swissmedic

Date: 22 January 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Abecma

International non-proprietary name: idecabtagene vicleucel

Pharmaceutical form: dispersion for infusion

Dosage strength(s): 260 to 500 x 10e6 CAR-positive viable T cells

Route(s) of administration: intravenous

Marketing authorisation holder: Bristol-Myers Squibb SA

Marketing authorisation no.: 67575

Decision and decision date: extension of therapeutic indication approved on 09.02.2024

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.

Table of contents

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)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a[decies] no. 2 of the TPA. Orphan drug 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 relapsed and refractory multiple myeloma who have received at least 2 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

2.2.2 Approved indication

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

- have received at least 2 therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and have demonstrated progression on or within 60 days of the last therapy

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	1 May 2023
Formal control completed	8 May 2023
List of Questions (LoQ)	1 September 2023
Response to LoQ	20 September 2023
Preliminary decision	29 November 2023
Response to preliminary decision	11 January 2024
Final decision	9 February 2024
Decision	approval

3 Clinical aspects

To further substantiate the advantage of therapy with Abecma over standard care – beyond the approval of Abecma for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies – the results of the ongoing study BB2121-MM-003 (KarMMa-3, MM-003) were submitted by the applicant.
KarMMa-3 is an ongoing Phase 3, open-label, multicentre, randomised, controlled study that compares the efficacy and safety of Abecma versus standard regimens in adult patients with relapsed and refractory multiple myeloma (RRMM) who have received 2 to 4 prior antimyeloma regimens including an immunomodulatory agent, a proteasome inhibitor, and daratumumab, and were refractory to the most recent prior antimyeloma regimen. A standard regimen was assigned to each patient prior to randomisation, contingent upon the patient's most recent antimyeloma treatment. The standard regimens consisted of daratumumab, pomalidomide, dexamethasone (DPd); daratumumab, bortezomib, dexamethasone (DVd); ixazomib, lenalidomide, dexamethasone (IRd); carfilzomib, dexamethasone (Kd); or elotuzumab, pomalidomide, dexamethasone (EPd). In patients randomised to the Abecma arm, the assigned standard regimen was to be used as bridging therapy, if clinically indicated. The study participants had to have had a progression of MM during or within 60 days of the previous therapy.

3.1 Efficacy

Progression-free survival (PFS) by Independent Review Committee (IRC) was defined as the primary endpoint of study MM-003. The key secondary endpoints of the study were ORR by IRC and OS, hierarchically tested.
Data from study MM-003 on PFS and ORR with a data cut-off of 18 April 2023 were submitted as part of this submission. In the ide-cel arm, 95.3 % of patients were refractory to the anti-CD38 antibody daratumumab, which is approved as a monotherapy and combination therapy for the treatment of multiple myeloma. In a clinical trial in patients with r/r MM, the PFS in the group treated with daratumumab, bortezomib, and dexamethasone was 16.7 months compared to 7.1 months in the control group (bortezomib and dexamethasone).
The primary endpoint PFS was achieved and ide-cel demonstrated superiority with 13.3 months compared to standard therapy (4.4 months). This result was independent of whether the patients had received 2, 3, or 4 previous lines of therapy. A better outcome was also shown for ORR and MRD negativity.
When evaluating the group-level mean change from baseline on EORTC QLQ-C30 pre-specified primary domains (fatigue, pain, physical functioning, cognitive functioning, and GHS/QoL), ide-cel consistently demonstrated clinically meaningful improvements compared with those of the standard regimens arm, which was stable or worsened over time.

3.2 Safety

The risk profile of ide-cel in study MM-003 was comparable to the risks of standard therapies and was in line with that observed to date. As of the 28 April 2023 data cut-off date, in the ITT population, similar proportions of subjects died in the ide-cel and standard regimens arms (41.7% vs 43.9%, respectively). The causes of death were similar between both arms, with the majority of deaths due to disease progression; a similar percentage died due to AEs in each arm.
In addition to the comparison with the control group, the data were compared with pooled safety data from studies CRB-401 and MM-001. In the ITT population, 29.5% of patients in the ide-cel arm and 25.8% of patients in the control arm died. The cause of death in the majority of cases in both groups was progression of the underlying disease.

As of the 28 April 2023 data cut-off date, any-grade SAEs were reported in 139 (55.8%) and 52 (41.3%) subjects in the ide-cel and standard regimens arms, respectively. Grade 3 or 4 SAEs were reported in 114 (45.8%) subjects in the ide-cel arm and 46 (36.5%) subjects in the standard regimens arm.

The most frequently reported SAEs in each arm were:

- ide-cel arm: pneumonia (6.8%), general physical health deterioration (6.8%), pyrexia (4.8%), CRS and febrile neutropenia (4.0%, each).
- standard regimens arm: pneumonia (4.8%), COVID-19 pneumonia and general physical health deterioration (3.2%, each), influenza and atrial fibrillation (2.4%, each).

Any-grade AEs were reported in 248 (99.6%) subjects in the ide-cel arm and 124 (98.4%) in the standard regimens arm. Grade 3 or 4 AEs were reported in 234 (94.0%) and 97 (77.0%) subjects in the ide-cel and standard regimens arms, respectively.

The most frequently reported (≥ 30% of subjects) any grade AEs were:
- Ide-cel arm: cytokine release syndrome (79.1%), neutropenia (78.7%), anaemia (66.3%), thrombocytopenia (55.4%), nausea (45.8%), diarrhoea (34.5%), hypokalaemia (32.1%), and hypophosphatemia (31.7%)
- Standard regimens arm: neutropenia (46.0%), anaemia (37.3%), and fatigue (34.9%)

In the ide-cel arm (Safety population), 197 (87.6%) subjects experienced at least 1 event of CRS. The median time to first onset of CRS AEs was 1.0 day (range 1.0 to 14.0 days) and the median duration was 4.0 days (range: 1.0 to 51.0 days). A small proportion of subjects had severe CRS (Grade 3: 6 subjects [2.7%]), Grade 4: 3 subjects [1.3%], and Grade 5: 2 subjects [0.9%]).

Based on the assessment of the type, frequency, and severity of AEs reported in pooled studies, the safety profile of ide-cel is similar regardless of the number of prior anti-MM therapies received. The proportion of subjects with SAEs and AESIs was lower in subjects with 2 versus ≥ 3 lines of therapy. The differences in favour of the third line of therapy are particularly evident in neurotoxicity. However, this difference could also be due to the fact that patients previously treated with ≥3 lines of therapy have a more advanced stage of the disease.

3.3 Final clinical benefit-risk assessment

Evidence is provided to conclude that the benefit-risk assessment for Abecma is positive for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior anti-myeloma therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti CD38 antibody, and were refractory to their previous regimen.

4 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.

5 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 two prior lines of therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression during or within 60 days after the last therapy.
- have received at least three prior lines of 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^2ntravenously (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

No dose adjustment is required in patients over 65 years of age (*See Section safety and efficacy in elderly patients*)

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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(s) 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. In clinical studies, the median time-to-onset of CRS was 1 day (range: 1 to 17 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>
</table>

<table>
<tr><th>CRS Grade[a]</th><th>Tocilizumab</th><th>Corticosteroids</th></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 hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity or Grade 4 transaminitis.</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).
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, including immune effector cell-associated neurotoxicity syndrome (ICANS), 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 3 days (range: 1 to 317 days, one patient developed encephalopathy at Day 317 as a result of worsening pneumonia and *Clostridium difficile* colitis) (see section “Undesirable effects”).

Parkinsonism

Grade 3 parkinsonism occurred after treatment with Abecma in a multiple myeloma study. Symptoms reported included tremor, dysphasia, bradykinesia, and parkinsonian-like reflexes. Monitor patients for signs and symptoms of neurotoxicity including symptoms of parkinsonism. There is insufficient information on the treatment of parkinsonism in patients following treatment with Abecma. Management of neurotoxicity including parkinsonism should be guided by institutional or standard clinical practice, and as determined by the treating physician.

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.

Neurologic Toxicity Grade[a]	**Corticosteroids and Antiseizure Medications**
	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.
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 ,CRB-401 and KarMMa-3 studies, in which 409 patients with relapsed and refractory multiple myeloma received Abecma (see section "Clinical efficacy"). In KarMMa (N = 128) and CRB-401 (N = 56), the median duration of follow-up (from Abecma infusion to data cutoff date) was 20.8 months. In KarMMa-3 (N = 225), the median duration of follow-up was 29.3 months.

The most common (incidence ≥ 20%) adverse reactions included CRS (84.6%), neutropenia (80.0%), anemia (63.6%), thrombocytopenia (55.0%), infections – pathogen unspecified, (43.8%), hypophosphataemia (33.3%), diarrhoea (33.0%), leukopenia (32.8%), hypokalaemia (32.0%), fatigue (29.8%), nausea (28.1%), lymphopenia (26.9%), pyrexia (24.7%), infections-viral (23.2%), headache (22.5%); hypocalcaemia (22.0%), hypomagnesaemia (21.3%), arthralgia (20.0%); other common adverse events occurring at lower frequency and considered clinically important included hypotension

(18.6%), upper respiratory tract infection (15.6%), hypogammaglobulinaemia (13.7%), febrile neutropenia (11.2%), pneumonia (11.0%), tremor (5.6%), somnolence (5.6%), encephalopathy (3.4%), syncope (3.2%) and aphasia (2.9%).

Serious adverse reactions occurred in 57.2% of patients. The most common (≥5%) serious adverse reactions included CRS (10.3%) and pneumonia (7.1%), other serious adverse events occurring at lower frequency and considered clinically important include febrile neutropenia (4.2%), pyrexia (3.7%), neutropenia (2.7%), sepsis (2.7%), confusional state (2.4%), haemophagocytic lymphohistiocytosis (1.7%), thrombocytopenia (1.5%), encephalopathy (1.5%),dyspnoea (1.5%), seizure (1.0%), mental status changes (1.0%), hypoxia (0.7%), and disseminated intravascular coagulation (0.5%).

The most common (≥5%) Grade 3 or 4 adverse reactions were neutropenia (77.3%), anemia (50.9%), thrombocytopenia (42.5%), leukopenia (31.5%), lymphopenia (25.9%), hypophosphataemia (19.8%), infections – pathogen unspecified. (15.2%), febrile neutropenia (10.5%), infections - viral (7.6%), pneumonia (6.8%), hypertension (6.6%) hypocalcaemia (5.6%) and infections bacterial (5.4%).

Adverse drug reactions observed in 409 patients treated with Abecma in the clinical studies within the allowed dose range of 150 to 540 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 in KarMMa) 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 (43.8%), infections – viral (23.2%), infections – bacterial (15.4%).

common: infections – fungal.

Blood and lymphatic system disorders

very common: Neutropenia (80.0%), anaemia (63.6%), thrombocytopenia (55.0%), leukopenia (32.8%), lymphopenia (26.9%), febrile neutropenia (11.2%).

common: Disseminated intravascular coagulation.

Immune system disorders

very common: Cytokine release syndrome (84.6%), hypogammaglobulinemia (13.7%).
common: Hemophagocytic lymphohistiocytosis.

Metabolism and nutrition disorders
very common: Hypophosphataemia (33.3%), hypokalaemia (32.0%), hypocalcaemia (22.0%), hypomagnesaemia (21.3%), decreased appetite (17.8%), hyponatraemia (13.9%), hypoalbuminaemia (11.5%).

Psychiatric disorders
very common: Insomnia (10.3%).
common: Delirium[b].

Nervous system disorders
very common: Encephalopathy[d] (23.5%), headache[c] (22.5%), dizziness[e] (16.1%).
common: Motor dysfunction[f], tremoraphasia[g], ataxia[h], seizure.
uncommon: Hemiparesis.

Cardiac disorders
very common: Tachycardia[i] (18.3%).
common: Atrial fibrillation.

Vascular disorders
very common: Hypotension[j] (18.6%), hypertension (13.9%).

Respiratory, thoracic and mediastinal disorders
very common: Cough[k] (18.8%), dyspnoea[l] (14.4%).
common: Hypoxia, pulmonary edema.

Gastrointestinal disorders
very common: Diarrhoea (33.0%), nausea (28.1%), constipation (18.3%), vomiting (15.2%).
common: Gastrointestinal hemorrhage[m].

Musculoskeletal and connective tissue disorders
very common: Arthralgia (20.0%).
common: Myalgia.

General disorders and administration site conditions

very common: Fatigue[n] (29.8%), pyrexia (24.7%), edema[o] (19.6%), chills (10.5%).
common: Asthenia.

Investigations

very common: Aspartate aminotransferase increased (12.2%), Alanine aminotransferase increased (11.2%).
common: Blood alkaline phosphatase increased, C-reactive protein increased.

[a] Infections and infestations System Organ Class Adverse Events are grouped by pathogen type and selected clinical syndromes.
[b] Delirium includes delirium, disorientation, agitation, hallucination, restlessness.
[c] Headache includes headache, head discomfort.
[d] Encephalopathy includes amnesia, bradyphrenia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dyscalculia, dysgraphia, encephalopathy, incoherent, lethargy, memory impairment, mental impairment, mental status changes, metabolic encephalopathy, neurotoxicity, somnolence, stupor.
[e] Dizziness includes dizziness, presyncope, syncope, vertigo.
[f] Motor dysfunction includes motor dysfunction, muscular spasms, muscular weakness.
[g] Aphasia includes aphasia, dysarthria, slow speech and speech disorder.
[h] Ataxia includes ataxia, dysmetria, 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, gingival bleeding, haematochezia, hemorrhoidal hemorrhage, melena, mouth haemorrhage.
[n] Fatigue includes fatigue, malaise.
[o] Edema includes edema, edema peripheral, face edema, generalized 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, CRB-401 and KarMMa-3), 3.2% of patients tested positive for pre-infusion anti-CAR antibodies and post-infusion anti-CAR antibodies were detected in 54.0% 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 84.6% of patients receiving Abecma. Grade 3 or higher CRS (Lee grading system, 2014) occurred in 5.1% of patients, with fatal (Grade 5) CRS reported in 0.7% of patients. The median time-to-onset, any grade, was 1 day (range: 1 to 17 days) and the median duration of CRS was 4 days (range: 1 to 63 days).
The most common manifestations of CRS (≥ 10%) included pyrexia (82.6%), hypotension (29.1%), tachycardia (24.7%), chills (18.8%), hypoxia (15.9%), headache (11.2%), and C-reactive protein increased (10.5%). 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 409 patients, 59.7% of patients received tocilizumab; 37.2% received a single dose while 22.5% received more than 1 dose of tocilizumab for treatment of CRS. Overall, 22.7% of patients received at least 1 dose of corticosteroids for treatment of CRS. Of the 92 patients in KarMMa and CRB-401 who received 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. Of the 225 patients in KarMMa-3 who received Abecma infusion, 71.6% of patients received tocilizumab and 28.4% received at least 1 dose of corticosteroids for the treatment of CRS.

Neurologic toxicities
In the pooled studies, of the 409 patients, independent of investigator attribution of neurotoxicity, the most frequent neurologic or psychiatric adverse reactions (≥ 5%) included headache (22.5%), dizziness (12.5%), confusional state (11.0%), insomnia (10.3%), anxiety (5.9%), tremor (5.6%), and somnolence (5.6%). Other neurological adverse reactions occurring at a lower frequency and considered clinically important included encephalopathy (3.4%) and aphasia (2.9%)

Neurotoxicity identified by the investigators, which was the primary method of assessing CAR T cell-associated neurotoxicity in the KarMMa and KarMMa-3 studies, occurred in 57(16.1%) of the 353 patients receiving Abecma, including Grade 3 or 4 in 3.1% of patients (with no Grade 5 events). The median time-to-onset of the first event was 3 days (range: 1 to 317; one patient developed encephalopathy at Day 317 as a result of worsening pneumonia and Clostridium Difficile colitis). The median duration was 3 days (range: 1 to 252; one patient developed neurotoxicity (highest grade 3) 43 days after ide-cel infusion which resolved after 252 days). Overall, 7.1% patients received at least 1 dose of corticosteroid for treatment of CAR T cell-associated neurotoxicity.
In KarMMa, across the target dose levels, 7.8% of 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.
In KarMMa-3, across all patients receiving Abecma infusion, 6.7% of patients received at least 1 dose of corticosteroid for treatment of CAR T cell-associated neurotoxicity.

Of the 353 patients in the KarMMa and KarMMa-3 studies the most common manifestations of investigator identified neurotoxicity (≥ 2%) included confusional state (8.5%), encephalopathy (3.4%), somnolence (2.8%) aphasia (2.5%), tremor (2.3%), disturbance in attention (2.0%) and dysgraphia (2.0%).
Immune effector-cell associated neurotoxicity syndrome (ICANS) has been identified as an adverse event during post-approval use of Abecma. Because reports are from a population of unknown size, an estimate of frequency cannot be made

Infections and febrile neutropenia
In the pooled studies, infections occurred in 62.8% of patients. Grade 3 or 4 infections occurred in 23.2% of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 15.2%, viral infections in 7.6%, bacterial infections in 4.6%, and fungal infections in 1.2% of patients. Fatal infections of unspecified pathogen were reported in 2.0 % of patients and 0.7% of patients had fatal fungal or viral infection and 0.2% of patients had fatal bacterial infection.
Febrile neutropenia (Grade 3 or 4) was observed in 10.8% 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, 151of the 395 patient s(38.2%) who had Grade 3 or 4 neutropenia and 164of the 230 patients (71.3%) 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 151 patients with neutropenia not resolved by month 1, 88.7% recovered from Grade 3 or 4 neutropenia with a median time to recovery from Abecma infusion of 1.9 months. Of the 164 patients with thrombocytopenia not resolved by month 1, 79.9% recovered from Grade 3 or 4 thrombocytopenia with the median time to recovery of 2.0 months. See section “Warnings and Precautions” for monitoring and management guidance.

Hypogammaglobulinemia
Hypogammaglobulinemia was reported in 13.7% of patients treated with Abecma in the pooled studies with a median time to onset of 90 days (range 1 to 326).

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

L01XL07

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-3

KarMMa-3 is an open-label, multicentre, randomised, controlled study that evaluated the efficacy and safety of Abecma, compared to standard therapy regimens, in adult patients with relapsed and refractory multiple myeloma who had received two to four prior anti multiple myeloma regimens including an immunomodulatory agent, a proteasome inhibitor, and daratumumab, and were refractory to the most recent prior antimyeloma regimen. A standard regimen was assigned to each patient prior to randomisation, contingent upon the patient's most recent antimyeloma treatment. The standard regimens consisted of daratumumab, pomalidomide, dexamethasone (DPd), daratumumab, bortezomib, dexamethasone (DVd), ixazomib, lenalidomide, dexamethasone (IRd), carfilzomib, dexamethasone (Kd), or elotuzumab, pomalidomide, dexamethasone (EPd). In patients randomised to the Abecma arm, the assigned standard regimen was to be used as bridging therapy, if clinically indicated.

The study included patients who achieved a response (minimal response or better) to at least 1 prior treatment regimen and had ECOG performance status of 0 or 1. The study excluded patients with serum creatinine clearance < 45 mL/min, serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times upper limit of normal, and left ventricular ejection fraction (LVEF) < 45%. Patients were also excluded if absolute neutrophil count < 1000/µL and platelet count < 75,000/µL in patients in whom < 50% of bone marrow nucleated cells are plasma cells and platelet count < 50,000/µL in patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells.

The median age of the study population was 63 years (range: 30 to 83 years); 40.9% were 65 years or older and 60.9% were men. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 48.2%, 1 in 50.5%, and 2 in 0.8% of patients.

Ninety percent of patients were refractory to an immunomodulatory drug (IMiD), 74% were refractory to a proteasome inhibitor (PI), and 95% were refractory to an anti-CD38 monoclonal antibody. Sixty-six percent were triple class refractory (refractory to a PI, an IMiD and an anti-CD38 monoclonal antibody).

Patients were randomised 2:1 to receive either Abecma (N = 254) or standard regimens (N = 132) for relapsed and refractory multiple myeloma. Randomisation was stratified by age, number of prior antimyeloma regimens and high-risk cytogenetics abnormalities. Patients receiving standard regimens were allowed to receive Abecma upon confirmed disease progression.

Patients randomised to Abecma were to receive lymphodepleting chemotherapy consisting of cyclophosphamide (300 mg/m2 IV infusion daily for 3 days) and fludarabine (30 mg/m2 IV infusion daily for 3 days) starting 5 days prior to the target infusion date of Abecma. Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd anticancer therapy for disease control (bridging therapy) was permitted between apheresis and until 14 days before the start of lymphodepleting chemotherapy.

Of the 254 patients randomised to Abecma, 249 (98%) patients underwent leukapheresis, and 225 (88.6%) patients received Abecma. Of the 225 patients, 192 (85.3%) patients received bridging therapy. Twenty-nine patients did not receive Abecma due to death (n = 4), adverse event (n = 5), patient withdrawal (n = 2), physician decision (n = 7), failure to meet lymphodepleting chemotherapy treatment criteria (n = 8) or manufacturing failure (n = 3).

The allowed dose range was 150 to 540 x 10^6 CAR-positive T cells. The median actual received dose was 445.3 x 10^6 CAR-positive T cells (range: 174.9 to 529.0 x 10^6 CAR-positive T cells). The median time from leukapheresis to product availability was 35 days (range: 24 to 102 days) and the median time from leukapheresis to infusion was 49 days (range: 34 to 117 days).

Of the 132 patients randomised to standard regimens, 126 (95.5%) patients received treatment. Six patients discontinued without receiving treatment due to disease progression (n = 1), patient withdrawal (n = 3), or physician decision (n = 2). Patients receiving a standard regimens were allowed to receive Abecma at investigator’s request, upon confirmed disease progression by the independent review committee (IRC) based on the International Myeloma Working Group (IMWG) criteria and

confirmed eligibility. Of the eligible patients, 69 (54.8%) underwent leukapheresis and 60 (47.6%) received Abecma.

The primary efficacy endpoint was progression free survival (PFS) according to the IMWG Uniform Response Criteria for Multiple Myeloma as determined by an Independent Review Committee (IRC).. Other efficacy measures included overall response rate (ORR), overall survival (OS) and patient-reported outcomes (PRO). In the intent-to-treat (ITT) population, the median duration of follow-up from randomization to data cutoff date was 18.6 months. The summary of the interim analysis efficacy results is shown in Table 3.

In the Abecma arm, the median duration of response (DOR) was 13.9 months (95% CI: 11.2, 17.8) in patients with partial response (PR) or better. In patients who achieved complete response (CR) or better, the median DOR was 20 months (95% CI: 15.8, 24.3).

Table 3. Summary of efficacy results from KarMMa-3 (intent-to-treat population)

	Abecma arm (N = 254)	**Standard regimens arm (N = 132)**
Progression free survival		
Number of events, n (%)	149 (58.7)	93 (70.5)
Median, months [95% CI][a]	13.3 [11.8, 16.1]	4.4 [3.4, 5.9]
Hazard ratio [95% CI][b]	0.49 [0.38, 0.65]	
One-sided p-value[c]	< 0.0001	
Overall response rate		
n (%)	181 (71.3)	55 (41.7)
95% CI (%)[d]	(65.7, 76.8)	(33.3, 50.1)
One-sided p-value[e]	< 0.0001	
CR or better (sCR+CR)	98 (38.5)	7 (5.3)
sCR	90 (35.4)	6 (4.5)
CR	8 (3.1)	1 (0.8)
VGPR	55 (21.7)	13 (9.8)
PR	28 (11.0)	35 (26.5)
MRD-negative status by NGS and ≥ CR		
MRD negativity rate, n (%)[f]	51 (20.1)	1 (0.8)
95% CI (%)[d]	(15.2, 25.0)	(0.0, 2.2)

CI=confidence interval; CR=complete response; MRD=minimal residual disease; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

[a] Kaplan-Meier estimate.

[b] Based on stratified univariate Cox proportional hazards model.

[c] One-sided p-value is based on stratified log-rank test.

[d] Two-sided Wald confidence interval.

[e] One-sided p-value based on stratified Cochran-Mantel-Haenszel (CMH) test.
[f] MRD negativity was defined as the proportion of all patients in the ITT population who achieved CR or stringent CR and are MRD negative at any timepoint within 3 months prior to achieving CR or stringent CR until the time of progression or death. Based on a threshold of 10^{-5} using ClonoSEQ, a next-generation sequencing (NGS) assay.

At the time of final PFS analysis (data cutoff 28-Apr-2023) with a median follow-up of 30.9 months, the median PFS for Abecma was 13.8 months (95% CI: 11.8, 16.1) versus standard regimens 4.4 months (95% CI: 3.4, 5.8); HR = 0.49 (95% CI: 0.38, 0.63), consistent with the interim analysis.

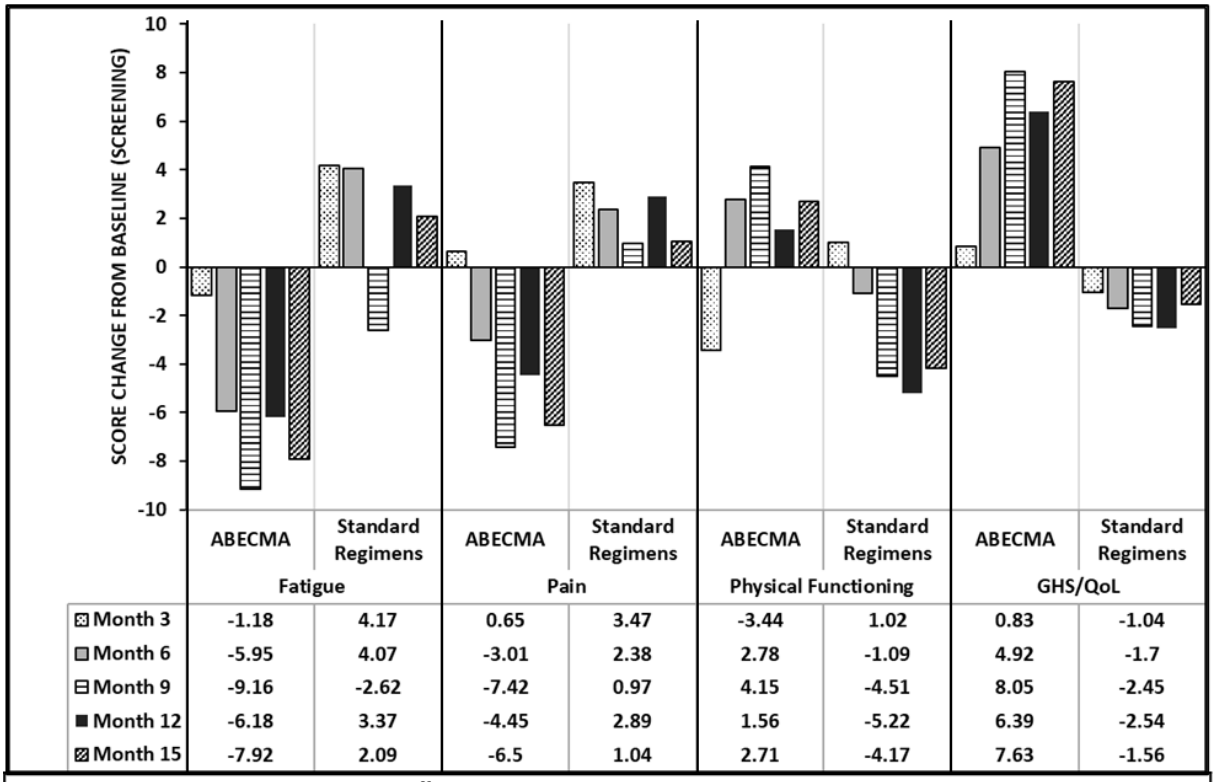
At this final PFS analysis, 74% of planned OS events were reached. Patients receiving standard regimens were allowed to receive Abecma upon confirmed disease progression.The OS data are therefore confounded by 74 (56.1%) patients from the standard regimen arm who received Abecma as a subsequent therapy. The median OS for Abecma was 41.4 months (95% CI: 30.9, NA) versus standard regimens 37.9 months (95% CI: 23.4, NA); HR = 1.01 (95% CI: 0.73, 1.40).

Patient-reported outcomes (PROs)

Descriptive analyses

Three PRO measures (EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D-5L) were completed at baseline (screening), monthly through month 24 and every 3 months thereafter. Of the questionnaire responders (Abecma n = 211; standard regimens n = 108), patients treated with Abecma showed trends towards improvements and differences in mean score changes from baseline compared to patients treated with standard regimens in most PRO domains, including fatigue, pain, physical functioning and GHS/QoL (see Figure 1).

Figure 1. EORTC QLQ-C30 - Mean score changes at month 3, 6, 9, 12 and 15 from baseline for fatigue, pain, physical functioning, and GHS/QoL domains in KarMMa-3 study



	Fatigue		Pain		Physical Functioning		GHS/QoL	
	ABECMA	Standard Regimens	ABECMA	Standard Regimens	ABECMA	Standard Regimens	ABECMA	Standard Regimens
Month 3	-1.18	4.17	0.65	3.47	-3.44	1.02	0.83	-1.04
Month 6	-5.95	4.07	-3.01	2.38	2.78	-1.09	4.92	-1.7
Month 9	-9.16	-2.62	-7.42	0.97	4.15	-4.51	8.05	-2.45
Month 12	-6.18	3.37	-4.45	2.89	1.56	-5.22	6.39	-2.54
Month 15	-7.92	2.09	-6.5	1.04	2.71	-4.17	7.63	-1.56

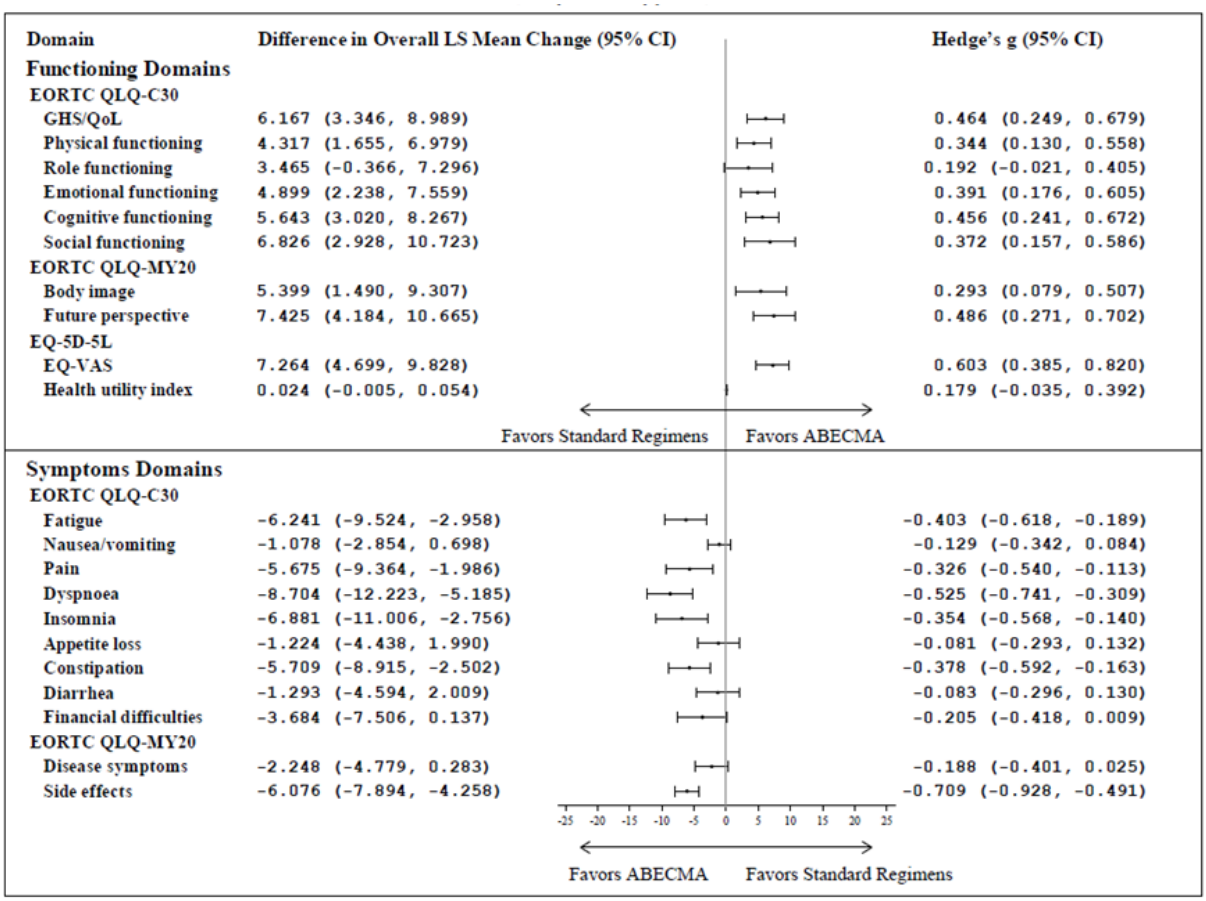
	Baseline (Screening)	Month 3	Month 6	Month 9	Month 12	Month 15
ABECMA Arm (N)	211	151	144	119	90	59
Standard Regimens Arm (N)	108	72	49	37	23	16

Negative score change from baseline represent improvement in symptoms for fatigue and pain domains, whereas positive score change from baseline represents better functioning for physical and GHS/QoL domains.

Constrained longitudinal data analyses (cLDA)

When comparing least square (LS) mean changes from baseline to month 25 using cLDA, the overall LS mean change scores favoured Abecma-treated patients for most of the three PRO measures' domains with meaningful effect sizes (Hedge's g > 0.2) (see Figure 2).

Figure 2. Forest plot of between-group differences in the cLDA overall LS mean change from baseline by treatment groupa,b,c in KarMMa-3 study (Abecma n = 211; standard regimens n = 108)



CI = Confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life-of-Core 30 Questionnaire; EORTC QLQ-MY20 = European Organization for Research and Treatment of Cancer Quality of Life-of-Questionnaire Multiple Myeloma Module; EQ-VAS = Visual Analogue Scale; GHS = Global health status; LS = Least square; QoL = Quality of Life.

[a] The guideline by Cohen (1998, 1992) for the interpretation of Hedge's g values is 0.20 to be indicative of small effects; 0.50 for medium effects, and 0.80 for large effects.

[b] Primary domains of interest: EORTC QLQ-C30 domains of global health status/quality of life (QoL), physical functioning, cognitive functioning, fatigue and pain; EORTC QLQ-MY20 domains of disease symptoms and side effects of treatment; EQ-5D-5L health utility index and EQ-VAS. Remaining domains considered secondary domains.

[c] Analysis did not include multiplicity adjustment.

PRO Time to Event Analyses

In the KarMMa-3 study, time to event analyses evaluated the time to confirmed clinically meaningful improvement and deterioration in PRO domains of interest, in patients treated with Abecma versus standard regimens, using the Kaplan-Meier estimate. Onset of deterioration or improvement was defined as change from baseline based on validated thresholds and confirmed by subsequent assessment ≥ 84 days after the onset. Hazards ratios (HR) were reported; HR<1.0 for deterioration and HR>1.0 for improvement favored Abecma. Patients treated with Abecma had significantly prolonged time to confirmed deterioration in most domains across all three PROs (i.e., HR<1.0). Abecma-treated patients also had shorter time to confirmed improvement for the majority of domains across the PRO measures (i.e., HR>1.0).

KarMMa

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 4: Total CAR-positive T cells dose with the corresponding dose range of CAR-positive viable T cells (x10^6)- KarMMa study

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 5: 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)**

	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)
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
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

	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 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 trials of Abecma, 163 (39.9%) patients were 65 years of age or older and 17 (4.2%) 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} from KarMMa and KarMMa-3 studies is provided in Table 6.

Table 6: Pharmacokinetic Parameters of Abecma in Patients with Relapsed/Refractory Multiple Myeloma

Pharmacokinetic Parameter	**Summary Statistic**	**KarMMa Study Total [150 to 450 x 10^6] CAR-Positive T Cells (Quantified by qPCR)a**	**KarMMa-3 Study Total [150 to 450 x 10^6] CAR-Positive T Cells (Quantified by ddPCR)b**
T_{max} (days)	Median (Range)	11 (7-30) N=127	11 (2-31) N=220
C_{max} (copies/µg)	Geometric mean (geometric CV%)	231,278 (178) N=127	115,701 (223) N=220
$AUC_{0\text{-}28days}$ (days*copies/ µg)	Geometric mean (geometric CV%)	2,860,340 (197) N=125	1,084,349 (231) N=218

$AUC_{0\text{-}28days}$ = area under the curve of the transgene level from time of dose to 28 days post-infusion; Cmax = the maximum transgene level; ddPCR = droplet digital polymerase chain reaction; qPCR = quantitative polymerase chain reaction; PK = pharmacokinetics;
T_{max} = time of maximum observed transgene level.
[a] The PK parameters of KarMMa study were determined by time course of transgene copies per microgram of DNA extracted from CD3+ sorted cells as quantified by quantitative polymerase chain reaction (qPCR).
[b] The PK parameters of KarMMa-3 study were determined by time course of transgene copies per microgram of DNA extracted from whole blood as quantified by droplet digital PCR (ddPCR).
Note: The PK parameters should not be directly compared between KarMMa and KarMMa-3 due to different primary PK assays used in these two studies

Abecma transgene levels were positively associated with objective tumor response (partial response or better). In KarMMa 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 responders (N = 93) was approximately 5.5-fold higher than non-responders (N = 32). In KarMMa-3, the median C_{max} levels in responders (N=180) were approximately 5.4-fold higher compared to the corresponding levels in non-responders (N=40). Median $AUC_{0\text{-}28days}$ in responders (N=180) was approximately 5.5-fold higher than non-responders (N=38).

Tocilizumab or Siltuximab and Corticosteroid Use
Some patients required tocilizumab or siltuximab and/or corticosteroid for the management of CRS. Abecma can continue to expand and persist following tocilizumab or siltuximab or corticosteroid administration (see Section”Warning and Precautions”).

In KarMMa, 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 $AUC_{0\text{-}28days}$).
In KarMMa-3, patients with CRS treated with tocilizumab or siltuximab had higher Abecma cellular expansion levels, as measured by 3.1-fold and 2.9-fold higher median Cmax (N=156) and $AUC_{0\text{-}28days}$ (N=155), respectively, compared to patients who did not receive tocilizumab or siltuximab (N=64 for $_{C}$max and N=63 for AUC0-28days).
Patients with CRS treated with corticosteroids had higher Abecma cellular expansion levels, as measured by 2.3-fold and 2.4-fold higher median Cmax (N=60) and AUC0-28days (N=60), respectively, compared to patients who did not receive corticosteroids (N=160 for Cmax and N=158 for AUC0-28days)

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: 30 to 81 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

Bristol-Myers Squibb SA, Steinhausen

Date of revision of the text

April 2024.