swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Abecma

International non-proprietary name: idecabtagene vicleucel, cell dispersion of 260 to 500 x 10^6 CAR-positive viable T cells

Pharmaceutical form: dispersion for infusion

Dosage strength(s): 1 or more infusion bags containing a cell dispersion of 260 to 500 x 10^6 CAR-positive viable T cells.

Each infusion bag contains 10-30 mL, 30-70 mL, or 55-100 mL of dispersion for infusion

Route(s) of administration: intravenous use (i.v.)

Marketing authorisation holder: Bristol-Myers Squibb SA, Steinhausen

Marketing authorisation no.: 67575

Decision and decision date: approved on 20.08.2021

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested the status of a new active entity for the active substance idecabtagene vicleucel, cell dispersion of 260 to 500 x 10^6 CAR-positive viable T cells of the medicinal product mentioned above.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan Status was granted on 15.08.2019.

2.2 Indication and dosage

2.2.1 Requested indication

Abecma is indicated for the treatment of adult patients with multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

2.2.2 Approved indication

Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Abecma is provided as a single dose for infusion containing a dispersion of chimeric antigen receptor (CAR)-positive T cells in 1 or more infusion bags. The target dose is 450 x 10^6 CAR-positive viable T cells within a range of 150 to 540 × 10^6 CAR-positive viable T cells.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	11 August 2020
Formal control completed	14 August 2020
List of Questions (LoQ)	23 October 2020
Response to LoQ	4 January 2021
Preliminary decision	10 June 2021
Response to preliminary decision	1 August 2021
Final decision	20 August 2021
Decision	approval

3 Medical context

Multiple myeloma is a largely incurable blood cancer characterised by the clonal proliferation of malignant plasma cells both within the bone marrow and at localised extramedullary sites termed plasmacytomas. The malignant proliferation of the plasma cell clone causes increasing levels of monoclonal protein (M-protein) in the serum and urine and may result in bone marrow failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcaemia, bone pain, and pathological fractures.

The estimated prevalence of MM in the EU in 2018 ranged from 1.79 to 3.61 in 10,000 persons. In Europe, 48,297 new cases of MM and 30,860 deaths due to MM were estimated in 2018.

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. With each relapse and each subsequent line of AMT, tumours typically recur more aggressively, leading to shorter response duration and ultimately, refractory MM, which is associated with shortened survival times. Furthermore, each line of therapy is associated with an increased risk of comorbidities, including treatment- and disease-related complications.

Progress has been made in improving OS in patients with MM. The increase in survival has been driven by the availability of newer therapies and novel combination approaches. However, even with optimal upfront therapy, most MM patients' progress or relapse, and further treatment is needed. Most patients with relapsed/refractory MM receive continuous therapy and therefore are at high risk to become refractory to all available drug classes, underscoring the need for drugs with a novel mechanism of action.

Despite the available treatment options for relapsed/refractory MM, there is no standard of care and no therapies approved or shown to be effective for patients with MM who have been exposed to an immunomodulatory agent, a PI, and an anti-CD38 antibody.

4 Quality aspects

Abecma is a customised, patient-specific *ex vivo* gene immunotherapy. T cells derived from the patient's peripheral blood are genetically engineered to express a specific chimeric antigen receptor directed against B-cell mature antigen (anti-BCMA CAR) that helps the body recognise and eliminate malignant cells. These modified immune cells are then infused back into the patient.

4.1 Drug substance

Abecma (idecabtagene vicleucel) is comprised of the autologous T cells, *ex vivo* genetically modified, using an integrating, replication-incompetent lentiviral vector carrying the transgene that encodes for the chimeric antigen receptor (CAR) directed against B-cell mature antigen (BCMA02) as a target for treatment of B-cell malignancies. Anti-BCMA02 chimeric antigen receptor contains an extracellular part consisting of the murine anti-BCMA02 single chain variable fragment, the human CD8α hinge region with transmembrane domain, linked to the intracellular co-stimulatory domains derived from the human 4-1BB and CD3ζ receptors.

Lentiviral vector anti-BCMA02 CAR LVV

Lentiviral vector (anti-BCMA02 CAR LVV) carrying the transgene for anti-BCMA02-CAR is used for an *ex vivo* gene transfer into the target cells. The vector is based on human immunodeficiency virus 1 (HIV1) containing necessary regulatory sequences and the anti-BCMA02-CAR transgene. The vector

is replication-incompetent, containing self-inactivating sequences, and pseudotyped with vesicular stomatitis virus (VSV) envelope glycoprotein.
The vector is produced in the production cell line after transient transfection with the mix of plasmids carrying the transgene and the sequences necessary for the production and assembly of the viral vector particles in the production cells. For the cells, a 2-tiered cell bank system was established and qualified according to ICH Q5.
The production cells are expanded, transfected with the plasmids, and the supernatant containing vector is collected, filtered, subjected to several purification steps, concentrated and, following sterile filtration, filled into the primary containers. Sufficient information on the vector manufacturing process and control strategy was provided. The process was validated, and the presented control strategy and data demonstrated that the manufacturing process is capable of producing vector batches consistently meeting predefined requirements.
The ability of anti-BCMA02 CAR LV vector to infect and stably integrate the transgene into the genome of the target cells was confirmed. Successful production and the activation of the functional anti-BCMA02 CAR in the human T cells upon transgene integration was shown.
The vector release specification contains a panel of tests to confirm identity, purity, biological activity of the encoded transgene, and to determine infectious titre. In addition to other safety parameters, absence of replication competent viruses is confirmed.
Analytical methods were described in sufficient detail. Non-compendial methods have been validated according to ICH guidelines, and compendial methods have been verified.
A proposed shelf-life for the anti-BCMA02 CAR LV vector under the proposed long-term storage condition was accepted.

Abecma (idecabtagene vicleucel, ide-cel)
Abecma is a customised, patient-specific *ex vivo* gene therapy derived from the patient's own peripheral blood cells collected by leukapheresis. One manufacturing run initiated from a single patient's leukapheresis corresponds to 1 batch of the drug product. Leukapheresis is performed in a qualified centre, and the cells withdrawn are transported under validated conditions to the manufacturing site for production of the process intermediate. The patient's cells undergo the cell enrichment procedure in order to concentrate the peripheral cells and reduce impurities. The enriched cell intermediate is cryopreserved and transported to the drug product manufacturing facility for further processing. Here, the cells undergo activation with suitable reagents followed by transduction using replication-incompetent lentiviral vector, the anti-BCMA02 CAR LVV. The cells are then expanded in the selective medium. The transduced and expanded cells are washed and concentrated prior to formulation into the final product.
The manufacturing process is continuous and proceeds directly to the drug product formulation and filling steps. The drug substance is not isolated, and an individual specification at this level was not established.
Overall, the manufacturing process, including process parameters and controls, was described in sufficient detail.

Manufacturing process changes during the process development, including new manufacturing sites, were adequately described, and supporting data from comparability studies between batches manufactured by proposed commercial process and clinical batches were provided.

Process performance qualification (PPQ) was performed using material from healthy donors. PPQ runs fulfilled predefined validation acceptance criteria for process parameters or process controls as well as release specifications. Transport of the leukapheresis material as well as transport of the cryopreserved intermediate in qualified shippers were validated. Extended characterisation of the PPQ batches demonstrated that the product's cellular composition is within expected ranges, based on the clinical batches, with an expected variability that can be attributed to the starting material variability.

The biological and physical properties, as well as the subcellular composition of Abecma and its impact on biological activity, were extensively characterised. Product-related and process-related impurities were addressed and, wherever applicable, their removal to acceptable levels was demonstrated.

4.2 Drug product

Abecma is a single-dose cell dispersion for infusion containing the recommended total dose of 260 to 500 x10^6 anti-BCMA02 CAR-expressing viable T cells in 1 or more infusion bags. The drug product is delivered cryopreserved in cryopreservation infusion bags from the manufacturing site to the clinical centre and, after thawing, is infused back into the patient.
Excipients used for the formulation of the drug product are sodium chloride, sodium gluconate, sodium acetate, potassium chloride, magnesium chloride, water for injection, and the cryopreservation medium (CryoStor CS10) containing dimethyl sulfoxide in a final concentration of 5% (v/v).
The primary container used for storage of Abecma is an ethylene vinyl acetate (EVA) cryopreservation bag. Three sizes of the same type of container can be used according to the calculated volume needed for the required dose. The suitability of the primary container was demonstrated. Each cryopreservation bag is placed into an individual aluminium cryocassette.

The manufacturing process for the drug product consists of the formulation of harvested cells, followed by filling into the primary containers, inspection, and labelling. After that, the drug product is cryopreserved and stored in the vapour phase of liquid nitrogen.
The manufacturing process was validated as a continuous process. The product is transported to the health care centres using qualified shippers in the vapour phase of liquid nitrogen and was appropriately validated.

The drug product release specification covers all relevant tests to confirm identity, purity, potency, and safety. Release criteria are based on the clinical experience in terms of safety and efficacy and the process capabilities with consideration of the high variability in the composition of autologous starting material. Analytical methods were adequately described. Non-compendial methods have been validated according to ICH guidelines and compendial methods verified for corresponding matrices.

The drug product is stored at temperatures not higher than -130 °C in the vapour phase of liquid nitrogen in the original container. A shelf-life of 12 months has been granted based on the data provided during assessment.
The drug product is thawed at 37 °C prior to administration. It is recommended that Abecma should be infused within 1 hour after the thawing. If more than 1 container comprises the dose, the bags are thawed and administered subsequently. Compatibility with commercial infusion sets was demonstrated.

Abecma is a cell-based therapy and not amenable to terminal sterilisation or viral inactivation. Thus, adventitious agent safety relies on the proper control and qualification of all materials used in the process in terms of adventitious agent safety, maintenance of the sterile process under aseptic conditions and in the closed systems, and the use of single-use disposables wherever possible. Aseptic processing was adequately validated. Confirmation of sterility at the level of the final product is available prior to administration. Sufficient information on the viral safety of the reagents as well as for the lentiviral vector was provided.
It can be concluded that the manufacturing process for both Abecma and the vector anti-BCMA02-CAR LVV incorporates adequate control measures to prevent contamination and maintain control with regard to adventitious agent contamination.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Idecabtagene vicleucel (ide-cel) is an autologous BCMA-targeting chimeric antigen receptor T cell (CAR-T) immunotherapy developed for the treatment of multiple myeloma (MM). A patient's T cells are genetically modified using a lentiviral vector coding for a B-cell maturation antigen (BCMA)-specific CAR. The CAR construct consists of a murine extracellular single-chain variable fragment (scFv), a CD8 alpha hinge, and a transmembrane domain fused to cytoplasmic signalling domains of CD137(4-1BB) and CD3. Immunohistochemistry (IHC) stainings of BCMA expression showed that BCMA+ cells represented 41% of the MM biopsies and 50% of the tumour tissues analysed. In vitro characterisation of ide-cel was performed to evaluate binding affinity, specificity, cell activation, and cytotoxicity against BCMA+ cells. Co-culturing of ide-cel with different tumour cells demonstrated BCMA-dependent interferon-gamma (INFγ) expression, proliferation, and cytotoxicity. To assess the in vivo pharmacology of ide-cel in a MM xenograft mouse model, immune-deficient NOD/SCID/IL-2Rγnull (NSG) mice were administered s.c. with RPMI-8226 MM cells followed by ide-cel administration at Day 18 or 39 post tumour injection. Ide-cel treatment resulted in a tumour burden reduction and increased survival of the NSG mice. In additional studies, the pharmacodynamics, pharmacokinetics and safety were assessed in immune deficient NSG mice with and without s.c. injected BCMA+ RPMI-8226 MM cells, followed by the i.v. administration of ide-cel. 1 x 10e7 BCMA+ RPMI-8226 tumour cells were injected in female NSG mice followed, at Day 25 post-tumour administration, by a single i.v. injection of 3 x 10e6 CAR+ bb612 anti-CD19Δ CAR T cells (negative control lacking the T cell signalling domains) or 3 x 10e6 CAR+ ide-cel anti-BCMA CAR-T cells. While a maximum of 60% of cells in MM xenografts expressed BCMA, treatment with ide-cel resulted in elimination of those malignancies. It is not fully understood whether BCMA-negative cells are recruited to the tumour or whether those cells are RPMI-8226 cells not expressing BCMA. In a xenograft model of lymphoma, the combined results of 2 studies with NSG mice injected with BCMA+ CD19+ Daudi human Burkitt's lymphoma cells and treated with ide-cel demonstrated a dose-dependent increase in body weights, inhibition of tumour growth, and increased survival. Although CD3+ T cells were detected in the liver, kidney, and bone marrow, their number was low. Peaked CD3+ T cells were observed in the spleen and lungs on Days 8 or 15, suggesting temporary residence of ide-cel in these tissues. A human equivalent dose of 2x10e6 CAR-T cells/kg was derived from the MM model.

5.2 Pharmacokinetics

The distribution of ide-cel was assessed in NSG mice in the presence or absence of BCMA+ cells. Since the CAR T cells are activated and proliferate upon binding to BCMA+ cells, the biodistribution studies performed with and without BCMA+ tumour xenograft allowed the specific effects of BMCA+ tumour cells to be evaluated on the distribution and persistence of ide-cel. CD3+ cell counts were measured in the bone marrow, kidney, liver, lung, and spleen. Following administration in NSG mice, ide-cel peripheral blood counts (CD3+/CAR+ T) peaked at Day 2 and then declined in all mice similarly. As expected, based on the mechanism of activation and proliferation of ide-cel upon interaction with BCMA+ cells, a second peak (ca. 20-fold higher) was observed in xenograft-bearing mice only at Day 11. A decrease in tumour burden was associated with a significant decrease in ide-cel counts. The kinetics of ide-cel in the peripheral blood of tumour-bearing animals paralleled cell counts in the non-tumour tissues, suggesting that the CD3+ cell kinetics in tissues is reflected by CD3+ cell counts in peripheral blood. The results of the biodistribution studies indicate that the peripheral blood ide-cel count correlates with CD3+ cell counts from MM tumours and other tissues and can be used as a relevant pharmacokinetics marker.

5.3 Toxicology

The nonclinical safety assessment of ide-cel consisted of investigations of the insertional mutagenesis potential of the vector, the evaluation of the transformation potential of transduced cells, and the

analysis of off-target bindings. The risk of insertional mutagenesis of the lentiviral vector (LVV) used in ide-cel was evaluated based on an insertion site analysis. The vector integration pattern of the anti-BCMA02 CAR LVV in the genome of CAR T cells was conducted with clinical ide-cel drug product lots. The LVV construct is designed to confer self-inactivating properties that block long terminal repeat-driven transcription of the transgene and nearby genes, improving the safety features of the anti-BCMA02 CAR LVV. Using insertion site analysis, the insertion profile of the LVV was demonstrated to be consistent with other LVV as reported in the literature. The analyses showed that the anti-BCMA02 CAR LVV has a reduced propensity for insertion in regulatory elements and preferentially integrates in the coding region of expressed genes, reducing the risk of gene dysregulation and consequently the risk of oncogenesis. No integration in the start site of known oncogenes was identified, and the integration profile proved to be highly polyclonal across tested samples. Overall, the integration site analysis did not reveal concerns related to integration site preferences or to the clonality of the integration profiles. IL-2 independent T cell growth is known to occur in malignant T cells and is indicative of T cell mutagenesis and transformation. Ide-cel was tested in vitro for its potential to growth in the absence of IL-2. Anti-BCMA02 CAR LVV transduced and untransduced T cells from patients and healthy donors were cultured with and without IL-2. No aberrant proliferation was observed in transduced or untransduced T cells irrespective of the donor condition. In addition, as compared to donor-dependent CAR+ expression in culture with IL-2, CAR+ expression did not increase in the absence of IL-2. The decrease in clonal diversity observed with all culture conditions was considered consequential to the decrease in clonal heterogeneity associated with reduction in cell number commonly observed in cell culture. Target and off-target binding of anti-BCMA antibodies in healthy human tissues was assessed in a GLP-compliant tissue cross-reactivity study. BCMA expression was reported in resident, migrating, and/or infiltrating mononuclear cells in the colon, fallopian tube, oesophagus, small intestine, stomach, lymph node, parathyroid, prostate, salivary gland, thymus, and tonsil. The binding of 4 anti-human BCMA antibodies to related and unrelated BCMA proteins was assessed using a cellular microarray of HEK293 cell lines. Cell lines were transfected with a vector coding for GFP and a human specific transgenic protein that is expressed on the cell surface. TNFRSF member or BCMA protein expression was not detected on normal HEK293 cell plasma membranes. The 4 anti-BCMA antibodies did not bind to any of the tested TNFRSF member proteins or to any of 358 other proteins, suggesting that those antibodies specifically bind to TNFRSF17/BCMA. CRS, neurotoxicity, cytopenias, and infections are the main safety concerns observed with the clinical use of ide-cel, and those effects could be linked to the mechanism of action of anti-BCMA CAR+ T cell products.

5.4 Nonclinical conclusions

The proof-of-principle was demonstrated using in vitro assays and tumour xenograft immunocompromised mouse models. Ide-cel binds specifically to BCMA and shows dose-dependent activation, proliferation, target cytolysis, and cytokine secretion against BCMA+ myeloma and lymphoma cell lines. Ide-cel targets both low and high BCMA+ expressing tumours and is inactive against BCMA-negative cells. CAR-T cell activation results in BCMA-specific IFN-γ release, target cell lysis, and ide-cel proliferation. The in vivo proof-of-concept was established in MM and lymphoma xenografts in NSG mice demonstrating BCMA-targeting CAR expression, exhibiting tumour volume reduction, elimination of BCMA+ tumours, decrease in soluble BCMA, and increase in survival. The administration of a single dose of ide-cel eliminated both subcutaneous and systemic tumours in NSG mice injected with BCMA+ cells. Due to its binding specificity, it is expected that ide-cel will eliminate both tumour and healthy plasma BCMA+ cells. The safety assessment of ide-cel focused on the risk of insertional mutagenesis derived from the use of lentiviral vector for the CAR genome integration and the potential of tumorigenic transformation of transduced cells. Analysis of the lentiviral integration profiles in transduced T cells demonstrated integration patterns similar to other lentivirus vectors with a high degree of polyclonality and no insertion site preference across the vector copy number in clinical studies, suggesting a low risk of insertional mutagenicity. IL-2 independent growth assays were used to assess the potential for aberrant CAR-T cell proliferation, and the results from this study indicate no T cell transformation. In addition, no substantial changes in ide-cel phenotypes,

CD4:CD8 ratio and clonal diversity were noted, suggesting a low tumorigenic risk. In conclusion, from a nonclinical point of view, the benefit outweighs the risk, and ide-cel can be approved.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Classical pharmacological concepts such as ADME and other pharmacokinetic and pharmacodynamic aspects are hardly applicable to adoptive cell therapies including CAR T cells. Pharmacokinetic parameters are used to describe cellular kinetics in terms of expansion ("absorption", "distribution") and persistence ("elimination"): whereas the maximum expansion and the time when the maximum expansion is reached are described by C_{max} and t_{max}, AUC, $t_{1/2}$, and t_{last} provide information about the persistence of CAR T cells.

The PK data from Study MM-001 were characterised using data corresponding to ≥ 3 months of follow-up after the last subject was infused with ide-cel. The key PK endpoints included area under the curve of the transgene level from time of dose to 28 days postinfusion ($AUC_{0\text{-}28days}$), maximum transgene level (C_{max}), and time of maximum observed transgene level (T_{max}).
Following ide-cel infusion, the CAR+ T cells proliferated and underwent rapid multi-log expansion, followed by a bi-exponential decline with initial peak expansion at a median T_{max} of ~ 11 days; T_{max} was generally consistent across the ide-cel target doses.

In general, cellular expansion parameters ($AUC_{0\text{-}28days}$ and C_{max}) increased with increasing ide-cel target dose from 150 to 450 × 10^6 CAR+ T cells. High variability (%CV ≥100%) was observed, leading to substantial overlap in exposures between the target doses.

Durable persistence of ide-cel (measured as detectable transgene level) was observed. Approximately 59% and 36% of ide-cel treated subjects had measurable CAR+ T cell levels at 6 months and 12 months postinfusion, respectively:

In summary, pharmacokinetic parameters are used to describe cellular kinetics in terms of expansion ("absorption", "distribution") and persistence ("elimination"). The available data suggest that, following peak expansion at ~ 11 days, the extent of cell expansion during the first month postinfusion ($AUC_{0\text{-}28days}$) represents the majority (65%) of total ide-cel exposure. Available PK data demonstrate that ide-cel can persist in peripheral blood for up to 1-year postinfusion.

Special populations / intrinsic factors

No studies in patients with renal and hepatic impairment were conducted. No paediatric patients were enrolled in in the study.

As part of study MM-001, several prespecified covariates were evaluated for their potential impact on cellular expansion parameters, including C_{max} and $AUC_{0\text{-}28days}$. These evaluations showed statistically significant associations of body weight and baseline sBCMA with $AUC_{0\text{-}28days}$ (and C_{max}); higher body weight was associated with lower exposures, and higher baseline sBCMA was associated with higher exposures. Based on the established relationship with body weight, $AUC_{0\text{-}28days}$ is predicted to be 28% lower in subjects weighing 97 kg (90th percentile of body weight distribution from subjects in Study MM-001) compared to subjects at the median weight of 76.4 kg, and is 46% higher in subjects weighing 58 kg (10th percentile of body weight distribution) compared to subjects at the median body weight. Based on the estimated power model, the effect of baseline sBCMA on $AUC_{0\text{-}28days}$ relative to a subject with median baseline sBCMA of 329 ng/mL would be predicted to translate into a 31% lower $AUC_{0\text{-}28days}$ in a subject at the 10th percentile of the baseline sBCMA distribution (37 ng/mL), and a 25% higher $AUC_{0\text{-}28days}$ in a subject at the 90th percentile (751.6 ng/mL). In view of the overall variability in cellular expansion between subjects, with geometric % CV > 100%, the magnitude of changes by body weight and sBCMA (up to 46% change) is considered relatively modest.
Additional covariates, such as age, race, ethnicity, sex, and ADA status, were not found to influence the cell expansion parameters.

Interactions
Ide-cel is a cellular product that is not cleared by the usual mechanisms that apply to small molecules or antibodies. Therefore, no pharmacokinetic drug-drug interactions are expected for adoptive cell therapies. No dedicated DDI studies have been performed.

Mechanism of action and primary pharmacology
Ide-cel is a genetically modified autologous T cell immunotherapy product consisting of T cells transduced with an anti-BCMA02 CAR LVV. Autologous T cells transduced ex vivo with the anti-BCMA02 CAR LVV express the anti-BCMA CAR on the T cell surface.

The CAR is comprised of a murine extracellular single-chain variable fragment (scFv) specific for recognising BCMA, followed by a human CD8α hinge and transmembrane domain fused to the T cell cytoplasmic signalling domains of CD137 (4-1BB) and CD3ζ chain, in tandem. Binding of ide-cel to BCMA-expressing target cells leads to signalling initiated by CD3ζ and 4-1BB domains and subsequent CAR+ T cell activation. Antigen-specific activation of ide-cel results in CAR+ T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.
Ide-cel is prepared from the patient's peripheral blood mononuclear cells (PBMCs), which are obtained via a standard leukapheresis procedure. After transduction, the T cells are expanded, harvested, and formulated as a dispersion for intravenous administration. The drug product is formulated and cryopreserved in a solution containing Plasma-Lyte A and CryoStor CS10, resulting in a final dimethyl sulfoxide (DSMO) concentration of 5%. A single dose of ide-cel drug product is filled in 1 or more infusion bags and thawed before infusion.

A real-time quantitative polymerase chain reaction (qPCR) assay has been validated to quantify ide-cel transgene copies in genomic deoxyribonucleic acid (gDNA). This assay was used to quantify ide-cel transgene isolated from CD3+ cells in clinical studies MM-001 and CRB-401 for cellular kinetics (PK) exposure analysis.

Immune responses to ide-cel were evaluated using an electrochemiluminescence (ECL) immunoassay that detects antidrug antibodies (ADAs) that bind to the extracellular domain (ECD) of the ide-cel CAR.

The ECL assay method was validated and used to detect ADA in clinical serum samples from studies MM-001 and CRB-401.

Secondary pharmacology (safety)
No delays in cardiac repolarisation are expected for adoptive cell therapies. No thorough QT/QTc studies have been performed.

Pharmacodynamic interactions with other medicinal products or substances
No dedicated studies were submitted.

Relationship between plasma concentration and effect
The relationship between cellular expansion parameters (C_{max}, $AUC_{0\text{-}28days}$, and $AUC_{0\text{-}3M}$) and key efficacy endpoints including overall response rate (ORR), very good partial response (VGPR) or better, complete response (CR) rate, and progression-free survival (PFS) were evaluated.
Increasing ide-cel exposure was positively correlated with higher efficacy responses. The median C_{max} level in responders (N = 93/127) was approximately 4.46-fold higher compared to the corresponding levels in non-responders (N = 34/127). The median $AUC_{0\text{-}28days}$ in responders (≥ PR; N = 93/125) was 5.47-fold higher than the corresponding levels in non-responders (N = 32/125). The median $AUC_{0\text{-}28days}$ was also 2.74-fold higher in subjects with VGPR or better (≥ VGPR; N = 67/125 vs. < VGPR; N = 58/125) and 1.86-fold higher in subjects with CR or better (≥ CR; N = 41/125 vs. < CR; N = 84/125). Increasing $AUC_{0\text{-}28days}$ was also associated with longer PFS; for each 2-fold increment in $AUC_{0\text{-}28days}$ the hazard ratio decreased by ~ 50% for PFS.

Several statistically significant covariates and baseline risk factors for each of the efficacy endpoints were identified, in addition to the impact of the exposure parameter. Sex was a predictor for ORR (higher ORR in females); baseline serum m-protein was a predictor for CR (higher CR rate for subjects with baseline serum m-protein level ≤ 10 g/L). Sex, baseline extramedullary plasmacytoma, baseline ferritin, and the use of steroids as last prior medication were predictors for PFS, with a lower hazard for progression or death (longer PFS) in females and subjects who received corticosteroids, and a higher hazard (shorter PFS) in subjects with extramedullary plasmacytoma or high baseline ferritin. Notably, body weight or body surface area were not found to be significant predictors on the exposure-response model, suggesting that weight does not exert an independent effect on efficacy responses, above and beyond its impact on initial cell expansion.

Relationship between plasma concentration and safety
Statistically significant exposure-response relationships were identified for the safety events of cytokine release syndrome requiring tocilizumab (tCRS) and cytokine release syndrome requiring corticosteroids (sCRS). Lower exposures (i.e. in the lowest quartile of observed exposures) were associated with lower rates of tCRS and sCRS.

No exposure-response trends were observed across the highest 3 quartiles for higher grade CRS, iiNT, or cytopenia. However, since the number of cases in each quartile is very low, it is not possible to come to any valid conclusion.

6.2 Dose finding and dose recommendation

Study CRB-401 was a first-in-human, 2-part, nonrandomised, open-label, multicentre Phase 1 study of ide-cel in subjects with relapsed or refractory MM. The study population enrolled in Study CRB-401 was heavily pretreated and had a high degree of refractoriness to prior AMTs, with 88.7% refractory to immunomodulatory agents, 83.9% refractory to PIs, and 80.6% refractory to anti-CD38 antibodies.
The primary objective of **Part A** (dose escalation) of Study CRB-401 was to determine the maximum tolerated dose (MTD) of ide-cel in subjects with MM whose tumours express high levels of BCMA (≥ 50% BCMA+ bone marrow plasma cells) and to select an RP2D. In Part A, ide-cel was administered to 21 subjects at a target dose of 50 (N = 3), 150 (N = 6), 450 (N = 9), or 800 (N = 3) × 10^6 CAR+ T cells. No dose-limiting toxicities were observed, and no MTD was identified.

In **Part B** (dose expansion), subjects with relapsed and refractory MM received ide-cel target dose levels of 150 to 450 × 10^6 CAR+ T cells, which was selected as the RP2D by the SRC for further examination of safety and efficacy.
Overall, AEs observed with ide-cel were expected toxicities consistent with the mechanism of action of CAR T cell therapies. Adverse events were generally manageable across the target dose levels of 150 to 450 × 10^6 CAR+ T cells. The most frequently reported Grade 3 or 4 AEs were from blood and lymphatic system disorders and included neutropenia, leukopenia, thrombocytopenia, anaemia, and lymphopenia. No subjects had Grade 4 or 5 CRS in this study. The frequencies of subjects with AEs were generally similar between the individual ide-cel target doses, except for CRS and neurological toxicity, which increased with increasing target dose.

The primary efficacy analyses (secondary endpoint) were based on investigator assessment of response. The ORR was 76.8% (95% CI: 63.6, 87.0) in subjects who received the ide-cel RP2D of 150 to 450 × 10^6 CAR+ T cells. In subjects who received the ide-cel RP2D of 150 to 450 × 10^6 CAR+ T cells, the median TTR was 1.02 months with a KM-estimated median DoR of 10.0 months in subjects who achieved at least a PR.
Although the numbers in the different dose-cohorts of study CRB-401 were too small for formal statistical comparisons and to reach any firm conclusion, based on experience gained from this study the target dose of 450 × 10^6 CAR+ T cells, within a range of 150 to 540 × 10^6 CAR+ T cells, was proposed.

In Study MM-001, frequent, deep, and durable responses were observed across the entire dose range and were numerically increased at the target dose of 450 × 10^6 CAR+ T cells. The ORR was > 70%, with > 30% of subjects achieving a response of CR or better and almost 25% of subjects achieving both CR or better and MRD-negative status. In a pooled analysis across Studies MM-001 and CRB-401 (N = 22) at the lower target dose of 150 × 10^6 CAR+ T cells, clinically meaningful efficacy was still observed including an ORR > 50%, a CR or better rate of > 30%, and a median DoR of > 10 months. According to the applicant, the ide-cel safety profile was generally manageable across the dose range of 150 to 540 × 10^6 CAR+ T cells and at the target dose of 450 × 10^6 CAR+ T cells. Taken together, these findings lead to the proposed ide-cel target dose and dose range.

In summary, the reviewer comes to the conclusion, that a real dose-finding process had not taken place. Numbers are too small to reach firm conclusions. Numerical trends in studies CRB-401 and MM-001 support the proposed ide-cel target dose of 450 × 10^6 CAR+ T cells and dose range of 150 to 540 × 10^6 CAR+ T cells, but formal statistical testing between different dose cohorts has not been done.

6.3 Efficacy

A single pivotal study – MM-001 – was submitted by the applicant. This study was an open-label, single-arm, multicentre, multinational, Phase 2 study to evaluate the efficacy and safety of ide-cel in subjects with relapsed/refractory MM 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.

140 subjects were enrolled in the study (i.e. underwent leukapheresis). Of these, 12 discontinued prior to receiving ide-cel infusion. Of the 12 discontinued subjects, 8 discontinued prior to starting LDC, with physician decision (3 subjects) and withdrawal by subject (2 subjects) being the most common reasons, and 1 subject each discontinuing due to AE, PD, and study drug manufacturing failure. 128 subjects were infused with ide-cel across the target dose levels of 150 to 450 x 10^6 CAR+ T cells, with an allowance of 20% over the target dose of 450 × 10^6 CAR+ T cells (i.e. up to 540 x 10^6 CAR+ T cells).
Of the 128 subjects who received ide-cel in this study, 4 subjects received a target dose of 150 x 10^6 CAR+ T cells, 70 subjects received a target dose of 300 x 10^6 CAR+ T cells, and 54 subjects received a target dose of 450 x 10^6 CAR+ T cells.
The primary objective of the study was to evaluate the efficacy, defined as ORR of ide-cel in subjects with relapsed/refractory MM. The secondary objectives included assessing additional efficacy outcomes, including the key secondary endpoint of CR rate, and safety.

The applicant also included supportive efficacy and safety data from Study CRB-401, with a data cutoff date of 22 Jul 2019, which is approximately 7 months after the last subject was infused with ide-cel. Safety data from the 224 subjects who received ide-cel infusion in Studies MM-001, CRB-401, MM-001-Japan, and MM-002 as of the data cutoff dates are included in the application.

The applicant was able to demonstrate that the clinical data from both the MM-001 and CRB-401 studies in subjects receiving 3 prior therapies support the positive benefit-risk in this group, justifying inclusion in the proposed indication. In Study MM-001, 11.4% (16/140) of subjects received 3 prior therapies. These 16 subjects shared similar key baseline characteristics to the overall treated population including frequent high-risk features. These subjects had a favourable benefit-risk profile with an overall response rate (ORR) of 68.8%, complete response rate (CRR) of 50.0%, and a median duration of response (DoR) of 8.0 months. Moreover, these subjects had the same level of refractoriness as the enrolled study populations: all were refractory to anti-CD38 antibody, and 93.8% were triple-refractory. Combining the experience in Study MM-001 and Study CRB-401, there were 23 subjects who had received only 3 prior therapies. Among these subjects, the ORR was 78.3% (18/23, 95% CI 56.3, 92.5) and the CRR was 52.2% (12/23, 95% CI 30.6, 73.2). The lower bound for these

response rates exceeded the study targets of >50% for ORR and >10% for CRR. Thus, it is justified to indicate the use of Abecma for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies.

A dose of 450 × 10^6 CAR+ T cells within a range of 150 to 540 × 10^6 CAR+ T cells to 300 to 460 × 10^6 CAR+ T cells was agreed and was aligned with the CHMP recommended dose considering the upper end of the dose range and CAR+ viable T cells dose units. The CHMP recommended dosage is for a target dose of 420 x 10^6 CAR+ viable T cells within a range of 260 to 500 x 10^6 CAR+ viable T cells, which equates to a 450 x 10^6 CAR+ T cell target dose within a range of 300 to 540 x 10^6 CAR+ T cells. The upper end of the dose range to 540 x 10^6 CAR+ T cells (equivalent to 500 x 10^6 CAR+ viable T cells) was maintained in order to maximise the number of patients receiving a dose closer to the target dose of 450 x 10^6 CAR+ T cells. This proposal is supported by the clinical data and the modelled dose range for ide-cel under the validated commercial fill strategy.

6.4 Safety

All subjects in the pooled analysis (N = 184) had at least 1 adverse event. 182 (98.9%) subjects had ≥ 1 Grade 3 or 4 AE. Serious AEs were reported for 127 (69.0%) subjects, and 29 (15.8%) subjects had AEs that led to death. Of 48 deaths observed, 33 occurred after initial ide-cel infusion and 15 deaths occurred after ide-cel retreatment. Most of the 48 deaths were attributed to the primary cause of death category of malignant disease under study or complication due to malignant disease under study (34 [18.5%].

A Grade 5 AE was reported in 29 (15.8%) subjects. The most frequently reported Grade 5 AE was general physical health deterioration (16 [8.7%] subjects), followed by respiratory failure and pneumonia (2 [1.1%] subjects each). All other Grade 5 AEs were reported for 1 (0.5%) subject each: bronchopulmonary aspergillosis, cardiac failure congestive, cardio-respiratory arrest, CRS, death, disease progression, gastrointestinal haemorrhage, pneumonia cytomegaloviral, and sepsis.

There are several known safety concerns that have been associated with, or observed after, treatment with approved anti-CD19 CAR T cell therapies. In the pooled analysis, secondary malignancies were reported for 17 (9.2%) of 184 ide-cel treated subjects. Taken together, these safety concerns (CRS, macrophage activation syndrome, infections, secondary malignancies) have to be covered adequately in the Prescribing Information and the Risk Management Plan and have to be followed up long-term.

Neurological toxicity is an expected AE associated with CAR T cell therapy. In the pooled analysis 74 subjects (40.2%) experienced at least 1 neurological toxicity-focused event. For 95 subjects (56.2%) the event persisted for 1-5 days, for 23 subjects (13.6%) 6-10 days, and for 33 subjects (10.7%) more than 10 days. Despite treatment, the events were still ongoing for 18 subjects (10.7%).

Cytopenias are common among patients treated with CAR T cell therapy. In the ide-cel-treated population, 96.7% of the 184 subjects had Grade 3 or 4 neutropenia, and 59.8% of the 184 subjects had Grade 3 or 4 thrombocytopenia within the first month after the infusion; for 32.5% (26/80) of the subjects their persistent Grade 3 or 4 thrombocytopenia did not recover, and of these, 53.8% (14/80) died, and 7 subjects (26.9%) had persistent Grade 3 or 4 thrombocytopenia.

6.5 Final clinical benefit-risk assessment

Evidence is provided to conclude that the risk-benefit assessment is positive for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti CD38 antibody, and have demonstrated disease progression on the last therapy. The addition of the clause ‘and have

demonstrated disease progression on the last therapy' reflects the fact that all subjects enrolled in Study MM-001 were refractory to their last regimen.

To further substantiate the advantage of therapy with Abecma over standard of care, the submission of the results of the still ongoing study BB2121-MM-003 (a Phase 3, Multicentre, Randomised, Open-label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3)) will need to be included as a condition once available.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Abecma was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Abecma®

Composition

Active substances

Idecabtagene vicleucel: A genetically modified autologous T cell immunotherapy consisting of T cells transduced with lentiviral vector (LVV) encoding a chimeric antigen receptor (CAR) that recognizes B-cell maturation antigen.

Excipients

Cryostor CS10 (5% DMSO; Dextran-40), sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride and water for injections.
Abecma contains up to 752 mg sodium and up to 274 mg potassium per dose.

Pharmaceutical form and active substance quantity per unit

Dispersion for infusion.
The finished product is composed of one or more infusion bags containing a colorless cell dispersion of 260 to 500 × 10^6 CAR-positive viableT cells.
The quantitative information regarding CAR-positive viable T cells/mL and volume are presented in the release for infusion certificate (RFI certificate) documentation accompanying Abecma.

Indications/Uses

Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma 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.

Dosage/Administration

Abecma must be administered in a qualified treatment centre with direct access to suitable intensive care monitoring facilities. Abecma therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for the administration and management of patients treated with Abecma, including treatment of cytokine release syndrome (CRS) and neurotoxicity.

A minimum of 2 doses of tocilizumab for use in the event of CRS and emergency equipment must be available prior to infusion of Abecma. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Abecma is intended for autologous use only.

Abecma is provided as a single dose for infusion containing a dispersion of chimeric antigen receptor (CAR)-positive T cells in one or more infusion bags. The target dose is 420 x 10^6 CAR-positive viable T cells within a range of 260 to 500 × 10^6 CAR-positive viable T cells.
See the accompanying Release for Infusion (RFI) Certificate for additional information pertaining to dose.

Pretreatment

Lymphodepleting chemotherapy consisting of cyclophosphamide 300 mg/m^2 intravenously (IV) and fludarabine 30 mg/m^2 IV should be administered for 3 days.
See the prescribing information of cyclophosphamide and fludarabine for information on dose adjustment in renal impairment.

Abecma is to be administered 2 days after completion of lymphodepleting chemotherapy up to a maximum of 9 days. The availability of Abecma must be confirmed prior to starting the lymphodepleting chemotherapy regimen. If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving Abecma.

Clinical assessment prior to infusion

Delay the infusion of Abecma up to 7 days if a patient has any of the following conditions:

- unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension) including those after preceding chemotherapies
- active infections or inflammatory disorders.
- Active graft-versus-host disease (GVHD).
- development of clinically significant worsening of multiple myeloma leading to medically significant organ dysfunction.

Premedication

To minimize the risk of infusion reactions, the patient should be pre-medicated with paracetamol (acetaminophen) (500 - 1000 mg orally) and diphenhydramine (12.5 mg intravenously or 25 to 50 mg) orally, or another H_1-antihistamine approximately 30 to 60 minutes before infusion of Abecma.

Prophylactic use of dexamethasone or other systemic corticosteroids should be avoided, as the use may interfere with the activity of Abecma. Therapeutic doses of corticosteroids should be avoided 72 hours prior to the start of lymphodepleting chemotherapy and following Abecma infusion except for the management of CRS, neurologic toxicities and other life-threatening emergencies (see section “Warning and Precautions”).

Monitoring

- Patients should be monitored at least daily for 10 days following Abecma infusion at the qualified healthcare facility for signs and symptoms of CRS and neurologic toxicities.
- After the first 10 days following infusion, the patient should be monitored at the physician’s discretion.
- Patients should be instructed to remain within proximity (max. 2 hours distance) of the appropriate clinical setting for at least 4 weeks following infusion.

Special populations

Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection

There is no clinical experience in patients with active HIV, HBV or HCV infection. Screening for HBV, active HIV and active HCV must be performed in accordance with clinical guidelines before collection of cells for manufacturing. Leukapheresis material from patients with active HIV or active HCV infection will not be accepted for Abecma manufacturing (see Section “Warnings and Precautions”).

Patients with impaired hepatic function

Hepatic impairment studies of Abecma were not conducted.

Patients with impaired renal function

Renal impairment studies of Abecma were not conducted.

Elderly patients

In the clinical trial of Abecma, 45 (35.2%) of the 128 patients in the KarMMa study were 65 years of age or older and 4/128 (3.1%) of patients were 75 years of age or older. No clinically important differences in safety or effectiveness of Abecma were observed between these patients and patients younger than 65 years of age.

Children and adolescents

The safety and efficacy of Abecma in pediatric or adolescent patients (under 18 years of age) have not been established.

Method of administration

Abecma is for intravenous use only.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Abecma should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation of Abecma for infusion

- Prior to preparation of Abecma, it must be confirmed that the patient's identity matches with the patient identifiers on the Abecma cassette(s) and infusion bag(s).
- The Abecma infusion bag must not be removed from the cassette if the information on the patient-specific label does not match the intended patient. The marketing authorization holder must be contacted if there are any discrepancies between the labels and the patient identifiers.
- The timing of Abecma thaw and infusion should be coordinated. The infusion time should be confirmed in advance and the start time of the thaw of Abecma adjusted so that it will be available for infusion when the patient is ready.
- Inspect the infusion bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, the marketing authorization holder must be contacted.
- Place the infusion bag inside a second sterile bag per local guidelines.
- If more than one infusion bag has been received for treatment, thaw each infusion bag one at a time.
- Thaw Abecma at approximately 37°C using an approved thaw device or water bath until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down and/or resuspend Abecma in new media prior to infusion.

Administration

- Do NOT use a leukodepleting filter.
- Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Central venous access may be utilized for the infusion of Abecma and is encouraged in patients with poor peripheral access.
- Confirm the patient's identity matches the patient identifiers on the Abecma infusion bag.
- Prime the tubing of the infusion set with sodium chloride 9 mg/mL (0.9%) solution for injection prior to infusion.
- Infuse Abecma within 1 hour from start of thaw.

- After the entire content of the infusion bag is infused, rinse the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection at the same infusion rate to ensure all product is delivered.
- Follow the same procedure for all subsequent infusion bags for the identified patient.

For special precautions for disposal, see section “Other information”.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.
Contraindications of the lymphodepleting chemotherapy must be considered.

Warnings and precautions

Cytokine Release Syndrome (CRS)
CRS, including fatal or life-threatening reactions, occurred following treatment with Abecma. The median time-to-onset of CRS was 1 day (range: 1 to 12 days) (see section “Undesirable effects”).

Monitoring and management of CRS
CRS should be identified based on clinical presentation. Patients should be evaluated for and treated for other causes of fever, hypoxia, and hypotension. CRS has been reported to be associated with findings of hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), and the physiology of the syndromes may overlap. MAS is a potentially life-threatening condition, and patients should be closely monitored for evidence of MAS. Treatment of MAS should be administered per institutional standards.
Ensure that a minimum of 2 doses of tocilizumab are available prior to infusion of Abecma. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.
Patients should be monitored at least daily for 10 days following Abecma infusion at the qualified healthcare facility for signs and symptoms of CRS. Patients should be monitored for signs or symptoms of CRS for at least 4 weeks after infusion.
At the first sign of CRS, institute treatment with supportive care, tocilizumab, and/or corticosteroids as indicated. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience CRS should be closely monitored for cardiac and organ function until resolution of symptoms. For severe or life-threatening CRS, consider intensive care unit level monitoring and supportive therapy.
Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time.
Earlier escalation (i.e. higher corticosteroid dose, alternative anticytokine agents, anti-T cell therapies) is recommended in patients with refractory CRS within 72 hours post Abecma infusion characterized

by persistent fever, end-organ toxicity (e.g. hypoxia, hypotension) and/or HLH/MAS not improving in grade within 12 hours of first line interventions.

Table 1: CRS grading and management guidance

<table>
<tr><th>CRS Grade[a]</th><th>Tocilizumab</th><th>Corticosteroids</th></tr>
<tr><td>Grade 1
Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).</td><td>If onset 72 hours or more after infusion, treat symptomatically.
If onset less than 72 hours after infusion, consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).</td><td>–</td></tr>
<tr><td rowspan="2">Grade 2
Symptoms require and respond to moderate intervention.
Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor, or Grade 2 organ toxicity.</td><td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).</td><td>Consider dexamethasone 10 mg IV every 12-24 hours.</td></tr>
<tr><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours).
If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day.
If steroids are initiated, continue steroids for at least 3 doses, and taper over a maximum of 7 days.
After 2 doses of tocilizumab, consider alternative anticytokine agents.
Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td></tr>
<tr><td rowspan="2">Grade 3
Symptoms require and respond to aggressive intervention.
Fever, oxygen requirement greater than or equal to 40% FiO_2 , or</td><td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).</td><td>Administer dexamethasone (e.g., 10 mg IV every 12 hours).</td></tr>
<tr><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours).</td></tr>
</table>

<table>
<tr><th>CRS Grade[a]</th><th>Tocilizumab</th><th>Corticosteroids</th></tr>
<tr><td>hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity or Grade 4 transaminitis.</td><td colspan="2">If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day.
If steroids are initiated, continue steroids for at least 3 doses, and taper over a maximum of 7 days.
After 2 doses of tocilizumab, consider alternative anticytokine agents.
Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.</td></tr>
<tr><td rowspan="2">Grade 4
Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD), or
Grade 4 organ toxicity (excluding transaminitis).</td><td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).</td><td>Administer dexamethasone 20 mg IV every 6 hours.</td></tr>
<tr><td colspan="2">After 2 doses of tocilizumab, consider alternative anticytokine agents.
Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.
If no improvement within 24 hours, consider methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) or anti-T cell therapies such as cyclophosphamide 1.5 g/m^2 or others.</td></tr>
</table>

[a] Lee criteria for grading CRS (Lee et al, 2014).

Neurologic toxicities

Neurologic toxicities, which may be severe or life-threatening, occurred following treatment with Abecma, including concurrently with CRS, after CRS resolution, or in the absence of CRS.
The median time-to-onset of the first event of investigator-identified neurotoxicity was 2 days (range: 1 to 10 days) (see section “Undesirable effects”).

Monitoring and management of neurologic toxicities

Monitor patients at least daily for 10 days following Abecma infusion at the qualified healthcare facility for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Monitor patients for signs or symptoms of neurologic toxicities for at least 4 weeks after infusion and treat promptly. If neurologic toxicity is suspected, manage according to the recommendations in Table 2, with supportive care and/or corticosteroids as needed. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities.
If concurrent CRS is suspected during the neurologic toxicity event, manage CRS according to the recommendations in Table 1, and use the more aggressive intervention for the two events specified in Table 1 and 2.

Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time.

Table 2. Neurologic toxicity grading and management guidance

Neurologic Toxicity Grade[a]	Corticosteroids and Antiseizure Medications
Grade 1	Start nonsedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe patient. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.
Grade 2	Start nonsedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 10 mg IV every 12 hours for 2-3 days, or longer for persistent symptoms. Consider taper for a total steroid exposure of greater than 3 days. Steroids are not recommended for isolated Grade 2 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to a maximum of 20 mg IV every 6 hours.
Grade 3	Start nonsedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 10 to 20 mg IV every 8 to 12 hours. Steroids are not recommended for isolated Grade 3 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided into 4 times a day; taper within 7 days). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 g/m^2.

Neurologic Toxicity Grade[a]	**Corticosteroids and Antiseizure Medications**
Grade 4	Start nonsedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g, repeated every 24 hours if needed; taper as clinically indicated). Consider cyclophosphamide 1.5 g/m^2. If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m^2.

[a] National Cancer Institute (United States) Common Terminology Criteria for Adverse Events criteria for grading neurologic toxicities.

Hypersensitivity reactions

Allergic reactions may occur with the infusion of Abecma. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) in Abecma.

Infections and febrile neutropenia

Abecma should not be administered to patients with active infections or inflammatory disorders. Severe, life-threatening, or fatal infections occurred in patients after Abecma infusion (see section “Undesirable effects”). Patients should be monitored for signs and symptoms of infection before and after Abecma infusion and treat appropriately. Prophylactic, pre-emptive, and/or therapeutic antimicrobials should be administered according to local institutional guidelines.

Febrile neutropenia was observed in patients after Abecma infusion (see section “Undesirable effects”) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

Viral reactivation

Cytomegalovirus (CMV) infection resulting in pneumonia and death has occurred following Abecma administration. Monitor and treat for CMV reactivation in accordance with clinical guidelines.
Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against plasma cells.
Screening for CMV, HBV, active HIV and active HCV must be performed in accordance with clinical guidelines before collection of cells for manufacturing.

Consider antiviral therapy to prevent viral reactivation per local institutional guidelines/clinical practice.

Prolonged cytopenias

Patients may exhibit prolonged cytopenias following lymphodepleting chemotherapy and Abecma infusion (see section “Undesirable effects”).

Blood counts should be monitored prior to and after Abecma infusion. Cytopenia should be monitored with myeloid growth factor and blood product transfusion support according to local institutional guidelines.

Hypogammaglobulinemia

Plasma cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with Abecma (see section “Undesirable effects”).

Immunoglobulin levels should be monitored after treatment with Abecma and managed per local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and immunoglobulin replacement.

Use of live vaccines

The safety of immunization with live viral vaccines during or following Abecma treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Abecma treatment, and until immune recovery following treatment with Abecma.

Secondary malignancies

Patients treated with Abecma may develop secondary malignancies. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy of T cell origin occurs, the marketing authorization holder should be contacted to obtain instructions on patient samples to collect for testing.

Blood, organ, tissue and cell donation

Patients treated with Abecma should not donate blood, organs, tissues and cells for transplantation.

Prior allogeneic stem cell transplantation

It is not recommended that patients receive Abecma within 4 months after an allogeneic stem cell transplant (SCT) because of the potential risk of Abecma worsening GVHD. Leukapheresis for Abecma manufacturing should be performed at least 12 weeks after allogeneic SCT.

Excipients

Abecma contains up to 33 mmol (752 mg) sodium per dose, equivalent to 37.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Abecma contains up to 7 mmol (274 mg) potassium per dose. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

Interactions

No interaction studies have been performed.

Drug/Laboratory Test Interactions

HIV and the lentivirus used to make Abecma have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received Abecma.

Pregnancy, lactation

Women of childbearing potential / Contraception in males and females

Pregnancy status of females with reproductive potential should be verified via pregnancy testing prior to starting treatment with Abecma.
There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Abecma.
See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

Pregnancy

There are no available data with Abecma use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with Abecma to assess whether it can cause fetal harm when administered to a pregnant woman.
It is not known if Abecma has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including plasma cell aplasia or hypogammaglobulinemia. Therefore, Abecma is not recommended for women who are pregnant, and pregnancy after Abecma infusion should be discussed with the treating physician. Assess immunoglobulin levels in newborns of mothers treated with Abecma.

Lactation

There is no information regarding the presence of Abecma in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Abecma and any potential adverse effects on the breastfed infant from Abecma or from the underlying maternal condition.

Fertility

There are no data on the effects of Abecma on fertility.

Effects on ability to drive and use machines

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving Abecma are at risk for altered or decreased consciousness or coordination in the 8 weeks following Abecma infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after Abecma infusion.

Undesirable effects

The safety data described in this section reflects the exposure to Abecma in the KarMMa and CRB-401 studies, in which 184 patients with relapsed and refractory multiple myeloma received Abecma (see section “Clinical efficacy”). The median duration of follow-up was 15.5 months.

The most common (incidence ≥ 20%) adverse reactions included neutropenia, CRS, anemia, thrombocytopenia, infections – pathogen unspecified, leukopenia, fatigue, diarrhea, hypokalemia, hypophosphatemia, nausea, lymphopenia, pyrexia, cough, hypocalcemia, viral infections, headache, hypomagnesemia, upper respiratory tract infection, arthralgia, oedema peripheral and decreased appetite; other common adverse events occurring at lower frequency and considered clinically important included hypogammaglobulinaemia (19.6%), febrile neutropenia (16.3%), pneumonia (10.3%), tremor (8.2%), somnolence (5.4%), aphasia (4.3%), encephalopathy (4.3%) and syncope (4.3%).

Serious adverse reactions occurred in 70.1% of patients. The most common (greater than or equal to 5%) serious adverse reactions included CRS (17.4%), pneumonia (7.1%), febrile neutropenia (6.0%) and pyrexia (6.0%); other serious adverse events occurring at lower frequency and considered clinically important include neutropenia (4.3%), sepsis (3.8%), thrombocytopenia (3.8%), confusional state (2.2%), dyspnoea (2.2%), hypoxia (1.6%), mental status changes (1.6%) and encephalopathy (1.6%).

The most common (greater than or equal to 5%) Grade 3 or 4 adverse reactions were neutropenia (88.6%), anemia (58.2%), thrombocytopenia (53.3%), leukopenia (45.1%), lymphopenia (30.4%), infections – pathogen unspecified. (17.9%), hypophosphataemia (17.4%), febrile neutropenia (14.7%), hypocalcaemia (7.1%), infections - viral (7.1%), pneumonia (6.0%), CRS (5.4%), hypertension (5.4%) and hyponatraemia (5.4%).

Adverse drug reactions occurred in patients treated with Abecma in the KarMMa and CRB-401 studies across the target dose levels of 150 to 450 x 10^6 CAR-positive T cells (see Table 3 in section "Clinical efficacy" for the corresponding dose range of CAR-positive viable T cells) are presented below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.

Infections and infestations[a]

very common: Infections – pathogen unspecified (53.8%), infections – viral (26.1%), infections – bacterial (14.1%).

common: infections – fungal.

Blood and lymphatic system disorders

very common: Neutropenia (91.3%), anaemia (70.7%), thrombocytopenia (66.8%), leukopenia (48.4%), lymphopenia (31.5%), febrile neutropenia (16.3%).

common: Disseminated intravascular coagulation.

Immune system disorders

very common: Cytokine release syndrome (81.0%), hypogammaglobulinemia (19.6%).

common: Hemophagocytic lymphohistiocytosis.

Metabolism and nutrition disorders

very common: Hypokalaemia (34.2%), hypophosphataemia (32.6%), hypocalcaemia (26.6%), hypomagnesaemia (22.3%), decreased appetite (19.6%), hypoalbuminaemia (19.6%), hyponatraemia (18.5%).

Psychiatric disorders

common: Insomnia, delirium[b].

Nervous system disorders

very common: Headache[c] (28.8%), encephalopathy[d] (27.2%), dizziness[e] (19.6%).

Common: Tremor, motor dysfunction[f], aphasia[g], ataxia[h], hemiparesis, seizure.

Cardiac disorders

very common: Tachycardia[i] (25.5%).

common: Atrial fibrillation.

Vascular disorders

very common: Hypotension[j] (25.0%), hypertension (13.0%).

Respiratory, thoracic and mediastinal disorders

very common: Cough[k] (27.7%), dyspnea[l] (15.8%).

Common: Hypoxia, pulmonary edema.

Gastrointestinal disorders

very common: Diarrhea (36.4%), nausea (32.6%), constipation (19.6%), vomiting (17.9%).

common: Gastrointestinal hemorrhage[m].

Musculoskeletal and connective tissue disorders

very common: Arthralgia (20.7%).

common: Myalgia.

General disorders and administration site conditions

very common: Fatigue[n] (41.3%), pyrexia (28.8%), edema[o] (25.0%), , chills (15.2%), asthenia (12.0%).

Investigations

very common: Blood alkaline phosphatase increased (13.6%), aspartate aminotransferase increased (12.5%).

common: Alanine aminotransferase increased, C-reactive protein increased.

[a] Infections and infestations System Organ Class Adverse Events are grouped by pathogen type.

[b] Delirium includes delirium, disorientation, hallucination.

[c] Headache includes headache, head discomfort.

[d] Encephalopathy includes amnesia, bradyphrenia, cognitive disorder, confusional state, disturbance in attention, dyscalculia, dysgraphia, encephalopathy, lethargy, memory impairment, mental status changes, metabolic encephalopathy, somnolence, toxic encephalopathy.

[e] Dizziness includes dizziness, presyncope, syncope, vertigo.

[f] Motor dysfunction includes motor dysfunction, muscular spasms, muscular weakness.

[g] Aphasia includes aphasia, dysarthria.

[h] Ataxia includes ataxia, gait disturbance

[i] Tachycardia includes sinus tachycardia, tachycardia.

[j] Hypotension includes hypotension, orthostatic hypotension.

[k] Cough includes cough, upper-airway cough syndrome.

[l] Dyspnea includes dyspnea, dyspnea exertional.

[m] Gastrointestinal hemorrhage includes gastrointestinal hemorrhage, hemorrhoidal hemorrhage, melena, mouth haemorrhage.

[n] Fatigue includes fatigue, malaise.

- Edema includes edema, face edema, generalized edema, peripheral edema, peripheral swelling.

Undesirable effects after market launch

Not applicable.

Description of selected undesirable effects

Immunogenicity

Abecma has the potential to induce anti-product antibodies. In clinical studies, humoral immunogenicity of Abecma was measured by determination of anti-CAR antibody in serum pre- and post-administration.

In the pooled studies (KarMMa and CRB-401), 4.3% of patients tested positive for pre-infusion anti-CAR antibodies and post-infusion anti-CAR antibodies were detected in 50.5% (of the patients. There is no evidence that the presence of pre-existing or post-infusion anti-CAR antibodies impact the cellular expansion, safety, or effectiveness of Abecma.

Cytokine release syndrome

In the pooled studies, CRS occurred in 81.0% of patients receiving Abecma. Grade 3 or higher CRS (Lee grading system) occurred in 5.4% of patients, with fatal (Grade 5) CRS reported in 0.5%of patients. The median time-to-onset, any grade, was 1 day (range: 1 to 17 days) and the median duration of CRS was 5 days (range: 1 to 63 days).

The most common manifestations of CRS included pyrexia (78.3%), hypotension (32.1%), tachycardia (25.5%), chills (23.4%), hypoxia (16.3%), C-reactive protein increased (16.3%), headache (14.7%), and fatigue (10.9%). Grade 3 or higher events that may be observed in association with CRS included atrial fibrillation, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).

Of the 184 patients 45.1% of patients received tocilizumab; 32.6% received a single dose while 12.5% received more than 1 dose of tocilizumab for treatment of CRS. Overall, across the target dose levels, 15.8% of patients received at least 1 dose of corticosteroids for treatment of CRS. Of the 92 patients at the target dose of 450 x 10^6 CAR-positive T cells, 54.3% of patients received tocilizumab and 22.8% received at least 1 dose of corticosteroids for treatment of CRS.

Neurologic toxicities

In the pooled studies, of the 184 patients, independent of investigator attribution of neurotoxicity, the most frequent neurologic or psychiatric adverse reactions included headache (28.8%), dizziness (15.2%), confusional state (13.0%), insomnia (9.8%), anxiety (8.2%), tremor (8.2%), and somnolence (6.5%). Other neurological adverse reactions occurring at a lower frequency and considered clinically important included aphasia (4.3%) and encephalopathy (4.3%).

Neurotoxicity identified by the investigators, which was the primary method of assessing CAR T cell-associated neurotoxicity in the KarMMa study only , occurred in 18.0% of the 128 patients receiving Abecma, including Grade 3 in 3.1% of patients (with no Grade 4 or 5 events). The median time-to-onset of the first event was 2 days (range: 1 to 10). The median duration was 3 days (range: 1 to 26). Overall, across the target dose levels, 7.8% patients received at least 1 dose of corticosteroid for treatment of CAR T cell-associated neurotoxicity, while at the target dose of 450 x 10^6 CAR-positive T cells, 14.8% of patients received at least 1 dose of corticosteroids. The most common manifestations of investigator identified neurotoxicity included confusional state (9.4%), encephalopathy (5.5%), aphasia (4.7%), hallucination (3.1%), and mental status changes (3.1%).

Infections and febrile neutropenia

In the pooled studies, infections occurred in 71.2% of patients. Grade 3 or 4 infections occurred in 23.4% of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 17.9%, viral infections in 7.1%, bacterial infections in 3.8%, and fungal infections in 0.5% of patients. Fatal infections of unspecified pathogen were reported in 1.6 % of patients and 0.5% of patients had fatal fungal or viral infection.

Febrile neutropenia (Grade 3 or 4) was observed in 14.7% of patients after Abecma infusion and may be concurrent with CRS.

Prolonged cytopenias

Patients may exhibit prolonged cytopenias following lymphodepleting chemotherapy and Abecma infusion. In the pooled studies, 62 of the 178 patients 34.8% who had Grade 3 or 4 neutropenia and 80 of the 110 72.7% patients who had Grade 3 or 4 thrombocytopenia during the first month following Abecma infusion had not resolved by last assessment during the first month. Among the 62 patients with neutropenia not resolved by month 1, 82.3% recovered from Grade 3 or 4 neutropenia with a median time to recovery from Abecma infusion of 1.9 months. Of the 80 patients with thrombocytopenia not resolved by month 1, 71.3% recovered from Grade 3 or 4 thrombocytopenia with the median time to recovery of 2.2 months. See section “Warnings and Precautions” for monitoring and management guidance.

Hypogammaglobulinemia

Hypogammaglobulinemia was reported in 19.6% of patients treated with Abecma in the pooled studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Abecma is administered only by trained medical personnel. The risks of overdose are unknown.

Properties/Effects

ATC code

Not yet assigned.

Mechanism of action

Abecma is a chimeric antigen receptor (CAR)-positive T cell therapy targeting B-cell maturation antigen (BCMA), which is expressed on the surface of normal and malignant plasma cells. 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 Abecma results in CAR-positive T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Pharmacodynamics

Not applicable.

Clinical efficacy

KarMMa was an open-label, single-arm, multicenter study that evaluated the efficacy and safety of Abecma in adult patients with relapsed and refractory multiple myeloma who had received at least three prior antimyeloma therapies including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

The study consisted of pretreatment (screening, leukapheresis, and bridging therapy [if needed]); treatment (lymphodepleting chemotherapy [LDC] and Abecma infusion); and post-treatment (ongoing) for a minimum of 24 months following Abecma infusion or until documented disease progression, whichever was longer. The LDC period was one 3-day cycle of cyclophosphamide (300 mg/m^2 IV infusion daily for 3 days) and fludarabine (30 mg/m^2 IV infusion daily for 3 days) starting 5 days prior to the target infusion date of Abecma. Patients were hospitalized for 14 days after Abecma infusion to monitor and manage potential CRS and neurotoxicity.

The Abecma -treated population had a high degree of refractoriness to prior antimyeloma treatments (AMTs): 84.4% of subjects were triple refractory (i.e., refractory to an immunomodulatory agent, a protease inhibitor, and an anti-CD38 antibody).

The target doses in the clinical study were 150, 300, or 450 x 10^6 CAR-positive T cells per infusion. The allowed dose range was 150 to 540 x 10^6 CAR-positive T cells. Table 3 below shows the target dose levels used in the clinical study based on total CAR-positive T cells and the corresponding range of actual dose administered defined as CAR-positive viable T cells.

Table 3: Total CAR-positive T cells dose with the corresponding dose range of CAR-positive viable T cells (x10^6)

Target dose based on total CAR-positive T cells, including both viable and non-viable cells (x10^6)	**CAR-positive viable T cells (x10^6) (min, max)**
150	133 to 181
300	254 to 299
450	307 to 485

Of 140 patients who underwent leukapheresis, 128 patients received Abecma. One of the 140 patients did not receive the product due to manufacturing failure. Eleven other patients were not treated with Abecma, due to physician decision (n=3), patient withdrawal (n=4), adverse events (n=1), progressive disease (n=1), or death (n=2), prior to receiving Abecma.

The median age of the study population was 60.5 years (range: 33 to 78 years); 35% were 65 years or older and 59% were men. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 45%, 1 in 53%, and 2 in 2% of patients.

Most patients (87.5%) treated with Abecma received bridging therapy for control of their multiple myeloma during the manufacturing process. The median time from leukapheresis to product availability was 32 days (range: 24 to 55 days) and the median time from leukapheresis to infusion was 40 days (range: 33 to 79 days). The median actual dose received across all target dose levels was 315.3 x10^6 CAR-positive cells (range: 150.5 to 518.4).

Efficacy was established on the basis of overall response rate (ORR), complete response (CR) rate, and duration of response (DOR), as determined by an independent review committee.
Another endpoint was Minimal Residual Disease (MRD) assessed using next-generation sequencing (NGS).

Efficacy results across the target dose levels of 150 to 450 x 10^6 CAR-positive T cells are shown in Table 4. In the primary analysis, based on the treated population, the ORR was 73.4 % (95% CI: 65.8, 81.1); the complete response (CR) rate was 32.8% (95% CI: 24.7, 40.9). In patients with partial

response (PR) or better, the median DOR was 10.6 months (95% CI: 8.0, 11.4). In those patients with CR or better, the median DOR was 23,3 months (95% CI: 11.4, 23,3). Median follow-up was 15.4 months for all treated patients (range 0.2, 24.2).

Of the 140 patients in the enrolled population, the ORR was 67.1% and the CR rate was 30%. Other efficacy outcomes for the enrolled population were consistent with those of the treated population.

Table 4: Summary of Efficacy based on the KarMMa study

	Enrolled Population (N=140)	**Treated Population Target Dose of Abecma (CAR-Positive T Cells)**			
		[150 x 10^6] (N=4)	**[300 x 10^6] (N=70)**	**[450 x 10^6] (N=54)**	**[150 to 450 x 10^6] (N=128)**
Overall Response Rate (SCR+CR+VGPR+PR), n (%)	**94 (67.1)**	**2 (50.0)**	**48 (68.6)**	**44 (81.5)**	**94 (73.4)**
95% CI[a]	59.4, 74.9	6.8, 93.2	56.4, 79.1	68.6, 90.7	65.8, 81.1
CR or better, n (%)	**42 (30.0)**	**1 (25.0)**	**20 (28.6)**	**21 (38.9)**	**42 (32.8)**
95% CI[a]	22.4, 37.6	0.6, 80.6	18.4, 40.6	25.9, 53.1	24.7, 40.9
VGPR or better, n (%)	**68 (48.6)**	**2 (50.0)**	**31 (44.3)**	**35 (64.8)**	**68 (53.1)**
95% CI[a]	40.3,56.9	6.8, 93.2	32.4, 56.7	50.6, 77.3	44.5, 61.8
Patients with MRD-negative[b] Status and ≥CR, n		**1**	**17**	**15**	**33**
Based on Treated Population, %	–	25.0	24.3	27.8	25.8
95% CI[a]		0.6, 80.6	14.8, 36.0	16.5, 41.6	18.5, 34.3
Based on Subjects with ≥CR, %		100	85.0	71.4	78.6
95% CI[a]		2.5, 100.0	62.1, 96.8	47.8, 88.7	63.2, 89.7
Time to Response[c], n	**94**	**2**	**48**	**44**	**94**
Median (months)	1	1	1	1	1
Min, max	0.5, 8.8	1.0, 1.0	0.5, 8.8	0.9, 2.0	0.5, 8.8

	Enrolled Population (N=140)	Treated Population Target Dose of Abecma (CAR-Positive T Cells)			
		[150 x 10^6] (N=4)	[300 x 10^6] (N=70)	[450 x 10^6] (N=54)	[150 to 450 x 10^6] (N=128)
Duration of Response[c] (PR or Better), n	**94**	**2**	**48**	**44**	**94**
Median[d] (months)	10.6	13.0	8.5	11.3	10.6
95% CI[a]	8.0, 11.4	2.8, 23.3	5.4, 10.9	10.3, NE	8.0, 11.4
Duration of Response (CR or Better), n	**42**	**1**	**20**	**21**	**42**
Median[d] (months)	23.3	23.3	16.2	NE	23.3
95% CI[a]	11.4, 23.3	NE, NE	8.0, NE	11.4, NE	11.4, 23.3
Overall Survival[e] (OS), months, n	**140**	**4**	**70**	**54**	**128**
Median (months)	21.4	18.2	NE	NE	NE
95% CI[a]	19.3, NE	9.4, NE	18.0, NE	NE, NE	18.9, NE
6 months Event-Free rate, %	87.4	100	89.6	86.9	88.8
12 Months Event-Free Rate, %	75.8	75.0	78.5	77.3	77.9

CAR=chimeric antigen receptor; CI=confidence interval; CR=complete response; max=maximum; Min=minimum; MRD=Minimal Residual Disease; NE=not estimable; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

[a] For Total ("Treated population" and "Enrolled population"): Wald CI; for individual target dose levels: Clopper-Pearson exact CI.

[b] Based on a threshold of 10^{-5} using a next-generation sequencing assay.

[c] Response is defined as achieving sCR, CR, VGPR, or PR according to IMWG criteria.

[d] Median is based on Kaplan-Meier estimation.

[e] OS was defined as time from leukapheresis date (enrolled population) or Abecma infusion (treated population) to death due to any cause.

Note: The target dose is 450 x 10^6 CAR-positive T cells within a range of 150 to 540 × 10^6 CAR-positive T cells. The 150 x 10^6 CAR-positive T cell dose is not part of the approved dose range.

Health-related quality of life (HRQoL)

HRQoL was assessed by the European Organization for Research and Treatment of Cancer-Quality of Life C30 questionnaire (EORTC-QLQ-C30) and multiple myeloma module (EORTC-QLQ-MY20) with a primary focus on fatigue, pain, physical functioning, cognitive functioning, global health/QoL, side effects and disease symptoms subscales. According to the results based on data obtained 10 months after Abecma infusion, patients treated with Abecma experienced clinically meaningful improvements in fatigue, pain, physical functioning and global health scores shortly after infusion, which became statistically significant (P<0.05) at multiple time points from month 3 through month 9 posttreatment with no deterioration in cognitive functioning, disease symptoms, or side effects. For most outcomes and observation points, a greater percentage of patients reported clinically meaningful improvement than deterioration.

Real World (RW) Evidence Study

RW Evidence (Study NDS-MM-003) was a non-interventional, retrospective study that collected data on real-world patients with relapsed and refractory multiple myeloma (RRMM) who received at least 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 antibody. From this group, patients were selected who met eligibility criteria as close as possible to the KarMMa study (i.e., lack of comorbidities and initiation of new therapy after becoming refractory to the last anti-myeloma therapy). ORR and overall survival (OS) were evaluated for the two groups, using propensity score methodology, to assess the comparative effectiveness of patients treated with available therapies compared to Abecma in the KarMMa study. The relative risk for ORR was 2.4 (95% CI: 1.7, 3.3), p<0.0001. The OS hazard ratio was 0.41 (95% CI 0.26, 0.65), significantly favoring the Abecma -treated cohort compared with the eligible RRMM cohort treated with available therapy (p = 0.0002).

Safety and efficacy in elderly patients

In the clinical trial of Abecma, 45 (35.2%) patients in the KarMMa study were 65 years of age or older and 4 (3.1%) were 75 years of age or older. No clinically important differences in the safety or effectiveness of Abecma were observed between these patients and patients younger than 65 years of age.

Pharmacokinetics

Absorption

Information is not relevant to Abecma (a CAR T cell product).

Distribution

Information is not relevant to Abecma (a CAR T cell product).

Metabolism

Information is not relevant to Abecma (a CAR T cell product).

Elimination

Information is not relevant to Abecma (a CAR T cell product).

Pharmacokinetics

Following Abecma infusion, the CAR-positive cells proliferate and undergo rapid multi-log expansion followed by a bi-exponential decline. The median time of maximal expansion in peripheral blood (T_{max}) occurred 11 days after infusion. Abecma can persist in peripheral blood for up to 1 year post-infusion. A summary of T_{max}, $AUC_{0\text{-}28days}$, and C_{max} by target dose level and across doses is provided in Table 5.

Table 5: Pharmacokinetic Parameters of Abecma by Target Dose Level in Subjects with Relapsed/Refractory Multiple Myeloma in the KarMMa Study

Pharmacokinetic Parameter	**Summary Statistic**	**[150 x 10^6] CAR-Positive T Cells**	**[300 x 10^6] CAR-Positive T Cells**	**[450 x 10^6] CAR-Positive T Cells**	**Total [150 to 450 × 10^6] CAR-Positive T Cells**
T_{max} (days)	Median (Range)	14 (11-14) N = 4	11 (7-30) N = 69	11 (7-28) N = 54	11 (7-30) N = 127
C_{max} (copies/µg)	Geometric mean (geometric CV%)	204,229 (169) N = 4	180,185 (210) N = 69	321,117 (126) N = 54	231,278 (178) N = 127
$AUC_{0\text{-}28days}$ (days*copies/µg)	Geometric mean (geometric CV%)	1,942,929 (154) N = 4	2,138,414 (215) N = 68	4,277,327 (152) N = 53	2,860,340 (197) N = 125

$AUC_{0\text{-}28days}$ = area under the curve of the transgene level from time of dose to 28 days post-infusion; C_{max} = the maximum transgene level; T_{max} = time of maximum observed transgene level.

Abecma transgene levels were positively associated with objective tumor response (partial response or better). The median C_{max} levels in responders (N = 93) were approximately 4.5-fold higher compared to the corresponding levels in non-responders (N = 34). Median $AUC_{0\text{-}28days}$ in responding subjects (N = 93) was approximately 5.5-fold higher than non-responders (N = 32).

Tocilizumab and Corticosteroid Use

Some patients required tocilizumab and/or corticosteroid for the management of CRS. Abecma can continue to expand and persist following tocilizumab or steroid administration (see Section 4.4).

Patients with CRS treated with tocilizumab had higher Abecma cellular expansion levels, as measured by 1.4-fold and 1.6-fold higher median C_{max} (N = 66) and $AUC_{0\text{-}28days}$ (N = 65), respectively, compared to patients who did not receive tocilizumab (N = 61 for C_{max} and N = 60 for $AUC_{0\text{-}28days}$). Patients with CRS treated with corticosteroids had higher Abecma cellular expansion levels, as measured by 1.7-fold and 2.2-fold higher median C_{max} (N = 18) and $AUC_{0\text{-}28days}$ (N = 18), respectively, compared to patients who did not receive corticosteroids (N = 109 for C_{max} and N = 107 for $AUC_{0\text{-}28days}$).

Kinetics in specific patient groups

Hepatic impairment

Hepatic impairment studies of Abecma were not conducted.

Renal impairment

Renal impairment studies of Abecma were not conducted.

Elderly patients

Age (range: 33 to 78 years) had no significant impact on expansion parameters.

Children and adolescents

The pharmacokinetics of Abecma in patients less than 18 years of age have not been evaluated.

Other intrinsic factors

Gender, race, and ethnicity had no significant impact on Abecma expansion parameters. Subjects with lower body weight had higher expansion. Due to high variability in pharmacokinetic cellular expansion, the overall effect of weight on the pharmacokinetics of Abecma is considered not to be clinically relevant.

Preclinical data

Due to the nature of this product, traditional toxicity, fertility, and pharmacokinetic studies with Abecma were not conducted.

Genotoxicity assays and carcinogenicity studies in rodents are not appropriate to assess the risk of insertional mutagenesis for genetically modified cell therapy products. No alternative adequate animal models are available.

In vitro expansion studies with CAR-positive T cells (Abecma) from healthy donors and patients showed no evidence for transformation and/or immortalisation of T cells. A genomic insertion site analysis of the lentiviral vector was performed on Abecma samples including patient lots and there

was no evidence for preferential integration near genes of concern or preferential outgrowth of cells harboring integration sites of concern.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expriry date (“EXP”) stated on the product label.
The volume intended for infusion within each bag must be completely infused within 1 hour from start of thaw.

Special precautions for storage

Store frozen in ethylene vinyl acetate cryopreservation bags in a container for cryogenic storage in the vapor phase of liquid nitrogen (≤ -130°C).
Keep out of the reach of children.
Instructions for handling

See section (“Dosing/Administration”).
Special precautions for handling and disposal

Abecma contains genetically modified human blood cells. It is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and Abecma may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Abecma to avoid potential transmission of infections.

Work surfaces which have or may have been in contact with Abecma must be decontaminated with appropriate disinfectant. Any unused medicinal product or material that has been in contact with Abecma (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

Authorisation number

67575 (Swissmedic)

Packs

The finished product is composed of one or more infusion bags containing a total cell dispersion of 260 to 500 x 10^6 CAR-positive viableT cells. Each infusion bag contains 10 – 30 mL (50 mL bags), 30 – 70 mL (250 mL bags) or 55 – 100 mL (500 mL bags) of cell dispersion. [A]

Each infusion bag of Abecma is individually packed in a metal cassette. Abecma is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry vapor shipper.
An RFI Certificate is affixed inside the shipper.

Marketing authorisation holder

Celgene GmbH, Zurich

Date of revision of the text

August 2021