27 February 2024
EMA/OD/0000141581
EMADOC-1700519818-1327771
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Carvykti (ciltacabtagene autoleucel; autologous human T cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen)
Treatment of multiple myeloma
EU/3/20/2252

Sponsor: Janssen - Cilag International N.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Autologous human T cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen
Other name(s)	Carvykti; CAR-T cell therapy - Nanjing; JNJ 4528; JNJ-68284528; LCAR-B38M
International Non-Proprietary Name	Ciltacabtagene autoleucel
Tradename	Carvykti
Orphan condition	Treatment of multiple myeloma
Sponsor's details:	Janssen - Cilag International N.V. Turnhoutseweg 30 2340 Beerse Antwerp Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Janssen - Cilag International N.V.
COMP opinion	22 January 2020
EC decision	28 February 2020
EC registration number	EU/3/20/2252
Post-designation procedural history	
Type II variation	
Rapporteur / Co-rapporteur	Jan Mueller-Berghaus / Marcos Timón
Applicant	Janssen - Cilag International N.V.
Application submission	25 May 2023
Procedure start	17 June 2023
Procedure number	EMA/H/C/0005095/II/0021
Invented name	Carvykti
Proposed therapeutic indication extension	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. Further information can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Carvykti
CHMP opinion	22 February 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Maria Elisabeth Kalland / Karri Penttila
Sponsor's report submission	20 June 2023
COMP discussion	13-15 February 2024

COMP opinion (adoption via written procedure)	27 February 2024

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing Autologous human T cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen was considered justified based on clinical data demonstrating a high overall response rate;
- the condition is chronically debilitating due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with a reduced life expectancy;
- the condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made;
- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Autologous human T cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who were heavily pre-treated with regimens including immunomodulators, proteasome inhibitors and anti-CD38 antibody, achieved high overall response rates including a high proportion of complete responses. The Committee considered that this constitutes a clinically relevant advantage.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of multiple myeloma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 4.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening due to development of hypercalcemia, renal insufficiency, anaemia, bone lesions, and reduced life expectancy;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Carvykti may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data that demonstrated improved and sustained complete response rates after treatment with Carvykti as compared to Abecma in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an

immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph) of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Carvykti, autologous human T cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen, ciltacabtagene autoleucel for treatment of multiple myeloma (EU/3/20/2252) is not removed from the Community Register of Orphan Medicinal Products.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Multiple myeloma (MM; also known as plasma cell myeloma) is a heterogeneous hematological B-cell malignancy characterized by dysregulated proliferation of plasma cells that clonally expand and accumulate in the bone marrow and/or at extramedullary sites, with potential for uncontrolled growth causing destructive osseous bone lesions, acute kidney injury, anemia, and hypercalcemia. The disease accounts for about 10-18% of all hematologic malignancies (Moreau et al., 2017; Siegel et al., 2020) and primarily affects older individuals (Howlader et al., 2020). The median age at onset of MM is around 72 years. The incidence rates increase with age, particularly after the age of 40 years, and are higher in men than in women with a ratio of around 3:2. The disease is often asymptomatic for a long time and therefore advanced at the time of diagnosis (Rajkumar et al., 2014).

The clonal plasma cells that cause MM are derived from post-germinal center B-cells. In a healthy individual, following antigen exposure (e.g., viral or bacterial infections), naive B-cells normally proliferate and subsequently undergo somatic hypermutation of the immunoglobulin (Ig)H and IgL VDJ sequences. This process produces long-lived plasma cells (a subset of plasma cells that provide long-lasting, sustained antibody production) that reside in the bone marrow and are an important component of humoral immunity. The development of an abnormal clonal plasma cell population mimics these normal biological processes but results in excessive amounts of intact immunoglobulins. In almost all patients, MM begins as an asymptomatic pre-malignant stage termed monoclonal gammopathy of unknown significance (MGUS), a clonal plasma cell dyscrasia present in 3% to 5% of people older than 65 years and in 10% of those older than 80 years. MGUS is associated with progression to active (symptomatic) MM, at a rate of approximately 1% to 2% per year, with a 20-year risk of progression to MM of approximately 18%. Only a few patients develop MM from the more advanced pre-malignant stage referred to as smouldering MM (SMM). The malignant proliferation of the plasma cell clone causes increasing levels of monoclonal protein (M-protein) in the serum and urine

and may result in bone marrow failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction. The level of M-protein in plasma serves as a reflection of the disease burden over time.

Among patients newly diagnosed with MM, approximately 3.3% present with extramedullary disease. Approximately 10% to 15% of patients with MM are diagnosed with concurrent immunoglobulin light chain amyloidosis during the course of their disease.

Approximately 86% of people with MM reveals a monoclonal protein in the serum protein electrophoresis, defined as the presence of an atypical antibody in the blood. A 24-hour urine protein test to quantify Bence-Jones protein is important to document the presence of baseline proteinuria and evaluate for evidence of secondary light-chain amyloidosis, which often manifests as nephrotic range proteinuria. CT or PET-CT are preferred for diagnosis of MM and should be used to evaluate patients with SMM when the clinical suspicion for MM is high (Cowan*, JAMA. 2022; 327(5): 464-477*).

The approved extension of the therapeutic 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 an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide*" falls within the scope of the designated orphan condition "Treatment of multiple myeloma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CAT/CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

MM is a largely incurable blood cancer characterized by the clonal proliferation of malignant plasma cells both within the bone marrow and at localized extramedullary sites termed plasmacytomas (Rajkumar, 2016a). The malignant proliferation of the plasma cell clone causes increasing levels of monoclonal protein (M-protein) in the serum and urine and may result in bone marrow failure, suppression of uninvolved immunoglobulin levels, and skeletal destruction.

The most common presenting symptoms of MM are fatigue, persistent bone pain, especially in the lower back or thorax, and opportunistic infections (often pneumococcal). Other common symptoms include pathologic fractures, spinal cord compression (from pathologic fracture), weakness, malaise, anaemia and/or bleeding, hypercalcemia, renal insufficiency, and neuropathies (Shah and Besa, 2018). Clinical complications of progressive MM include recurrent infections due to decreased production of antibodies, cytopenias (especially anaemia, but also thrombocytopenia, and neutropenia), renal failure due to the protein overload, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures (Munshi et al., 2012).

Over the past 20 years, substantial progress has been made in improving response rates, durability of responses and ultimately the overall survival (OS) of patients with MM through the development and availability of novel non-chemotherapy targeted treatment options. The more recently approved targeted therapies (anti-CD38, anti-SLAMF7, anti-BCMA) and immunotherapeutic approaches (such as CAR-T cell products) have led to substantial improvement in patient outcomes. However, despite recent advances in treatment, MM remains an incurable disease (Nadeem and Anderson, 2020) and most MM patients, even those who initially respond to treatment, are expected to progress or relapse with a median survival of approximately 8-10 years (Gulla & Anderson, 2020). In addition, each subsequent line of therapy renders patients with MM more refractory to treatment. For instance, the prognosis of patients with MM who have received at least 3 prior lines of therapy, who have become

double refractory to an immunomodulatory drug (IMiD; lenalidomide or pomalidomide) and a proteasome inhibitor (PI; bortezomib or carfilzomib), and who have been exposed to an alkylating agent, is very poor with an event-free survival and OS of only 5 and 13 months, respectively (Kumar et al., 2017). It is hence acknowledged that the condition remains a serious and potentially fatal disease that is largely incurable despite advances in treatment.

The sponsor has not identified any substantial changes in the seriousness of MM since the orphan designation was granted in 2020 and the criteria was reviewed and considered maintained at the time of the conditional marketing authorisation (CMA) on 25-May-2022. Although four new anti-myeloma therapies (teclistamab, melphalan flufenamide, talquetamab, and elranatamab) have been authorised in the EU since the marketing authorisation of Carvykti, they are all approved for the treatment of MM patients who are triple-class exposed or triple- or higher-class refractory in the fourth- and later lines setting, which has resulted in a therapeutic vacuum for patients in early line relapse.

The COMP has previously accepted that MM is chronically debilitating due to the development of hypercalcemia, renal insufficiency, anaemia and/or bleeding, frequent infections, and bone lesions, and life-threatening in nature due to the poor survival of patients with relapsed and refractory (RR) disease. The seriousness of MM earlier acknowledged by the COMP remains acceptable for this procedure.

Number of people affected or at risk

At the time of maintenance of the orphan designation in 2022, the COMP concluded that the condition was estimated to be affecting approximately 4.6 in 10,000 persons in the European Union (EU).

The sponsor selected the interactive web-based European Cancer Information System (ECIS) database and contemporary literature as the primary and most relevant sources for the estimation of the current incidence and prevalence of MM in the EU. The estimated crude incidence of MM for the 27 EU member states (EU27) was reported by ECIS to be 0.79 per 10,000 persons in 2022. The sponsor noted that males have a higher estimated crude incidence of MM than females in the EU27 with 0.86 versus 0.72 per 10,000 persons, respectively (ECIS; 2022 data).

The sponsor highlighted that a median overall survival (mOS) for the whole MM population has not been reported and that it is influenced by various factors such as age, International Staging System (ISS) stage at diagnosis, and line of treatment. To approximate the most comprehensive and up to date estimates of mOS, the sponsor utilized data from recent publications. Based on these data, the mOS for ISS stage I/II patients, who represent 60-70% of all MM patients, is approximately 7 years. For ISS stage III patients, who represent 30-40% of all MM patients, the mOS is approximately 1-4 years (Blimark et al., 2018, Cho et al., 2017; Greipp et al., 2005; Kastritis et al., 2017; Szabo et al., 2019, Usmani et al., 2018; Verelst et al., 2018).

Using the varying distributions of 30/70% and 40/60% for ISS stage I/II and stage III and mOS of 1-4 years for ISS stage III, a mOS of 4.6 to 6.1 years for the entire patient population can be estimated, which results in a prevalence estimate within the range of 3.63 to 4.82 per 10,000 persons. The mOS for the whole MM population is therefore estimated to be 5.8 years ([7 years*0.6) + (4 years*0.4)]. Using the standard formula P (point prevalence) = I (incidence) × D (mean duration) for indirectly establishing the prevalence, the prevalence of MM is estimated to be (0.79*5.8) = **4.58 per 10,000** persons in the EU. It should be noted that the weighted mOS calculated above is comparable to the mOS of 5.7 years (95% CI: 5.4, 6.3) which was reported for 3,449 MM patients diagnosed between 2004-2017 and seen at the Mayo Clinic in the US (Nandakumar et al., 2019).

Data from the International Agency for Research on Cancer (IARC)'s Globocan surveillance project (2020 data), the Association of the Nordic Cancer Registries (NORDCAN v9.3; Larønningen et al., 2023), the Netherlands Cancer Registry (IKNL; 2023 data), and the Czech National Cancer Registry (CNCR; 2023 data) were consulted as secondary sources of information for the estimation of the prevalence.

A 5-year prevalence of 3.08 per 10,000 people in the EU27 was estimated based on data from the Globocan database. However, the 5-year prevalence only represents a partial prevalence. It was noted that 5 years of surveillance may not be long enough to capture everyone with prevalent MM as survival of MM has improved in recent years due to novel treatments. The 10-year- and complete prevalence estimates will therefore better reflect the actual prevalence of MM, especially as patients live longer with the disease. Table 1 presents the 10-year partial prevalence and complete prevalence estimates from the EU population-based cancer registries. The EU-based registries provided slightly higher 10-year and total prevalence estimates, with an average 10-year prevalence of 4.03 per 10,000 persons and an average total prevalence of **4.39 per 10,000** persons across the five EU countries.

Table 1. 10-year and total prevalence of MM from population-based cancer registries in EU countries.

Country	10-year prevalence (number)	10-year prevalence per 10,000 persons	Total prevalence (number)	Total prevalence per 10,000 persons
Denmark	3093	5.26	3577	6.08
Finland	1731	3.12	2181	3.93
Sweden	4149	3.97	4962	4.75
Netherlands	6530	3.75	7462[a]	4.29
Czech Republic	NR	NR	3107	2.90
Average	---	**4.03**	---	**4.39**

EU=European Union; NR=not reported
[a]20-year prevalence reported from the Netherlands Cancer Registry
Sources:
https://nordcan.iarc.fr/en/dataviz/prevalence_table?years=2021&years_available=1943_2021&sexes=0&cancers=380
https://nkr-cijfers.iknl.nl/viewer/prevalentie-per-jaar?language=en&viewerId=c64bd8f1-8e0d-4bfd-a7ca-4be54770c5ae
https://www.mzcr.cz/wp-content/uploads/2022/07/NOPL-CR-2030-annexe-1-summary-of-analytical-study.pdf

Based on the review of the epidemiological data sources found and the assumptions made for the calculations as presented above, the sponsor considered that **4.6 per 10,000** people is the most contemporary, conservative estimate of the prevalence of MM in the EU. The sponsor concluded that the true prevalence for MM remain below the orphan designation threshold of 5 per 10,000 persons. The proposed estimate is in line with the prevalence figures accepted in recent designations and for the latest orphan maintenance procedures evaluated for MM. The prevalence estimate presented by the sponsor is based on comparable data sources, but with a focus on more recent data, to those used in the estimation accepted for the orphan maintenance of cilta-cel at the time of the CMA in 2022. The COMP therefore came to the same conclusion for this procedure, that MM affects **approximately 4.6 in 10,000** people in the EU.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are several medicinal products authorised in the European Community for treatment of MM. Central marketing authorisations (MAs) include doxorubicin (Caelyx pegylated liposomal), daratumumab (Darzalex), carfilzomib (Kyprolis), bortezomib (Velcade and generics), lenalidomide (Revlimid and generics), thalidomide (generics), panobinostat (Farydak), elotuzumab (Empliciti), ixazomib (Ninlaro), pomalidomide (Imnovid), dexamethasone (Neofordex and generics), isatuximab (Sarclisa), selinexor (Nexpovio), idecabtagene vicleucel (hereinafter referred to as ide-cel, Abecma (CMA in Aug-2021), ciltacabtagene autoleucel (hereinafter referred to as cilta-cel, Carvykti; CMA in May-2022), melphalan flufenamide (Pepaxti), teclistamab (Tecvayli; CMA in Aug-2022), talquetamab (Talvey; CMA in Aug-2023), and elranatamab (Elrexfio; CMA in Dec-2023).).

Several products are also authorised at the national level for treatment of MM, including carmustine, cyclophosphamide, doxorubicin, bendamustine, epirubicin, melphalan and vincristine. As defined by their approved therapeutic indications, these medicines are approved for use across the MM continuum (i.e., from newly diagnosed to heavily RR disease) and are often used in combination.

Carvykti (cilta-cel) was granted a conditional MA in the EU (Product No. EMEA/H/C/005095) on 25-May-2022 and is authorised for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received *at least three prior therapies*, including an IMiD, a PI and an anti CD38 mAb and have demonstrated disease progression on the last therapy. This indication extension of cilta-cel is intended to include treatment of adult patients with RRMM in two earlier lines after at least one therapy, including an IMiD and a PI, who have demonstrated disease progression on the last therapy and are refractory to lenalidomide.

The European Hematology Association (EHA) and European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment and follow-up of MM describe some of the recommended treatment options available for RRMM patients at first relapse, which is primarily determined by the first-line treatment received and refractoriness to specific agents (Figure 1; Dimopoulos et al., 2021). Of the medicinal products authorised in the EU for the treatment of MM, the products presented in Table 2 are authorised in the relapsed/refractory setting. The current treatment options for lenalidomide-refractory patients in second line of therapy are the approved combination regimens with either pomalidomide (PVd), daratumumab (DVd), or selinexor (SVd) plus bortezomib and dexamethasone, daratumumab in combination with pomalidomide and dexamethasone (DPd), or daratumumab (DKd) or isatuximab (IsaKd) in combination with carfilzomib and dexamethasone.

Ninlaro (ixazomib citrate) is also authorised in the second- and later lates setting, but as a regimen in combination with lenalidomide and dexamethasone, and hence is not an alternative treatment option for lenalidomide-refractory patients. Moreover, the medicinal products panobinostat (Farydak), elotuzumab (Empliciti) for those who are refractory to lenalidomide, ide-cel (Abecma), teclistamab (Tecvayli), talquetamab (Talvey), elranatamab (Elrexfio), and melphalan flufenamide (Pepaxti), are approved for the treatment of patients with RRMM in either the third- or fourth- and later lines setting. These medicines have therefore more restricted therapeutic indications as compared to that currently applied for cilta-cel. The proposed extension of the indication for cilta-cel hence includes a broader patient population than the one approved for the above-mentioned medicinal products.

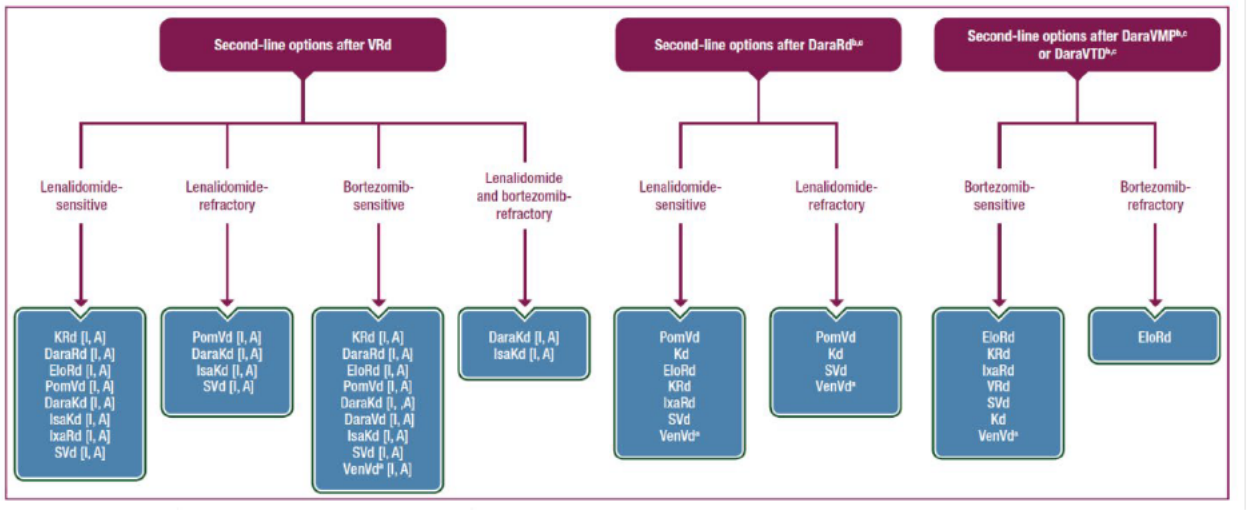

Figure 1. EHA-ESMO Guideline on the Treatment of MM at First Relapse.

The three different flow-charts shown in this figure depict three different scenarios – depending on the first-line treatment given (from left to right):

- Second-line options after VRd first-line treatment
- Second-line options after DaraRd first-line treatment and
- Second-line options after DaraVMP or DaraVTD first-line treatment.

Dara=daratumumab; Elo=elotuzumab; Isa=isatuximab; K=carfilzomib; Kd=carfilzomib/dexamethasone; PomVd=pomalidomide/bortezomib/dexamethasone; Rd=lenalidomide/dexamethasone; S=selinexor; Vd=bortezomib/dexamethasone; VMP=bortezomib/melphalan/prednisone; VRd=bortezomib/lenalidomide/dexamethasone; Ven=venetoclax; VTD=bortezomib/thalidomide/dexamethasone. (Dimopoulos 2021a).

a Patients with t(11;14).

b Patients who progress while on monthly Dara are considered as Dara-refractory.

c All recommendations for patients who receive front-line therapy with Dara-based therapies are based on panel consensus as there are no trials evaluating regimens in second-line therapy that include patients refractory or exposed to Dara.

Table 2. Products approved for relapsed/refractory MM treatment in the EU.

EU Agency Product Number	Product Name (INN)	Approved Therapeutic Indication	Significant Benefit Discussion Needed?
EMEA/H/C/000539	Velcade (bortezomib)	As monotherapy, or in combination with pegylated liposomal doxorubicin or dexamethasone, for the treatment of adult patients with progressive MM who have received at least 1 prior therapy and who have already undergone or are unsuitable for hematopoietic stem cell transplantation.	Yes, complete overlap of product indication with the proposed cilta-cel indication.
EMEA/H/C/003790	Kyprolis (carfilzomib)	In combination with daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone for the treatment of adult patients with MM who have received at least 1 prior therapy.	Yes, complete overlap of product indication with the proposed cilta-cel indication.
EMEA/H/C/003844	Ninlaro (ixazomib)	In combination with lenalidomide and dexamethasone for the treatment of adult patients with MM who have received at least 1 prior therapy.	No, despite the overlap of product indication with the proposed cilta-cel indication, ixazomib is indicated in combination with lenalidomide, while cilta-cel is indicated in lenalidomide-refractory patients.
EMEA/H/C/000717	Revlimid (lenalidomide)	In combination with dexamethasone for the treatment of MM in adult patients who have received at least 1 prior therapy.	No, despite the overlap of product indication with the proposed cilta-cel indication, cilta-cel is indicated in lenalidomide--refractory patients.

EMEA/H/C/002682	Imnovid (pomalidomide)	In combination with bortezomib and dexamethasone in the treatment of adult patients with MM who have received at least 1 prior treatment regimen including lenalidomide; in combination with dexamethasone for the treatment of adult patients with RRMM who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.	Yes, complete overlap of product indication with the proposed cilta-cel indication.
EMEA/H/C/004077	Darzalex (daratumumab)	In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with MM who have received at least 1 prior therapy; in combination with pomalidomide and dexamethasone for the treatment of adult patients with MM who have received 1 prior therapy containing a PI and lenalidomide and were lenalidomide-refractory, or who have received at least 2 prior therapies that included lenalidomide and a PI and have demonstrated disease progression on or after the last therapy; or as monotherapy for the treatment of adult patients with RRMM, whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy.	Yes, complete overlap of product indication with the proposed cilta-cel indication.
EMEA/H/C/004977	Sarclisa (isatuximab)	In combination with pomalidomide and dexamethasone, for the treatment of adult patients with RRMM who have received at least 2 prior therapies including lenalidomide and a PI and have demonstrated disease progression on the last therapy; and in combination with carfilzomib and dexamethasone, for the treatment of adult patients with MM who have received at least 1 prior therapy.	Yes, complete overlap of product indication with the proposed cilta-cel indication.
EMEA/H/C/003725	Farydak (panobinostat)	In combination with bortezomib and dexamethasone for the treatment of adult patients with relapsed and/or refractory MM who have received at least 2 prior regimens including bortezomib and an IMiD.	No, product indication covers only patients with relapsed and/or refractory MM from the third line onwards.
EMEA/H/C/003967	Empliciti (elotuzumab)	In combination with lenalidomide and dexamethasone for the treatment of MM in adult patients who have received at least 1 prior therapy; and in combination with pomalidomide and dexamethasone for the treatment of adult patients with RRMM who have received at least 2 prior therapies including lenalidomide and a PI and have demonstrated disease progression on the last therapy.	No, despite the overlap of product indication with the proposed cilta-cel indication in patients who had received at least 1 prior therapy, cilta-cel is indicated in lenalidomide--refractory patients. The additional product indication covers only patients with relapsed and/or refractory MM from the third line onwards.
EMEA/H/C/000089	Caelyx pegylated liposomal (doxorubicin)	In combination with bortezomib for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplant.	No, despite the overlap of product indication with the proposed cilta-cel indication, the product is not considered standard of care in the treatment setting and it is not recommended per ESMO guidelines. The approved indication is also restricted to MM patients who are ineligible for bone marrow transplant.
EMEA/H/C/005330	Celdoxome pegylated liposomal (doxorubicin)		
EMEA/H/C/005681	Pepaxti (melphalan flufenamide)	In combination with dexamethasone, for the treatment of adult patients with MM who have received at least 3 prior lines of therapies, whose disease is refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to	No, product indication covers only patients with relapsed and/or refractory MM from the fourth line onwards.

		progression should be at least 3 years from transplantation.	
EMEA/H/C/005127	Nexpovio (selinexor)	In combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received at least 1 prior therapy; and in combination with dexamethasone for the treatment of MM in adult patients who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, 2 IMiDs and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.	Yes, complete overlap of product indication with the proposed cilta-cel indication.
EMEA/H/C/004662	Abecma (idecabtagene vicleucel)	For the treatment of adult patients with RRMM who have received at least 3 prior therapies, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	No, product indication covers only patients with relapsed and/or refractory MM from the fourth line onwards.
EMEA/H/C/005865	Tecvayli (teclistamab)	As monotherapy for the treatment of adult patients with RRMM, who have received at least 3 prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	No, product indication covers only patients with relapsed and/or refractory MM from the fourth line onwards.
EMEA/H/C/005864	Talvey (talquetamab)	As monotherapy for the treatment of adult patients with RRMM, who have received at least 3 prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	No, product indication covers only patients with relapsed and/or refractory MM from the fourth line onwards.
EMEA/H/C/005908	Elrexfio (elranatamab)	As monotherapy for the treatment of adult patients with RRMM, who have received at least 3 prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	No, product indication covers only patients with relapsed and/or refractory MM from the fourth line onwards.

In conclusion, the approved triplet regimens with the anti-CD38 therapies daratumumab (Darzalex; DVd, DPd, and DKd) and isatuximab (Sarclisa; IsaKd), the selective XPO1-mediated nuclear export inhibitor selinexor (Nexpovio; SVd), and pomalidomide (Imnovid; PVd) are all considered satisfactory methods of treatment relevant for a discussion on the significant benefit of cilta-cel in the target MM population as their indications are covering the indication extension proposed for cilta-cel.

Significant benefit

The sponsor did not receive any protocol assistance from EMA regarding the evidence needed to demonstrate significant benefit of cilta-cel over satisfactory methods of treatment for patients with relapsed and lenalidomide-refractory MM who have received at least one prior therapy.

The claim of significant benefit is based on the results from an ongoing, open-label, multicenter, randomised, controlled phase 3 study MMY3002 (also referred to as CARTITUDE-4), which is used to obtain the pivotal evidence for cilta-cel in the parallel variation application for an extension of the indication to include treatment of adult patients with RRMM in two earlier treatment lines. The study was designed to determine whether treatment with cilta-cel provides a benefit compared to standard of care therapy (PVd or DPd) in patients with relapsed and lenalidomide-refractory MM who had received 1 to 3 prior lines of therapy, including an IMiD and PI, and had documented disease progression. Enrolled patients were randomised in a 1:1 ratio to arm A (standard therapy with PVd or DPd; N=211 ITT/n=208 mITT) or arm B (sequence of apheresis, at least 1 cycle of bridging therapy, lymphodepletion, and cilta-cel infusion; N=208) and stratified by investigator's choice (PVd vs. DPd),

ISS staging at screening (I vs. II vs. III), and number of prior lines of therapy (1 vs. 2 or 3 prior anti-myeloma regimens).

The primary endpoint was progression-free survival (PFS) per validated computer algorithm according to the International Myeloma Working Group (IMWG) response criteria (Durie et al., 2015, Kumar et al., 2016, Rajkumar et al., 2011). Key secondary endpoints were complete response (CR)/ stringent CR (sCR) rate, overall response rate (ORR), overall minimal residual disease (MRD) negativity rate, OS, and time to worsening of symptoms in the MySIm-Q total symptom score, which were tested sequentially using a hierarchical procedure to control type I error rate at a 2-sided significance level of 0.05 (overall). Other secondary endpoints included duration of response (DoR), PFS on next line of therapy (PFS2), time to subsequent anti-myeloma treatment, rate of sustained MRD negativity, and time to disease progression. The enrolled (intent to treat [ITT]) population was defined as the primary analysis population. The data cut-off (DCO) date for the efficacy data provided from study MMY3002, which corresponds to the protocol-specified interim analysis of PFS, was 01-Nov-2022. At this DCO, the median duration of follow-up was 15.9 months.

The sponsor pursued two different approaches to establish the significant benefit of cilta-cel over the satisfactory methods of treatment.

- Conducted efficacy analysis based on clinical data from the pivotal study MMY3002:
    - Comparative analysis of cilta-cel versus the approved regimen DPd and PVd.
    - An analysis of treatment outcomes with cilta-cel in study MMY3002 participants who had failed prior treatment with daratumumab, isatuximab, bortezomib, carfilzomib, and pomalidomide.
- Performed matching-adjusted indirect comparisons (MAIC) of efficacy outcomes across clinical studies, between participants treated with cilta-cel in study MMY3002 and participants treated with the approved combination regimens with isatuximab (IsaPd) and selinexor (SVd) in their respective registrational studies. However, the triplet regiment with isatuximab plus pomalidomide and dexamethasone which is included in the conducted MAIC is authorised in the third- and later lines for MM patients who are lenalidomide-refractory and hence will not be further discussed.

Significant benefit of cilta-cel over the triplet regimens with daratumumab (DPd) and pomalidomide (PVd)

Direct comparison of DPd or PVd versus cilta-cel in study MMY3002 (sub-group analyses)

Per protocol, participants in both treatment arms were to receive a standard regimen (DPd or PVd), either as study treatment (for participants randomised to arm A) or as bridging therapy following apheresis and prior to cilta-cel infusion (for participants randomised to arm B). These two standard regimens were used as comparators in the control arm A of study MMY3002.

A subgroup analysis of the primary endpoint was conducted per regimen included in the comparator arm based on computerised algorithm by investigator's choice of DPd or PVd. HR was 0.26 (95% CI: 0.18, 0.39; CPW method) or 0.31 (95% CI: 0.13, 0.72; CPW method) for participants randomised to arm B who received either DPd or PVd, respectively, as bridging therapy prior to cilta-cel infusion versus arm A participants who received either DPd or PVd as study treatment.

Subgroup analyses of the rate of CR or better and ORR were also conducted based on computerised algorithm by investigator's choice of DPd or PVd for the ITT analysis set. The rate of CR or better was 75.3% or 57.7% in arm B for participants who received either DPd or PVd, respectively, as bridging

therapy followed by cilta-cel as study treatment, and 24.0% or 7.1% in arm A for participants who received either DPd or PVd as study treatment with an odds ratio of 9.6 (95% CI: 6.0, 15.5) or 17.7 (95% CI: 3.5, 91.0), respectively. The ORR was also higher for arm B than for arm A with an value of 86.8% (95% CI: 81.0, 91.4) or 69.2% (95% CI: 48.2, 85.7) in arm B for participants who received either DPd or PVd, respectively, as bridging therapy followed by cilta-cel as study treatment and 69.4% (95% CI: 62.2, 76.0) or 53.6% (95% CI: 33.9, 72.5) in arm A for participants who received either DPd or PVd as study treatment with an odds ratio of 2.9 (95% CI: 1.7, 4.9) or 2.0 (95% CI: 0.6, 6.0), respectively.

Based on the outcome of the direct comparison of cilta-cel to DPd and PVd in the randomised phase 3 study MMY3002, the sponsor considered that the documentation of statistically significant and clinically meaningful improvement of PFS and CR or better deep response rates, and higher ORR in patients treated with cilta-cel establishes the claim of significant benefit over these two standard regimens.

The clinical data derived from the pivotal, comparative study MMY3002 demonstrated the ability of cilta-cel to prolong PFS and improve deep response rates. The COMP considered this sufficient to support the basis of significant benefit based on a clinically relevant advantage in terms of improved efficacy in comparison to the authorised regimens with daratumumab (DPd) and pomalidomide (PVd) for adult patients with relapsed and lenalidomide-refractory MM who have received at least one prior therapy.

Significant benefit over daratumumab (DVd and DKd) and isatuximab (IsaKd)

The analysis of the treatment outcomes with cilta-cel in study MMY3002 participants who had failed prior treatment with daratumumab, bortezomib, and carfilzomib is based on the 208 participants randomised to arm B in study MMY3002 who comprised the ITT analysis set for this treatment arm. Table 3 provides the median PFS and 12-month PFS rate, while Table 4 presents the ORR, based on the anti-myeloma therapies that participants received prior to enrolment and treatment with cilta-cel in study MMY3002, especially for those participants who were exposed to these prior therapies (left) and for those participants whose disease was refractory to these prior therapies (right).

The median PFS was 19.3 months (95% CI: 13.2, NE) and 18.0 months (95% CI: 9.3, 22.8) for participants who were refractory to bortezomib (n=55) and for participants who were refractory to daratumumab (n=48), respectively. The 12-month PFS rates >50% were observed among participants who were refractory to the PIs bortezomib (65.2%; 95% CI: 51.0, 76.2) and carfilzomib (72.5%; 95% CI: 58.1, 82.7), and among participants who were refractory to the anti-CD38 antibody daratumumab (55.8%; 96% CI: 40.6, 68.6).

Table 3. Cilta-cel PFS based on computerized algorithm by prior therapies and refractory status for MM; ITT analysis set, Arm B (Study MMY3002).

	Arm B					
	EVT/N[a]	Median PFS (95% CI) exposed in any 1 to 3 prior lines	12-month PFS Rate (%) exposed in any 1 to 3 prior lines	EVT/N[a]	Median PFS (95% CI) refractory to any prior 1 to 3 lines	12-month PFS Rate (%) refractory to any prior 1 to 3 lines
		(months)	(95% CI)		(months)	(95% CI)
Analysis set: intent-to-treat	208					
Prior exposed to				Refractory to		
IMiD						
Lenalidomide	65/208	NE (22.8, NE)	75.9 (69.4, 81.1)	65/208	NE (22.8, NE)	75.9 (69.4, 81.1)
Pomalidomide	3/8	NE (1.1, NE)	60.0 (19.5, 85.2)	3/8	NE (1.1, NE)	60.0 (19.5, 85.2)
PI						
Bortezomib	62/203	NE (22.8, NE)	76.8 (70.3, 82.0)	26/55	19.3 (13.2, NE)	65.2 (51.0, 76.2)
Carfilzomib	26/77	NE (19.2, NE)	75.2 (63.9, 83.4)	20/51	NE (15.6, NE)	72.5 (58.1, 82.7)
Ixazomib	4/21	NE (NE, NE)	85.7 (62.0, 95.2)	3/15	NE (12.6, NE)	86.7 (56.4, 96.5)
Anti-CD38 Ab						
Daratumumab	26/51	19.2 (9.7, NE)	58.5 (43.7, 70.6)	26/48	18.0 (9.3, 22.8)	55.8 (40.6, 68.6)
Isatuximab	1/2	NE (2.1, NE)	50.0 (0.6, 91.0)	1/2	NE (2.1, NE)	50.0 (0.6, 91.0)
Cytotoxic antibiotics and related substances						
Doxorubicin	12/22	16.4 (2.1, NE)	59.1 (36.1, 76.2)	2/4	13.4 (2.9, NE)	75.0 (12.8, 96.1)

Key: Arm B = 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.
Key: EVT=event; CI=confidence interval; NE=not estimable.
[a] Number of PFS events / number of subjects who were exposed (left) or refractory (right) to this particular prior therapy.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

For participants who were refractory to bortezomib, carfilzomib, and daratumumab, the ORR was 74.6% (95% CI: 61.0, 85.3), 80.4% (95% CI: 66.9, 90.2), 68.8% (95% CI: 53.8, 81.3), respectively.

The sponsor concluded that the efficacy of cilta-cel in study MMY3002 demonstrated improved PFS outcomes and higher ORR results in patients who had previously been exposed to and were refractory to daratumumab, bortezomib, and carfilzomib, and highlighted the significant benefit of cilta-cel over these agents.

Table 4. Cilta-cel ORR on computerized algorithm by prior therapies and refractory status for MM; ITT analysis set, Arm B (Study MMY3002).

	Exposed			Refractory	
	EVT/N[a]	ORR, % (95% CI)		EVT/N[a]	ORR, % (95% CI)
Analysis set: intent-to-treat	176/208	84.62 (78.98; 89.23)		176/208	84.62 (78.98; 89.23)
Prior exposed to			Refractory to		
IMiD			**IMiD**		
Lenalidomide	176/208	84.62 (78.98;89.23)	Lenalidomide	176/208	84.62 (78.98; 89.23)
Pomalidomide	6/8	75.00 (34.91; 96.81)	Pomalidomide	6/8	75.00 (34.91; 96.81)
PI			**PI**		
Bortezomib	173/203	85.22 (79.58; 89.50)	Bortezomib	41/55	74.55 (61.00; 85.33)
Carfilzomib	64/77	83.12 (72.86; 90.86)	Carfilzomib	41/51	80.39 (66.88; 90.18)
Ixazomib	18/21	85.71 (63.66; 96.95)	Ixazomib	13/15	86.67 (59.54; 98.34)
Anti-CD38 Ab			**Anti-CD38 Ab**		
Daratumumab	36/51	70.59 (56.17; 82.51)	Daratumumab	33/48	68.75 (53.75; 81.34)
Isatuximab	1/2	50.00 (1.26; 98.74)	Isatuximab	1/2	50.00 (1.26; 98.74)

Key: Arm B = 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.
Key: EVT=event; CI=confidence interval; ORR=overall response rate
[a] Number of PFS events / number of subjects who were exposed (left) or refractory (right) to this particular prior therapy.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

The efficacy analysis in the subset of patients who had received some of the satisfactory methods of treatment before study entry in arm B of study MMY3002 demonstrated that cilta-cel offered a clinical meaningful benefit for those patients who had progressed or relapsed and were refractory after prior treatment with daratumumab, bortezomib, and carfilzomib, as they achieved improved PFS outcomes and higher ORR to cilta-cel. The COMP agreed that the responses observed in these subgroups of patient constitute a clinically relevant advantage and establish the significant benefit of cilta-cel over regimens based on daratumumab, bortezomib, and carfilzomib for adult patients with relapsed and lenalidomide-refractory MM in the second- and later lines setting, and hence the triple regimens with daratumumab (DVd and DKd) and isatuximab (IsaKd).

Significant benefit of cilta-cel over the triplet regimen with selinexor (SVd)

The sponsor has conducted analyses using the MAIC approach to assess the efficacy of cilta-cel in comparison to selinexor by comparing the efficacy outcomes across the two clinical studies, between patients treated with cilta-cel in CARTITUDE-4 (N=208) versus those treated with selinexor in BOSTON (N=195). The outcomes included in the comparative analyses were the primary endpoint of PFS, and the secondary endpoints of ORR, rate of ≥VGPR and ≥CR. To account for confounding bias due to lack of randomisation, imbalances between patient populations from the two studies on prognostic patient/ disease characteristics were adjusted for using the approach of unanchored MAIC.

Comparisons of clinical outcomes between studies are prone to bias due to confounding, as observed differences in outcomes may be induced by imbalances in prognostic factors of the non-randomised patient cohorts being compared. The method of unanchored MAIC allows adjustment for this potential confounding when patient-level data are available for the treatment of interest and aggregate-level results are available for the comparator studies (Signorovitch et al., 2012). The approach is conceptually similar to inverse probability weighting (Hernán et al., 2020), where "counterfactual" outcomes for cilta-cel, are compared to observed outcomes from the comparator studies, as if CARTITUDE-4 would have enrolled similar patients as the comparator studies.

Table 5 shows an overview of the available data from BOSTON and identifies its more restrictive eligibility criteria versus CARTITUDE-4, as well as the impact on available patient numbers from the cilta-cel arm when these eligibility criteria are applied to CARTITUDE-4.

Table 5. Analysis sets for CARTITUDE-4 and the BOSTON study for selinexor.

Comparator	Study	No. patients	Eligibility criteria applied to CARTITUDE-4	Number of cilta-cel patients included in the analyses from CARTITUDE-4
SVd	BOSTON	195	Patients with more than 3 prior lines of therapy excluded	208

SVd: selinexor, bortezomib, dexamethasone

Selinexor: The BOSTON study is a global, phase 3, randomised study of QW selinexor in combination with bortezomib and dexamethasone (SVd) versus BIW Vd after 1 to 3 prior anti-myeloma regimens. The primary endpoint was PFS, determined by an IRC and assessed in the ITT population. Secondary

endpoints include ORR, OS and PFS, DoR, PFS on subsequent therapy, time to next anti-myeloma therapy, time to response, incidence of grade 2 or higher peripheral neuropathy events, and patient-reported peripheral neuropathy (as determined by EORTC QLQ-CIPN20 outcomes). Randomisation was stratified by treatment with prior PI therapies, number of prior anti-myeloma regimens (1 vs. > 1) and Revised International Staging System (R-ISS; Stage III vs. I or II). The publication by Grosicki and colleagues (Grosicki et al., 2020) was used as input in the comparative analyses.

Unanchored matching-adjusted indirect comparisons

The prognostic factors to be considered in the analyses were a priori identified and ranked by importance, based on input from independent clinical experts, which is reassuring. The following factors were identified as most prognostic: refractory status (not reported in BOSTON), cytogenetic risk, ISS/ R-ISS disease stage, presence of plasmacytomas/ extramedullary disease (not reported in BOSTON), and these were considered for the base case (BC) analyses. As a sensitivity analysis, the following factors were additionally included, as they were reported for BOSTON: number of prior lines, time since diagnosis, age, prior stem cell transplant (SCT), ECOG score, race, gender, and creatinine clearance.

To quantify the differences in outcomes between CARTITUDE-4 and BOSTON on response rates and PFS, individual patient-level data (IPD) were derived from the results in BOSTON, by reconstructing reported data for ORR and rate of CR and by simulating PFS from digitally scanned published Kaplan Meier curves using the validated algorithm method previously published by Guyot and colleagues (Guyot et al., 2012). The derived IPD were then pooled with available IPD from CARTITUDE-4 to estimate the relative efficacy of cilta-cel versus selinexor for the response and PFS outcomes, using logistic regression and Cox regression to estimate odds ratios (OR) and hazard ratios (HR), respectively.

The unanchored MAIC approach to adjust for imbalances in patient characteristics between the patient populations in the two clinical studies, involved the following steps:

1. Eligibility criteria from BOSTON were applied to the CARTITUDE-4 population whereby only patients from CARTITUDE-4 satisfying the eligibility criteria from BOSTON were included in the comparative analyses. All patients treated with cilta-cel in CARTITUDE-4 were considered eligible and were therefore included in the analyses.
2. Patient-level data from CARTITUDE-4 were then weighted such that their baseline characteristics matched the summary-level baseline characteristics as reported for BOSTON. This approach is a form of propensity score weighting in which patients from CARTITUDE-4 are weighted by their inverse odds of being in that group versus the selinexor cohort. The propensity score model was estimated using the generalized method of moments, including baseline risk factors which were commonly available in CARTITUDE-4 and BOSTON (Signorovitch et al., 2012). After applying this matching algorithm, the baseline characteristics for the reweighted CARTITUDE-4 population were balanced versus the comparator BOSTON population (Table 6).
3. Finally, the weighted IPD for the cilta-cel arm from CARTITUDE-4 was pooled with the simulated IPD for the selinexor arm from BOSTON (as described above) and analysed using weighted logistic regression and weighted Cox proportional hazards regression to estimate OR and HR (including 95% CIs), reflecting the relative benefit for cilta-cel versus selinexor on ORR/≥CR and PFS.

Table 6. Baseline characteristics for CARTITUDE-4 adjusted to BOSTON

		Cilta-cel (CART-4)	SVd (BOSTON)	Cilta-cel Adjusted[1]
N patients		208	195	208
Refractory Status	<tri-refractory	76%		
	Tri/quad-refr	19%		
	Penta-refr	5%		
	%double refr			
	% >=tri-refr			
	Refr to PI	50%		
Cytogenetic Risk	High	59%	54%	54%
ISS stage	I	65%	50%	50%
	II	29%	34%	34%
	III	6%	16%	16%
R-ISS stage	I			
	II			
	III			
EMD	Yes	20%		

EMD=extramedullary disease; ISS=International Staging System; R-ISS=Revised International Staging System. Double-refractory: refractory to 2 classes of treatment. Triple class refractory: refractory to 1 IMiD + 1 PI + 1 anti-CD38. Quadruple-refractory: refractory to 1 PI, 2 IMiD and 1 anti-CD38 or 2 PIs, 1 IMiD and 1 anti-CD38. Penta-refractory: refractory to at least 2 PIs + at least 2 IMiDs + 1 anti-CD38.
[1] CARTITUDE-4 population adjusted to the BOSTON study.

The sponsor noted that the adjusted HR based on the MAIC approach showed significantly better PFS outcomes for cilta-cel versus selinexor corresponding to a reduction in the risk of disease progression or death when treated with cilta-cel of 39% when compared to selinexor (HR: 0.61 [95% CI: 0.43, 0.87; p=0.0068]). This result demonstrates that the improvement in PFS for cilta-cel versus selinexor is both statistically significant and clinically relevant. Table 7 summarizes the unadjusted and adjusted PFS HR (95% CI) alongside the medians for cilta-cel and selinexor.

Table 7. Median PFS by treatment, and Hazard Ratio for Cilta-cel versus Selinexor

		Hazard Ratio (95% CI) for Cilta-cel vs. Comparator	
	Median PFS [95% CI]	**Unadjusted**	**Adjusted: base case**
Cilta-cel	NE [22.8; NE][a]	-	-
SVd	13.3 [10.3;18.3]	0.54 [0.39;0.74]	0.61 [0.43;0.87]

CI=confidence interval; NE=not estimable; PFS=progression-free survival.
SVd: selinexor, bortezomib, dexamethasone; dex: dexamethasone
[a] Median was formally reached, however at a time-point where only 3 patients were still at risk. Based on parametric survival extrapolations, expected median is estimated to be beyond 27 months, across different and best fitting parametric modelling approaches.

The response rates were numerically higher for cilta-cel versus selinexor for both ≥VGPR and ≥CR. Table 8 shows observed response rates and the results for the adjusted comparisons based on the MAIC approach, expressed as OR and ratios of response. The results demonstrated that the response

ratios or odds for patients treated with cilta-cel to respond to treatment compared to patients treated with selinexor are 1.8- or 4.6-fold and 4.3- or 12.7-fold (with the lower limits of the CI above 1) more likely to achieve ≥VGPR and ≥CR, respectively, when treated with cilta-cel versus selinexor.

The sponsor stated that the results from the sensitivity analyses that were conducted were generally consistent with the 'base case' comparative estimates, which confirmed the conclusions on superior outcomes for cilta-cel versus selinexor on PFS (HR=0.59) and response rates with a RR of 1.10/4.22 for the triplet regimen with selinexor (SVd).

The sponsor stated that the reported results demonstrate that patients treated with cilta-cel are statistically significantly more likely to achieve a meaningful increase in PFS, to respond and have at least a VGPR and respond deeply to treatment (≥CR) when compared with selinexor. Based on this evidence, the sponsor concluded that the documentation of a meaningful extended survival without disease progression (PFS) and favorable response in terms of ≥VGPR and ≥CR with cilta-cel compared with selinexor justifies the claim of significant benefit of cilta-cel over this triplet regimen.

Table 8. Observed and adjusted response rates, by treatment.

a. ORR	**Observed Response**	**Adjusted Comparisons**		
		Odds Ratio [95% CI][a]	**Cilta-cel Adjusted[b]**	**Relative Risk [95% CI][c]**
Cilta-cel	84.60%	1.00	-	-
SVd	76.90%	1.61 [0.97;2.66]	82.6%	1.07 [0.97;1.19]
b. ≥VGPR	**Observed Response**	**Adjusted Comparisons**		
		Odds Ratio [95% CI][a]	**Cilta-cel Adjusted [b]**	**Relative Risk [95% CI][c]**
Cilta-cel	81.3%	1.00	-	-
SVd	44.6%	4.63 [2.87;7.47]	78.9%	1.77 [1.49;2.10]
c. ≥CR	**Observed Response**	**Adjusted Comparisons**		
		Odds Ratio [95% CI][a]	**Cilta-cel Adjusted [b]**	**Relative Risk [95% CI][c]**
Cilta-cel	73.10%	1.00	-	-
SVd	16.90%	12.68 [7.66;21.00]	72.1%	4.26 [3.08;5.89]

CI=confidence interval; CR=complete response; ORR=overall response rate; VGPR=very good partial response
SVd: selinexor, bortezomib, dexamethasone; dex: dexamethasone
Note: response rates for cilta-cel are based on infused patients.
[a] Odds ratio for cilta-cel versus comparators, based on logistic regression.
[b] 'Cilta-cel adjusted' is the estimated response rate for cilta-cel, after matching population to the comparator.
[c] Relative risk is equal to the ratio of the adjusted response rates for cilta-cel versus comparators.

The COMP considered that the efficacy data from CARTITUDE-4 combined with the presented results of the unanchored MAIC comparing to the ITT population from BOSTON provided adequate evidence to support the claim for significant benefit of cilta-cel based on better efficacy in terms of improvement in PFS and deeper response rates to treatment compared to the triplet regimen with selinexor (SVd) in patients with relapsed and lenalidomide-refractory MM who have received at least one prior therapy.

Conclusion

In conclusion, the COMP agreed that the claim of significant benefit based on a clinically relevant advantage for cilta-cel over the authorised triplet regimens with pomalidomide in combination with bortezomib and dexamethasone (PVd), daratumumab in combination with either bortezomib and

dexamethasone (DVd), pomalidomide and dexamethasone (DPd), or carfilzomib and dexamethasone (DKd), isatuximab plus carfilzomib and dexamethasone (IsaKd), and selinexor in combination with bortezomib and dexamethasone (SVd) is established based on the data provided. The COMP concluded that the data presented are considered sufficient to support maintenance of the orphan designation of Carvykti (cilta-cel) for the treatment of adult patients with relapsed and lenalidomide-refractory MM who received at least one prior therapy.

4. COMP position adopted on 27 February 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of multiple myeloma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 4.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to development of hypercalcemia, renal insufficiency, anaemia and/or bleeding, frequent infections, and bone lesions, and life-threatening due to poor survival of patients with relapsed and refractory disease;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Carvykti, the assumption that Carvykti may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical study data which demonstrated an improvement in progression free survival, which were associated with sustained and deeper responses, after treatment with Carvykti as compared to the authorised triple regimens with daratumumab (DPd), pomalidomide (PVd), and selinexor (SVd) in adult patients with relapsed and refractory multiple myeloma, who have received at least one prior therapy and are refractory to lenalidomide. In addition, clinically meaningful benefits in response to Carvykti were shown in subgroups of patients who had progressed or relapsed and were refractory to prior treatment with regimens based on daratumumab, bortezomib, and carfilzomib, which are components of the approved triple regimens with daratumumab (DVd and DKd) and isatuximab (IsaKd).

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Carvykti, autologous human T cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen, ciltacabtagene autoleucel for treatment of multiple myeloma (EU/3/20/2252) is not removed from the Community Register of Orphan Medicinal Products.