the additional risk minimisation activity:** In order to minimise the risks associated with the treatment of ide-cel, hospitals and their associated centres who have HCPs that are expected to prescribe, dispense and administer ide-cel must complete the educational programme by being provided with information in accordance with the agreed HCP Educational Programme. **Target audience and planned distribution path**: The target audience is HCPs who are expected to prescribe and/or dispense and/or administer ide-cel. **Plans to evaluate the effectiveness of the interventions and criteria for success:** PSUR as per EU guidance, GVP (E+R) Criteria for Success: Process indicator: Quantification of provision of product to only qualified sites only if the HCPs involved in the treatment of a patient have received the educational programme.
Additional Risk Minimisation **HCP Educational Programme**	**Objectives:** All HCPs who are expected to prescribe, dispense, and administer ide-cel shall be provided with an HCP guide, which will contain information about: • identification of CRS and serious neurological adverse reactions including ICANS; • management of the CRS and serious neurological adverse reactions including ICANS; • adequate monitoring of CRS and serious neurological adverse reactions including ICANS; • provision of all relevant information to patients; • ensuring immediate on-site access to 1 dose of tocilizumab per patient prior to ide-cel infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site; • risk of secondary malignancy of T-cell origin; • contact details for tumour sample testing after development of a secondary malignancy of T cell origin. • provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study; • ensure that adverse reactions are adequately and appropriately reported; • ensure that detailed instructions about the thawing procedure are provided.

Table 5.2-1: Additional Risk Minimisation Measures

	Rationale for the additional risk minimisation activity: The HCP educational tool is designed to minimise the risk of CRS and Neurotoxicity including ICANS and provide information on the management of the risk and the necessary steps to prevent life-threatening or fatal CRS and/or Neurotoxicity including ICANS. This tool is also designed to increase awareness of the risk of secondary malignancy of T-cell origin. **Target audience and planned distribution path**: The target audience is HCPs who are expected to prescribe, dispense and administer ide-cel. Proposed Actions: • Distribution in a targeted manner of Educational Programme tools to HCPs expected to use the product within qualified centres. **Plans to evaluate the effectiveness of the interventions and criteria for success:** PSUR as per EU guidance, GVP (E+R) Method of assessment: • AE reports to be reviewed on an ongoing basis. AEs to be summarised at the time of the PSUR • Assessment through PASS To monitor and estimate adherence to early intervention guide for CRS and Neurotoxicity including ICANS (ie, ide-cel use) Criteria for Success: Outcome indicator: Absence of fatal outcome due to CRS, or fatal outcome due to Neurotoxicity
Additional Risk Minimisation **Patient Educational Programme**	**Objectives:** All patients who receive ide-cel shall be provided with a patient card, which will contain the following key messages: • the risks of CRS and serious neurological adverse reactions associated with ide-cel; • the need to report the symptoms of suspected CRS and neurotoxicity including ICANS to their treating doctor immediately; • the need to remain in the proximity of the location where ide-cel was received for at least 2 weeks following ide-cel infusion; • the need to carry the patient card at all times; • a reminder to patients to show the patient card to all HCPs, including in conditions of emergency, and a message for HCPs that the patient is using ide-cel; • fields to record contact details of the prescriber and batch number. **Rationale for the additional risk minimisation activity:** To educate patients on the risk of CRS and neurotoxicity including ICANS and encourage patients to carry the patient card with them at all times to minimise the risk of CRS and neurotoxicity including ICANS and provide education on the early symptoms of the risks and the necessary step to call or see the treating physician to prevent life-threatening or fatal CRS and/or neurotoxicity including ICANS. **Target audience and planned distribution path**: The target audience is the patient who will receive ide-cel. Proposed Actions: Distribution of patient card by HCP prescribing/dispensing and/or administering ide-cel depending on national healthcare system. **Plans to evaluate the effectiveness of the interventions and criteria for success:** PSUR as per EU guidance, GVP (E+R)

Table 5.2-1: Additional Risk Minimisation Measures

	Criteria for Success: Outcome indicator: Absence of fatal outcome due to CRS, or fatal outcome due to neurotoxicity

5.3 Summary of Risk Minimisation Measures

A summary of risk minimisation measures and pharmacovigilance activities by safety concern is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Cytokine release syndrome	**Routine Risk Minimisation Activities:** SmPC Sections 4.2 and 4.4, PL Sections 2 and 3 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire
	Additional Risk Minimisation Activities: • Educational programme for HCPs and patients • Controlled distribution programme	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Neurologic toxicity including ICANS	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 4.4 and 4.7, PL Section 2– warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire
	Additional Risk Minimisation Activities: • Educational programme for HCPs and patients • Controlled distribution programme	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Cytopenias	**Routine Risk Minimisation Activities:** SmPC Section 4.4, PL Sections 2 and 4 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Hypogammaglobulinaemia	**Routine Risk Minimisation Activities:** SmPC Sections 4.4 and 4.6 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Infections	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 4.4 and PL Sections 2, 3 and 4 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: • Educational programme for HCPs (need to coordinate ide-cel thawing and its infusion) • Controlled distribution programme	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Secondary malignancy of T-cell origin	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – warnings, advice and management discussed Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire
	Additional Risk Minimisation Activities: • Educational programme for HCPs	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006) Long-term follow-up study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable
Important Potential Risks		
Secondary malignancies (except secondary	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – warnings and advice discussed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
malignancy of T-cell origin)	Ide-cel is administered by an HCP	Specific adverse drug reaction follow-up questionnaire
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006) Long-term follow-up study (GC-LTFU-001)
Tumour lysis syndrome	**Routine Risk Minimisation Activities:** Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006)
Aggravation of graft versus host disease	**Routine Risk Minimisation Activities:** SmPC Section 4.4 and PL Section 2 – warnings, advice and management discussed Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** Included under the category of Other AEs considered related to ide-cel treatment in PASS (BB2121-MM-006)
Generation of replication competent lentivirus	**Routine Risk Minimisation Activities:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** LTFU study (GC-LTFU-001)
Immunogenicity	**Routine Risk Minimisation Activities:** SmPC Section 4.2 and PL Section 3 – premedication with paracetamol and diphenhydramine or another H1-antihistamine SmPC Section 4.8 – listed as an ADR	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** None

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing Information		
Impact on pregnancy and lactation	**Routine Risk Minimisation Activities:** SmPC Section 4.6 and PL Section 2 – warnings, advice and management discussed Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006) for pregnancy events
Long-term safety	**Routine Risk Minimisation Activities:** SmPC Annex II – long-term registry discussed Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** PASS (BB2121-MM-006) Long-term follow-up study (GC-LTFU-001)
Safety in elderly patients (≥ 75 years)	**Routine Risk Minimisation Activities:** SmPC Section 4.2 – No dose adjustment necessary Ide-cel is administered by an HCP	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional Risk Minimisation Activities: None	**Additional pharmacovigilance activities:** None

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ABECMA

This is a summary of the Risk Management Plan (RMP) for Abecma. The RMP details important risks of Abecma, how these risks can be minimised, and how more information will be obtained about Abecma's risks and uncertainties (missing information).

Abecma's Summary of Product Characteristics (SmPC) and the associated package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how Abecma should be used.

This summary of the RMP for Abecma should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Abecma's RMP.

I. The medicine and what it is used for

Abecma is authorised for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. It contains idecabtagene vicleucel as the active substance and it is given by infusion.

Further information about the evaluation of Abecma's benefits can be found in the Abecma's EPAR, including in its plain-language summary, available on the European Medicines Agency website.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Abecma, together with measures to minimise such risks and the proposed studies for learning more about Abecma's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Abecma, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Abecma is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Abecma are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Abecma. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	Cytokine release syndrome
	Neurologic toxicity including ICANS
	Cytopenias
	Hypogammaglobulinaemia
	Infections
	Secondary malignancy of T-cell origin
Important potential risks	Secondary malignancies (except secondary malignancy of T-cell origin)
	Tumour lysis syndrome
	Aggravation of GVHD
	Generation of replication competent lentivirus
	Immunogenicity
Missing information	Impact on pregnancy and lactation
	Long-term safety
	Safety in elderly patients (≥ 75 years)

II.B Summary of important risks

Important identified risks

Cytokine Release Syndrome	
Evidence for linking the risk to the medicine	In the pooled analysis (n = 409), 346 (84.6%) subjects who received Abecma had ≥ 1 CRS event. CRS has likewise been reported with CD19 directed CAR T providing further evidence of a class risk. MAS (PT of HLH) was reported for 9 (2.2%) subjects in the pooled analysis: 2 (0.5%) subjects had a maximum severity of Grade 2, 2 (0.5%) had a maximum severity of Grade 3, and 5 (1.2%) had a maximum severity of Grade 4. CRS is considered an important identified risk due to its frequency and the potential for serious outcomes, including death, if untreated. Thus, further evaluation of frequency, severity, seriousness and outcome of this risk in the postmarketing period is warranted. Macrophage activation syndrome and HLH are potentially life-threatening. Cytokine release syndrome has been reported in a few cases to be associated with findings of MAS/HLH, and the physiology of the syndromes may overlap.
Risk factors and risk groups	In the pooled analysis 346 (84.6%) subjects who received Abecma had ≥ 1 CRS event. An exploratory analysis of baseline predictors for CRS in Study MM-003 no correlation of baseline soluble BCMA, body weight, or dose with CRS requiring tocilizumab or CRS requiring steroids. However, higher odds ratio of CRS (Gr3+) was associated with higher level of baseline soluble BCMA and with lower body weight. Macrophage activation syndrome is usually associated with more severe forms of CRS.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Sections 4.2 and 4.4, PL Sections 2 and 3 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Abecma is administered by an HCP **Additional Risk Minimisation Activities:** • HCP educational material • Patient card • Controlled distribution programme
Additional pharmacovigilance activities	Postauthorisation safety study (BB2121-MM-006)
Neurologic Toxicity including ICANS	
Evidence for linking the risk to the medicine	Neurologic toxicity including ICANS is considered an important identified risk due to its seriousness and its potential for associated disability, including death, if left untreated. In addition to CRS, neurologic toxicity is an expected acute AE associated with CAR T cell therapy. The diagnosis is based on clinical signs and symptoms in the absence of definitive diagnostic tests. Neurologic toxicity is primarily managed with supportive care for low grade toxicity, and corticosteroids are frequently used for more severe neurologic toxicity. In order to enable a side-by-side comparison and pooling of data across Studies MM-001, CRB-401, and MM-003, a Neurologic Toxicity-Focused AEs search approach was required that included selected PTs of neurologic toxicity events as determined by the MAH with consideration of biological/pharmacological plausibility for a drug-event relationship, known neurologic toxicities reported with this class of drug and consistent with published guidelines for CAR T cell-associated encephalopathy, and clinical judgement. In the pooled analysis, 153 (37.4%) subjects who received Abecma had ≥ 1 Neurologic Toxicity – Focused AE on or after Abecma infusion. Neurologic Toxicity – Focused AEs reported for ≥

Important identified risks

	5% of subjects were confusional state (11.0%), insomnia (10.3%), tremor (5.6%), and somnolence (5.6%).
Risk factors and risk groups	In the pooled analysis, 153 (37.4%) subjects who received Abecma had ≥ 1 Neurologic Toxicity – Focused AE on or after Abecma infusion. Neurologic Toxicity - Focused AEs were reported for 32.3% of subjects in the pooled analysis within the first 8 weeks and for 8.6% of subjects > 8 weeks after Abecma infusion. In Study MM-001, there was no correlation of pre-infusion soluble biomarkers with investigator-identified neurotoxicity events, and no association of serum BCMA levels with any grade investigator-identified neurotoxicity events.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 4.4 and 4.7, PL Section 2– warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Abecma is administered by an HCP **Additional Risk Minimisation Activities:** • HCP educational material • Patient card • Controlled distribution programme
Additional pharmacovigilance activities	Postauthorisation safety study (BB2121-MM-006)
Cytopenias	
Evidence for linking the risk to the medicine	**Evidence Source(s) and Strength of Evidence:** The AE category of Cytopenia – Overall and sub-category names refer to not only the individual PT, but also includes AE PTs relating to the defined medical condition/concept of neutropenia, thrombocytopenia, and anaemia. In the pooled analysis, 379 (92.7%) subjects who received Abecma had ≥ 1 Cytopenia – Overall AE. The 3 most commonly reported events were neutropenia, anaemia, and thrombocytopenia. Cytopenias (eg, neutropenia, anaemia, and thrombocytopenia) were among the most frequently reported Grade 3 or 4 AEs, and most of these events were reported within the first 8 weeks after Abecma infusion. As anaemia was considered less severe and more manageable compared with neutropenia and thrombocytopenia, this section focuses on neutropenia and thrombocytopenia. In the pooled analysis, Cytopenia – Neutropenia AEs were reported for 87.8% of subjects who received Abecma. Cytopenia – Neutropenia AEs were reported for 86.8% of subjects within the first 8 weeks and for 37.2% of subjects > 8 weeks after Abecma infusion. 83.6% of subjects had ≥ 1 Grade 3 or 4 Cytopenia – Neutropenia AE. No subject had a Grade 5 Cytopenia – Neutropenia AE. The frequency of subjects with Grade 3 or 4 Cytopenia – Neutropenia AEs was 81.9% within the first 8 weeks and 25.6% > 8 weeks after Abecma infusion. In the pooled analysis, Cytopenia – Thrombocytopenia AEs were reported for 59.9% of subjects who received Abecma. • Cytopenia – Thrombocytopenia AEs were reported for 55.3% of subjects within the first 8 weeks and for 29.1% of subjects > 8 weeks after Abecma infusion. • Grade 3 or 4 Cytopenia – Thrombocytopenia AEs were reported for 47.7% of subjects, with Grade 4 events reported for 34.5% of subjects. No subject had a Grade 5 Cytopenia - Thrombocytopenia AE. The frequency of subjects with Grade 3 or 4 Cytopenia - Thrombocytopenia AEs was 42.5% within the first 8 weeks and 19.7% > 8 weeks after Abecma infusion.

Important identified risks

Risk factors and risk groups	Cytopenias are common in both advanced MM patients and in patients treated with CAR T therapy. Contributing factors in RRMM patients include progressive myeloma, prior AMTs, concomitant medications, LDC, and post-infusion toxicities, such as CRS and infection. In the pooled analysis, the frequency of subjects with Grade 3 or 4 Cytopenia – Overall was 90.5% within the first 8 weeks and 40.0% > 8 weeks after infusion.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4, PL Sections 2 and 4 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Abecma is administered by an HCP **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	Postauthorisation safety study (BB2121-MM-006)
Hypogammaglobulinaemia	
Evidence for linking the risk to the medicine	Hypogammaglobulinaemia is considered an important identified risk due to the expected off-tumour, on-target toxicity of plasma cell aplasia from Abecma which may result in some degree of hypogammaglobulinaemia and associated immunosuppression. Hypogammaglobulinaemia is a known risk factor for development of infections in MM patients. The expected duration of plasma cell aplasia is unknown, but may persist much longer than Abecma CAR+ T cells remain in the body. Prolonged plasma cell aplasia is expected to result in hypogammaglobulinaemia which can also be observed as a manifestation of myeloma itself. Hypogammaglobulinaemia may increase the risk of bacterial and other infections including opportunistic infections and viral reactivation. Intravenous Ig replacement may be needed to maintain adequate IgG levels. The use of prophylactic antibiotics may also be necessary. In the pooled analyses, hypogammaglobulinaemia was reported in 14.4% of subjects treated with Abecma.
Risk factors and risk groups	The destruction of non-tumour BCMA+ plasma cells in healthy tissues, or "on-target/ off-tumour" toxicity, may result in some degree of hypogammaglobulinaemia and associated immunosuppression. Therefore, the MOA for Abecma may play a role in subjects developing hypogammaglobulinaemia.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Sections 4.4 and 4.6 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Abecma is administered by an HCP **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	Postauthorisation safety study (BB2121-MM-006)
Infections	
Evidence for linking the risk to the medicine	Infections are a major cause of morbidity in patients with MM with approximately 25% of patients presenting with recurrent infections and serious infections reported for > 75% of patients. In the pooled analysis, 252 (61.6%) subjects who received Abecma had Infections – Overall. The most frequently (≥ 5% of subjects) reported PTs were upper respiratory tract infection (14.9%), pneumonia (10.3%), and urinary tract infection (6.1%). Grade 3 or 4 Infections were reported for 22.0% of subjects, with 16.1% of subjects experiencing Grade 3 events.

Important identified risks

	Infections represent an identified risk of treatment with Abecma and may include bacterial, fungal, pneumocystis, viral reactivation and symptomatic viral infections (eg, cytomegalovirus, HBV, respiratory viruses and other viruses). Risk factors for infection include immune dysfunction from myeloma, LDC (ie, fludarabine and cyclophosphamide) associated lymphopenia and myelosuppression, and Abecma treatment-associated toxicities. Cytokine release syndrome may exacerbate and delay recovery from cytopenias, and treatment of CRS and neurotoxicity with corticosteroids may also increase infection risk. Plasma cell aplasia following Abecma treatment is an expected on-target toxicity of BCMA-targeted CAR T cell therapies and may result in chronic hypogammaglobulinaemia. Infections including life-threatening and fatal have been reported after Abecma including bronchopulmonary aspergillosis, pneumonia cytomegaloviral, pneumonia, fungal infection, and mucormycosis.
Risk factors and risk groups	Risk factors for the development of infection include immunocompromised state resulting from neutropenia, lymphopenia, chemotherapy, immunosuppressive drugs, and hypogammaglobulinaemia. Cytokine release syndrome may exacerbate and delay recovery from cytopenias, and treatment of CRS and neurotoxicity with corticosteroids may increase infection risk. Finally, plasma cell aplasia following Abecma treatment is an expected on-target toxicity of BCMA targeted CAR T cell therapies and may result in chronic hypogammaglobulinaemia, which may further the risk of infection.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Sections 4.2, 4.4 and PL Sections 2, 3 and 4 – warnings, advice and management discussed SmPC Section 4.8 and PL Section 4 – listed as an ADR Abecma is administered by an HCP **Additional Risk Minimisation Activities:** • HCP educational material • Controlled distribution programme
Additional pharmacovigilance activities	Postauthorisation safety study (BB2121-MM-006)
Secondary Malignancy of T-cell origin	
Evidence for linking the risk to the medicine	No insertional mutagenesis or malignancies from insertional oncogenesis have been reported or identified as of the cutoff date in the clinical study setting. In the pooled analysis, no secondary malignancies of T-cell origin have been reported after ide-cel infusion, including initial infusion and retreatment as of the data cutoff dates (07-Apr-2020 [CRB-401, MM-001] and 18-Apr-2022 [MM-003]). One case of secondary malignancy of T-cell origin was received for ide-cel from a study not summarized in this RMP (Study BB2121-MM-002) and was coded to the PT of large granular lymphocytosis (T-LGL). The subject was diagnosed with Grade 3 T-LGL approximately 6 weeks after ide-cel infusion for RRMM. In this case, transgene testing and insertion site analysis indicated the level of CAR+ cells detected in circulation were within expected range relative to time from infusion, and highly polyclonal. No predominant clone was identified, suggesting no involvement from insertional oncogenesis. A causal relationship has not been found between ide-cel and T-cell malignancy. The product information for Abecma has been updated based on a class-warning regarding the occurrence of secondary malignancies of T-cell origin with CAR-T cell therapies and PRACs assessment that an at least reasonable possibility for a causal relationship for the class exists.
Risk factors and risk groups	The risk factors and risk groups described below for secondary hematologic malignancies that are not of T-cell origin are likely also applicable to secondary T-cell malignancies.

Important identified risks

	Much is unknown about the T-cell lymphomas after CAR T therapy in the cases received, including important patient characteristics such as age, prior therapies (including prior autologous or allogeneic stem cell transplantation), immune status, and other clinical features as well as the time from CAR-T infusion to the development of T cell lymphoma. The clinical status of the patients in terms of immunosuppression, previous therapy, conditioning chemotherapy, and evidence of prior clonal hematopoiesis is also unknown. Related to the product, the vector copy number, integration site analysis and detection of the CAR transgene in the T cell lymphomas are all crucial information for analysis. These data are critical to determine any possible biological or causal relationship with CAR-T cells but can be difficult to obtain as measurements of CAR expression or integration are not commercially available as clinical diagnostic assays.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – warnings, advice and management discussed Abecma is administered by an HCP **Additional Risk Minimisation Activities:** • Educational programme for HCPs
Additional pharmacovigilance activities	Postauthorisation safety study (BB2121-MM-006) Long-term follow-up study (GC-LTFU-001) Transgene assay service testing of secondary malignancies with insertion site analysis as applicable

Important potential risks

Secondary Malignancies (except secondary malignancy of T-cell origin)	
Evidence for linking the risk to the medicine	In the pooled analysis, other secondary malignancies were reported for 31 (7.6%) subjects who received Abecma. The most common secondary malignancies were basal cell carcinoma (8 [2.0%] subjects), MDS and squamous cell carcinoma (5 [1.2%] subjects each), and breast cancer and malignant melanoma (3 [0.7%] subjects each). Anal cancer, bladder cancer, Bowen's disease, leukemia, lung adenocarcinoma, metastases to CNS, rectal adenocarcinoma, renal cancer, and small intestine adenocarcinoma were reported for 1 (0.2%) subject each.
Risk factors and risk groups	While none of the following may be exclusive, there may be several explanations why patients develop secondary malignancies: • Prior treatments for B-cell lymphoma (eg, alkylating agents, immunomodulatory drugs, autologous HCT, and/or other therapies), • Patient's exposure to lymphodepleting chemotherapy prior to CAR T-cell infusion, • Pre-existing mutations, • Hereditary. The occurrence of secondary malignancies (except secondary malignancy of T-cell origin) in cancer patients has increased as improvements in cancer therapies and cancer detection have led to larger number of long-term cancer survivors. Results of a population-based study of 19,791 patients with MM showed that a prior malignancy diagnosis was associated with a significantly increased risk of developing a subsequent malignancy. Results of another large, population-based study (including 8740 patients with MM) showed that the risk of developing any secondary malignancy is 26% higher in patients with MM compared with the general population, with an 11-fold increased risk of developing acute myeloid leukaemia and MDS, and a 2-fold increased risk of developing nonmelanoma skin cancer. In general, the risk of developing cancer is greater in older than in younger patients. In the pooled analysis, the median age of all subjects was 61.0 years.

Important potential risks

	At present after surviving from a primary malignancy, 17% to 19% patients develop SMN. This is due to three reasons: continued lifestyle, genetic susceptibility, and treatment modality. In the United States National Cancer Institute's SEER programme, it was observed that proportion of SMNs was doubled in the last three decades (9% in 1975 through 1979 to 19% in 2005 through 2009). Interventions to reduce the risk of SMN can be considered during or following treatment for the first cancer. Lifestyle interventions after treatment such as quitting smoking, reduce alcohol consumption, regular exercise and weight loss may be effective in reducing the incidence of SMNs.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4 – warnings, advice and management discussed Abecma is administered by an HCP **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	Postauthorisation safety study (BB2121-MM-006) Long-term follow-up study (GC-LTFU-001)

Tumour Lysis Syndrome	
Evidence for linking the risk to the medicine	Because Abecma has anti-neoplastic activity, complications of TLS may occur, therefore TLS is considered an important potential risk for Abecma.
Risk factors and risk groups	Based on the MOA for this risk, patients with high disease burden are at increased risk of developing TLS.
Risk minimisation measures	**Routine Risk Minimisation Activities:** Abecma is administered by an HCP **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	Postauthorisation safety study (BB2121-MM-006)

Aggravation of Graft Versus Host Disease	
Evidence for linking the risk to the medicine	There is a theoretical risk of inducing or aggravating GVHD in patients with prior allo-HSCT.
Risk factors and risk groups	Patients with active GVHD from prior HSCT.
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.4 and PL Section 2 – warnings, advice and management discussed Abecma is administered by an HCP **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	Included under the category of Other AEs considered related to Abecma treatment in PASS (BB2121-MM-006)

Important potential risks

Generation of Replication Competent Lentivirus	
Evidence for linking the risk to the medicine	Lentiviral vectors used to transduce host autologous T cells for Abecma manufacture are engineered to be replication-incompetent and self-inactivating. There have been no reports of RCL generated during lentiviral vector manufacturing from Abecma and there have been no Abecma subjects who have shown evidence of RCL. RCL has not been detected in third-generation lentiviral vector products manufactured for clinical use suggesting that current vector design and vector product screening provide a high level of assurance regarding the absence of replicating virus. The potential generation of RCL during manufacturing remains a theoretical possibility that cannot be entirely excluded and RCL has the potential to increase the possibility of Abecma transgene mediated transformation. However, all available evidence suggests that the overall risk is very low.
Risk factors and risk groups	No known risk factors or risk groups.
Risk minimisation measures	**Routine Risk Minimisation Activities:** None **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	LTFU study (GC-LTFU-001)
Immunogenicity	
Evidence for linking the risk to the medicine	In the pooled analysis 70 (17.1%) subjects who received Abecma had ≥ 1 immunogenicity event. In Study MM-001, of the 128 subjects who received Abecma across the target dose levels of 150 to 450 × 106 CAR+ T cells, 5 (3.9%) were positive for ADAs prior to Abecma infusion (ie, pre-positive), 122 (95.3%) were negative for ADAs prior to Abecma infusion (ie, pre-negative), and 1 (0.8%) subject was missing data pre-infusion. The 5 subjects who were pre-positive were also positive for ADAs after Abecma infusion (ie, post-positive). As of the Safety Update data cutoff date (16-Oct-2019), 62 (48.4%) of 128 subjects were negative for ADAs prior to Abecma infusion and became positive for ADAs after Abecma infusion (ie, pre-negative to post-positive). In Study CRB-401, of the 56 subjects who received Abecma across the target dose levels of 150 to 450 × 106 CAR+ T cells, 3 (5.4%) subjects were positive for ADAs prior to Abecma infusion (ie, pre-positive), and 50 (89.3%) subjects were negative for ADA prior to Abecma infusion (ie, pre-negative), and 3 (5.4%) subjects were missing pre-infusion data. As of the Safety Update data cutoff date (22-Jul-2019), 31 (55.4%) of 56 subjects were negative for ADAs prior to Abecma infusion and became positive for ADAs after Abecma infusion (ie, pre-negative to post-positive). In Study MM-003, of the 225 subjects who received Abecma, the proportion of subjects with pre-existing ADAs was low and 2/5 subjects remained positive. The treatment emergent positive rate with 56.9% with an onset of antibody response in the majority of subjects starting at Month 4 and beyond. No immunogenicity adverse events specific to the development of ADA (PTs of antibody test abnormal, antibody test positive, inhibiting antibodies, inhibiting antibodies positive, neutralising antibodies, and neutralising antibodies positive) nor specifically attributed to ADA were identified, therefore, no definitive conclusions regarding the association of ADA positivity with immunogenicity adverse events can be drawn.
Risk factors and risk groups	No known risk factors or risk groups.

Important potential risks

Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.2 and PL Section 3 – premedication with paracetamol and diphenhydramine or another H1-antihistamine SmPC Section 4.8 – listed as an ADR **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	None

Missing information

Pregnancy and Lactation	
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.6 and PL Section 2 – warnings, advice and management discussed Abecma is administered by an HCP **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	Postauthorisation safety study (BB2121-MM-006) for pregnancy events
Long-term Safety	
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Annex II – long-term registry discussed Abecma is administered by an HCP **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	Postauthorisation safety study (BB2121-MM-006) Long-term follow-up study (GC-LTFU-001)
Safety in Elderly Patients (≥ 75 Years)	
Risk minimisation measures	**Routine Risk Minimisation Activities:** SmPC Section 4.2 – No dose adjustment necessary Abecma is administered by an HCP **Additional Risk Minimisation Activities:** None
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Postauthorisation Safety Study BB2121-MM-006

Primary Objective

- To characterise the incidence and severity of selected ADRs, as outlined in the SmPC, in patients treated with Abecma in the postmarketing setting and to monitor for potential clinically important events that have not yet been identified as part of the Abecma safety profile.

Secondary Objective

- To assess survival in patients treated with Abecma in the postmarketing setting.

II.C.2 Other studies in post-authorisation development plan

Long-term Follow-up Study GC-LTFU-001

Primary Objectives:

- To assess the risk of delayed AEs following exposure to genetically modified (GM) T cells
- To monitor for long-term persistence of GM T cells, including analysis of vector integration sites, as appropriate
- To monitor for generation of replication competent retroviruses

Additional Pharmacovigilance Measures in Postauthorisation Development Plan:

Transgene assay service testing of secondary malignancies with insertion site analysis as applicable

Primary Objective:

- Tumour tissue sample testing from patients that develop a secondary malignancy of T-cell origin

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of Contents

Additional Questions

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ADVERSE EVENT REPORT QUESTIONNAIRE **Cytokine Release Syndrome (CRS)** **NOTE: INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED.**		
PATIENT DEMOGRAPHICS		
Patient's initials: _____ Gender: ☐ Male ☐ Female	Patient's date of birth (dd/Mmm/yyyy): _____/_____/_____ OR Patient's age: _____ years	Study Protocol ID (if applicable): _____

SUSPECT PRODUCTS: Please provide suspect product(s) information (those products which are suspected to be associated with one or more adverse events).			
	Suspect Product #1 (CAR T Cell Product)	**Suspect Product #2**	**Suspect Product #3**
Product name	☐ Lisocabtagene maraleucel (Breyanzi) ☐ Idecabtagene vicleucel (Abecma) ☐ Other: _____		
Dose and regimen			
Route of administration			
Indication			
Treatment start date (dd/Mmm/yyyy)			
Treatment stop date (dd/Mmm/yyyy)			
Treatment duration (if start/stop dates unknown)			
Lot/batch number(s)			
Expiration date(s)			

Additional Questions

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CRS - Adverse Event (AE)			
Event	**Start Date**	**Stop Date**	**Outcome**
CRS			
CRS-associated AE - list all below			
CRS-associated organ - specific AE (hepatic, renal, pulmonary, or cardiac) - list all below			

Overall CRS Grade per Lee, et al (2014) - choose one based on most severe symptom		
☐	Grade 1	Temperature ≥ 38.5 °C/101.3 °F
☐	Grade 2	Oxygen requirement < 40% FiO_2 or Hypotension responsive to intravenous fluids or single low-dose vasopressor or Grade 2 organ toxicity
☐	Grade 3	Oxygen requirement ≥ 40% FiO_2 or Hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
☐	Grade 4	Life-threatening hypotension or Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
☐	Grade 5	Death

Seriousness Criteria (check all that apply)	
☐ Death Date of death (dd/Mmm/yyyy): ____/____/____ Cause of death: _____ Was autopsy performed? ☐ Yes ☐ No If yes, please provide autopsy report if available.	☐ Required or ☐ Prolonged hospitalization Admission date (dd/Mmm/yyyy): ___/____/____ Discharge date (dd/Mmm/yyyy): ___/____/____
☐ Life-threatening	☐ Congenital anomaly/birth defect
☐ Persistent or significant disability/incapacity	☐ Medically important event
	☐ Non-serious

Additional Questions

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Causality Assessment
In your opinion, what is the causal relationship between CRS and the CAR T therapy? ☐ Related ☐ Not related **If not related, please provide the cause of the CRS.**
Were alternate causes for the signs and symptoms ruled out? ☐ Yes ☐ No **If yes, please describe how these were ruled out.**

CRS Treatment

Was tocilizumab administered? ☐ Yes ☐ No

Dose	Therapy Dates (dd/Mmm/yyyy)	Response

Were corticosteroids (CS) administered? ☐ Yes ☐ No

Name of CS	Route	Dose	Therapy Dates (dd/Mmm/yyyy)	Response

Were anti-hypotension medications administered (ie, pressors)? ☐ Yes ☐ No

Name of Pressor	Dose	Therapy Dates (dd/Mmm/yyyy)	Response

Additional Questions

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Were any other treatments administered? ☐ Yes ☐ No

Name of Treatment	Route	Dose	Therapy Dates (dd/Mmm/yyyy)	Response

Relevant Medical History

If no relevant medical history, please indicate so here: ☐ No relevant medical history

Please list relevant medical history below, including any infection history or treatment for infection, and any history (including severity and previous treatment) of hepatic, renal, pulmonary, or cardiac disease or impairment.

Disease State	Start Date

Concomitant Medications

Please list concomitant medications below. If the list is too long, please attach a printout of the patient's medications.

Drug Name	Indication	Dose/Frequency	Start Date	Stop Date

Please provide any supplemental information on a separate page.

Signature of Person Completing Form:	
Name of Person Completing Form (Print):	**Date Completed (dd/Mmm/yyyy):**
E-mail Address:	**Phone Number:**

Additional Questions

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Additional Questions

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ADVERSE EVENT REPORT QUESTIONNAIRE
Neurotoxicity (NT)

NOTE: INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED.

PART A:
PATIENT DEMOGRAPHICS

Patient's initials: _____ Gender: ☐ Male ☐ Female	Patient's date of birth (dd/Mmm/yyyy): _____/_____/_____ OR Patient's age: _____ years	Study Protocol ID (if applicable): _____

Patient's Relevant Medical History

If no relevant medical history, please indicate so here: ☐ No relevant medical history

Please list relevant medical history below, including any history of seizure disorder or other neurologic disorders, CNS involvement of cancer, and presence of implants or medical devices in the CNS.

Disease State	Start Date

Concomitant Medications

Please list concomitant medications below. If the list is too long, please attach a printout of the patient's medications.

Drug Name	Indication	Dose/ Frequency	Start Date	Stop Date

--- See next page ---

Additional Questions

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PART B: SUSPECT PRODUCTS			
Suspect CAR T Cell Product	**Infusion date (dd/Mmm/yyyy)**	**Indication**	**Batch/JOIN number**
☐ Lisocabtagene maraleucel (Breyanzi) ☐ Idecabtagene vicleucel (Abecma) ☐ Other: _____			

OTHER SUSPECT PRODUCTS: Please provide suspect product(s) information (those products which are suspected to be associated with one or more adverse events).		
	Suspect Product #1	**Suspect Product #2**
Product name		
Dose and regimen		
Route of administration		
Indication		
Treatment start date (dd/Mmm/yyyy)		
Treatment stop date (dd/Mmm/yyyy)		
Treatment duration (if start/stop dates unknown)		
Expiration date(s)		
Batch/LOT number		

--- See next page ---

Additional Questions

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PART C:
NEUROLOGIC ADVERSE EVENTS

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Please complete the following details if the patient expierienced ICANS

	Start Date (dd/Mmm/yyyy)	Stop Date (dd/Mmm/yyyy)	Grading assessment[b]	Seriousness Criteria[b]	Outcome[c]	Causality[d]
ICANS						

Please describe the ICANS Sign and Symptoms

ICANS sign or symptom	Start Date (dd/Mmm/yyyy)	Stop Date (dd/Mmm/yyyy)	Grading assessment[b]	Seriousness Criteria[b]	Outcome[c]

Non-ICANS Neurologic Adverse Events

Please enter details regarding non-ICANS Neurologic Adverse Event(s) below, if any.

Non-ICANS Neurologic Adverse Event	Start Date (dd/Mmm/yyyy)	Stop Date (dd/Mmm/yyyy)	Grading assessment[b]	Seriousness Criteria[b]	Outcome[c]	Causality[d]

Key	[a]Grading assessment:	[b]Seriousness Criteria	[c]Outcome	[d]Causality
	1 = Grade 1 2 = Grade 2 3 = Grade 3 4 = Grade 4 5 = Grade 5	D = Death LT = Life-threatening H = Initial or prolonged hospitalization S = Significant disability or incapacity M = Medically significant N/A = Not applicable (non-serious)	1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 6 = Unknown	1= Related 2= Not related

CEREBRAL EDEMA

Additional Questions

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Was any cerebral edema identified? ☐ Yes ☐ No

Did the patient experience cerebral edema in the context of ICANS ? ☐ Yes ☐ No

Please describe

- **how it was identified.**
- **the cerebral edema treatment.**

If one of the neurologic adverse events resulted in death, please provide the following information.

Date of death (dd/Mmm/yyyy): _____/_____/_____

Cause of death: _____

Was an autopsy performed? ☐ Yes ☐ No If yes, please provide the autopsy report if available.

If one of the neurologic adverse events resulted in hospitalization, please provide the following information.

Admission date (dd/Mmm/yyyy): _____/_____/_____

Discharge date (dd/Mmm/yyyy): _____/_____/_____

DIAGNOSTIC RESULTS

Please add as many lines as needed.

Test name [e.g. spinal fluid results, brain imagin, other]	**Date of Test (dd/Mmm/yyyy)**	**Findings**

Additional Event Information

In your opinion, what is the causal relationship between the neurologic adverse events and the BMS CAR T therapy?

☐ Related ☐ Not related

Additional Questions

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If not related, what was the cause of the the neurologic adverse events?

Were alternative causes for the signs and symptoms ruled out? ☐ Yes ☐ No

If yes, please describe how these alternate causes were ruled out.

Neurologic adverse events treatment

Was tocilizumab administered? ☐ Yes ☐ No

Dose	Therapy Dates	Response

Were anti-epileptics administered? ☐ Yes ☐ No

Name of Anti-Epileptic	Route	Dose	Therapy Dates	Response

Were corticosteroids (CS) administered? ☐ Yes ☐ No

Name of CS	Route	Dose	Therapy Dates	Response

Were any other treatments administered? ☐ Yes ☐ No

Name of Treatment	Route	Dose	Therapy Dates	Response

Please provide any supplemental information on a separate page.

Additional Questions

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Signature of Person Completing Form:	
Name of Person Completing Form (Print):	**Date Completed (dd/Mmm/yyyy):**
E-mail Address:	**Phone Number:**

Additional Questions

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Additional Questions

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ADVERSE EVENT REPORT QUESTIONNAIRE **Secondary Malignancy** **NOTE: INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED.**		
PATIENT DEMOGRAPHICS		
Patient's initials: _____ Gender: ☐ Male ☐ Female	Patient's date of birth (dd/Mmm/yyyy): _____/_____/_____ OR Patient's age: _____ years	Study Protocol ID (if applicable): _____

SUSPECT PRODUCTS: Please provide suspect product(s) information (those products which are suspected to be associated with one or more adverse events).			
	Suspect Product #1 (CAR T Cell Product)	**Suspect Product #2**	**Suspect Product #3**
Product name	☐ Lisocabtagene maraleucel (Breyanzi) ☐ Idecabtagene vicleucel (Abecma) ☐ Other: _____		
Dose and regimen			
Route of administration			
Indication			
Treatment start date (dd/Mmm/yyyy)			
Treatment stop date (dd/Mmm/yyyy)			
Treatment duration (if start/stop dates unknown)			
Lot/batch number(s)			
Expiration date(s)			

Additional Questions

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SECONDARY MALIGNANCY

If not previously reported, please provide the information below regarding the secondary malignancy.

Secondary Malignancy	Start Date (dd/Mmm/yyyy)	Stop Date (dd/Mmm/yyyy)	CTCAE Grade[a]	Seriousness Criteria[b]	Outcome[c]

Key:	[a]CTCAE Grade	[b]Seriousness Criteria	[c]Outcome
	1 = Grade 1 (mild) 2 = Grade 2 (moderate) 3 = Grade 3 (severe) 4 = Grade 4 (life-threatening) 5 = Grade 5 (fatal) Please indicate CTCAE version used.	D = Death LT = Life-threatening H = Initial or prolonged hospitalization S = Significant disability or incapacity M = Medically significant N/A = Not applicable (non-serious)	1 = Recovered/resolved 2 = Recovering/resolving 3 = Not recovered/not resolved 4 = Recovered/resolved with sequelae 5 = Fatal 6 = Unknown

If the event resulted in death, please provide the following information.

Date of death (dd/Mmm/yyyy): _____/_____/_____

Cause of death: _____

Was an autopsy performed? ☐ Yes ☐ No If yes, please provide the autopsy report if available.

If the event resulted in hospitalization, please provide the following information.

Admission date (dd/Mmm/yyyy): _____/_____/_____

Discharge date (dd/Mmm/yyyy): _____/_____/_____

Diagnostic Results - indicate N/A if not performed

Date of Test (dd/Mmm/yyyy)	Pathology: specify tissue type (including any additional analysis, molecular markers, etc.)	Imaging or Other Diagnostic Results

Additional Questions

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Additional Event Information
Please indicate any pre-existing factors that may have contributed to the development of a secondary malignancy.
In your opinion, what is the causal relationship between the secondary malignancy and the CAR T therapy? ☐ Related ☐ Not related **If related, were alternate causes for the secondary malignancy ruled out?** ☐ Yes ☐ No **If yes, please describe how these alternate causes were ruled out.** **If not related, what was the cause of the secondary malignancy?**
Were any treatments administered for the secondary malignancy? ☐ Yes ☐ No **If yes, please indicate treatment details below.**

Name of Treatment	Route	Dose	Therapy Dates (dd/Mmm/yyyy)	Response

Relevant Medical History
If no relevant medical history, please indicate so here: ☐ No relevant medical history
Please include any prior cancer history with dates of diagnosis and stage of disease, specific agents of all cytotoxic chemotherapy or targeted therapy regimens, as well as therapeutic radiation exposure.

Diagnosis and Stage	Treatment Regimen	Therapy Dates (dd/Mmm/yyyy)	Response

Additional Questions

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Please indicate any other risk factors for a secondary malignancy below.	
History of tobacco use? ☐ Yes ☐ No	If yes, please indicate number of pack-years:
History of environmental exposure (eg, asbestos, radiation)? ☐ Yes ☐ No	If yes, please describe:
History of hereditary cancer syndromes? ☐ Yes ☐ No	If yes, please describe:
Family history of cancer? ☐ Yes ☐ No	If yes, please describe:
Any other risk factors for a secondary malignancy? ☐ Yes ☐ No	If yes, please describe:

Concomitant Medications

Please list concomitant medications below. If the list is too long, please attach a printout of the patient's medications.

Drug Name	Indication	Dose/Frequency	Start Date (dd/Mmm/yyyy)	Stop Date (dd/Mmm/yyyy)

Please provide any supplemental information on a separate page.

Signature of Person Completing Form:	
Name of Person Completing Form (Print):	**Date Completed (dd/Mmm/yyyy):**
E-mail Address:	**Phone Number:**

Additional Questions

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ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Availability of Tocilizumab and Site Qualification via the Controlled Distribution Programme

The MAH will ensure that hospitals and their associated centres that dispense ide-cel are qualified in accordance with the agreed controlled distribution programme by:

- ensuring immediate, on-site access to 1 dose of tocilizumab per patient prior to ide-cel infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on site;
- healthcare professionals (HCPs) involved in the treatment of a patient have completed the educational programme.

Educational Programme

HCP Educational Programme

All HCPs who are expected to prescribe, dispense, and administer ide-cel shall be provided with an HCP guide, which will contain information about:

- identification of CRS and serious neurologic adverse reactions including ICANS;
- management of CRS and serious neurologic adverse reactions including ICANS;
- adequate monitoring of CRS and serious neurologic adverse reactions including ICANS;
- provision of all relevant information to patients;
- ensuring immediate, on-site access to 1 dose of tocilizumab per patient prior to ide-cel infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site;
- risk of secondary malignancy of T-cell origin;
- contact details for tumour sample testing after development of a secondary malignancy of T cell origin.
- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study;
- ensure that adverse reactions are adequately and appropriately reported;
- ensure that detailed instructions about the thawing procedure are provided

Patient Educational Programme

All patients who receive ide-cel shall be provided with a patient card, which will contain the following key messages:

- the risks of CRS and serious neurologic adverse reactions associated with ide-cel;
- the need to report the symptoms of suspected CRS and neurotoxicity including ICANS to their treating doctor immediately;

- the need to remain in the proximity of the location where ide-cel was received for at least 2 weeks following ide-cel infusion;
- the need to carry the patient card at all times;
- a reminder to patients to show the patient card to all HCPs, including in conditions of emergency, and a message for HCPs that the patient is using ide-cel;
- fields to record contact details of the prescriber and batch number.