SUMMARY OF PRODUCT CHARACTERISTICS

▼ 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 adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

CARVYKTI 3.2 × 10^6 – 1 × 10^8 cells dispersion for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

CARVYKTI (ciltacabtagene autoleucel) is a genetically modified autologous cell-based product, containing T cells transduced *ex vivo* using a replication incompetent lentiviral vector encoding an anti-B cell maturation antigen (BCMA) chimeric antigen receptor (CAR), comprising two single domain antibodies linked to a 4-1BB costimulatory domain and a CD3-zeta signaling domain.

2.2 Qualitative and quantitative composition

Each patient-specific infusion bag of CARVYKTI contains ciltacabtagene autoleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti-BCMA chimeric antigen receptor (CAR-positive viable T cells) (see section 4.2). The medicinal product is packaged in one infusion bag containing a cell dispersion for infusion of 3.2 × 10^6 to 1 × 10^8 CAR-positive viable T cells suspended in a cryopreservative solution.

An infusion bag contains 30 mL or 70 mL of dispersion for infusion.

The cellular composition and the final cell number is dependent on patient body weight and varies between individual patient batches. In addition to T cells, Natural Killer (NK) cells may be present.

The quantitative information of the medicinal product including the total viable cell concentration, volume of dispersion and total number of CAR+ cells per bag and supplied dose is presented in the Lot Information Sheet included with the cryo cassette used for transport of CARVYKTI.

Excipient(s) with known effect

Each dose of CARVYKTI contains 0.05 mL of dimethyl sulfoxide (DMSO) per mL and residual kanamycin (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dispersion for infusion

A colourless to white, including shades of white, yellow, and pink, dispersion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

CARVYKTI must be administered in a qualified treatment centre.

Therapy should be initiated under the direction and supervision of a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with CARVYKTI.

Prior to infusion, the qualified treatment centre must have at least 1 dose of tocilizumab available for use in the event of cytokine release syndrome (CRS), with access to an additional dose within 8 hours of each previous dose (see section 4.4). In the exceptional case where tocilizumab is not available due to a shortage that is listed in the National Health Authority shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.

Emergency equipment must be available prior to infusion and during the recovery period.

Posology

CARVYKTI is intended for autologous use (see section 4.4).
Treatment consists of a single dose for infusion containing a dispersion of CAR-positive viable T cells in one infusion bag.

The target dose is 0.75×10^6 CAR-positive viable T cells/kg of body weight (not exceeding 1×10^8 CAR-positive viable T cells).

Patients 100 kg and below: $0.5 - 1 \times 10^6$ CAR-positive viable T cells/kg body weight.
Patients above 100 kg: $0.5 - 1 \times 10^8$ CAR-positive viable T cells (non-weight based).

See the accompanying Lot information sheet (LIS) for additional information pertaining to dose.

Bridging therapy
Consider bridging therapy according to prescriber's choice prior to infusion with CARVYKTI to reduce tumour burden or stabilise the disease (see section 4.4).

Pre-treatment (lymphodepleting regimen)
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) (see section 5.1).

The availability of CARVYKTI should be confirmed prior to starting the lymphodepleting regimen.

A lymphodepleting regimen of cyclophosphamide 300 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous should be administered daily for 3 days. CARVYKTI infusion should be administered 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, thereby resulting in delays to CARVYKTI dosing, the lymphodepleting regimen should be re-administered after a minimum of 21 days following the first dose of the first lymphodepleting regimen.

For dose modifications of cyclophosphamide and fludarabine, see corresponding Summaries of Product Characteristics of cyclophosphamide and fludarabine.

Premedication

The following pre-infusion medications should be administered to all patients 30 to 60 minutes prior to CARVYKTI infusion:

- Antipyretic (oral or intravenous paracetamol 650 to 1,000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

The use of prophylactic systemic corticosteroids should be avoided as it may interfere with the activity of CARVYKTI.

Special populations

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

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)
There is currently no experience with manufacturing CARVYKTI for patients testing positive for HIV, active HBV, or active HCV. Screening for HBV, HCV and HIV and other infectious agents must be performed before collection of cells for manufacturing.
HIV-positive patients treated with CARVYKTI should be advised on the importance of continuing with antiretroviral therapy, according to local institutional guidelines/clinical practice.

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

Method of administration

CARVYKTI is for intravenous use only.

Do NOT use a leukodepleting filter.

Preparation of CARVYKTI for infusion

Prior to infusion and during the recovery period, the availability of tocilizumab and emergency equipment must be ensured.

Before infusion, it must be confirmed that the patient's identity matches the unique patient information on the CARVYKTI cryo cassette, infusion bag and on the Lot Information Sheet. (see section 4.4).

The medicinal product must not be thawed until it is ready to be used. The timing of CARVYKTI thaw and infusion should be coordinated; the infusion time should be confirmed in advance, and the start time for thaw must be adjusted so that CARVYKTI is available for infusion when the patient is ready. The medicinal product should be administered immediately after thawing and the infusion should be completed within 2.5 hours of thawing.

For detailed instructions on preparation, administration, accidental exposure and disposal of CARVYKTI, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy and supportive therapy should be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability, the name of the medicinal product, the batch number and the name of the treated patient should be kept for a period of 30 years after the expiry date of the medicinal product.

General

Autologous use

CARVYKTI is intended solely for autologous use and must not under any circumstances, be administered to other patients. CARVYKTI must not be infused if the information on the product labels and Lot Information Sheet does not match the patient's identity.

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,
- grade ≥ 3 non-haematologic toxicities of cyclophosphamide and fludarabine lymphodepletion regimen, except for Grade 3 nausea, vomiting, diarrhoea, or constipation. CARVYKTI infusion should be delayed until resolution of these events to Grade ≤ 1,
- active graft versus host disease.

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. There is no experience of use of CARVYKTI in patients with CNS involvement of myeloma or other pre-existing, clinically relevant CNS illnesses.
The efficacy/safety of CARVYKTI in patients previously exposed to other anti-BCMA treatments is unknown.
There is limited evidence available on efficacy/safety of CARVYKTI in re-treated patients.

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.

Monitoring after infusion
Patients should be monitored daily for 14 days after the CARVYKTI infusion at a qualified clinical facility, and then periodically for an additional 2 weeks after CARVYKTI infusion, for signs and symptoms of CRS, neurologic events and other toxicities (see section 4.4).
Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

Cytokine release syndrome
Cytokine release syndrome, including fatal or life-threatening reactions, can occur after CARVYKTI infusion.

Nearly all patients experienced CRS after CARVYKTI infusion, with majority of these being Grade 1 or Grade 2 *(*see section 4.8*)*. The median time from CARVYKTI infusion (Day 1) to onset of CRS was 7 days (range: 1 to 23 days). Approximately 83% of patients experienced CRS onset after Day 3 of receiving the CARVYKTI infusion.

In almost all cases, duration of CRS ranged from 1 to 18 days (median duration, 4 days). Eighty-nine percent of patients had a CRS duration of $\leq$ 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. Potentially life-threatening complications of CRS may include cardiac dysfunction, neurologic toxicity and haemophagocytic lymphohistiocytosis (HLH). 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. 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.

The infusion of CARVYKTI should be delayed if the patient has unresolved serious adverse reactions from preceding lymphodepleting or bridging therapies (including cardiac toxicity and pulmonary toxicity), rapid disease progression and clinically significant active infection (see section 4.2). Appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any active infections should be ensured prior to CARVYKTI infusion. Infections may also occur concurrently with CRS and may increase the risk of a fatal event.

The availability of at least one dose of tocilizumab for use in the event of CRS should be ensured prior to infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the MHRA Central Alerting System, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion. Patients should be monitored for signs and symptoms of CRS daily for 14 days after the CARVYKTI infusion at a qualified clinical facility, and then periodically for an additional two weeks after CARVYKTI infusion.

Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, the patient should be immediately evaluated for hospitalisation and treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids should be instituted as indicated in Table 1 below.

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 (see section 4.2).

Management of cytokine release syndrome associated with CARVYKTI
If CRS is suspected, manage according to the recommendations in Table 1. Supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) should be administered as appropriate. Laboratory testing to monitor for disseminated intravascular coagulation (DIC), haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function should be considered. 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 HLH that remain 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

CRS Grade[a]	Tocilizumab[b]	Corticosteroids[f]
Grade 1 Temperature ≥38 °C[c]	Tocilizumab 8 mg/kg intravenously (IV) over 1 hour (not to exceed 800 mg) may be considered.	N/A
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, or, Grade 2 organ toxicity.	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 litre or increasing supplemental oxygen.	Consider methylprednisolone 1 mg/kg intravenously (IV) twice daily or dexamethasone (e.g., 10 mg IV every 6 hours).
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose of dexamethasone (20 mg IV every 6 to 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.	
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.	Per Grade 2	Administer methylprednisolone 1 mg/kg IV twice daily or dexamethasone (e.g., 10 mg IV every 6 hours).
	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.	
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-	Per Grade 2	Administer dexamethasone 20 mg IV every 6 hours.
	After 2 doses of tocilizumab, consider alternative anti-cytokine	

Table 1: CRS grading and management guidance

CRS Grade[a]	Tocilizumab[b]	Corticosteroids[f]
venous haemodialysis (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), or, Grade 4 organ toxicity (excluding transaminitis).	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).	

[a] Based on ASTCT 2019 grading system (Lee et.al, 2019), modified to include organ toxicity.
[b] Refer to tocilizumab prescribing information for details. Consider alternative measures (see Sections 4.2. and 4.4).
[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 (for example, anti-IL1 such as anakinra) 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

Neurologic toxicities occur frequently following treatment with CARVYKTI and can be fatal or life-threatening (see section 4.8). Neurologic toxicities included ICANS, movement and neurocognitive toxicity (MNT) with signs and symptoms of parkinsonism, Guillain-Barré syndrome, peripheral neuropathies and cranial nerve palsies. Patients should be counselled on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Patients should be instructed 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, concurrent with CRS, following resolution of CRS or in the absence of CRS.

Symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state.

Reduction of baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumour burden should be considered, which may mitigate the risk of developing neurologic toxicity (see section 4.8). Patients should be monitored for signs or symptoms of ICANS for four weeks after infusion. At the first sign of ICANS, the patient should be immediately evaluated for hospitalisation and treatment instituted with supportive care as indicated in Table 2 below. Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening. Continue to monitor patients for signs and symptoms of neurologic toxicities after recovery from CRS and/or ICANS.

Management of neurologic toxicity associated with CARVYKTI
At the first sign of neurologic toxicity including ICANS, neurology evaluation should be considered. Rule out other causes of neurologic symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities.

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.

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 generalised, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised intracranial pressure (ICP): focal/local oedema 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, or raised ICP / cerebral oedema, with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad	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 oedema 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.

EEG=Electroencephalogram; ICE=Immune Effector Cell-Associated Encephalopathy
Note: ICANS grade and management is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral oedema), 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 as in Table 3 below.

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

[d] Intracranial haemorrhage with or without associated oedema 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.

Table 3: Immune Effector Cell-Associated Encephalopathy (ICE) assessment

Immune Effector Cell-Associated Encephalopathy (ICE) Tool[a]	
	Points
Orientation: Orientation to year, month, city, hospital	4
Naming: Name 3 objects (e.g., point to clock, pen, button)	3
Following commands: (e.g., 'Show me 2 fingers' or 'Close your eyes and stick out your tongue')	1
Writing: Ability to write a standard sentence	1
Attention: Count backwards from 100 by ten	1

[a] ICE-Tool Scoring:

- Score 10: No impairment
- Score 7-9: Grade 1 ICANS
- Score 3-6: Grade 2 ICANS
- Score 0-2: Grade 3 ICANS
- Score 0: patient unarousable and unable to perform ICE assessment: Grade 4 ICANS

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 tumour burden at baseline (bone marrow plasma cell ≥80% or serum M-spike ≥ 5 g/dL or serum free light chain ≥ 5,000 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.
Patients should be monitored 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 section 4.8).

Patients should be monitored for GBS. Patients presenting with peripheral neuropathy should be evaluated for GBS. Treatment with intravenous immunoglobulin (IVIG) and escalation to plasmapheresis should be considered, depending on toxicity severity.

Peripheral neuropathy
Occurrence of peripheral neuropathy, including sensory, motor, or sensorimotor, have been reported in trials of CARVYKTI.

Patients should be monitored for signs and symptoms of peripheral neuropathies. Management with short-course systemic corticosteroids should be considered, 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.

Patients should be monitored for signs and symptoms of cranial nerve palsies. Management with short-course systemic corticosteroids should be considered, 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 or lower by Day 30 (see section 4.8).

Blood counts should be monitored prior to and after CARVYKTI infusion. For thrombocytopenia, supportive care with transfusions should be considered. 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 section 4.8).

Patients should be monitored for signs and symptoms of infection prior to and during treatment with CARVYKTI and treated appropriately. Prophylactic antimicrobials should be administered 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. Patients should be counselled 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 treated with medicinal products directed against B cells.

There is currently no experience with manufacturing CARVYKTI for patients testing positive for HIV, active HBV, or active HCV. Screening for HBV, HCV and HIV and other infectious agents must be performed before collection of cells for manufacturing (see section 4.2).

Reactivation of John Cunningham (JC) virus, leading to progressive multifocal leukoencephalopathy (PML), has been reported in patients treated with CARVYKTI who have also received prior treatment with other immunosuppressive medications. Cases with fatal outcome have been reported.

Hypogammaglobulinaemia

Hypogammaglobulinaemia may occur in patients receiving CARVYKTI.

Immunoglobulin levels should be monitored after treatment with CARVYKTI; IVIG should be administered for IgG <400 mg/dL. Manage according to standard guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection.

Immune-mediated enterocolitis

Patients may develop immune-mediated enterocolitis, which may emerge several
months after CARVYKTI infusion. Some cases may be refractory to treatment with
corticosteroids, and other treatment options may be relevant to consider. There were
events of gastrointestinal perforation, including fatal outcomes.

Secondary malignancies including of myeloid and T-cell origin
Patients treated with CARVYKTI may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19- directed CAR T-cell therapy, including CARVYKTI. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-, directed CAR T-cell therapy. There have been fatal outcomes.

Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), including cases with fatal outcomes, have occurred in patients after CARVYKTI infusion (see section 4.8).

Patients should be monitored life-long for secondary malignancies. In the event a secondary malignancy occurs, the company should be contacted for reporting and to obtain instructions on patient samples to collect for testing of secondary malignancy of T-cell origin. In patients with HIV infection, contact the company for the testing of secondary malignancies, including those of non T-cell origin.

Interference with serological testing
Due to limited and short spans of identical genetic information between the lentiviral vector used to create CARVYKTI and HIV, some HIV nucleic acid tests (NAT) may give a false positive result
Blood, organ, tissue and cell donation
Patients treated with CARVYKTI should not donate blood, organs, tissues and cells for transplantation. This information is provided in the Patient Alert Card which should be given to the patient.

Hypersensitivity
Allergic reactions may occur with infusion of CARVYKTI. Serious hypersensitivity reactions, including anaphylaxis, may occur 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.

Long-term follow-up
Patients are expected to enroll and be followed in a registry in order to better understand the long-term safety and efficacy of CARVYKTI.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic or pharmacodynamic drug interaction studies have been performed with CARVYKTI.

The co-administration of agents known to inhibit T cell function has not been formally studied. The co-administration of agents known to stimulate T cell function has not been investigated and the effects are unknown.

Some patients in the clinical trials on CARVYKTI 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_{0-28d}, 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.

Live vaccines

The safety of immunisation 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Pregnancy status for females of childbearing potential should be verified prior to starting treatment with CARVYKTI.

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.

See the prescribing information for lymphodepleting chemotherapy for information on the need for contraception in patients who receive the lymphodepleting chemotherapy.

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 hypogammaglobulinaemia. Assessment of immunoglobulin levels in newborns of mothers treated with CARVYKTI should be considered.

Breast-feeding

It is unknown whether CARVYKTI is excreted in human milk. Women who are breast-feeding should be advised of the potential risk to the breast-fed infant.

Following administration of CARVYKTI, the decision to consider breast-feeding should be discussed with the treating physician.

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 (see section 5.3).

4.7 Effects on ability to drive and use machines

CARVYKTI has major influence on the 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 (see section 4.4). Patients should be advised 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.

4.8 Undesirable effects

Summary of the safety profile

The safety of CARVYKTI was evaluated in 396 adult patients with multiple myeloma infused with CARVYKTI in three open label clinical trials: Study MMY2001 (N=106), which included patients from the main Phase 1b/2 cohort (United States; n=97) and an additional cohort (Japan; n=9), Phase 2 Study MMY2003 (N=94) and Phase 3 Study MMY3002 (N=196). Patients who complete Study MMY2001, MMY2003, or MMY3002 are eligible to enroll in a separate long-term follow-up study (MMY4002).

The most common CARVYKTI adverse reactions (≥20%) were neutropenia (90%), pyrexia (85%), CRS (83%), thrombocytopenia (60%), anaemia (60%), musculoskeletal pain (40%), fatigue (35%), leukopenia (34%), hypotension (34%), hypogammaglobulinaemia (33%), diarrhea (32%), upper respiratory tract infection (32%), transaminase elevation (26%), headache (25%), nausea (23%), and cough (22%).

Serious adverse reactions occurred in 44% of patients; serious adverse reactions reported in ≥2% of patients were CRS (11%), pneumonia (9%), sepsis (5%), viral infection (5%), neutropenia (4%), cranial nerve palsies, (4%), ICANS (4%), encephalopathy (3%), upper respiratory tract infection (3%), bacterial infections (2%), gastroenteritis (2%), febrile neutropenia (2%), thrombocytopenia (2%), haemophagocytic lymphohistiocytosis (2%), motor dysfunction (2%), dyspnea (2%), diarrhea (2%), and renal failure (2%).

The most common (≥5%) Grade ≥ 3 non-haematological adverse reactions were transaminase elevation (11%), pneumonia (11%), febrile neutropenia (8%), sepsis (7%), pyrexia (7%), Gamma-glutamyltransferase increased (6%), hypotension (6%), bacterial infection (5%), and hypogammaglobulinaemia (5%).

The most common (≥20%) Grade ≥3 haematological abnormalities were neutropenia (89%), thrombocytopenia (45%), anaemia (44%), lymphopenia (36%), and leukopenia (33%).

Tabulated list of adverse reactions

Table 4 summarises the adverse reactions that occurred in patients receiving CARVYKTI.

Within each system organ class, the adverse reactions are ranked by frequency. Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness. 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 4: Adverse reaction in patients with multiple myeloma treated with CARVYKTI

System organ class	Frequency	Adverse Reaction	Incidence (%)	
			All grades	grade ≥ 3
Infections and infestations	Very common	Bacterial infection[*#]	14	5
		Upper respiratory tract infection[*]	32	2
		Viral infection[*]	19	4
		Pneumonia[*#]	14	11
	Common	Sepsis[1#]	9	7
		Gastroenteritis[2]	6	1
		Urinary tract infection[3]	5	2
		Fungal infection[*]	3	<1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Secondary malignancy of myeloid origin[#]	4	4
	Uncommon	Secondary malignancy of T-cell origin	1	1
Blood and lymphatic system disorders	Very common	Neutropenia[*]	90	89
		Thrombocytopenia	60	45
		Anemia[4]	60	44
		Leukopenia	34	33
		Lymphopenia	38	36
		Coagulopathy[5]	12	3

Table 4: Adverse reaction in patients with multiple myeloma treated with CARVYKTI

System organ class	Frequency	Adverse Reaction	Incidence (%)	
			All grades	grade ≥ 3
	Common	Febrile neutropenia	8	8
		Lymphocytosis	3	1
Immune system disorders	Very common	Hypogammaglobulinaemia[*]	33	5
		Cytokine release syndrome[#]	83	4
	Common	Haemophagocytic lymphohistiocytosis[#]	3	2
Metabolism and nutrition disorders	Very common	Hypocalcaemia	16	3
		Hypophosphataemia	17	4
		Decreased appetite	16	1
		Hypokalaemia	17	2
		Hypoalbuminaemia	11	<1
		Hyponatraemia	10	2
		Hypomagnesaemia	12	<1
		Hyperferritinemia[6]	10	2
Psychiatric disorders	Common	Delirium[7]	3	<1
		Personality changes[8]	3	1
Nervous system disorders	Very common	Encephalopathy[9#]	14	3
		Immune effector cell-associated neurotoxicity syndrome[#]	11	2
		Motor dysfunction[10]	13	2
		Dizziness[*]	13	1
		Headache	25	0
		Sleep disorder[11]	10	1
	Common	Aphasia[12]	5	<1
		Cranial nerve palsies[14]	7	1
		Paresis[14]	1	<1
		Ataxia[15]	4	<1
		Tremor[*]	5	<1

Table 4: Adverse reaction in patients with multiple myeloma treated with CARVYKTI

System organ class	Frequency	Adverse Reaction	Incidence (%)	
			All grades	grade ≥ 3
		Neurotoxicity[#]	1	1
		Neuropathy peripheral[16]	7	1
	Uncommon	Guillain-Barre syndrome	<1	<1
Cardiac disorders	Very common	Tachycardia[*]	14	1
	Common	Cardiac arrhythmias[17]	4	2
Vascular disorders	Very common	Hypotension[*]	34	6
		Hypertension	11	4
		Haemorrhage[18#]	11	2
	Common	Thrombosis[*]	4	1
		Capillary leak syndrome	1	0
Respiratory, thoracic and mediastinal disorders	Very common	Hypoxia[*]	13	4
		Dyspnoea[19#]	14	3
		Cough[*]	22	0
Gastrointestinal disorders	Very common	Diarrhoea[20]	32	3
		Nausea	23	<1
		Vomiting	12	0
		Constipation	15	0
	Common	Abdominal pain[*]	9	0
		Immune-mediated entercolitis		
Hepatobiliary disorders	Common	Hyperbilirubinaemia	3	1
Skin and subcutaneous tissue disorders	Common	Rash[*]	9	0
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[*]	40	3

Table 4: Adverse reaction in patients with multiple myeloma treated with CARVYKTI

System organ class	Frequency	Adverse Reaction	Incidence (%)	
			All grades	grade ≥ 3
Renal and urinary disorders	Common	Renal failure[21]	7	4
General disorders and administration site conditions	Very common	Pyrexia	85	7
		Fatigue[*]	35	4
		Chills	15	0
		Oedema[22]	16	1
		Pain[*]	11	1
Investigations	Very common	Transaminase elevation[*]	26	11
		Gamma-glutamyltransferase increased	10	6
	Common	C-reactive protein increased	7	1
		Blood alkaline phosphatase increased	8	3

Adverse reactions are reported using MedDRA version 26.1

Contains fatal outcome(s).

* Based on grouped term.

1 Sepsis includes bacteraemia, bacterial sepsis, candida sepsis, device related bacteraemia, enterococcal bacteraemia, enterococcal sepsis, haemophilus sepsis, neutropenic sepsis, pseudomonal bacteraemia, pseudomonal sepsis, sepsis, septic shock, staphylococcal bacteraemia, streptococcal sepsis, systemic candida, and urosepsis.

2 Gastroenteritis includes enterocolitis bacterial, enterocolitis infectious, enterocolitis viral, enterovirus infection, gastroenteritis, gastroenteritis cryptosporidial, gastroenteritis rotavirus, gastroenteritis salmonella, gastroenteritis viral, gastroenteritis escherichia coli gastrointestinal infection, and large intestine infection.

3 Urinary tract infection includes cystitis, escherichia urinary tract infection, urinary tract infection, urinary tract infection bacterial, and urinary tract infection viral.

4 Anaemia includes anaemia, hypochromic anaemia, iron deficiency anaemia and pallor.

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

6 Hyperferritinemia includes hyperferritinaemia, and serum ferritin increased.

7 Delirium includes agitation, delirium, disorientation, euphoric mood, hallucination, irritability, and restlessness.

8 Personality changes includes affect lability, apathy, flat affect, indifference, personality change, and reduced facial expression.

9 Encephalopathy includes amnesia, bradyphrenia, cognitive disorder, 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.

10 Motor dysfunction includes agraphia, bradykinesia, cogwheel rigidity, coordination abnormal, dysgraphia, extrapyramidal disorder, eyelid ptosis micrographia, motor dysfunction, muscle rigidity, muscle spasms, muscle tightness, muscular weakness, myoclonus, parkinsonism posture abnormal and stereotypy.

11 Sleep disorder includes hypersomnia, insomnia, sleep disorder, and somnolence.

12 Aphasia includes dysarthria, slow speech, and speech disorder.

13 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.

14 Paresis includes paresis, hemiparesis, and peroneal nerve palsy.

15 Ataxia includes balance disorder, dysmetria, and gait disturbance.

16 Neuropathy peripheral includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

17 Cardiac arrhythmias include atrial fibrillation, atrial flutter, atrioventricular block complete, atrioventricular block second degree, supraventricular tachycardia, ventricular extrasystoles, and ventricular tachycardia.

18 Haemorrhage includes catheter site haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, contusion, epistaxis, eye contusion, gastrointestinal haemorrhage, haematemesis, haematochezia, haematoma, haematuria, haemoptysis, infusion site haematoma, lower gastrointestinal haemorrhage, oral contusion, post procedural, haemorrhage, pulmonary haemorrhage, retinal haemorrhage, retroperitoneal haemorrhage, subarachnoid haemorrhage, and Subdural haematoma.

19 Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure, tachyponea and wheezing.

20 Diarrhoea includes colitis, and diarrhoea.

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

22 Oedema includes face oedema, fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral, palatal oedema, periorbital oedema, peripheral swelling, pulmonary congestion, pulmonary oedema, scrotal oedema, and swollen tongue.

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 section 5.1). 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 haemorrhage in the context of HLH or DIC and 3 due to fatal infections).

Description of selected adverse reactions

Cytokine release syndrome

CRS was reported in 83% of patients (n=330); 79% (n=314) of patients had CRS events that were Grade 1 or Grade 2, 4% (n=15) of patients had Grade 3 or Grade 4 CRS events and <1% (n=1) of patients had a Grade 5 CRS event. Ninety-eight percent of patients (n=324) 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 (82%), hypotension (28%), Aspartate aminotransferase (AST) increased (12%), and hypoxia (10%). See section 4.4 for monitoring and management guidance.

Neurologic toxicities

Neurologic toxicity occurred in 23% of patients (n=90); 5% (n=22) of patients had Grade 3 or Grade 4 neurologic toxicity and 1% (n=3) of patients had Grade 5 neurologic toxicity (one due to ICANS, one due to neurologic toxicity with ongoing parkinsonism, and one due to encephalopathy). In addition,

eleven patients had fatal outcomes with ongoing neurologic toxicity at the time of death; eight deaths were due to infection (including two deaths in patients with ongoing signs and symptoms of parkinsonism, as discussed below), and one death each due to respiratory failure, cardio-respiratory arrest and intraparenchymal hemorrhage. See section 4.4 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=8) 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 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 90 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 38.0days (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). 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), 28 patients developed peripheral neuropathy, presenting as sensory, motor, or sensorimotor neuropathies. Median time of onset of symptoms was 58 days (range: 1 to 914 days), median duration of peripheral neuropathies was 142 days (range: 1 to 1062 days) including those with ongoing neuropathy. Of these 28 patients, 5 experienced Grade 3 or Grade 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 23 with ≤ Grade 2 peripheral neuropathy, peripheral neuropathy resolved with no

treatment reported in 7 patients and following treatment with duloxetine in 3 patients, and was ongoing in the other 9 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 61 days (range: 1 to 443 days) following onset of symptoms.

Prolonged and recurrent cytopenias

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 (28%), 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 5 lists the incidences of Grade 3 or Grade 4 cytopenias occurring after dosing not resolved to Grade 2 or lower by Day 30 and Day 60, respectively.

Table 5: Incidences of prolonged and recurrent cytopenias following treatment with CARVYKTI (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%)	111 (29%)	44 (11%)	81 (21%)
Lymphopenia	394 (99%)	97 (25%)	45 (12%)	91 (23%)
Anemia	184 (46%)	10 (3%)	10 (3%)	26 (7%)

[a] The laboratory result with the worst toxicity grade is 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 < 50,000 cells/µL.

Neutropenia: Grade 3/4 - Neutrophil count < 1,000 cells/µL.

Lymphopenia: Grade 3/4 - Lymphocytes count < 0.5×10^9 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 patients.

Serious infections

Infections occurred in 54% of patients (n=213); 18% of patients (n=73) 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 4% of patients (n=17). 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 section 4.4 for monitoring and management guidance.

Hypogammaglobulinaemia
In the pooled studies (N=396), hypogammaglobulinaemia occurred in 34% of patients, with 5% of patients experiencing Grade 3 hypogammaglobulinaemia. Laboratory IgG levels fell below 500 mg/dL after infusion in 91% (360/396) of patients treated with CARVYKTI. Hypogammaglobulinaemia either as an adverse reaction or a laboratory IgG level below 500 mg/dL occurred in 92% (364/396) of patients after infusion. Fifty- eight percent of patients received IVIG post CARVYKTI for either an adverse reaction or prophylaxis. See section 4.4 for monitoring and management guidance.

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 the pooled studies (n=363), 23% (83/363) of patients with appropriate samples were positive for treatment-emergent anti-CAR antibodies. There was no clear evidence that the observed anti-CAR antibodies impact CARVYKTI kinetics of initial expansion and persistence, efficacy or safety.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the:
Yellow Card Scheme
Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, 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.

Pharmacodynamic effects

In vitro co-culture experiments demonstrated that ciltacabtagene autoleucel-mediated cytotoxicity and cytokine release (interferon-gamma, [IFN-γ], tumour necrosis factor alpha [TNF-α], interleukin [IL]-2) were BCMA-dependent.

Clinical efficacy and safety

CARTITUDE-1 (Study MMY2001)
MMY2001 was an open label, single-arm, multicentre, Phase 1b/2 study evaluating the efficacy and safety of CARVYKTI for the treatment of adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior lines of antimyeloma therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on or within 12 months after the last regimen. Patients with known active, or prior history of significant central nervous system (CNS) disease including CNS multiple myeloma, patients previously exposed to other anti-BCMA treatments, allogeneic stem cell transplant within 6 months before apheresis or ongoing treatment with immunosuppressants, creatinine clearance < 40 mL/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.

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 medicinal 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 to 167 days).

Following leukapheresis and prior to administration of CARVYKTI, 73 of the 97 patients (75%) received bridging therapy. The most commonly used agents as bridging therapies (≥20% of patients) included dexamethasone: 62 patients (63.9%), bortezomib: 26 patients (26.8%), cyclophosphamide: 22 patients (22.7%), and pomalidomide: 21 patients (21.6%).

CARVYKTI was administered as a single IV infusion 5 to 7 days after the start of a lymphodepleting chemotherapy (cyclophosphamide 300 mg/m2 intravenously daily

and fludarabine 30 mg/m2 intravenously daily for 3 days). Ninety-seven patients received CARVYKTI at a median dose of 0.71 × 106 CAR-positive viable T cells/kg (range: 0.51 to 0.95 × 106 cells/kg). All patients were hospitalised for the CARVYKTI infusion and for a minimum of 10 days afterward.

Table 6: Summary of patient demographic and baseline characteristics

Analysis set	**All Treated (N=97)**	**All Leukapheresed (N=113)**
Age (years)		
Category n (%)		
< 65	62 (64)	70 (62)
65 – 75	27 (28)	34 (30)
> 75	8 (8)	9 (8)
Median (range)	61.0 (43; 78)	62 (29; 78)
Sex		
Male n (%)	57 (59)	65 (57.5)
Female n (%)	40 (41)	48 (42.5)
Race		
American Indian or Alaska native	1 (1)	1 (1)
Asian	1 (1)	1 (1)
Black or African American	17 (17.5)	17 (15)
Native Hawaiian or other Pacific islander	1 (1)	1 (1)
White	69 (71)	83 (73.5)
Multiple	0	0
Not reported	8 (8)	10 (9)
ECOG score prior to infusion n (%)		
0	39 (40)	55 (49)
1	54 (56)	58 (51)
2	4 (4)	-
ISS staging at study baseline n (%)		
N	97	58
I	61 (63)	32 (55)
II	22 (23)	21 (36)
III	14 (14)	5 (9)
Creatinine Clearance/eGFR (MDRD) (mL/min/1.73m^2) Median (range)	88.44 (41.8, 242.9)	73.61 (36.2, 177.8)
Time since initial multiple myeloma diagnosis to enrollment (years) Median (range)	5.94 (1.6; 18.2)	5.73 (1.0; 18.2)
Presence of extramedullary plasmacytomas n (%)		
Yes	13 (13)	NA[a]
No	84 (87)	NA[a]
Cytogenetic risk at study baseline n (%)		
Standard risk	68 (70)	70 (62)
High risk	23 (24)	28 (25)
Del17p	19 (20)	22 (19.5)
T(4;14)	3 (3)	5 (4)
T(14;16)	2 (2)	3 (3)
Unknown	6 (6)	15 (13)

Table 6: Summary of patient demographic and baseline characteristics

Analysis set	All Treated (N=97)	All Leukapheresed (N=113)
Tumour BCMA expression (%) Median (range)	80 (20; 98)	80 (20; 98)
Number of lines of prior therapies for multiple myeloma Median (range)	6 (3,18)	5 (3, 18)
Prior treatment with PI+IMiD+anti-CD38 antibodies n (%)	97 (100)	113 (100)
Prior autologous SCT n (%)	87 (90)	99 (88)
Prior allogeneic SCT n (%)	8 (8)	8 (7)
Refractory at any point to prior therapy n (%)	97 (100)	113 (100)
Refractory to PI+IMiD+anti-CD38 antibody n (%)	85 (88)	100 (88.5)
Refractory to last line of prior therapy n (%)	96 (99)	112 (99)

ECOG= Eastern Cooperative Oncology Group; ISS= International Staging System; PI= Proteasome inhibitor; IMiD= Immunomodulatory drug; SCT= Stem cell transplant; NA= not applicable.

[a] Plasmacytomas were not assessed until prior to lymphodepletion.

Efficacy results were based on overall response rate as determined by the Independent Review Committee assessment using IMWG criteria (see Table 7).

Table 7: Efficacy results for Study MMY2001

Analysis set	All Treated (N=97)	All Leukapheresed (N=113)
Overall Response Rate (sCR[a] + VGPR + PR) n (%) 95% CI (%)	95 (97.9) (92.7, 99.7)	95 (84.1) (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) (months) Median (95% CI)	NE (28.3, NE)	-
DOR if best response is sCR[a] (months) Median (95% CI)	NE (28.3, NE)	-
Time to Response (months) Median (Range)	0.95 (0.9; 10.7)	-
MRD negativity rate n (%)[c] 95% CI (%)	56 (57.7) (47.3, 67.7)	56 (49.6) (40.0, 59.1)
MRD negative patients with sCR n (%)[c] 95% CI (%)	42 (43.3) (33.3, 53.7)	42 (37.2) (28.3, 46.8)

CI=confidence interval; MRD= Minimal Residual Disease; NE= not estimable

Notes: Based on a median duration of follow up of 28 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.

[c] 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. MRD negativity rate [(%) 95% CI] in evaluable patients (n=61) was 91.8% (81.9%, 97.3%).

CARTITUDE-4 (Study MMY3002)
MMY3002 is a Phase 3 randomised, open label, multicentre 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 randomised 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).

The trial excluded patients with known active or prior history of central nervous system involvement, clinical signs of meningeal involvement of multiple myeloma, a history of Parkinson's disease or other neurodegenerative disorder, previous exposure to other anti BCMA treatments or CAR T cell therapy directed at any target, allogenic stem cell transplant within 6 months before apheresis or ongoing treatment with immunosuppressants, or autologous stem cell transplant within 12 weeks before apheresis.

Of the 419 patients who were randomised (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: 28 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 randomised to the CARVYKTI arm underwent apheresis. Following apheresis and prior to administration of CARVYKTI, all 208 randomised 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/m2 intravenously daily and fludarabine 30 mg/m2 intravenously daily for 3 days) at a median dose of 0.71×106 CAR-positive viable T-cells/kg (range: 0.39 to 1.07×106 cells/kg).

The primary efficacy measure was progression-free survival (PFS) analysed based on the Intent-To-Treat Analysis Set. After a median follow-up of 15.9 months, median PFS was 11.8 months (95% CI: 9.7, 13.8) for the standard of care arm and NE (95% CI: 22.8, NE) for the CARVYKTI arm (Hazard ratio: 0.26 [95% CI: 0.18, 0.38], p-value <0.0001). 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 standard of care arm. In the CARVYKTI arm, the estimated median duration of response (DOR) has not been reached. In the standard of care arm, the estimated median DOR was 16.6 months (95% CI: 12.9, NE). After a median follow-up of 15.9 months, median overall survival (OS) was NE (95% CI: NE, NE) for the CARVYKTI arm

and 26.7 months (95% CI: 22.5, NE) for the standard of care arm (Hazard ratio: 0.78 [95% CI: 0.50, 1.20]; p-value = 0.2551).

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%).

MMY3002 updated efficacy results

At the protocol specified second interim analysis in Study MMY3002 at a median follow-up of 33.6 months, median PFS was not reached in the CARVYKTI arm. Median OS was not reached for either arm. A one time infusion of CARVYKTI demonstrates a statistically significant improvement in OS for participants treated with CARVYKTI as compared with standard of care therapy. PFS results are presented in Table 8 and Figure 1. OS results are presented in Table 8 and Figure 2.

Table 8: Summary of efficacy results for Study MMY3002 (Intent-To-Treat Analysis Set)

	CARVYKTI (N=208)	**Standard of Care (N=211)**
Progression-Free Survival[a,b]		
Number of events, n (%)	89 (42.8)	153 (72.5)
Median, months [95% CI][c]	NE [34.5, NE]	11.8 [9.7, 14.0]
Hazard ratio [95% CI][d]	0.29 [0.22, 0.39]	
Complete Response or Better Rate[b,e], % [95% CI]	73.1 [66.5, 79.0]	21.8 [16.4, 28.0]
p-value[f]	<0.0001	
Overall Response Rate (ORR)[b,e], % [95% CI]	84.6 [79.0, 89.2]	67.3 [60.5, 73.6]
p-value[f]	<0.0001	
Overall MRD Negativity Rate[e], % [95% CI]	60.6 [53.6, 67.3]	15.6 [11.0, 21.3]
p-value[g]	<0.0001	
Overall Survival (OS)[a]		
Number of events (%)	50 (24.0%)	83 (39.3%)
Number of censored (%)	158 (76.0%)	128 (60.7%)
Median, months [95% CI][c]	NE [NE, NE]	NE [37.75, NE]
Hazard ratio [95% CI][h]	0.55 [0.39, 0.79]	
p-value[i]	0.0009	

Key: NE=not estimable, CI = confidence interval.

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

[a] Second Interim analysis (data cut-off: 01 May 2024), with a median duration of follow-up of 33.6 months.

[b] Per the International Myeloma Working Group (IMWG) consensus, as assessed by computerised algorithm

[c] Kaplan-Meier estimate

[d] Based on a stratified Cox proportional hazards model, including only PFS events that occurred more than 8 weeks post-randomisation. A hazard ratio <1 indicates an advantage for the 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 randomised.

[e] Primary analysis (data cut-off: 01 November 2022), with a median duration of follow-up of 15.9 months.

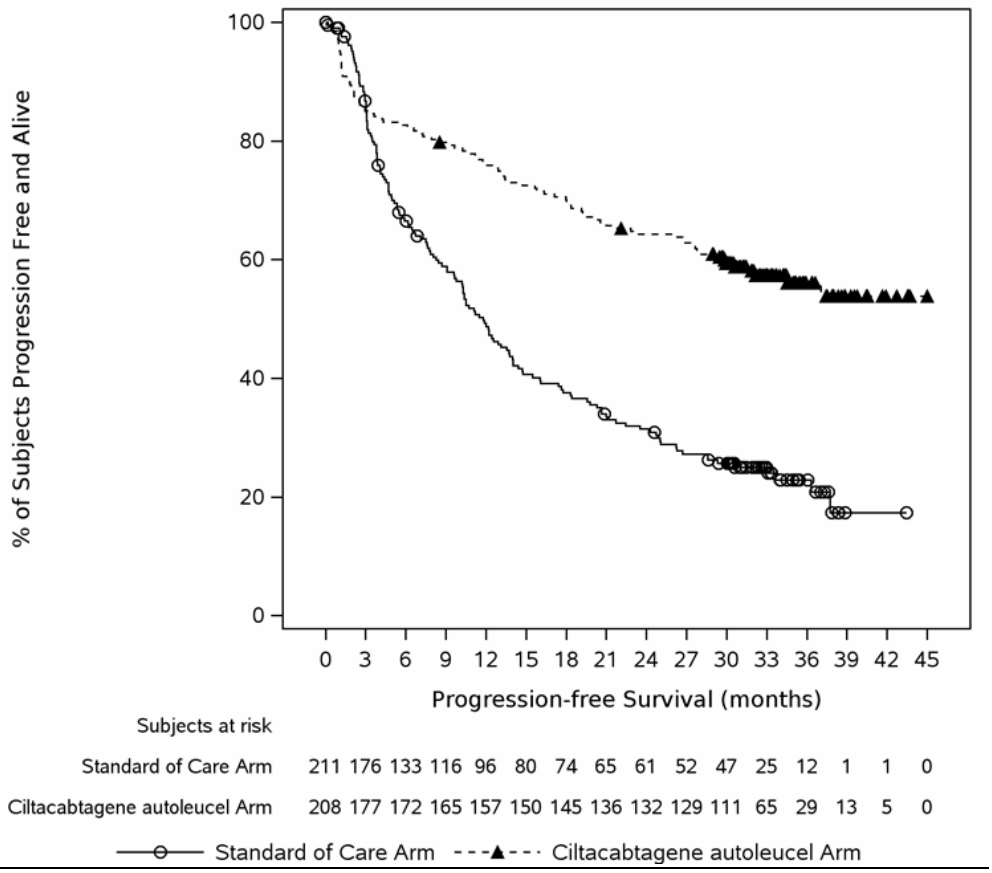
[f] Stratified Cochran-Mantel-Haenszel Chi-Squared test

[g] Fisher's exact test

[h] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized. A hazard ratio <1 indicates an advantage for the CARVYKTI arm.

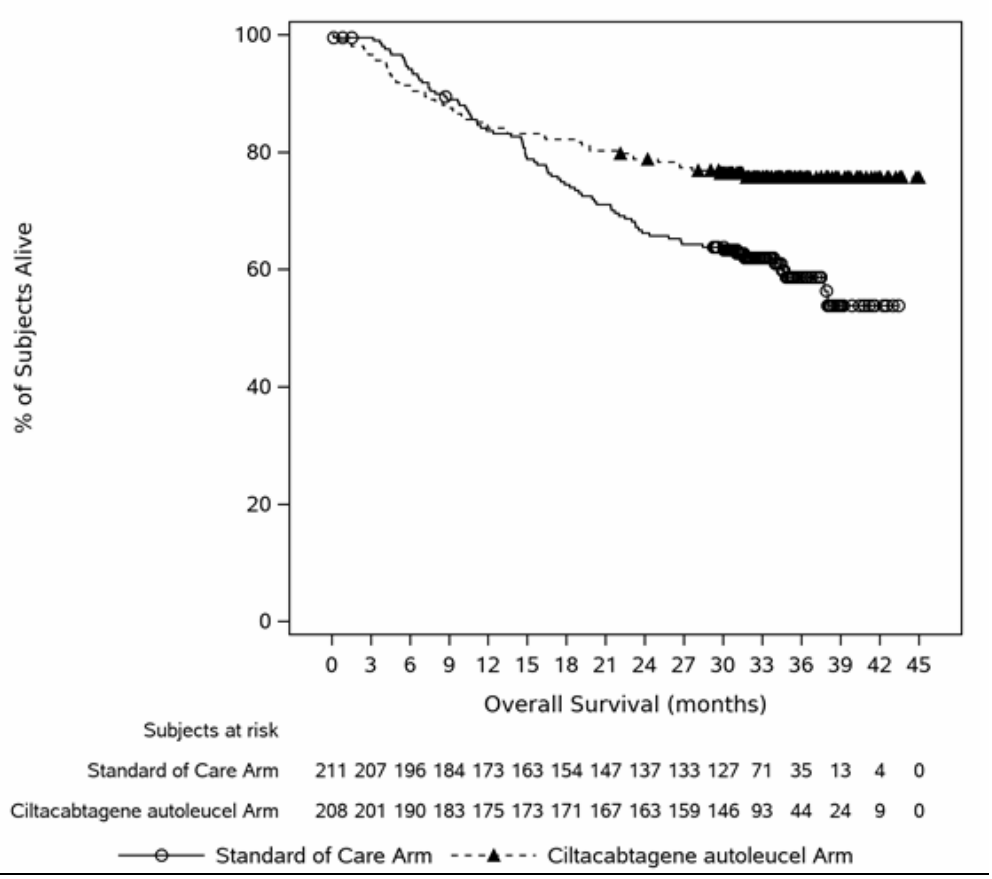
[i] p-value is based on the log-rank test stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized.

Figure 1: Kaplan-Meier Plot for updated PFS results; Intent-to-Treat Analysis Set (Study MMY3002)



Notes: PFS based on the second interim analysis with a median duration of follow up of 33.6 months. Intent-to-treat analysis set consists of subjects who were randomized in the study.
Key: Standard of Care Arm = PVd or DPd; Ciltacabtagene autoleucel Arm = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd=pomalidomide-bortezomib-dexamethasone; DPd=daratumumab-pomalidomide-dexamethasone.

Figure 2: Kaplan-Meier Plot for updated Overall Survival results; Intent-to-Treat Analysis Set (Study MMY3002)



Notes: OS based on the second interim analysis with a median duration of follow up of 33.6 months. Intent-to-treat analysis set consists of subjects who were randomized in the study.
Key: Standard of Care Arm = PVd or DPd; Ciltacabtagene autoleucel Arm = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd=pomalidomide-bortezomib-dexamethasone; DPd=daratumumab-pomalidomide-dexamethasone.

Paediatric population
The licensing authority has waived the obligation to submit the results of studies with CARVYKTI in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 9: Pharmacokinetic parameters of CARVYKTI in patients with multiple myeloma

Parameter	Summary Statistics	N=97
C_{max} (copies/µg genomic DNA)	Mean (SD), n	48692 (27174), 97
t_{max} (day)	Median (range), n	12.71 (8.73 – 329.77), 97
AUC_{0-28d} (copies*day/µg genomic DNA)	Mean (SD), n	504496 (385380), 97
AUC_{0-last} (copies*day/µg genomic DNA)	Mean (SD), n	1098030 (1387010), 97
AUC_{0-6m} (copies*day/µg genomic DNA)	Mean (SD), n	1033373 (1355394), 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 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.

Special populations

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.

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).

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.

5.3 Preclinical safety data

CARVYKTI comprises engineered human T cells; therefore, there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for medicinal product development were not performed.

Carcinogenicity and mutagenicity

No genotoxicity or carcinogenicity studies have been performed.

The risk for insertional mutagenesis occurring during the manufacturing of CARVYKTI 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 samples from 6 multiple myeloma patients and from 3 samples from 3 healthy donors. There was no evidence for preferential integration near genes of concern.

Reproductive toxicology

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

No studies have been conducted to evaluate the effects of CARVYKTI on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS5

6.2 Incompatibilities

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

6.3 Shelf life

9 months.

Once thawed: maximum 2.5 hours at room temperature (20 °C to 25 °C).
CARVYKTI infusion must be administered immediately after thawing and completed within 2.5 hours.

Thawed medicinal product should not be shaken, refrozen or refrigerated.

6.4 Special precautions for storage

CARVYKTI must be stored and transported in the vapour phase of liquid nitrogen (≤ -120 °C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration. Do not re-freeze after thawing.

Keep infusion bag in the aluminium cryo cassette.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Ethylene vinyl acetate (EVA) infusion bag with sealed addition tube and two available spike ports containing either 30 mL (50 mL bag) or 70 mL (250 mL bag) of cell dispersion.

Each infusion bag is packed in an aluminium cryo cassette.

6.6 Special precautions for disposal

CARVYKTI should not be irradiated as irradiation could inactivate the medicinal product.

Precautions to be taken before handling or administering the medicinal product

CARVYKTI should be transported within the facility in closed, break-proof and leak-proof containers.

This medicinal product contains human blood cells. Healthcare professionals handling CARVYKTI should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

CARVYKTI must remain ≤ -120 °C at all times, until the content of the bag is thawed for infusion.

Preparation prior to administration

The timing of CARVYKTI thaw and infusion should be coordinated; the infusion time should be confirmed in advance, and the start time for thaw must be adjusted so that CARVYKTI is available for infusion when the patient is ready. Once thawed, the medicinal product should be administered immediately and the infusion should be completed within 2.5 hours.

- Prior to CARVYKTI preparation, patient identity should be confirmed by matching the patient's identity with the patient identifiers on the CARVYKTI cryo cassette and Lot Information Sheet. The CARVYKTI infusion bag should

not be removed from the cryo cassette if the information on the patient-specific label does not match the intended patient.

- Once patient identification is confirmed, the CARVYKTI infusion bag should be removed from the cryo cassette.
- The infusion bag should be inspected for any breaches of container integrity such as breaks or cracks before and after thawing. Do not administer if the bag is compromised and contact Janssen-Cilag Ltd.

Thawing

- The infusion bag should be placed inside a sealable plastic bag prior to thawing.
- CARVYKTI should be thawed at 37 °C±2 °C using either a water bath or dry thaw device 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.
- The infusion bag should be removed from the sealable plastic bag and wiped dry. The contents of the infusion bag should be gently mixed to disperse clumps of cellular material. If visible cell clumps remain, the contents of the bag should continue to be gently mixed. Small clumps of cellular material should disperse with gentle manual mixing. CARVYKTI must not be pre-filtered into a different container, washed, spun down, and/or resuspended in new media prior to infusion.
- Once thawed, the medicinal product should not be re-frozen or refrigerated.

Administration

- CARVYKTI is for autologous single use only.
- Prior to infusion and during the recovery period, ensure tocilizumab and emergency equipment are available for use.
- Confirm the patient's identity with the patient identifiers on the CARVYKTI infusion bag and Lot Information Sheet. Do not infuse CARVYKTI if the information on the patient-specific label does not match the intended patient.
- Once thawed, the entire contents of the CARVYKTI bag should be administered by intravenous infusion within 2.5 hours at room temperature (20 °C to 25 °C), using infusion sets fitted with an in-line filter. The infusion usually takes less than 60 minutes.
- 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 for injection to ensure all medicinal product is delivered.

<u>Precautions to be taken for the disposal of the medicinal product</u>

Unused medicinal product and all material that has been in contact with CARVYKTI (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

Accidental exposure

In case of accidental exposure local guidelines on handling of human-derived material should be followed. Work surfaces and materials which have potentially been in contact with CARVYKTI must be decontaminated with appropriate disinfectant.

7 MARKETING AUTHORISATION HOLDER

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UK

8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

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