swissmedic

Date: 23 January 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Carvykti

International non-proprietary name: ciltacabtagene autoleucel

Pharmaceutical form:	dispersion for infusion
Dosage strength(s):	The finished product is packaged in one infusion bag containing a dispersion for infusion of 3.2 x 10^6 to 1 x 10^8 CAR-positive viable T cells suspended in a cryopreservative solution
Route(s) of administration:	for intravenous use only
Marketing authorisation holder:	Janssen-Cilag AG
Marketing authorisation no.:	67956
Decision and decision date:	extension of therapeutic indication approved on 21 October 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.

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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) and information regarding procedure

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 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on14 May 2020.

2.2 Indication and dosage

2.2.1 Requested indication

CARVYKTI is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least one prior therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide

2.2.2 Approved indication

CARVYKTI is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and are refractory to lenalidomide.

2.2.3 Requested dosage

Summary of the requested standard 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	2 August 2023
Formal control completed	14 August 2023
List of Questions (LoQ)	12 December 2023
Response to LoQ	10 April 2024
Preliminary decision	12 June 2024
Response to preliminary decision	1 September 2024
Final decision	21 October 2024
Decision	approval

3 Medical context

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 1-2% of all cancers and 10-15% of haematological neoplasms. Incidence increases with age, and the median age at onset of MM is approximately 70 years, with approximately two thirds of patients aged older than 65 years.
MM is an incurable disease. Patients will ultimately relapse even if they achieve prolonged and deep initial responses to frontline therapy. Survival rates have improved for patients with MM over the last 5 years based on novel agents such as immunomodulatory drugs, proteasome inhibitors, chemotherapy, or novel antibodies. Nevertheless, relapse remains inevitable, indicating an ongoing need for new therapeutic approaches, particularly in lenalidomide-refractory patients in the second and later line setting.

4 Clinical aspects

4.1 Clinical pharmacology

To further substantiate the advantage of therapy with Carvykti in earlier treatment lines – beyond the approval of Carvykti for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies – the applicant submitted the results of the ongoing study MMY3002 (CARTITUDE-4).
CARTITUDE-4 is an ongoing phase 3, randomised, open-label, multicentre study in participants with relapsed and lenalidomide-refractory multiple myeloma treated with 1 to 3 prior lines of therapy to determine whether treatment with cilta-cel would provide efficacy benefit compared to investigator's choice of PVd or DPd (determined prior to screening based on participant's prior exposure to anti-myeloma therapies).
Participants randomised to the comparator arm received PVd (21-day cycles) or DPd (28-day cycles) until confirmed disease progression, death, intolerable toxicity, withdrawal of consent, or end of study.
Participants randomised to the cilta-cel arm received a sequence of apheresis, bridging therapy with PVd or DPd, a conditioning regimen, and cilta-cel infusion.

4.2 Dose finding and dose recommendation

N/A

4.3 Efficacy

The primary endpoint PFS and response-related secondary endpoints (CR or better, ORR) were determined using a validated computer algorithm. Other secondary endpoints were MRD negativity and OS. Safety data were periodically reviewed by an independent data monitoring committee (IDMC).
Data from study MMY3002 on PFS and response-related secondary endpoints with a data cut-off of 1 November 2022 were submitted as part of this submission. In the cilta-cel arm, 23.1 % of patients had previously been exposed to the anti-CD38 antibody daratumumab, which is approved as a monotherapy and combination therapy for the treatment of multiple myeloma.
At a median follow-up of 15.9 months, the median PFS was 11.8 months (95% CI: 9.7, 13.8) for the comparator arm and not evaluable (95% CI: 22.8, NE) for the cilta-cel arm. PFS results were robust across multiple sensitivity and supplementary analyses and highly consistent across all pre-specified

subgroups (including key subgroups of one prior line of therapy, ISS Stage III, high tumour burden, and high-risk cytogenetics).
Statistically significant improvement was also observed for the major secondary efficacy endpoints CR or better, ORR and MRD negativity rate (10-5). OS data were not yet mature.
Updated data on OS and PFS, with a data cut-off of May 2024 were submitted during the review.

4.4 Safety

The overall safety profile of cilta-cel in study 68284528MMY3002 (CARTITUDE-4) in Arm B (cilta-cel arm) was consistent with previous experience, showing improvements in the rates and severity of CRS, ICANS, and MNTs compared to earlier pivotal studies (MMY2001). The study included 208 participants in each arm (standard of core arm (A) & cilta-cel arm (B)). In Arm B, 176 received cilta-cel as study treatment, and 20 received cilta-cel as subsequent therapy after bridging treatment due to disease progression before cilta-cel infusion. All participants experienced at least one TEAE of any grade. Serious TEAEs occurred in 81 (38.9%) of participants in Arm A and 92 (44.2%) in Arm B, of which 70 (33.7%) in Arm A and 67 (32.2%) in Arm B were grades 3-4. Grade 3 or 4 TEAEs were reported for 94.2% and 96.6% of participants in Arm A and Arm B, respectively. TEAEs leading to death were reported in 5 participants (2.4%) in Arm A including 4 infections (including COVID-19, PML, respiratory tract infection, septic shock, 1 each (0.5%), and 1 (0.5%) pulmonary embolism, while there were 10 (4.8%) in Arm B, including 9 infections (4.3%), 7 (3.4%) COVID-19 pneumonia, 1 (0.5%) each of pneumonia, neutropenic sepsis, and respiratory failure)). CRS of any grade was observed in 76.1% of Arm B participants, with 1.1% experiencing grade 3, and no grade 4 or 5 events. CAR-T related neurotoxicity (ICANS and other neurotoxicities) was reported in 20.5%, with 8 patients (4.5%) experiencing ICANS, mostly grades 1-2, and no grade 3-5. Movement and neurocognitive (MNT) AEs of grade 1 were experienced by 1 subject (0.6%). Cytopenias were the most common TEAEs, with over 80% experiencing grades 3-4 (86.1% and 93.8% in Arm A & B, respectively), including persistent lymphopenia, neutropenia, thrombocytopenia, and anaemia. Hypogammaglobulinemia was reported in 71.6% of Arm A, and 90.9% of Arm B patients, including 1 (0.5%) in Arm A, and 15 (7.2%) in Arm B, were TEAE grade 3 respectively, with no grade 4 or 5 in either arm. TEAE of infections were reported for 148 participants (71.2%) in Arm A and 127 participants (61.1%) in Arm B, of which 47 (22.6%) participants were grades 3-4 in each arm, while 4 (1.9%) in Arm A, and 9 (4.3%) in Arm B were grade 5. Secondary primary malignancies were reported in 14 (6.7%) of subjects in Arm A and 9 (4.3%) in Arm B, including haematologic malignancies (0.0% in arm A, and 3 (1.4%) in Arm B (including 1 (0.5%) each of MDS, AML, and PTCL unspecified)) and other SPMs, some with fatal outcomes. Higher rates of CRS, HLH, DIC, and neurotoxicity were observed in the 20 early progressor patients who received cilta-cel as subsequent therapy, with some deaths related to these events.

4.5 Final clinical benefit risk assessment

A favourable benefit-risk ratio can be concluded for the use of ciltacabtagene autoleucel in the treatment of patients with r/rMM who have received at least two prior lines of therapy, including a PI, an immunomodulatory agent, and an anti-CD38 antibody, and who are refractory to lenalidomide.

5 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.

6 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Carvykti 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.

CARVYKTI®

Composition

Active substances

Ciltacabtagene autoleucel is an immunotherapy with genetically modified autologous T-cells transduced with a lentiviral vector (LVV) encoding a chimeric antigen receptor (CAR) and directed against the B-cell maturation antigen (BCMA).

Excipients

Cryostor CS5 which contains dimethyl sulfoxide.

Pharmaceutical form and active substance quantity per unit

Dispersion for infusion
The finished product is packaged in one infusion bag containing a dispersion for infusion of 3.2×10^6 to 1×10^8 CAR-positive viable T-cells suspended in a cryopreservative solution.

Indications/Uses

CARVYKTI is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma:

- who have received at least two prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and are refractory to lenalidomide.
- who have received at least three prior therapies, with at least a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Dosage/Administration

For autologous use only. For intravenous use only.
CARVYKTI must be administered in a qualified treatment centre with direct access to appropriate intensive care units. CARVYKTI therapy must be initiated under the direction and supervision of a healthcare professional experienced in the treatment of haematological malignancies and trained for the administration and management of patients treated with CARVYKTI, including the treatment of cytokine release syndrome (CRS) and neurotoxicity.

A single dose of CARVYKTI is 0.5-1.0×10^6 CAR-positive viable T-cells per kg body weight up to a maximum of 1×10^8 CAR-positive viable T-cells suspended in a patient-specific infusion bag.
In addition to T-cells, CARVYKTI may contain natural killer cells.

Usual dosage

Adults (≥18 years)

The information on pre-treatment and premedication should be taken into account (see «ADMINISTRATION SCHEDULE»).
CARVYKTI is provided as a single-dose for infusion containing a suspension of chimeric antigen receptor (CAR)-positive viable T-cells.
The dose is 0.5-1.0×10^6 CAR-positive viable T-cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T-cells per single infusion.

Patients with hepatic disorders

No studies have been conducted on the use of CARVYKTI in patients with hepatic impairment.

Patients with renal disorders

No studies have been conducted on the use of CARVYKTI in patients with renal impairment.

Elderly patients

No dose adjustment is required in patients ≥65 years of age.

Children and adolescents (17 years of age and younger)

The safety and efficacy of CARVYKTI in children aged below 18 years of age have not been established.
No data are available.

ADMINISTRATION SCHEDULE

Preparing Patient for CARVYKTI Infusion

Confirm availability of CARVYKTI prior to starting the lymphodepleting regimen.

Lymphodepleting regimen

Administer a lymphodepleting regimen of cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days. Administer CARVYKTI infusion 5 to 7 days after the start of the lymphodepleting regimen. If resolution of toxicities due to the lymphodepleting regimen to Grade 1 or lower takes more than 14 days, resulting in delays to CARVYKTI dosing, re-administration of the lymphodepleting regimen should be considered after a minimum of 21 days following the first dose of the first -lymphodepleting regimen. For dose modifications, see

corresponding manufactures prescribing information of fludarabine and cyclophosphamide, respectively.
Lymphodepleting regimen must be delayed if a patient has serious adverse reactions from preceding bridging therapies (including clinically significant active infection, cardiac toxicity, and pulmonary toxicity).

Clinical assessment prior to CARVYKTI infusion

CARVYKTI infusion should be delayed if a patient has any of the following conditions:

- clinically significant active infection or inflammatory disorders.
- Persistent serious adverse events (especially pulmonary or cardiac adverse reactions or hypotension), including those after previous chemotherapy.
- Grade ≥ 3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning except for Grade 3 nausea, vomiting, diarrhoea, or constipation. CARVYKTI infusion should be delayed until resolution of these events to Grade ≤ 1.
- Development of clinically significant worsening of multiple myeloma leading to medically significant organ dysfunction or clinical deterioration following chemotherapy for lymphodepletion.
- Active graft versus host disease.

Premedication

Administer the following pre-infusion medications to all patients (30 to 60 mins) prior to CARVYKTI infusion:

- Antipyretics (oral or intravenous paracetamol/acetaminophen 650 to 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Avoid use of prophylactic systemic corticosteroids as it may interfere with the activity of CARVYKTI.

Preparation of CARVYKTI for infusion

This medicinal product contains genetically modified human blood cells. Healthcare professionals working with CARVYKTI must take appropriate precautions (wearing gloves and protective goggles) to avoid potential transmission of infectious diseases.

Preparation of CARVYKTI for infusion

Do not thaw the product until it is ready to be used. Coordinate the timing of CARVYKTI thaw and infusion. Confirm the infusion time in advance and adjust the start time for thaw so that CARVYKTI is available for infusion when the patient is ready.

- Confirm patient identity: Prior to CARVYKTI preparation, match the patient's identity with the patient identifiers on the CARVYKTI cassette. Do not remove the CARVYKTI product bag from the cassette if the information on the patient-specific label does not match the intended patient.
- Once patient identification is confirmed, remove the CARVYKTI product bag from the cassette.

- Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing and thereafter. Do not administer if the bag is compromised and follow the local guidelines (or contact the company).
- Place the infusion bag inside a sealable plastic bag (preferably sterile) prior to thawing.
- Thaw CARVYKTI at 37°C ± 2°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Total time from start of thaw until completion of thawing should be no more than 15 minutes.
- Remove the infusion bag from the sealable plastic bag and wipe dry. 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 pre-filter into a different container, wash, spin down, and/or resuspend CARVYKTI in new media prior to infusion.
- Once thawed, the CARVYKTI infusion must be administered and completed within 2.5 hours at room/ambient temperature (20°C to 25°C).
- Do not re-freeze or refrigerate thawed product.

Administration

- Administer CARVYKTI at a certified healthcare facility.
- Prior to infusion and during the recovery period, ensure 2 doses of tocilizumab in case of a cytokine release syndrome and emergency equipment are available for use. The treatment centre must have access to an additional dose within 8 hours after administration of the last dose of tocilizumab.
- Confirm the patient's identity with the patient identifiers on the infusion bag. Do not infuse CARVYKTI if the information on the patient-specific label does not match the intended patient.
- Once thawed, administer the entire contents of the CARVYKTI bag by intravenous infusion within 2.5 hours using infusion sets fitted with an in-line filter.
- Do NOT use a leukodepleting filter.
- Gently mix the contents of the bag during CARVYKTI infusion to disperse cell clumps.
- After the entire content of the product bag is infused, flush the administration line inclusive of the in-line filter, with sodium chloride 9 mg/mL (0.9%) solution (normal saline) to ensure all product is delivered.

For special precautions for disposal, see *Instructions for handling.*

Monitoring after infusion

Monitor patients daily for 14 days after the CARVYKTI infusion at a certified healthcare facility and then periodically, at the decision of the doctor, for an additional two weeks after CARVYKTI infusion for signs and symptoms of cytokine release syndrome (CRS), neurologic events and other toxicities (see *Warnings and Precautions*).

Instruct patients to remain within proximity (maximum of 2 hours away) of a certified healthcare facility for at least 4 weeks following infusion.

Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify CRS based on clinical presentation (see *Warnings and Precautions*)
If CRS is suspected, manage according to the recommendations in Table 1. Administer supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) as appropriate. Consider laboratory testing to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function. Other monoclonal antibodies targeting cytokines (for example, anti-IL1 and/or anti-TNFα) or therapy directed at reduction and elimination of CAR-T-cells may be considered for patients who develop high grade CRS and hemophagocytic lymphohistiocytosis (HLH) that remains severe or life-threatening following prior administration of tocilizumab and corticosteroids.
If concurrent neurologic toxicity is suspected during CRS, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2,
- Tocilizumab according to the CRS grade in Table 1,
- Anti-seizure medication according to the neurologic toxicity in Table 2

Table 1: CRS Grading and Management Guidance

<table>
<tr><th>CRS Grade[a]</th><th>Tocilizumab[b]</th><th>Corticosteroids[f]</th></tr>
<tr><td>Grade 1
Temperature ≥ 38°C[c]</td><td>Tocilizumab 8 mg/kg intravenously (IV) over 1 hour (not to exceed 800 mg) may be considered</td><td>N/A</td></tr>
<tr><td>Grade 2
Symptoms require and respond to moderate intervention.

Temperature ≥ 38°C[c] with:

Hypotension not requiring vasopressors,
and/or,

Hypoxia requiring oxygen via cannula[e] or blow-by,</td><td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).

Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids up to 1 liter or increasing supplemental oxygen.</td><td>Consider methylprednisolone 1 mg/kg intravenously (IV) twice daily or dexamethasone (e.g., 10 mg IV every 6 hours).</td></tr>
<tr><td></td><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose of dexamethasone (20 mg IV every 6 to 12 hours).</td></tr>
</table>

<table>
<tr><td>or,

Grade 2 organ toxicity.</td><td colspan="2">After 2 doses of tocilizumab, consider alternative anti-cytokine agents.[d]

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.

Temperature ≥38°C[c] with:

Hypotension requiring one vasopressor with or without vasopressin,
and/or,

Hypoxia requiring oxygen via high-flow nasal cannula[e], facemask, non-rebreather mask, or Venturi mask,

or,

Grade 3 organ toxicity or Grade 4 transaminitis.</td><td>Per Grade 2</td><td>Administer methylprednisolone 1 mg/kg IV twice daily or dexamethasone (e.g., 10 mg IV every 6 hours).</td></tr>
<tr><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose 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 IV every 12 hours.

After 2 doses of tocilizumab, consider alternative anti-cytokine agents.[d]

Do not exceed 3 doses of 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).

Temperature ≥38°C[c] with:

Hypotension requiring multiple vasopressors (excluding vasopressin),
and/or,

Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation),</td><td>Per Grade 2</td><td>Administer dexamethasone 20 mg IV every 6 hours.</td></tr>
<tr><td colspan="2">After 2 doses of tocilizumab, consider alternative anti-cytokine agents[d]. 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 IV, repeat every 24 hours if needed; taper as clinically indicated) or other immunosuppressants (e.g. other anti-T cell therapies).</td></tr>
</table>

or, Grade 4 organ toxicity (excluding transaminitis).	

[a] Based on ASTCT 2019 grading system (Lee et.al, 2019), modified to include organ toxicity.

[b] Refer to tocilizumab prescribing information for details.

[c] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anti-cytokine therapy (e.g., tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause.

[d] Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.

[e] Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.

[f] Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days.

Neurologic Toxicities

Neurological toxicities, which may be serious or life-threatening, have occurred after treatment with CARVYKTI, including concurrently with CRS, after resolution of CRS and without CRS (see section «Adverse Effects – Description of selected adverse reactions – Neurological toxicities»).
General management for neurologic toxicity e.g., Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) is summarized in Table 2.
At the first sign of neurologic toxicity, including ICANS, other causes of neurological symptoms should be excluded. Patients should be monitored for signs or symptoms of neurological toxicities for at least 4 weeks after infusion and treated immediately. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities (see «Warnings and Precautions»).

If concurrent CRS is suspected during the neurologic toxicity event, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2,
- Tocilizumab according to CRS grade in Table 1,
- Anti-seizure medication according to neurologic toxicity in Table 2.

Patients should be instructed to seek immediate medical attention if signs or symptoms of neurological toxicity occur at any time.

Table 2: Guideline for management of ICANS

ICANS Grade[a]	**Corticosteroids**
Grade 1 ICE score 7-9[b] or depressed level of consciousness: awakens spontaneously.	Consider dexamethasone[c] 10 mg intravenously every 6 to 12 hours for 2 to 3 days Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.
Grade 2	

ICE score-3-6[b] or depressed level of consciousness: awakens to voice	Administer dexamethasone[c] 10 mg intravenously every 6 hours for 2-3 days, or longer for persistent symptoms. Consider steroid taper if total corticosteroid exposure is greater than 3 days. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.
Grade 3 ICE score-0-2[b] (If ICE score is 0, but the patient is arousable (e.g. awake with global aphasia) and able to perform assessment) or depressed level of consciousness: awakens only to tactile stimulus, or seizures, either: any clinical seizure, focal or generalized, that resolves rapidly, or non-convulsive seizures on EEG that resolve with intervention, or raised intracranial pressure (ICP): focal/local edema on neuroimaging[d].	Administer dexamethasone[c]10 mg-20 mg intravenously every 6 hours. If no improvement after 48 hours or worsening of neurologic toxicity, escalate dexamethasone[c] dose to at least 20 mg intravenously every 6 hours; taper within 7 days, OR escalate to high-dose methylprednisolone (1 g/day, repeat every 24 hours if needed; taper as clinically indicated). Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.
Grade 4 ICE score-0[b] (Patient is unarousable and unable to perform ICE assessment) or depressed level of consciousness either: patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or stupor or coma, or seizures, either: life-threatening prolonged seizure (>5 min), or repetitive clinical or electrical seizures without return to baseline in between, or motor findings[e]: deep focal motor weakness such as hemiparesis or paraparesis,	Administer dexamethasone[c] 10 mg-20 mg intravenously every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g/day, repeated every 24 hours if needed; taper as clinically indicated). Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. If raised ICP/cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g/day, repeat every 24 hours if needed; taper as clinically indicated), and consider neurology and/or neurosurgery consultation

or raised ICP / cerebral edema, with signs/symptoms such as: diffuse cerebral edema on neuroimaging, or decerebrate or decorticate posturing, or cranial nerve VI palsy, or papilledema, or Cushing's triad	

Note: ICANS grade and management is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema), not attributable to any other cause.

[a] ASTCT 2019 criteria for grading Neurologic Toxicity (Lee et.al, 2019),

[b] If patient is arousable and able to perform Immune Effector Cell-associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

[c] All references to dexamethasone administration are dexamethasone or equivalent

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

[e] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

Mode of administration

For intravenous use only.

Contraindications

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

Warnings and precautions

General

Patients with active or prior history of significant central nervous system (CNS) disease or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Rapidly progressing disease

When considering patients for CARVYKTI treatment, physicians should assess the impact of rapidly progressing disease on the ability of patients to receive CAR-T infusion. Some patients may not benefit from CARVYKTI treatment due to potential increased risk of early death if disease progresses rapidly during bridging therapy.

Cytokine Release Syndrome (CSR)

Cytokine release syndrome, including fatal or life-threatening reactions, can occur after CARVYKTI infusion.
In Study MMY2001, 95% of patients experienced CRS after CARVYKTI infusion with majority of these being Grade 1 or Grade 2 (90%) (see «Undesirable effects»). The median time from CARVYKTI infusion (Day 1) to onset of CRS was 7 days (range of 1 to 12 days). Approximately 90% of patients experienced onset of CRS after Day 3 of receiving the CARVYKTI infusion.
In almost all cases, duration of CRS ranged from 1 to 14 days (median duration 4 days), with 88% of patients having a CRS duration of ≤ 7 days.
In Study MMY3002, 151/196 (77%) experienced CRS after CARVYKTI infusion with majority of these being Grade 1 or Grade 2 (see «Undesirable effects»). The median time from CARVYKTI infusion (Day 1) to onset of CRS was 8 days (range of 1 to 23 days). In all cases, duration of CRS ranged from 1 to 17 days (median duration 3 days), with 89% of patients having a CRS duration of ≤ 7 days.
Clinical signs and symptoms of CRS may include but are not limited to fever (with or without rigors), chills, hypotension, hypoxia, and elevated liver enzymes. Risk factors for severe CRS include high pre-infusion tumour burden, active infection and early onset of fever or persistent fever after 24 hours of symptomatic treatment. Infections may also occur concurrently with CRS and may increase the risk of a fatal event. Potentially life-threatening complications of CRS may include cardiac dysfunction, neurologic toxicity, and HLH. CRS has been reported to be associated with findings of haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) and the physiology of the syndromes may overlap. Patients who develop HLH may have an increased risk of severe bleeding. Patients should be closely monitored for signs or symptoms of these events, including fever and treatment should be according to institutional standards.
Appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any active infections should be ensured prior to CARVYKTI infusion.
Ensure that at least two doses of tocilizumab are available prior to infusion of CARVYKTI. Monitor patients for signs and symptoms of CRS daily for 14 days after the CARVYKTI infusion at a certified healthcare facility and then periodically for an additional two weeks after CARVYKTI infusion.
Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated in Table 1 (see «Dosage/Administration»).
Evaluation for HLH should be considered in patients with severe or unresponsive CRS. For patients with high pre-infusion tumour burden, early onset of fever, or persistent fever after 24 hours, early tocilizumab should be considered. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), should be avoided during CRS. Consider reducing

baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumour burden.

Neurologic toxicities

Neurologic toxicities occur frequently following treatment with CARVYKTI and can be fatal or life-threatening (see «Undesirable effects»). Neurologic toxicities included ICANS, movement and neurocognitive toxicity with signs and symptoms of parkinsonism, Guillain-Barré Syndrome, peripheral neuropathies and cranial nerve palsies. Counsel patients on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Instruct patients to seek immediate medical attention for further assessment and management if signs or symptoms of any of these neurologic toxicities occur at any time.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

Patients receiving CARVYKTI may experience fatal or life-threatening ICANS following treatment with CARVYKTI, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state.

Consider reducing baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumor burden which may mitigate the risk of developing neurologic toxicity (see «Undesirable effects»). Monitor patients for signs or symptoms of ICANS for four weeks after infusion. At the first sign of ICANS, immediately evaluate patient for hospitalization and institute treatment with supportive care as indicated in Table 2 (see «Dosage/Administration»). Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening.

Movement and Neurocognitive Toxicity with Signs and Symptoms of Parkinsonism

Neurologic toxicity of movement and neurocognitive toxicity with signs and symptoms of parkinsonism has been reported in trials of CARVYKTI. A cluster of symptoms with variable onset spanning more than one symptom domain was observed, including movement (e.g., micrographia, tremor, bradykinesia, rigidity, stooped posture, shuffling gait), cognitive (e.g., memory loss, disturbance in attention, confusion), and personality change (e.g., reduced facial expression, flat affect, masked facies, apathy), often with subtle onset (e.g., micrographia, flat affect), that in some patients progressed to an inability to work or care for oneself. Most of these patients presented a combination of two or more factors such as high tumor burden (bone marrow plasma cell ≥80% or serum M-spike ≥ 5 g/dL or serum free light chain ≥ 5000 mg/L), prior Grade 2 or higher CRS, prior ICANS, and high CAR-T-cell expansion and persistence. Treatment with levodopa/carbidopa (n=4), was not effective in improving symptomatology in these patients.

Monitor patients for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures.

Guillain-Barré Syndrome

Guillain-Barré Syndrome (GBS) has been reported after treatment with CARVYKTI. Symptoms reported include those consistent with Miller-Fisher variant of GBS, motor weakness, speech disturbances, and polyradiculoneuritis (see Adverse Reactions).
Monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment with intravenous immunoglobulin (IVIG) and escalate to plasmapheresis, depending on toxicity severity.

Peripheral Neuropathy

Occurrence of peripheral neuropathy, including sensory, motor, or sensorimotor, have been reported in trials of CARVYKTI.
Monitor patients for signs and symptoms of peripheral neuropathies. Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Cranial Nerve Palsies

Occurrence of 7th, 3rd, 5th, and 6th cranial nerve palsy, some of which were bilateral, worsening of cranial nerve palsy after improvement, and occurrence of peripheral neuropathy in patients with cranial nerve palsy have been reported in trials of CARVYKTI.
Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Prolonged and Recurrent Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and CARVYKTI infusion and should be managed according to local guidelines. In trials of CARVYKTI, nearly all patients had one or more Grade 3 or 4 cytopenic adverse reactions. Most patients had a median time from infusion to first onset of Grade 3 or 4 cytopenia of less than two weeks with the majority of patients recovering to ≤Grade 2 by Day 30 (see «Undesirable effects»).
Monitor blood counts after CARVYKTI infusion. For thrombocytopenia consider supportive care with transfusions. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after CARVYKTI or until CRS has resolved.

Serious Infections and febrile neutropenia

Serious infections, including life-threatening or fatal infections, occurred in patients after CARVYKTI infusion (see «Undesirable effects»).

Monitor patients for signs and symptoms of infection, employ surveillance testing prior to and during treatment with CARVYKTI and treat patients appropriately. Administer prophylactic antimicrobials according to local guidelines. Infections are known to complicate the course and management of concurrent CRS. Patients with clinically significant active infection should not start CARVYKTI treatment until the infection is controlled.
In the event of febrile neutropenia, infection should be evaluated and managed appropriately with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.
Patients treated with CARVYKTI may be at an increased risk of severe/fatal COVID-19 infections. Counsel patients on the importance of prevention measures.

Viral reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia.
There is currently no experience with manufacturing CARVYKTI for patients testing positive for HIV, active HBV, or active HCV. Screening for HBV, HCV, HIV and other infectious agents must be performed in accordance with local clinical guidelines before collection of cells for manufacturing.

Hypogammaglobulinemia

Hypogammaglobulinemia may occur in patients receiving CARVYKTI.
Monitor immunoglobulin levels after treatment with CARVYKTI and administer IVIG for IgG<400 mg/dL. Manage per local clinical guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection.

Live vaccines

The safety of immunization with live viral vaccines during or following CARVYKTI 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 CARVYKTI treatment, and until immune recovery following treatment with CARVYKTI.

Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies. A case of CAR positive T cell lymphoma has been reported in an ongoing study. Monitor life-long for secondary malignancies. In the event that a secondary hematologic malignancy occurs, contact the company for reporting and to obtain instructions on patient samples to collect for testing. In patients with HIV infection, contact the company for the testing of all types of secondary malignancy, including those of non T cell origin.

Hypersensitivity

Allergic reactions may occur with infusion of CARVYKTI. Serious hypersensitivity reactions, including anaphylaxis, may also be due to the dimethyl sulfoxide (DMSO), or residual kanamycin in CARVYKTI.

Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction. Treat promptly and manage patients appropriately according to the severity of the hypersensitivity reaction.

Blood, organ, tissue and cell donation

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

Interactions

No interaction studies have been performed with CARVYKTI.
HIV and the lentivirus used to make CARVYKTI have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests (NATs) may yield false-positive results in patients who have received CARVYKTI.

Pregnancy, lactation

Pregnancy

There are no available data on the use of CARVYKTI in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with CARVYKTI. It is not known whether CARVYKTI has the potential to be transferred to the foetus and cause foetal toxicity. Therefore, CARVYKTI is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised there may be risks to the foetus.
Pregnancy after CARVYKTI therapy should be discussed with the treating physician.
Pregnant women who have received CARVYKTI may have hypogammaglobulinemia. Assessment of immunoglobulin levels in new-borns of mothers treated with CARVYKTI should be considered.

Females and males of reproductive potential

Pregnancy testing

Pregnancy status for females of child-bearing age should be verified prior to starting treatment with CARVYKTI.

Contraception

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with CARVYKTI.
In clinical trials, female patients of childbearing potential were advised to practice a highly effective method of contraception, and male patients with partners of childbearing potential or whose partners were pregnant, were instructed to use a barrier method of contraception until one year after the patient has received CARVYKTI infusion.
See the prescribing information for lymphodepleting chemotherapy for information on the need for contraception in patients who receive the lymphodepleting chemotherapy.

Breast-feeding

There is no information regarding the presence of CARVYKTI 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 CARVYKTI and any potential adverse effects on the breastfed infant from CARVYKTI or from the underlying maternal condition.

Fertility

There are no data on the effect of CARVYKTI on fertility. Effects of CARVYKTI on male and female fertility have not been evaluated in animal studies.

Effects on ability to drive and use machines

Due to the potential for neurologic events, patients receiving CARVYKTI are at risk for altered or decreased consciousness or coordination in the 8 weeks following CARVYKTI infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery during this initial period and in the event of new onset of any neurological symptoms.

Undesirable effects

Summary of the safety profile

The safety data described in this section reflect the exposure to CARVYKTI in three open label clinical trials in which 396 adult patients with multiple myeloma received CARVYKTI infusion (see «Clinical Efficacy»): Study MMY2001 (N=106), which included patients from the main Phase 1b/2 cohort (United States; n = 97; with a median duration of follow-up of 27.7 months)) and an additional cohort (Japan; n = 9), Phase 2Study MMY2003 (n = 94) and Phase 3 Study MMY3002 (N=196).
The most common CARVYKTI adverse reactions (≥ 20%) were neutropenia, pyrexia , CRS, thrombocytopenia, anemia, musculoskeletal pain, fatigue, lymphopenia, leukopenia, hypotension, diarrhea, upper respiratory tract infection, hypogammaglobulinemia, transaminase elevation, headache, nausea, and cough.
Serious adverse reactions occurred in 41% of patients; serious adverse reactions reported in ≥ 5% of patients were CRS (11%), pneumonia (7%) and sepsis (5%).
The most common (≥ 10%) Grade ≥ 3 non-haematological adverse reaction was transaminase elevation (11%).
The most frequent (≥ 25%) Grade ≥ 3 haematological abnormalities were neutropenia (88%), thrombocytopenia (44%), anemia (44%), lymphopenia (33%), and leukopenia (32%).

Below are the adverse reactions that occurred in patients receiving CARVYKTI summarised .
Within each MedDRA system organ class, the adverse reactions are ranked by frequency, with the

most frequent reactions first, using the following convention: 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); not known (cannot be estimated from the available data).

Table 3: Adverse reactions in patients with multiple myeloma treated with CARVYKTI (N = 396)

System Organ Class	Frequency	Adverse Reaction	Incidence (%)	
			All Grades	Grade ≥ 3
Infections and infestations	Very common	Upper respiratory tract infection[1]	30	2
		Viral infection[2]	17	4
		Bacterial infection[3#]	13	5
		Pneumonia[4#]	12	9
	Common	Sepsis[5#]	9	7
		Gastroenteritis[6]	6	1
		Urinary tract infection[7]	5	1
		Fungal infection[8]	3	<1
Blood and lymphatic system disorders	Very common	Neutropenia	89	88
		Thrombocytopenia	60	44
		Anemia[9]	60	44
		Lymphopenia	34	33
		Leukopenia	33	32
		Coagulopathy[10]	12	3
	Common	Febrile neutropenia	8	8
		Lymphocytosis[11]	3	1
Immune system disorders	Very common	Cytokine release syndrome[#]	83	4
		Hypogammaglobulinemia[12]	29	5
	Common	Hemophagocytic lymphohistiocytosis[#]	3	2
Metabolism and nutrition disorders	Very common	Hypophosphatemia	17	4
		Hypokalemia	17	2
		Hypocalcemia	16	3
		Decreased appetite	15	1
		Hypomagnesemia	12	<1
		Hypoalbuminemia	11	<1
		Hyponatremia	10	2
		Hyperferritinemia[13]	10	2
Psychiatric disorders	Common	Delirium[14]	3	<1
		Personality changes[15]	3	1
Nervous system disorders	Very common	Headache	24	0
		Motor dysfunction[16]	13	2

		Dizziness[17]	13	1
		Immune effector cell-associated neurotoxicity syndrome[#]	11	2
		Encephalopathy[18#]	10	2
		Sleep disorders[19]	10	1
	Common	Cranial nerve palsies[20]	7	1
		Neuropathy peripheral[21]	7	1
		Aphasia[22]	5	<1
		Tremor[23]	5	<1
		Ataxia[24]	4	<1
		Neurotoxicity[#]	1	1
		Paresis[25]	1	<1
	Uncommon	Guillain-Barre syndrome	<1	<1
Cardiac disorders	Very common	Tachycardia[26]	13	1
	Common	Cardiac arrhythmias[27]	4	2
Vascular disorders	Very common	Hypotension[28]	33	6
		Hypertension	11	4
		Hemorrhage[29#]	10	2
	Common	Thrombosis[30]	4	1
		Capillary leak syndrome	1	0
Respiratory, thoracic and mediastinal disorders	Very common	Cough[31]	21	0
		Dyspnea[32#]	14	3
		Hypoxia[33]	13	4
Gastrointestinal disorders	Very common	Diarrhea[34]	31	3
		Nausea	23	<1
		Constipation	15	0
		Vomiting	12	0
	Common	Abdominal pain[35]	8	0
Hepatobiliary disorders	Common	Hyperbilirubinemia	3	1
Skin and subcutaneous tissue disorders	Common	Rash[36]	9	0
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[37]	38	3
Renal and urinary disorders	Common	Renal failure[38]	6	4
General disorders and administration site conditions	Very common	Pyrexia	84	6
		Fatigue[39]	35	4
		Edema[40]	16	1
		Chills	14	0

		Pain[41]	11	1
Investigations	Very common	Transaminase elevation[42]	25	11
		Gamma-glutamyltransferase increased	10	6
	Common	Blood alkaline phosphatase increased	8	3
		C-reactive protein increased	7	1

Adverse events are reported using MedDRA version 25.0

[#] Contains fatal event/s.

[1] Upper respiratory tract infection includes bronchitis, nasal congestion, nasopharyngitis, pharyngeal inflammation, pharyngitis, respiratory tract congestion, respiratory tract infection, rhinitis, rhinorrhoea, rhinovirus infection, sinus congestion, sinusitis, upper respiratory tract infection, viral pharyngitis, and viral upper respiratory tract infection.

[2] Viral infection includes adenovirus infection, adenovirus test positive, asymptomatic covid-19, covid-19, coronavirus infection, cytomegalovirus infection, cytomegalovirus infection reactivation, cytomegalovirus syndrome, cytomegalovirus viraemia, hepatitis b reactivation, herpes simplex reactivation, herpes virus infection, herpes zoster, herpes zoster disseminated, human herpesvirus 6 infection, human rhinovirus test positive, influenza, lymphadenitis viral, metapneumovirus infection, oral herpes, parainfluenzae virus infection, parvovirus b19 infection, parvovirus infection, respiratory syncytial virus infection, respiratory tract infection viral, and rotavirus infection.

[3] Bacterial infection includes abscess limb, bordetella infection, breast cellulitis, bronchitis bacterial, campylobacter infection, catheter site infection, cellulitis, chalazion, citrobacter infection, clostridium difficile colitis, clostridium difficile infection, device related infection, enterococcal infection, escherichia infection, folliculitis, hordeolum, klebsiella infection, lung abscess, perichondritis, perirectal abscess, post procedural infection, pyelonephritis acute, salmonellosis, sinusitis bacterial, skin infection, soft tissue infection, staphylococcal infection, superinfection bacterial, tooth infection, vascular access site infection, and vascular device infection.

[4] Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, covid-19 pneumonia, lower respiratory tract infection, lung infiltration, metapneumovirus pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia moraxella, pneumonia pseudomonal, pneumonia streptococcal, and pneumonia viral.

[5] Sepsis includes bacteremia, bacterial sepsis, candida sepsis, device related bacteremia, enterococcal bacteremia, haemophilus sepsis, neutropenic sepsis, pseudomonal bacteremia, pseudomonal sepsis, sepsis, septic shock, staphylococcal bacteremia, streptococcal sepsis, systemic candida, and urosepsis.

[6] Gastroenteritis includes enterocolitis bacterial, enterocolitis infectious, enterocolitis viral, enterovirus infection, gastroenteritis, gastroenteritis cryptosporidial, gastroenteritis rotavirus, gastroenteritis salmonella, gastroenteritis viral, gastrointestinal infection, and large intestine infection.

[7] Urinary tract infection includes cystitis, escherichia urinary tract infection, urinary tract infection, urinary tract infection bacterial, and urinary tract infection viral.

[8] Fungal infection includes candida infection, cerebral aspergillosis, oral candidiasis, sinusitis aspergillus, tongue fungal infection, and vulvovaginal candidiasis.

[9] Anemia includes anemia and iron deficiency anemia.

[10] Coagulopathy includes activated partial thromboplastin time prolonged, blood fibrinogen decreased, coagulation test abnormal, coagulopathy, disseminated intravascular coagulation, hypofibrinogenemia, international normalised ratio increased, prothrombin level increased, and prothrombin time prolonged.

[11] Lymphocytosis includes lymphocyte count increased, and lymphocytosis.

[12] Hypogammaglobulinaemia includes blood immunoglobulin G decreased, and hypogammaglobulinaemia.

[13] Hyperferritinemia includes hyperferritinaemia, and serum ferritin increased.

[14] Delirium includes agitation, delirium, disorientation, euphoric mood, hallucination, irritability, and restlessness.

[15] Personality changes includes flat affect, indifference, personality change, and reduced facial expression.

[16] Motor dysfunction includes agraphia, dysgraphia, eyelid ptosis, micrographia, motor dysfunction, muscle rigidity, muscle spasms, muscle tightness, muscular weakness, myoclonus, and parkinsonism.

[17] Dizziness includes dizziness, dizziness exertional, dizziness postural, presyncope, syncope, and vertigo.

[18] Encephalopathy includes amnesia, bradyphrenia, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, lethargy, memory impairment, mental impairment, mental status changes, psychomotor retardation, and slow response to stimuli.

[19] Sleep disorders includes hypersomnia, insomnia, sleep disorder, and somnolence.

[20] Cranial nerve palsies include Bell`s palsy, cranial nerve paralysis, facial nerve disorder, facial paralysis, facial paresis, iiird nerve paralysis, trigeminal palsy, and VIth nerve paralysis.

[21] Neuropathy peripheral includes neropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

[22] Aphasia includes aphasia, dysarthria, slow speech, and speech disorder.

[23] Tremor includes resting tremor and tremor.

[24] Ataxia includes ataxia, balance disorder, dysmetria, and gait disturbance.

[25] Paresis includes hemiparesis, paresis, and peroneal nerve palsy.

[26] Tachycardia includes sinus tachycardia, and tachycardia.

[27] Cardiac arrhythmias include atrial fibrillation, atrial flutter, atrioventricular block second degree, supraventricular tachycardia, ventricular extrasystoles, and ventricular tachycardia.

[28] Hypotension includes hypotension and orthostatic hypotension.

[29] Hemorrhage includes catheter site haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, contusion, epistaxis, eye contusion, haematemesis, haematochezia, haematoma, haematuria, haemoptysis, lower gastrointestinal haemorrhage, pulmonary haemorrhage, retinal haemorrhage, retroperitoneal haemorrhage, subarachnoid haemorrhage, and subdural haematoma.

[30] Thrombosis includes deep vein thrombosis, device related thrombosis, embolism, jugular vein thrombosis, pulmonary embolism, and venous thrombosis limb.

[31] Cough includes cough, productive cough, and upper-airway cough syndrome.

[32] Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure, tachypnoea, and wheezing.

[33] Hypoxia includes hypoxia and oxygen saturation decreased.

[34] Diarrhoea includes colitis and diarrhoea.

[35] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and dyspepsia.

[36] Rash includes bullous haemorrhagic dermatosis, dermatitis exfoliative generalised, dermatitis psoriasiform, drug eruption, erythema, pityriasis lichenoides et varioliformis acuta, rash, rash erythematous, rash maculo-papular, rash pustular, rash vesicular, and urticaria.

[37] Musculoskeletal pain includes arthralgia, back pain, bone pain, joint stiffness, muscle strain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, myositis, neck pain, non-cardiac chest pain, osteoarthritis, pain in extremity, rotator cuff syndrome, spinal pain, and tendonitis.

[38] Renal failure includes acute kidney injury, blood creatinine increased, chronic kidney disease, renal failure, and renal impairment.

[39] Fatigue includes asthenia, fatigue, and malaise.

[40] Oedema includes face oedema, fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral, palatal oedema, periorbital oedema, peripheral swelling, pulmonary congestion, and pulmonary oedema.

[41] Pain includes anorectal discomfort, catheter site pain, ear pain, eye pain, flank pain, fracture pain, inflammatory pain, odynophagia, pain, pain in jaw, pain of skin, pelvic pain, proctalgia, rhinalgia, sacral pain, sinus pain, testicular pain, and toothache.

[42] Transaminase elevation includes alanine aminotransferase increased, and aspartate aminotransferase increased.

Of the 196 patients in Study MMY3002, 20 patients who had higher risk disease progressed early and rapidly on bridging therapy prior to infusion with CARVYKTI and received CARVYKTI as subsequent therapy (see Clinical Studies). In these patients, MNT was reported in one patient (5%) and was mild in severity (Grade 1 or 2). CRS was reported at a higher rate for Grade 3 and Grade 4 (25%), including events of CRS complicated by HLH (10%) or DIC (10%). ICANS was reported at a higher rate (35%) and severity (10%) for Grade 3. Five patients died of fatal events related to CARVYKTI (2 due to hemorrhage in the context of HLH or DIC and 3 due to fatal infections).

Description of selected adverse reactions

Cytokine release syndrome

In the pooled studies (N=396), CRS was reported in 83% of patients (n=330); 79% (n=314) CRS events were Grade 1 or Grade 2, 4% (n=15) Grade 3 or 4, and <1% (n=1) was Grade 5. Ninety-eight percent of patients (n=323) recovered from CRS.
The duration of CRS was ≤18 days for all but one patient who had a duration of CRS of 97 days complicated by secondary HLH with a subsequent fatal outcome. The most frequent (≥10%) signs or symptoms associated with CRS included pyrexia (81%), hypotension (28%), Aspartate aminotransferase (AST) increased (12%) and hypoxia (10%). See «Warnings and Precautions» for monitoring and management guidance.

Neurologic toxicities

In the pooled studies (N=396), neurologic toxicity occurred in 23% (n=89) of patients with 5% (n=21) being Grade 3 or Grade 4 and 1% Grade 5 (n=3; one due to ICANS, one due to movement and neurocognitive toxicity with signs and symptoms of parkinsonism, and one due to encephalopathy). In addition, eleven patients had fatal outcomes with ongoing neurologic toxicity at the time of death; ten deaths were due to infection. Including two deaths in patients with ongoing signs and symptoms of parkinsonism, as discussed below, and one death was due to respiratory failure. See «Warnings and Precautions» for monitoring and management guidance.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

In the pooled studies (N=396), ICANS occurred in 11% of patients (n=45), with 2% (n=7) experiencing Grade 3 or 4 ICANS and <1% (n = 1) Grade 5 ICANS. Symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state. The median time from CARVYKTI infusion to first onset of ICANS was 8.0 days (range: 2 to 15 days, except for 1 patient with onset at 26 days) and the median duration was 3 days (range 1 to 29 days, except for 1 patient who had a subsequent fatal outcome at 40 days).

Movement and Neurocognitive Toxicity with Signs and Symptoms of Parkinsonism

Of the 89 patients in the pooled studies (N=396) experiencing any neurotoxicity, nine male patients had neurologic toxicity with several signs and symptoms of parkinsonism, distinct from ICANS. The maximum toxicity grades of parkinsonism were: Grade 1 (n=1) Grade 2 (n=2), Grade 3 (n=6). The median onset of parkinsonism was 38 days (range: 14 to 914 days) from infusion of CARVYKTI. One patient (Grade 3) died of neurologic toxicity with ongoing parkinsonism 247 days after administration of CARVYKTI, and two patients (Grade 2 and Grade 3) with ongoing parkinsonism died of infectious causes 162 and 119 days after administration of CARVYKTI. One patient recovered (Grade 3). In the remaining 5 patients, symptoms of parkinsonism were ongoing up to 996 days after administration of

CARVYKTI. All 9 patients had a history of prior CRS (n=1 Grade 1; n=6 Grade 2; n=1 Grade 3; n=1 Grade 4), while 6 of 9 patients had prior ICANS (n=5 Grade 1; n=1 Grade 3).

Guillain-Barré Syndrome

In the pooled studies (N=396), one patient was reported to have GBS after treatment with CARVYKTI. Although GBS symptoms improved after receiving treatment with steroids and IVIG, the patient died 139 days after administration of CARVYKTI due to encephalopathy post gastroenteritis with ongoing GBS symptoms.

Peripheral Neuropathy

In the pooled studies (N=396), 27 patients developed peripheral neuropathy, presenting as sensory, motor, or sensorimotor neuropathies. Median time of onset of symptoms was 57 days (range: 1 to 914 days), median duration of peripheral neuropathies was 140 days (range: 1 to 766 days) including those with ongoing neuropathy. Of these 27 patients, 5 experienced Grade 3 or 4 peripheral neuropathy (which resolved in 1 patient with no treatment reported, and was ongoing in the other 4 patients, including one patient who improved after treatment with dexamethasone); of the remaining 22 with ≤ Grade 2 peripheral neuropathy, peripheral neuropathy resolved with no treatment reported in 6 patients, and following treatment with duloxetine in 2 patient, and was ongoing in the other 10 patients.

Cranial Nerve Palsies

In the pooled studies (N=396), 27 patients experienced cranial nerve palsies. Median time to onset was 22 days (range: 17 to 101 days) following infusion of CARVYKTI, and median time to resolution was 56 days (range: 1 to 209 days) following onset of symptoms.

Prolonged and recurrent Cytopenias

In the pooled studies (N=396), Grade 3 or 4 cytopenias at Day 1 after dosing, not resolved to Grade 2 or lower by Day 30 following CARVYKTI infusion, included thrombocytopenia (33%), neutropenia (29%) lymphopenia (25%) and anemia (3%). After Day 60 following CARVYKTI, 23%, 21%, 7% and 4% of patients had an occurrence of Grade 3 or 4 lymphopenia, neutropenia, anemia and thrombocytopenia respectively, after initial recovery of their Grade 3 or 4 cytopenia.

Table 4 lists the incidences of Grade 3 or 4 cytopenias occurring after dosing not resolved to Grade 2 or lower by Day 30 and Day 60 respectively.

Table 4: Incidences of prolonged and recurrent cytopenias following treatment with CARVYKTI in the pooled studies (N=396)

	Grade 3/4 (%) after Day 1 Dosing	Initial Grade 3/4 (%), not Recovered[a] to ≤ Grade 2 by Day 30	Initial Grade 3/4 (%), not Recovered[a] to ≤ Grade 2 by Day 60	Occurrence of Grade 3/4 (%) > Day 60 (after Initial Recovery[a] of Grade 3/4)
Thrombocytopenia	191 (48%)	132 (33%)	76 (19%)	14 (4%)
Neutropenia	381 (96%)	114 (29%)	44 (11%)	81 (21%)
Lymphopenia	391 (99%)	98 (25%)	46 (12%)	90 (23%)
Anemia	180 (46%)	11 (3%)	12 (3%)	26 (7%)

[a] The laboratory result with the worst toxicity grade will be used for a calendar day. Recovery definition: must have 2 consecutive Grade ≤2 results on different days if recovery period ≤10 days.

Notes: Lab results assessed after Day 1 until Day 100 for MMY2001 and MMY2003 or Day 112 for MMY3002, or the start of subsequent therapy, whichever occurs first, are included in the analysis.

Thrombocytopenia: Grade 3/4 – Platelets count <50000 cells/µL.

Neutropenia: Grade 3/4 - Neutrophil count <1000 cells/µL.

Lymphopenia: Grade 3/4 - Lymphocytes count <0.5 x 10^9 cells/L.

Anemia: Grade 3 – hemoglobin <8g/dL. Grade 4 not defined by laboratory count per NCI-CTCAE v5.

Percentages are based on the number of treated subjects.

Serious Infections

Infections occurred in 206 patients (52%) in the pooled studies (N=396); 66 (17%) experienced Grade 3 or Grade 4 infections, and fatal infections (COVID-19 pneumonia, pneumonia, sepsis, Clostridium difficile colitis, septic shock, bronchopulmonary aspergillosis, pseudomonal sepsis, neutropenic sepsis, and lung abscess) occurred in 17 patients (4%). The most frequently reported (≥2%) Grade 3 or higher infections were pneumonia, COVID-19 pneumonia, and sepsis. Febrile neutropenia was observed in 6% of patients with 2% experiencing serious febrile neutropenia. See «Warnings and Precautions» for monitoring and management guidance.

Hypogammaglobulinemia

In the pooled studies (N=396) hypogammaglobulinemia was reported in 30% of patients with 5% of patients experiencing Grade 3 hypogammaglobulinemia; laboratory IgG levels fell below 500 mg/dL after infusion in 91% (359/396) of patients treated with CARVYKTI. Fifty-three percent of patients received IVIG post CARVYKTI for either an adverse reaction or prophylaxis. See «Warnings and Precautions» for monitoring and management guidance.

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 EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There are no data regarding the signs or sequelae of overdose with CARVYKTI.

Properties/Effects

ATC code

L01XL05

Mechanism of action

CARVYKTI is a BCMA-directed, genetically modified autologous T-cell immunotherapy, which involves reprogramming a patient's own T-cells with a transgene encoding a chimeric antigen receptor (CAR) that identifies and eliminates cells that express BCMA. BCMA is primarily expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B-cells and plasma cells. The CARVYKTI CAR protein features two BCMA-targeting single domain antibodies designed to confer high avidity against human BCMA, a 4-1BB co-stimulatory domain and a CD3-zeta (CD3ζ) signaling cytoplasmic domain. Upon binding to BCMA expressing cells, the CAR promotes T-cell, activation, expansion and elimination of target cells.
In vitro co-culture experiments demonstrated that ciltacabtagene autoleucel-mediated cytotoxicity and cytokine release (interferon-gamma, [IFN-γ], tumor necrosis factor alpha [TNF-α], interleukin [IL]-2) were BCMA-dependent.

Pharmacodynamics

After a single infusion of CARVYKTI, expansion of CAR-positive T-cells coincided with decreases of serum soluble BCMA, serum M-protein, and/or free light chains. Across all patients, levels of IL-6, IL-10, IFN-γ and IL-2 receptor alpha increased post-infusion and peaked at Days 7–14. The serum levels of all cytokines generally returned to baseline levels within 2-3 months post-infusion.

Immunogenicity

The immunogenicity of CARVYKTI has been evaluated using a validated assay for the detection of binding antibodies against CARVYKTI pre-dose and at multiple timepoints post-infusion. In Study MMY2001, 19 of 97 patients (19.6%) were positive for anti-CAR antibodies. In Study MMY3002, 37 of 176 patients (21%) were positive for anti-CAR antibodies.
There was no clear evidence to suggest that the observed anti-CAR antibodies impact CARVYKTI kinetics of initial expansion and persistence, efficacy, or safety.

Clinical efficacy

Study MMY2011

MMY2001 was an open label trial evaluating CARVYKTI for the treatment of patients with relapsed or refractory multiple myeloma who previously received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on or after the last regimen.

In total, 113 patients underwent leukapheresis; CARVYKTI was manufactured for all patients. Sixteen patients were not treated with CARVYKTI (n=12 after leukapheresis and n=4 after lymphodepleting therapy), due to either withdrawal by patient (n=5), progressive disease (n=2) or death (n=9).
Of the 97 patients treated, the median time from the day after receipt of leukapheresis material at manufacturing facility to release of product for infusion was 29 days (range 23 to 64 days) and the median time from initial leukapheresis to CARVYKTI infusion was 47 days (range 41 days to 167 days).
Following leukapheresis and prior to administration of CARVYKTI, 73 of the 97 patients treated (75%) received bridging therapy. The most commonly used agents as bridging therapies (≥20% of patients) included dexamethasone: 62 patients (64%), bortezomib: 26 patients (27%), cyclophosphamide: 22 patients (23%), and pomalidomide: 21 patients (22%).
CARVYKTI was administered as a single IV infusion 5 to 7 days after the start of a lymphodepleting chemotherapy (cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days). Ninety-seven patients received CARVYKTI at a median dose of 0.71×10^6 CAR-positive viable T-cells/kg (range: 0.51 to 0.95×10^6 cells/kg). All patients were hospitalized for CARVYKTI infusion and for a minimum of 10 days afterward.
Of the 113 patients that underwent leukapheresis, 58% were male, 74% were Caucasian and 15% were African-American. The median patient age was 62 years (range: 29 to 78 years). Patients had received a median of 5 (range: 3 to 18) prior lines of therapy and 88% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-nine percent of patients were refractory to their last line of prior therapy and 89% were refractory to a proteasome inhibitor (PI), immunomodulatory agent, and anti-CD38 antibody.
Of the 97 patients treated, 59% were male, 71% were Caucasian and 18% were Black or African-American. The median patient age was 61 years (range: 43 to 78 years). Patients had received a median of 6 (range: 3 to 18) prior lines of therapy and 90% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-nine percent of patients were refractory to their last line of prior therapy and 88% were refractory to a proteasome inhibitor (PI), immunomodulatory agent, and anti-CD38 antibody.
Patients with known active, or prior history of significant central nervous system (CNS) disease including CNS multiple myeloma, allogenic stem cell transplant within 6 months before apheresis or ongoing treatment with immunosuppressants, creatinine clearance < 40mL/min, absolute lymphocyte concentration < 300/µL, hepatic transaminases > 3 times the upper limit of normal, cardiac ejection fraction < 45%, or with active serious infection were excluded from the trial.
Efficacy results were based on overall response rate as determined by the Independent Review Committee assessment using IMWG criteria (see Table 5).

Table 5: Efficacy results for Study MMY2001

	All Treated (N=97)	All Leukapheresed (N=113)
Overall Response Rate (sCR[a] + VGPR + PR), n (%)	95 (97.9)	95 (84.1)
95% CI (%)	(92.7; 99.7)	(76.0, 90.3)
Stringent complete response (sCR[a]) n (%)	80 (82.5)	80 (70.8)
Very good partial response (VGPR) n (%)	12 (12.4)	12 (10.6)
Partial response (PR) n (%)	3 (3.1)	3 (2.7)
Duration of Response (DOR)[b]		
Number of responders	95	-
DOR (Months): Median (95% CI)	NE (23.3; NE)	
Number of responders with sCR[a]	80	-
DOR if best response is sCR[a] (Months): Median (95% CI)	NE (28.3; NE)	
Number of responders with VGPR or better	92	-
DOR if best response is VGPR or better (Months): Median (95% CI)	NE (24.4; NE)	
Time to Response (months)		
Number of responders	95	-
Median	0.95	
Range	(0.9; 10.7)	
Time to sCR[a] (months)		
Number of responders with sCR[a]	80	-
Median	2.89	
Range	(0.9; 17.8)	

Notes: Based on a median duration of follow up of 27.7 months

[a] All complete responses were stringent CRs

[b] The estimated DOR rate was 60.3% (95% CI: 49.6%, 69.5%) at 24 months and 51.2% (95% CI: 39.0%, 62.1%) at 30 months

NE = not estimable

Table 6: Summary of MRD negativity rate

	All Treated (N=97)	All Leukapheresed (N=113)
MRD negativity rate, n (%)	56 (57.7)	56 (49.6)
95% CI (%)	(47.3, 67.7)	(40.0, 59.1)
MRD negative patients with sCRn (%)[a]	42 (43.3)	42 (37.2)
95% CI (%)	(33.3. 53.7)	(28.3, 46.8)
	Evaluable patients (N=61)	
MRD negativity rate, n (%)	56 (91.8)	-
95% CI (%)	(81.9, 97.3)	-

MRD= Minimal Residual Disease

Notes:Based on a median duration of follow up of 27.7 months

[a] Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death / progression / subsequent therapy (exclusive) are considered. All complete responses were stringent CRs.

With a median duration of follow-up of 27.7 months, median Progression Free Survival (PFS) was not reached (95% CI: 24.5, not estimable). The 12-month PFS rate (95% CI) was 76.3% (66.5%, 83.6%). The 24-month PFS rate (95% CI) was 62.7% (52.2%, 71.5%).

For patients who achieved sCR (all complete responses were stringent CRs), median PFS was not reached (95% CI: 30.1%, not estimable) with an estimated 12-month PFS rate of 88.8% (95% CI: 79.5%, 94.0%). The 24-month PFS rate was 73.5% (95% CI: 62.3%, 81.9%).

Median overall survival (OS) was not reached (95% CI: not estimable, not estimable). The OS rate at 12 months was 87.6% (95% CI: 79.2%, 92.8%). The 24-month OS rate was 76.2% (95% CI: 66.5%, 83.5%).

Health-related quality of life (HRQoL) was evaluated by the EORTC QLQ-C30 and completed at baseline (n=63) and during the post-infusion phase. The adjusted mean (95% CI) change from baseline in the EORTC QLQ-C30 Pain subscale was -1.9 (-8.5, -4.6) at day 7, -9.9 (-16.5, -3.3) at day 28, -6.3 (-12.9, -0.4) at day 56, -9.4 (-16.3, -2.5) at day 78, and -10.5 (-17.3, -3.8) at day 100, indicating overall reduction in pain following CARVYKTI infusion. Clinically meaningful improvements at Day 100 were seen in 72.2% of patients for the pain subscale, 53.8% for the fatigue subscale, 57.7% for the physical functioning subscale, and 53.7% for the global health status subscale.

Study MMY3002

MMY3002 is a Phase 3 randomized, open label, multicenter trial evaluating the efficacy of CARVYKTI for the treatment of patients with relapsed and lenalidomide-refractory multiple myeloma, who previously received at least 1 prior line of therapy including a proteasome inhibitor and an immunomodulatory agent. A total of 419 patients were randomized to received either a sequence of apheresis, bridging therapy, lymphodepletion and CARVYKTI (n=208) or standard of care which included physician’s choice of daratumumab, pomalidomide and dexamethasone or bortezomib, pomalidomide and dexamethasone (n=211).

Patients with known active or prior history of central nervous system involvement, patients who exhibit clinical signs of meningeal involvement of multiple myeloma and patients with a history of Parkinson’s disease or other neurodegenerative disorder, were excluded from the trial.

Of the 419 patients who were randomized (208 to CARVYKTI and 211 to standard of care), 57% were male, 75% were Caucasian, 3% were Black or African-American, and 7% were Hispanic or Latino. The median patient age was 61 years (range: 27 to 80 years). Patients had received a median of 2 (range: 1 to 3) prior lines of therapy and 85% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-nine percent of patients were refractory to their last line of prior

therapy. Forty-eight percent were refractory to a proteasome inhibitor (PI) and 100% were refractory to an immunomodulatory agent.

All 208 patients randomized to the CARVYKTI arm underwent apheresis. Following apheresis and prior to administration of CARVYKTI, all 208 randomized patients received protocol mandated bridging therapy (standard of care). Of these 208 patients, 12 were not treated with CARVYKTI due to progressive disease (n=10) or death (n=2), and 20 progressed prior to infusion with CARVYKTI but were able to receive CARVYKTI as subsequent therapy.

In the 176 patients that received CARVYKTI as study treatment, the median time from the day after receipt of apheresis material at manufacturing facility to release of product for infusion was 44 days (range: 25 to 127 days) and the median time from first apheresis to CARVYKTI infusion was 79 days (range: 45 days to 246 days).

CARVYKTI was administered as a single IV infusion 5 to 7 days after the start of a lymphodepleting chemotherapy (cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days) at a median dose of 0.71×10^6 CAR-positive viable T-cells/kg (range: 0.39 to 1.07×10^6 cells/kg).

The primary efficacy measure was progression-free survival (PFS) analyzed based on the Intent-To-Treat Analysis Set (see Table 7 and Figure 1). After a median follow-up of 15.9 months, median PFS was 11.8 months (95% CI: 9.7, 13.8) for the comparator arm and NE (95% CI: 22.8, NE) for CARVYKTI arm (Hazard ratio: 0.26 [95% CI: 0.18, 0.38]). The estimated PFS rate at 12 months was 75.9% (95% CI: 69.4%, 81.1%) in the CARVYKTI arm and 48.6% (95% CI: 41.5%, 55.3%) in the comparator arm. In the CARVYKTI arm, the estimated median duration of response (DOR) has not been reached. In the comparator arm, the estimated median DOR was 16.6 months (95% CI: 12.9, NE).

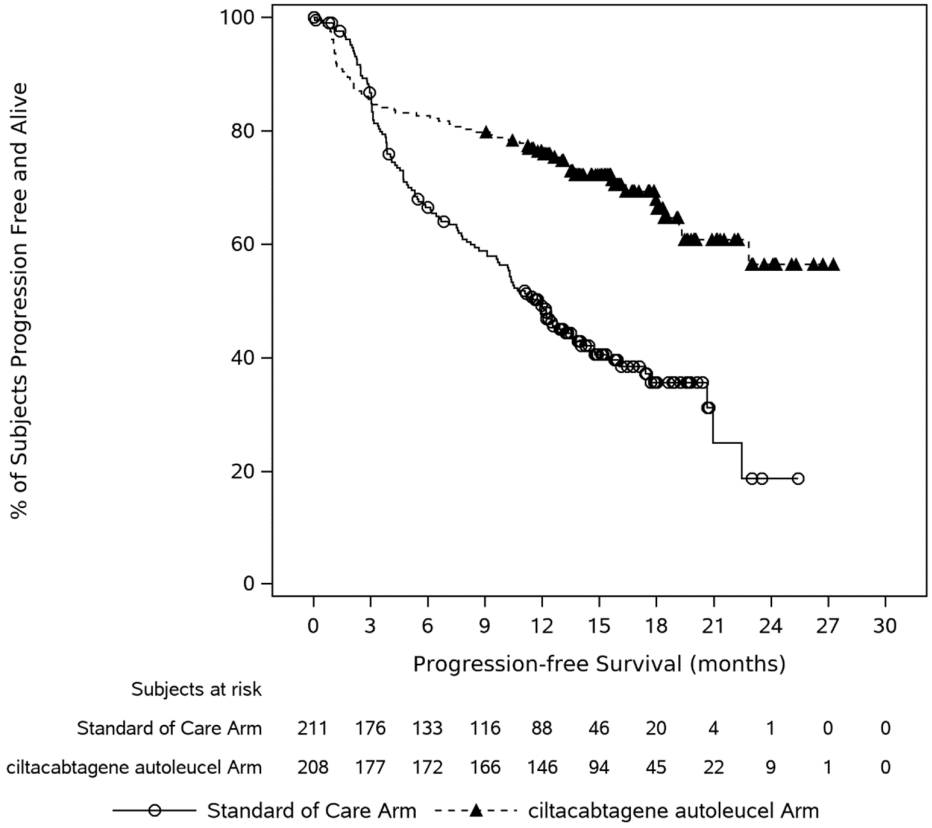
Table 7: Efficacy results for Study MMY3002 (Intent-To-Treat Analysis Set)

	CARVYKTI (N=208)	**Comparator (N=211)**
Progression-Free Survival[a]		
Number of events, n (%)	65 (31.3)	122 (57.8)
Median, months [95% CI][b]	NE [22.8, NE]	11.8 [9.7, 13.8]
Hazard ratio [95% CI][c]	0.26 [0.18, 0.38]	
p-value[d]	<0.0001	
Complete Response or Better Rate[a], % [95% CI]	73.1 [66.5, 79.0]	21.8 [16.4, 28.0]
p-value[e]	<0.0001	
Overall Response Rate (ORR)[a], % [95% CI]	84.6 [79.0, 89.2]	67.3 [60.5, 73.6]
p-value[e]	<0.0001	
Overall MRD Negativity Rate, % [95% CI]	60.6 [53.6, 67.3]	15.6 [11.0, 21.3]
p-value[f]	<0.0001	
Overall Survival (OS)		
Number of events, n (%)	39 (18.8)	47 (22.3)
Median, months [95% CI][b]	NE [NE, NE]	26.7 [22.5, NE]
Hazard ratio [95% CI][g]	0.78 [0.50, 1.20]	

p-value[h]	0.2551

NE=not estimable; CI=confidence interval; MRD=minimal residual disease
Notes: Based on a median duration of follow up of 15.9 months
[a] Per the International Myeloma Working Group (IMWG) consensus, as assessed by computerized algorithm
[b] Kaplan-Meier estimate
[c] Based on a stratified Cox proportional hazards model, including only PFS events that occurred more than 8 weeks post-randomization. A hazard ratio <1 indicates an advantage for CARVYKTI Arm. For all stratified analyses, stratification was based on investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized.
[d] Stratified weighted log-rank test (weight of 0 in the log-rank statistic for the first 8 weeks post-randomization, and 1 afterwards)
[e] Stratified Cochran-Mantel-Haenszel Chi-Squared test
[f] Fisher's exact test
[g] Based on a stratified Cox proportional hazards model. A hazard ratio <1 indicates an advantage for CARVYKTI Arm.
[h] Stratified log-rank test.

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3002 (Intent-To-Treat Analysis Set)



Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Of the 176 patients who received CARVYKTI as study treatment, the median progression free survival (PFS) was not estimable (95% CI: not estimable, not estimable) with a 12 months PFS rate of 89.7%. The overall response rate (ORR) in these patients was 99.4% (95% CI: 96.9%, 100.0%). The rate of CR/sCR was 86.4% (95% CI: 80.4%, 91.1%).

Of the 20 patients who experienced early and rapid disease progression and received CARVYKTI as subsequent therapy, after CARVYKTI infusion, the median PFS was 7.39 months (95% CI: 1.61, not estimable) with 12-month PFS rate of 39.4% (95% CI: 18.6, 59.7), ORR of 65% (95% CI: 40.8%, 84.6%), and CR/sCR of 40% (95% CI: 19.1%, 63.9%).

In the 208 patients who were randomized to receive CARVYKTI a delay in median time to worsening of multiple myeloma symptoms was reported compared to the 211 who were randomized to receive

standard of care (23.7 months vs 18.9 months, respectively) as measured with the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q).

Pharmacokinetics

CARVYKTI pharmacokinetics (PK) was assessed in 97 adult patients with relapsed or refractory multiple myeloma in Study MMY2001 receiving a single CARVYKTI infusion at the median dose of 0.71×10^6 CAR positive viable T-cells/kg (range: 0.51×10^6 to 0.95×10^6 cells/kg).
Following a single infusion, CARVYKTI exhibited an initial expansion phase followed by a rapid decline and then a slower decline. However, high interindividual variability was observed.

Table 8: Pharmacokinetic Parameters of CARVYKTI in patients with multiple myeloma

Parameter	Summary Statistics	Patetients (N=97)
C_{max} (copies/µg genomic DNA)	Mean (SD), n	48’692 (27’174), 97
t_{max} (day)	Median (range), n	12,71 (8,73 - 329,77), 97
$AUC_{0\text{-}28d}$ (copies*day/µg genomic DNA)	Mean (SD), n	504’496 (385’380), 97
$AUC_{0\text{-}last}$ (copies*day/µg genomic DNA)	Mean (SD), n	1’098’030 (1'387’010), 97
$AUC_{0\text{-}6m}$ (copies*day/µg genomic DNA)	Mean (SD), n	1’033’373 (1’355’394), 96
$t_{1/2}$ (day)	Mean (SD), n	23,5 (24,2), 42
t_{last} (day)	Median (range), n	125,90 (20,04 – 702,12), 97

After the cell expansion, the persistence phase of the CARVYKTI levels was observed for all patients. At the time of analysis (n=65), the median time for CAR transgene levels in peripheral blood to return to the pre-dose baseline level was approximately 100 days (range: 28-365 days) post-infusion. The PK of CARVYKTI was assessed in 176 adult patients with lenalidomide refractory multiple myeloma in MMY3002 and were generally consistent with those in Study MMY2001.
Detectable CARVYKTI exposures in bone marrow indicate a distribution of CARVYKTI from systemic circulation to bone marrow. Similar to blood transgene levels, bone marrow transgene levels declined over time and exhibited high interindividual variability.
Some patients required tocilizumab, corticosteroids and anakinra for management of CRS. CARVYKTI continues to expand and persist following tocilizumab administration. In Study MMY2001, patients treated with tocilizumab (n=68) had 81% and 72% higher CARVYKTI C_{max} and $AUC_{0\text{-}28d}$, respectively, as compared to patients (n=29) who did not receive tocilizumab. Patients who received

corticosteroids (n=28) had 75% and 112% higher C_{max} and AUC_{0-28d}, respectively, compared with patients who did not receive corticosteroids (n=69). In addition, patients who received anakinra (n=20) had 41% and 72% higher C_{max} and AUC_{0-28d}, respectively, compared with patients who did not receive anakinra (n=77). In Study MMY3002, the results related to tocilizumab and corticosteroid were consistent with Study MMY2001.

Absorption

NA

Distribution

NA

Metabolism

NA

Elimination

NA

Kinetics in specific patient groups

The pharmacokinetics of CARVYKTI (C_{max} and AUC_{0-28d}) were not impacted by age (range 27-78 years), including patients <65 years of age (n=215; 64.8%), 65-75 years (n=105; 31.6%) and >75 years of age (n=12; 3.6%).
Similarly, the pharmacokinetics of CARVYKTI (C_{max} and AUC_{0-28d}) were not impacted by gender, body weight, and race.

Hepatic impairment

Hepatic impairment studies of CARVYKTI were not conducted. CARVYKTI C_{max} and AUC_{0-28d} were similar in patients with mild hepatic dysfunction [(total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase >ULN) or (ULN < total bilirubin ≤ 1.5 times ULN)] and patients with normal hepatic function.

Renal impairment

Renal impairment studies of CARVYKTI were not conducted. CARVYKTI C_{max} and AUC_{0-28d} in patients with mild renal dysfunction (60 mL/min ≤ creatinine clearance [CRCL] < 90 mL/min) or moderate renal dysfunction (30 mL/min ≤ creatinine clearance < 60 mL/min) were similar to patients with normal renal function (CRCL ≥ 90 mL/min).

Preclinical data

Nonclinical safety assessment of CARVYKTI confirmed the on-target specificity of CARVYKTI to BCMA.

Carcinogenicity

No genotoxicity or carcinogenicity studies have been performed.
The risk for insertional mutagenesis occurring during the manufacturing of ciltacabtagene autoleucel following transduction of autologous human T-cells with an integrating lentiviral vector (LV) was assessed by evaluating the integration pattern of the vector in pre-infusion CARVYKTI. This genomic insertional site analysis was performed on CARVYKTI products from 7 patients and 3 healthy volunteers. There was no evidence for preferential integration near genes of concern.
The potential for enhanced proliferation of CARVYKTI was assessed in an *in vitro* cytokine independent growth assay. Integration of LV into primary T-cell genome during transduction did not lead to cytokine independent uncontrolled growth in the absence of IL-2 (the cytokine that regulates T-cell growth and promotes T-cell survival) of CARVYKTI.

Reproductive toxicity

No reproductive and developmental toxicity animal studies have been conducted with CARVYKTI.

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 expiry date ("EXP") stated on the pack.

Special precautions for storage

Store ≤ -120°C, e.g., in a container for cryogenic storage in the vapour phase of liquid nitrogen.
Store in the original packaging containing the cassette protecting the infusion bag.
Once thawed, the product should be administered immediately, and the infusion should be completed within 2.5 hours at room/ambient temperature (20°C to 25°C). Thawed product should not be shaken, refrozen or refrigerated.
Keep out of reach of children.

Instructions for handling

Do not irradiate as this could lead to inactivation of the product.
CARVYKTI should be transported within the facility in closed, break-proof, leak-proof containers.
CARVYKTI contains human blood cells that are genetically modified with replication incompetent lentiviral vector. Follow universal precautions and local guidelines for handling and disposal of unused medicinal product or all material that has been in contact with CARVYKTI (solid and liquid waste) to avoid potential transmission of infectious diseases.

Authorisation number

67956 (Swissmedic)

Packs

Ethylene vinyl acetate (EVA) infusion bag with sealed addition tube and two available spike ports containing either 30 mL or 70 mL of cell dispersion [A].
Each infusion bag is individually packed in an aluminium cryo cassette.

Component Type	Mandatory content and placement instructions
Cassette	Do not irradiate. Do NOT use leukocyte depleting filter. Intravenous use For autologous use only. Properly identify intended recipient and product. <u>Storage conditions:</u> Store and transport frozen ≤ -120°C in vapour phase of liquid nitrogen. Do not thaw the product until use. Do not shake. Do not refreeze. Do not refrigerate.
Infusion Bag	For intravenous use only For autologous use only Verify Patient ID

Marketing authorisation holder

Janssen-Cilag AG, Zug

Date of revision of the text

October 2024