BRISTOL-MYERS SQUIBB RESEARCH & DEVELOPMENT

SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR ABECMA® (IDECABTAGENE VICLEUCEL)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of ABECMA® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, eg by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of ABECMA® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Bristol-Myers Squibb SA is fully responsible for the accuracy and correctness of the content of the published summary RMP for ABECMA®.

1 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.

1.1 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 three 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.

1.2 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.

1.3 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
	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)

1.3.1 Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risks

Cytokine Release Syndrome	
Evidence for linking the risk to the medicine	In the pooled analysis from MM-001 and CRB-401 clinical studies, 149 (81.0%) subjects who received Abecma across the target dose levels of 150 to 450 × 10^6 CAR+ T cells had ≥ 1 CRS event. CRS has likewise been reported with CD19 directed CAR T providing further evidence of a class risk. Macrophage activation syndrome (PT of haemophagocytic lymphohistiocytosis) was reported for 4 (2.2%) subjects in the pooled analysis: 1 (1.4%) subject who received Abecma at a target dose of 300 × 10^6 CAR+ T cells and 3 (3.3%) subjects who received Abecma at a target dose of 450 × 10^6 CAR+ T cells. Macrophage activation syndrome was reported in 2 (1.1%) subjects at a maximum severity of Grade 2 and in 2 (1.1%) subjects at a maximum severity of Grade 4. Grade 4 MAS AEs reported for the 2 subjects were ongoing at the time of their deaths. 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 haemophagocytic lymphohistiocytosis (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 for the MM-001 and CRB-001 clinical studies, 149 (81.0%) subjects who received Abecma across the target dose levels of 150 to 450 × 10^6 CAR+ T cells had ≥ 1 CRS event. The frequency of subjects with CRS increased with target dose: 40.9%, 75.7%, and 94.6% of subjects who received Abecma at a target dose of 150, 300, and 450 × 10^6 CAR+ T cells, respectively. An exploratory analysis of baseline predictors for CRS in Study MM-001 showed no correlation of pre-infusion immune-related soluble factors, or clinical markers of inflammation (C-reactive protein or ferritin) with any grade CRS, CRS requiring tocilizumab, or CRS requiring steroids. However, elevated serum BCMA concentration pre-infusion was associated with CRS requiring corticosteroids. Macrophage activation syndrome is usually associated with more severe forms of CRS.
Risk minimization 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 adverse drug reaction (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	
Evidence for linking the risk to the medicine	Neurologic toxicity 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.

Important identified risks

	In order to enable a side-by-side comparison and pooling of data across Studies MM-001 and CRB-401, 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, 77 (41.8%) subjects who received Abecma across the target dose levels of 150 to 450 × 10^6 CAR+ T cells had ≥ 1 Neurologic Toxicity – Focused AE on or after Abecma infusion. Neurologic Toxicity – Focused AEs reported for ≥ 5% of subjects were confusional state (13.0%), insomnia (9.8%), tremor (8.2%), and somnolence (6.5%). The frequencies of Neurologic Toxicity – Focused AEs were similar for subjects who received Abecma at a target dose of 300 and 450 × 10^6 CAR+ T cells (42.9% and 44.6%, respectively) and higher than for those who received Abecma at a target dose of 150 × 10^6 CAR+ T cells (27.3%).
Risk factors and risk groups	In the pooled analysis, the frequencies of Neurologic Toxicity – Focused AEs were similar for subjects who received Abecma at a target dose of 300 and 450 × 10^6 CAR+ T cells (42.9% and 44.6%, respectively) and higher than for those who received Abecma at a target dose of 150 × 10^6 CAR+ T cells (27.3%). Neurologic Toxicity – Focused AEs were reported for 33.6% of subjects in Study MM-001 within the first 8 weeks and for 9.8% 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 minimization 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 Study MM-001, 124 (96.9%) subjects who received Abecma across the target dose levels of 150 to 450 × 10^6 CAR+ T cells 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 in the Abecma treated population in Study MM-001, and most of these events were reported within the first 8 weeks after Abecma infusion. Across the target dose levels, the reports of Grade 3 or 4 neutropenia and thrombocytopenia were predominantly

Important identified risks

Grade 4, while the reports of anaemia were primarily Grade 3. As anaemia was considered less severe and more manageable compared with neutropenia and thrombocytopenia, this section focuses on neutropenia and thrombocytopenia.

In Study MM-001, Cytopenia – Neutropenia AEs were reported for 94.5% of subjects who received Abecma across the target dose levels of 150 to 450 × 10^6 CAR+ T cells. At the target doses of 150, 300, and 450 × 10^6 CAR+ T cells, Cytopenia – Neutropenia AEs were reported for 100%, 94.3%, and 94.4% of subjects, respectively. Cytopenia – Neutropenia AEs were reported for 93.8% of subjects within the first 8 weeks and for 38.5% of subjects > 8 weeks after Abecma infusion.

Almost all subjects (93.0%) had ≥ 1 Grade 3 or 4 Cytopenia – Neutropenia AE. No subject had a Grade 5 Cytopenia – Neutropenia AE. At the target doses of 150, 300, and 450 × 10^6 CAR+ T cells, Grade 3 or 4 Cytopenia – Neutropenia AEs were reported for 100%, 91.4%, and 94.4% of subjects, respectively. The frequency of subjects with Grade 3 or 4 Cytopenia – Neutropenia AEs was 92.2% within the first 8 weeks and 23.0% > 8 weeks after Abecma infusion.

Most (87.5%) subjects received colony-stimulating factors (eg, filgrastim and pegfilgrastim) during the study.

In Study MM-001, Cytopenia – Thrombocytopenia AEs were reported for 65.6% of subjects who received Abecma across the target dose levels of 150 to 450 × 10^6 CAR+ T cells. At the target doses of 150, 300, and 450 × 10^6 CAR+ T cells, frequency of Cytopenia

- Thrombocytopenia AEs did not increase with increased target dose (100%, 64.3%, and 64.8%, respectively). Cytopenia – Thrombocytopenia AEs were reported for 61.7% of subjects within the first 8 weeks and for 32.8% of subjects > 8 weeks after Abecma infusion. Grade 3 or 4 Cytopenia – Thrombocytopenia AEs were reported for 53.9% of subjects, with Grade 4 events reported for 45.3% of subjects. No subject had a Grade 5 Cytopenia
- Thrombocytopenia AE. At the target doses of 150, 300, and 450 × 10^6 CAR+ T cells, Grade 3 or 4 Cytopenia – Thrombocytopenia AEs were reported for 75.0%, 51.4%, and 55.6% of subjects, respectively. The frequency of subjects with Grade 3 or 4 Cytopenia
- Thrombocytopenia AEs was 51.6% within the first 8 weeks and 22.1% > 8 weeks after Abecma infusion.

Approximately half (49.2%; 63/128) of all subjects received platelet transfusions during the study, and the median number of transfusions among subjects who received it was 6 (range: 1 to 40). Thrombopoietin mimetics were also received by 3.1% of subjects during the study.

Analyses of time to recovery of neutropenia and thrombocytopenia presented in this section are based on laboratory values rather than cytopenia reported by investigators on the AE CRF. Time to Grade 3 or 4 cytopenia (neutropenia or thrombocytopenia) recovery after Abecma infusion was evaluated for subjects with last laboratory assessment within Month 1 indicating Grade 3 or 4 cytopenia (ie, subjects with persistent Grade 3 or 4 cytopenia). Recovery from cytopenia was defined as returning to ≤ Grade 2 severity after Month 1.

In Study MM-001, across the target dose levels of 150 to 450 × 10^6 CAR+ T cells, 125 (97.7%) of 128 subjects had Grade 3 or 4 neutropenia within Month 1 of the Abecma infusion date. Of these 125 subjects, 52 (41.6%) had not recovered at Month 1 (ie, persistent neutropenia). For 43 (82.7%) of these 52 subjects, their Grade 3 or 4 neutropenia recovered to Grade 0 to 2 after Month 1; the median time to recovery in these subjects was 1.9 months (range: 1.2 to 5.6). For 9 (17.3%) of the 52 subjects, their persistent Grade 3 or 4 neutropenia did not recover (1 subject at 150 × 10^6 CAR+ T cells, 3 subjects at 300 × 10^6 CAR+ T cells, and 5 subjects at 450 × 10^6 CAR+ T cells); the reasons that the Grade 3 or 4 neutropenia did not recover were death (7 subjects) and lost to follow-up (2 subjects). No subject had ongoing persistent Grade 3 or 4 neutropenia as of the data cutoff date.

Across the target dose levels of 150 to 450 × 10^6 CAR+ T cells, 83 (64.8%) of 128 subjects had Grade 3 or 4 thrombocytopenia within Month 1 of the Abecma infusion date. Of these 83 subjects, 62 (74.7%) had not recovered at Month 1 (ie, persistent thrombocytopenia). For 43 (69.4%) of

Important identified risks

	the 62 subjects, their persistent Grade 3 or 4 thrombocytopenia recovered to Grade 0 to 2 after Month 1; the median time to recovery in these subjects was 2.1 months (range: 1.2 to 13.8). For 19 (30.6%) of the 62 subjects, their persistent Grade 3 or 4 thrombocytopenia did not recover (2 subjects at 150×10^6 CAR+ T cells, 9 subjects at 300×10^6 CAR+ T cells, and 8 subjects at 450×10^6 CAR+ T cells); the reasons that the Grade 3 or 4 thrombocytopenia did not recover were death (13 subjects) and lost to follow-up (4 subjects); 2 (10.5%) subjects had ongoing persistent Grade 3 or 4 thrombocytopenia as of the data cutoff date.
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. At the target doses of 150, 300, and 450×10^6 CAR+ T cells, Grade 3 or 4 Cytopenia – Overall AEs were reported for 95.5%, 95.7%, and 94.6% of subjects, respectively. The frequency of subjects with Grade 3 or 4 Cytopenia – Overall was 95.1% within the first 8 weeks and 41.5% > 8 weeks after infusion.
Risk minimization 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 immunoglobulin (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 21.2% 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 mechanism of action (MOA) for Abecma may play a role in subjects developing hypogammaglobulinaemia.
Risk minimization 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

Important identified risks

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, 131 (71.2%) subjects who received Abecma across the target dose levels of 150 to 450 × 106 CAR+ T cells had Infections – Overall. The most frequently (≥ 5% of subjects) reported PTs were upper respiratory tract infection (21.7%), pneumonia (10.3%), urinary tract infection (8.7%), influenza (7.1%), and sinusitis (6.0%). Overall, the frequency of Infections was similar at the target doses of 150, 300, and 450 × 106 CAR+ T cells (72.7%, 67.1%, and 73.9%, respectively). Grade 3 or 4 Infections were reported for 23.4% of subjects, with 18.5% of subjects experiencing Grade 3 events. 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. The frequencies of Infections – Overall were similar across the target dose levels: 72.7%, 67.1%, and 73.9% at the target doses of 150, 300, and 450 × 106 CAR+ T cells, respectively. The frequency of Infections did not appear to increase over time: 39.1% of subjects experienced Infections – Overall within the first 8 weeks, 27.8% of subjects > 8 to ≤ 16 weeks, and 29.2% of subjects > 16 weeks to ≤ 6 months after infusion.
Risk minimization 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)

Important potential risks

Secondary Malignancies	
Evidence for linking the risk to the medicine	Secondary malignancies from Abecma is considered an important potential risk based on the theoretical risk of vector insertional mutagenesis leading to oncogenesis. No insertional mutagenesis or malignancies of T cell origin have been reported or identified to date in the clinical study setting. In the pooled analysis, no secondary malignancies from insertional oncogenesis have been reported after Abecma infusion, including initial infusion and retreatment, as of the data cut off dates. Other secondary malignancies were reported for 16 (8.7%) of 184 subjects who received Abecma across the target dose levels of 150 to 450 × 106 CAR+ T cells. Fifteen (8.2%) subjects developed secondary malignancies after initial Abecma infusion. Almost one-half of the secondary malignancies were basal cell carcinomas (6 [3.3%] subjects); myelodysplastic syndrome (MDS) was reported for 2 (1.1%) subjects and Bowen's disease for 2 (1.1%) subjects. Anal cancer, bladder cancer, breast cancer, lung adenocarcinoma, malignant melanoma, and squamous cell carcinoma were reported for 1 (0.5%) subject each. Two subjects in Study CRB-401 had multiple malignancies, including 1 subject who had both basal cell skin carcinoma and bladder cancer and another who had both basal cell skin carcinoma and malignant melanoma.
Risk factors and risk groups	The occurrence of secondary malignancies 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. At present after surviving from a primary malignancy, 17% to 19% patients develop second malignant neoplasm (SMN). This is due to three reasons: continued lifestyle, genetic susceptibility, and treatment modality. In the United States National Cancer Institute's Surveillance, Epidemiology and End Results (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. For Studies MM-001 and CRB-401, there appears to be low risk of insertional mutagenesis leading to oncogenesis of Abecma within the vector copy number range that was characterised (up to 16.4 copies/CAR+ T cell). Although viral insertional mutagenesis is a potential risk in CAR T production, Abecma reduces the risk by the lentiviral nature and self-inactivating design of the vector and by transducing mainly mature peripheral blood T cells as opposed to stem/progenitor cells.
Risk minimization 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

Important potential risks

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
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 minimization 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 minimization 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 minimization 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 from MM-001 and CRB-401 clinical studies, 41 (22.3%) subjects who received Abecma across the target dose levels of 150 to 450 × 10^6 CAR+ T cells had ≥ 1 immunogenicity event. Rash was reported for 13 (7.1%) subjects in the pooled analysis: 4 (5.7%) subjects who received Abecma at a target dose of 300 × 10^6 CAR+ T cells and 9 (9.8%) subjects who received Abecma at a target dose of 450 × 10^6 CAR+ T cells. Infusion related reaction was reported for 9 (4.9%) subjects in the pooled analysis: 5 (7.1%) subjects who received Abecma at a target dose of 300 × 10^6 CAR+ T cells and 3 (3.3%) subjects who received Abecma at a target dose of 450 × 10^6 CAR+ T cells. In Study MM-001, of the 128 subjects who received Abecma across the target dose levels of 150 to 450 × 10^6 CAR+ T cells, 5 (3.9%) were positive for antidrug antibodies (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 × 10^6 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). 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

Important potential risks

	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.
Risk minimization 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 minimization 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 minimization 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 minimization measures	**Routine Risk Minimisation Activities:** SmPC Section 4.2 – No dose adjustment necessary Abecma is administered by an HCP **Additional Risk Minimisation Activities:** None

Missing information

Additional pharmacovigilance activities	None

1.3.2 Post-Authorisation Development Plan

1.3.2.1 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.

Postauthorisation Efficacy Study BB2121-MM-003

Primary Objective

- Compare the efficacy of Abecma to standard regimens in subjects with RRMM as measured by progression-free survival.

Secondary Objectives

- Evaluate the safety of Abecma compared to standard regimens in subjects with RRMM
- Evaluate additional efficacy parameters of Abecma compared to standard regimens in subjects with RRMM
- Characterise the expansion and persistence of CAR+ T cells, in the peripheral blood (cellular kinetics-pharmacokinetics)
- Evaluate the percentage of subjects who attain minimal residual disease negative status by next generation sequencing
- Evaluate the impact of Abecma compared to standard regimens on the changes in health-related quality of life
- Evaluate the impact of Abecma on health utility values compared with standard regimens.

1.3.2.2 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