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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

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# 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) | 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.<br>Turnhoutseweg 30<br>2340 Beerse<br>Antwerp<br>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 |
| **Marketing authorisation procedural history** | |
| Rapporteur / Co-rapporteur | Jan Mueller-Berghaus / Marcos Timón |
| Applicant | Janssen-Cilag International N.V. |
| Application submission | 29 April 2021 |
| Procedure start | 20 May 2021 |
| Procedure number | EMA/H/C/0005095 |
| Invented name | Carvykti |
| Proposed therapeutic indication | Carvykti is indicated for the treatment of 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.<br>Further information on Carvykti 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 | 24 March 2022 |
| **COMP review of orphan medicinal product designation procedural history** | |
| COMP rapporteur(s) | Karri Penttila / Maria Elisabeth Kalland |
| Sponsor's report submission | 20 May 2021 |
| COMP discussion and adoption of list of questions | 15-17 March 2022 |
| Oral explanation | 12 April 2022 |
| COMP opinion | 13 April 2022 |

# 2. Grounds for the COMP opinion

**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 sponsor Janssen-Cilag International N.V. submitted on 21 October 2019 an application for designation as an orphan medicinal product to the European Medicines Agency for a 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 for treatment of multiple myeloma (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- 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.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this 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 as an orphan medicinal product for the orphan condition: treatment of multiple myeloma".

# 3. Review of criteria for orphan designation at the time of marketing authorisation

## 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 multiple myeloma (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 therapeutic indication "*Carvykti is indicated for the treatment of 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"* 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 (B/R) assessment of the CAT/CHMP.

**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).

Substantial progress has been made during the last decade in improving the overall survival (OS) of patients with MM through the development and availability of new approved treatment options. Despite optimal upfront therapy and recent advances in treatment, MM remains an incurable disease and most MM patients progress or relapse, and further treatment is needed. In addition, each subsequent line of therapy renders the patient more refractory to treatment. The prognosis of patients with MM who have received at least 3 prior lines of therapy, who have become double refractory to IMiDs (lenalidomide or pomalidomide) and PIs (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 therefore 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 changes in the seriousness of MM since the orphan designation was granted in 2020. 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 or refractory (r/r) disease. The seriousness of MM earlier acknowledged by the COMP remains acceptable for this procedure.

**Number of people affected or at risk**

The sponsor has accessed the European Cancer Information System (ECIS) database and contemporary literature as the primary and most relevant sources for the estimation of the incidence and prevalence of MM in the EU. The estimated crude incidence for the 27 EU member states (EU27)

was reported to be 0.80 per 10,000 persons (ECIS 2020). The sponsor noted that males have a higher estimated crude incidence of MM than females in the EU27 with 0.92 per 10,000 persons versus 0.69 per 10,000 persons, respectively.

Data from the International Agency for Research on Cancer (IARC)'s Globocan surveillance project (2020 data), the CancerMPact program of Kantar Health for the 4 most populous EU countries comprising approximately 58% of the EU population, which are Germany, France, Italy, and Spain (including Robert Koch Institute, ITACAN, InVS in France, and IARC; 2020 data), and the Association of the Nordic Cancer Registries (NORDCAN; 2020 data) were consulted as secondary sources of information for the estimation of the prevalence.

Based on the review of the epidemiological data sources found, the sponsor concluded on a point prevalence for MM of **4.34 per 10,000** people in the EU. The proposed estimate was indirectly calculated using the most current European incidence derived from ECIS 2020 data and the highest median survival duration of 5.42 years reported among MM patients aged 65 years or younger who were diagnosed between 2001-2006 at the Mayo Clinic in the US (Kumar et. al., 2008; Turesson et al., 2018). The sponsor also referred to median OS data reported in the Swedish Myeloma Registry from 2008-2015 (Blimark et al., 2018), but did not use them for establishing the disease duration of MM. The sponsor emphasised that the prevalence estimates will vary from the proposed value according to the age group and treatment line considered for the survival estimate, as the duration of the disease between different age groups and treatment lines is different.

Moreover, a 5-year prevalence of 3.08 per 10,000 people in the EU27 was estimated based on data from the Globocan database. The EU country registries provided slightly higher 10-year and total prevalence estimates, with an average 10-year prevalence in four of the most populous EU countries of 3.52 per 10,000 persons and an average total prevalence in the three Nordic EU countries (Denmark, Finland, and Sweden) of 3.68 per 10,000 persons. The 10-year prevalence and complete prevalence estimates were considered to better reflect the actual prevalence of MM, especially as patients live longer with the disease.

The main concern here is that the disease duration used for establishing the prevalence indirectly by the standard formula P=I×D is somewhat lower than the median OS values reported in recent procedures assessed over the last year. Higher estimates for the median OS of the whole MM population ranging from 5.8-6.2 years have been used in prevalence figures recently accepted for MM (Fonseca et al., 2017; Greipp et al., 2005; Cho et al., 2017; Kastritis et al., 2017; Usmani et al., 2018). The impact of the rapidly evolving therapeutic field and improved survival in recent years are reflected in these estimates. The sponsor then claimed to use a publication from 2018 to establish overall median survival. The survival data reported in this publication is considered to be outdated and more recent publications such as that reported by Cowan and colleagues this year (Cowan*, JAMA*. 2022; 327(5): 464-477) indicate that there could be higher median survival of around 10 years in the US. Europe may not be far behind. The sponsor also briefly discussed in a sensitivity analysis the estimated median OS of 5.8 years used for the prevalence figure accepted for the orphan maintenance of Abecma in 2021 but considered this as a more conservative estimate.

The sponsor puts forward the following argument: considering the totality of the data from multiple sources, their estimates show that the true complete prevalence of MM ranges from 3.5 per 10,000 to 4.64 per 10,000. Given ECIS is a well-established source on cancer incidence, and the sponsor's estimation of survival is based on a recent comprehensive literature review (Turesson et al., 2018) reporting a median survival of 5.42 years among those under the age of 65 years, the sponsor maintains the complete prevalence of MM to be 4.34 (0.8*5.42) persons.

The COMP was of the opinion that the median survival proposed might be a bit low and does not reflect the current situation in Europe. The sponsor should therefore use a more current figure and provide an updated prevalence estimate.

## 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**

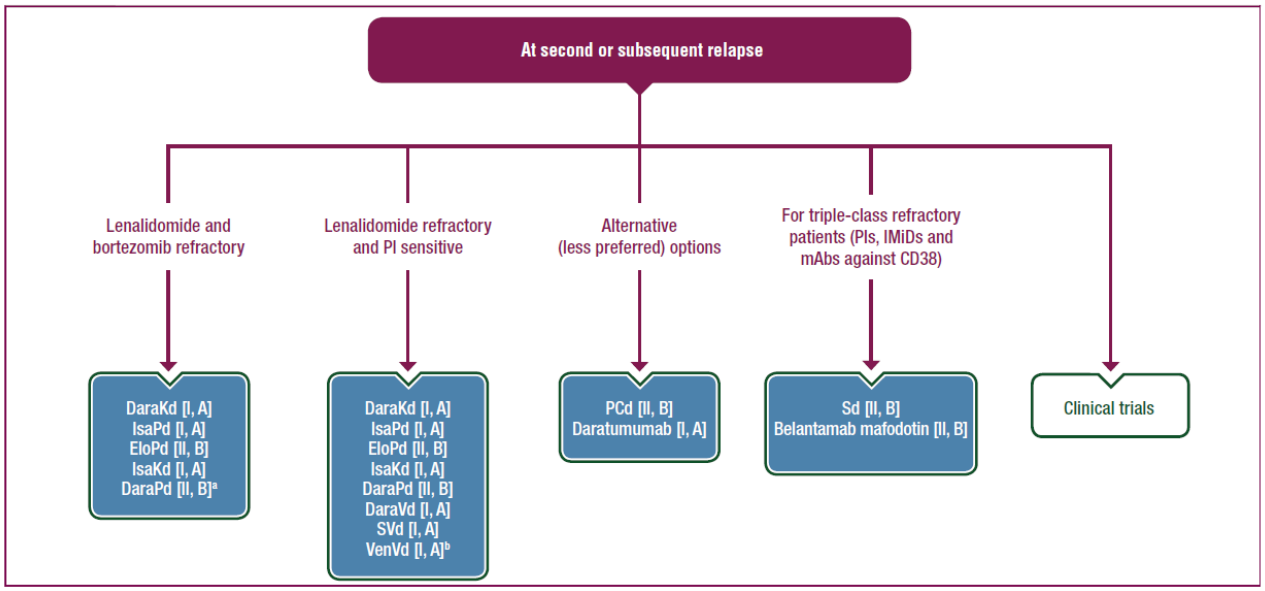
There are several medicinal products authorised in the European Community for treatment of MM. Central marketing authorisations include daratumumab (Darzalex), carfilzomib (Kyprolis), bortezomib (Velcade and generics), doxorubicin (Caelyx), interferon-α-2b (IntronA/ Alfatronol), lenalidomide (Revlimid and generics), thalidomide (generics), panobinostat (Farydak), elotuzumab (Empliciti), ixazomib (Ninlaro), pomalidomide (Imnovid), dexamethasone (generics), isatuximab (Sarclisa), belantamab mafodotin (Blenrep), selinexor (Nexpovio), and the most recently approved CAR-T cell product idecabtagene vicleucel (hereinafter referred to as ide-cel, Abecma; CMA in Aug-2021). In addition, several products are authorised at the national level for the treatment of MM, including carmustine, cyclophosphamide, doxorubicin, bendamustine, epirubicin, melphalan and vincristine.

The recently updated European Hematology Association (EHA) and European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up of MM describe recommended treatment options available for r/r MM patients in the third- and later lines setting (Dimopoulos, Ann Oncol. 2021; 32(3): 309-322). The EHA-ESMO guidelines distinguishes between treatment of elderly patients in the non-transplant setting, and younger or more fit patients in good clinical condition who are eligible for autologous stem-cell transplantation (ASCT) in the transplant setting. Treatments are discussed as regards to front-line treatment, consolidation, maintenance, and r/r disease. According to the guidelines, the selection of a proper regimen in third- or subsequent lines of therapy for any given patient depends on several parameters such as prior exposure, refractoriness, and sensitivity to specific agents or classes of agents in prior lines of therapy.

The treatment algorithm for MM is evolving rapidly and the therapeutic field for the management of the condition is continually changing. Currently, the following agents are specifically authorised in the r/r MM setting in the EU:

- Second- and later lines: bortezomib, carfilzomib, ixazomib, lenalidomide, pomalidomide, daratumumab, isatuximab, and elotuzumab.
- Third- and later lines: pomalidomide, daratumumab, isatuximab, elotuzumab, and panobinostat.
- Fourth- and later lines: ide-cel.
- Fifth- and later lines: belantamab and selinexor.

**Figure 1.** EHA-ESMO Guideline on the Treatment of Multiple Myeloma at Second or Subsequent Relapse




Dara=daratumumab; Elo=elotuzumab; IMiD=immunomodulatory drug; Isa=isatuximab; Kd=carfilzomib/dexamethasone; mAb=monoclonal antibody; MM=multiple myeloma; PCd=pomalidomide/cyclophosphamide/dexamethasone; Pd=pomalidomide/dexamethasone; PI=proteasome inhibitor; S=selinexor; Sd=selinexor/dexamethasone; Vd=bortezomib/dexamethasone; Ven=venetoclax. (Dimopoulos 2021).
a Phase 3 data were presented at the American Society of Hematology (ASH) annual meeting in December 2020 (Dimopoulos 2020).
b For patients with t(11;14) or high BCL2 levels.

**Table 1:** ESMO 2021 Recommendations for multiple myeloma patients who receive a third or subsequent line of therapy

| **Regimen** | **Indication** | **Approval Status** |
|---|---|---|
| Daratumumab/Carfilzomib/ Dexamethasone **(DaraKd)** | Carfilzomib in combination with daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy | Regimen authorised in European Union, Norway, Iceland and Liechtenstein. |
| Daratumumab/Pomalidomide/ Dexamethasone **(DaraPd)** | In combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy | Regimen authorised in European Union, Norway, Iceland and Liechtenstein. |

**Table 1:** ESMO 2021 Recommendations for multiple myeloma patients who receive a third or subsequent line of therapy

| **Regimen** | **Indication** | **Approval Status** |
|---|---|---|
| Daratumumab/Velcade/ Dexamethasone **(DaraVd)** | Daratumumab in combination with bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. | Daratumumab indication authorised in European Union, Norway, Iceland and Liechtenstein. |
| Isatuximab/Carfilzomib/ Dexamethasone **(IsaKd)** | Isatuximab is indicated, in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. | Isatuximab indication authorised in European Union, Norway, Iceland and Liechtenstein. |
| Isatuximab/Pomalidomide/ Dexamethasone **(IsaPd)** | Isatuximab is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy. | Isatuximab indication authorised in European Union, Norway, Iceland and Liechtenstein. |
| Elotuzumab/Pomalidomide/ Dexamethasone **(EloPd)** | Elotuzumab is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy | Elotuzumab indication authorised in European Union, Norway, Iceland and Liechtenstein. |
| Selinexor/Dexamethasone **(Sd)** (Group 2 regimen) | Selinexor is indicated in combination with dexamethasone for treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy | Selinexor indication authorised in European Union, Norway, Iceland and Liechtenstein. |
| Selinexor/Velcade/ Dexamethasone **(SVd)** | See approval status | Regimen **not currently authorised** |

**Table 1:** ESMO 2021 Recommendations for multiple myeloma patients who receive a third or subsequent line of therapy

| **Regimen** | **Indication** | **Approval Status** |
|---|---|---|
| | | in European Union, Norway, Iceland and Liechtenstein. |
| Venetoclax/Velcade/ Dexamethasone **(VenVd)** | See approval status | Regimen **not currently authorised** in European Union, Norway, Iceland and Liechtenstein. |
| Pomalidomide/Cyclophosphamide/ Dexamethasone **(PCd)** | See approval status | Regimen **not currently authorised** in European Union, Norway, Iceland and Liechtenstein. |
| Belantamab Mafadotin monotherapy (Group 2 agent) | Belantamab as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least 4 prior therapies and whose disease is refractory to at least 1 PI, 1 immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy | Belantamab indication authorised in European Union, Norway, Iceland and Liechtenstein |
| Idecabtagene vicleucel monotherapy (Group 2 agent) | Idecabtagene vicleucel is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. | Idecabtagene vicleucel indication authorised in European Union, Norway, Iceland and Liechtenstein. |
| Melphalan flufenamide/Dexamethasone (Group 2 regimen) | See approval status | Regimen **not currently authorised** in European Union, Norway, |

**Table 1:** ESMO 2021 Recommendations for multiple myeloma patients who receive a third or subsequent line of therapy

| **Regimen** | **Indication** | **Approval Status** |
|---|---|---|
| | | Iceland and Liechtenstein.<br><br>This regimen is currently under review by the EMA. |

The sponsor's product ciltacabtagene autoleucel (hereinafter referred to as cilta-cel; Carvykti) is intended to treat patients with r/r MM who have received at least three prior therapies, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38-directed antibody, and have demonstrated disease progression on the last therapy. In this disease setting, ide-cel (Abecma) for triple-class exposed patients (prior treatment history with a PI, an IMiD, and an anti-CD38 antibody) in fourth- or later lines, and belantamab (Blenrep) for triple-class refractory patients (refractory to a PI, an IMiD, and an anti-CD38 antibody) and selinexor (Nexpovio) for penta-refractory patients (refractory to two PIs, two IMiDs, and an anti-CD38 antibody) in fifth- or later lines, could be used. The approved therapeutic indications for these three medicinal products are presented below:

*Abecma* (ide-cel; an anti-BCMA CAR-T cell product) *is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.*

*Blenrep* (belantamab mafodotin; an anti-BCMA mAb) *is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.*

*Nexpovio* (selinexor; a selective XPO1-mediated nuclear export inhibitor) *is indicated in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.*

Of these products, only Abecma is considered relevant for a discussion on the significant benefit of cilta-cel in MM since the two latter products only covers either triple- or penta-class refractory patients with r/r MM in later treatment lines.

**Significant benefit**

The sponsor argued that cilta-cel is of significant benefit over existing methods of treatment for the target patient population based on the improved and deepened ORR and prolonged PFS observed in the pivotal study CARTITUDE-1. They came for protocol assistance (PA) and raised a question on significant benefit which the COMP discussed. The challenge with this condition and the multiple choices have been that the treatment landscape has emerging quickly over the last couple of years making establishing significant benefit more challenging. The sponsor was therefore reminded by the EMA in the PA that the most recent therapeutic alternatives for the intended patient population will need to be evaluated for demonstrating significant benefit at the time of MA to maintain the orphan medicinal product status. The sponsor confirmed that they have complied with the EMA recommendations.

The sponsor has provided an indirect comparison to each of the recently approved products in the r/r MM setting to which the studied patient population in the pivotal study CARTITUDE-1 had not been exposed to prior to study entry to support significant benefit based on a clinically relevant advantage in terms of improved efficacy. An indirect comparison to the approved BCMA-directed CAR-T cell product ide-cel (Abecma) is presented below.

CARTITUDE-1 is an ongoing, open-label, multicenter, single-arm phase 1b/2 study designed to evaluate the efficacy and safety of cilta-cel in adult patients with r/r MM in the fourth- and later lines setting. Among 143 patients who consented, 113 completed apheresis and were considered enrolled into the study (ITT), of which 97 patients (85.8%) received cilta-cel infusion (mITT). The primary endpoint for the phase 2 part is overall response rate (ORR), defined as the proportion of patients who achieved a partial response (PR) or better (i.e., stringent complete response [sCR] + CR + very good PR [VGPR] + PR) as assessed by an independent review committee (IRC) according to the international myeloma working group (IMWG) response criteria (Kumar et al., 2016). Secondary efficacy endpoints included VGPR/CR/sCR rates, minimal residual disease (MRD) negative rate as defined by the IMWG response criteria, clinical benefit rate (CBR; ORR + MR [minimal response]), time-to-response (TTR), duration of response (DOR), progression-free survival (PFS), and OS.

The patients who received cilta-cel infusion in the pivotal study were young (median age 61 years [range: 43-78]), but heavily pre-treated since the median number of prior lines of therapy was 6 (range: 3-18) and around half of the patients (50.5%; 49/97) had received at least 5 prior lines of therapy. Among the treated patients, 88.7% (86/97) was double-class refractory (refractory to a PI and an IMiD), 87.6% (85/97) was triple-class refractory, and 42.3% (41/97) was penta-class refractory. All patients had received a prior anti-CD38-directed treatment and all except for one of the treated patients (99.0%; 96/97) were refractory to this therapy. In addition, 99.0% (96/97) were refractory to their last line of prior therapy, and 99.0%, 94.8%, 91.8%, 85.6%, and 29.9% had previously been exposed to lenalidomide (81.4% refractory), bortezomib (68.0% refractory), pomalidomide (83.5% refractory), carfilzomib (64.9% refractory), and ixazomib (27.8% refractory), respectively, and 89.7% had underwent a prior ASCT and 8.2% an allogenic SCT. Furthermore, 23.7%, 21.6%, 11.3%, and 8.2% had been exposed to prior treatment with elotuzumab (19.6% refractory), thalidomide (8.2% refractory), panobinostat (8.2% refractory), and isatuximab (7.2% refractory).

<u>Indirect comparison to Abecma</u>

The sponsor has conducted an indirect comparison of the outcomes between patients treated with cilta-cel (Carvykti) in CARTITUDE-1 (N=97) versus patients treated with ide-cel (Abecma) in KarMMa (N=128). To account for confounding bias due to lack of randomization, imbalances between patient populations from the two pivotal studies on prognostic patient/disease characteristics were adjusted for

using the approach of unanchored MAIC. The prognostic factors to be considered in the analyses were a priori identified and ranked by importance, based on input from independent clinical experts. This is considered appropriate based on the single-arm trial design of the two clinical studies.

KarMMa (also referred to as MM-001) is an open-label, multicenter, multinational, single-arm phase 2 study evaluating the efficacy and safety of ide-cel in adult patients with r/r MM in the fourth- and later lines setting (NCT03361748; clinicaltrials.gov, NCT03361748). The study served as the basis for the approval in the EU of ide-cel for use in adult patients with r/r MM after three or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38-directed antibody. Of 140 enrolled patients, 128 received lymphodepleting therapy and were subsequently treated with ide-cel at doses between 150.5 and 518.4 x $10^6$ anti-BCMA CAR+ T-cells (Munshi et al., 2021). The primary efficacy endpoint of ORR was defined using IMWG criteria and adjudicated by an IRC. Secondary efficacy endpoints included CR rate (defined as a key secondary endpoint), TTR, DOR, MRD negative rate, time to progression (TTP), PFS, and OS.

The sponsor claimed that a secondary analysis using a similar comparison including all enrolled patients from CARTITUDE-1 versus the same patient population as mentioned for KarMMa was not possible as the latter study did not report results for all enrolled patients. This is not correct as the clinical outcomes for the enrolled patient population in KarMMa have been reported in the approved SmPC and are also accessible in the published EPAR for Abecma.

To quantify the differences in outcomes between CARTITUDE-1 and KarMMa on response rates and PFS, individual patient-level data (IPD) were derived from the results in KarMMa, by reconstructing reported data for ORR and CR or better and by simulating PFS from digitally scanned published Kaplan Meier curves using the validated algorithm published by Guyot and colleagues (Guyot et al., 2012; Saluja et al., 2019; Latimer et al., 2011). The derived IPD were then pooled with available IPD from CARTITUDE-1 to estimate the relative efficacy of cilta cel versus ide-cel 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 KarMMa were applied to the CARTITUDE-1 population whereby only patients from CARTITUDE-1 satisfying the eligibility criteria from KarMMa were included in the comparative analyses. Only one patient treated with cilta-cel in CARTITUDE-1 who were not refractory to the last line of prior therapy was considered ineligible and 96 (99.0%) of the 97 treated patients in CARTITUDE-1 were therefore included in the analyses.
2. Patient-level data from CARTITUDE-1 were then weighted such that their baseline characteristics matched the summary-level baseline characteristics as reported for KarMMa. This approach is a form of propensity score weighting in which patients from CARTITUDE-1 are weighted by their inverse odds of being in that group versus the ide-cel cohort. The propensity score model was estimated using the generalized method of moments, including baseline risk factors which were commonly available in CARTITUDE-1 and KarMMa (Signorovitch et al., 2012). This process was done only for the infused patient population from CARTITUDE-1. After applying this matching algorithm, the baseline characteristics for the reweighted CARTITUDE-1 population were balanced versus the comparator KarMMa population.
3. Finally, the weighted IPD for CARTITUDE-1 were pooled with the simulated IPD for KarMMa (as described above) and analysed using weighted logistic regression and weighted Cox

proportional hazards regression to estimate ORs and HRs (including 95% CIs), reflecting the relative benefit for cilta-cel versus ide-cel on ORR/≥CR and PFS.

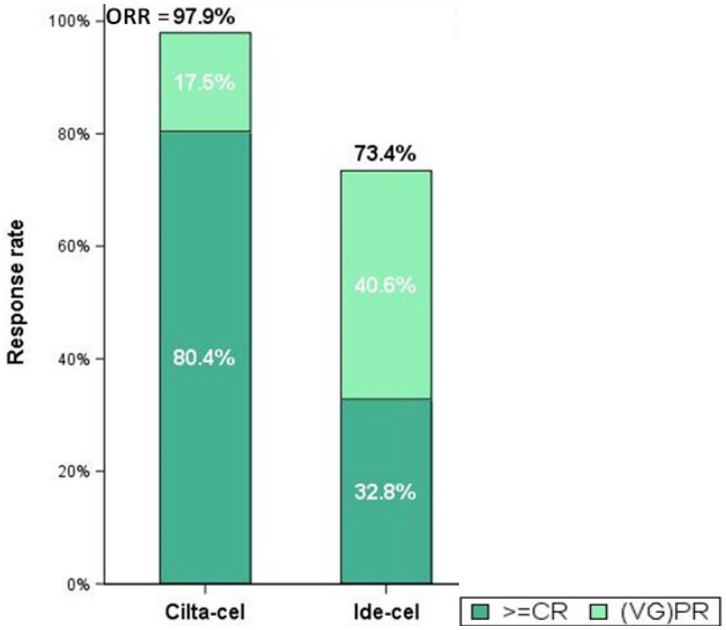
**Table 2.** Baseline characteristics for CARTITUDE-1 (mITT) adjusted to KarMMa

| | | **Cilta-cel (CARTITUDE-1)** | **Ide-cel (KarMMa)** | **Cilta-cel Adjusted[1]** |
|---|---|---|---|---|
| **N patients** | | 97 | 128 | 96 |
| **Refractory Status** | <tri-refractory | 12% | 16% | 16% |
| | Tri-quad-refractory | 45% | 58% | 58% |
| | Penta-refractory | 42% | 26% | 26% |
| **Cytogenetic Risk** | High | 25% | 35% | 35% |
| | Standard | 75% | 65% | 65% |
| **R-ISS stage** | I | 34% | 11% | 11% |
| | II | 59% | 72% | 72% |
| | III | 7% | 17% | 17% |
| **Plasma-cytomas** | Yes | 20% | 39% | 39% |
| | No | 80% | 61% | 61% |

R-ISS=Revised International Staging System
1CARTITUDE-1 population adjusted to the pivotal study KarMMa for ide-cel.

The sponsor noted following their analysis that the response rates are substantially higher for cilta-cel versus ide-cel for both ORR and CR. The results demonstrated that the odds for patients treated with cilta-cel to respond to treatment compared to patients treated with ide-cel are 1.4- and 2.2-fold higher (with the lower limits of the CIs above 1) in terms of ORR and ≥CR, respectively.

**Figure 2.** Observed Response Rates (IRC) Based on Published Results




The adjusted HRs based on the MAIC approach showed significantly better PFS outcomes for cilta-cel versus ide-cel corresponding to a reduction in the risk of progression or death when treated with cilta-cel of 67% when compared to ide-cel (HR: 0.33 [95% CI: 0.20, 0.54; p<0.0001]).

**Table 3.** Median PFS by Treatment and HR for cilta-cel versus ide-cel

| | | **Hazard Ratio (95% CI) for cilta-cel vs ide-cel** | |
|---|---|---|---|
| | **Median PFS (95% CI)** | **Unadjusted** | **Adjusted** |
| **Cilta-cel** | 22.8 (22.8; NE)[a] | - | - |
| **Ide-cel** | 8.8 (5.6; 11.6) | 0.23 (0.15; 0.36) | 0.33 (0.20; 0.54) |

CI=confidence interval; PFS=progression-free survival. [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.

Prior to adjustment, the HR for DOR for cilta-cel versus ide-cel was 0.33 (95% CI: 0.21, 0.52; p<0.0001). The effect of cilta-cel was statistically significantly superior to ide-cel after base case adjustment (HR: 0.48 [95% CI: 0.28, 0.81; p=0.0058]). The Grambsch-Therneau test (Grambsch 1994) for violation of the proportional hazards assumption was non-significant for the base case adjusted analysis (p=0.11), indicating that the proportional hazards assumption was not violated.

PFS data was available for all 124 patients in KarMMa who received infusion with the 300 x $10^6$ and 450 x $10^6$ anti-BCMA CAR+ T-cells dose cohorts, whereas OS data was only available in the public domain for 123 of these patients (the available data removed one patient who received a non-conforming product that did not meet the product release specifications for ide-cel) (Lin et al., 2021).

Prior to adjustment, the HR for cilta-cel versus ide-cel was 0.26 (95% CI: 0.17, 0.40; P<0.0001) for PFS and 0.39 (95% CI: 0.23, 0.66; P=0.0004) for OS. The effect of cilta-cel for PFS was statistically significantly superior to ide-cel after base case adjustment (HR: 0.36 [95% CI: 0.22, 0.59; P<0.0001]). For OS, the estimated treatment effect was in favor of cilta-cel (HR: 0.54 [95% CI: 0.29, 1.01; p=0.0527]), but with widened CIs overlapping 1. The Grambsch-Therneau test for violation of

the proportional hazards assumption was non-significant for both outcomes in the base case adjusted analysis (PFS: p=0.60; OS: p=0.17), indicating that the proportional hazard assumption was not violated.

Additional comparative analysis between cilta-cel versus ide-cel by sub-population was also presented. The comparisons for both ORR and ≥CR were in favour of cilta-cel across all reported sub-populations, and consistent with the results observed for the overall population, with all lower CIs above 1 for all OR estimates. The results for PFS were consistently in favour of cilta-cel for the reported subgroups, with HR ranging between 0.17 and 0.30, and all upper CIs below 1. The point estimates for the OS HR varied between 0.21 and 0.94, all favouring cilta-cel over ide-cel. While the upper CI for the overall population was below 1, HR estimates by subgroup were less stable with wider confidence intervals, compared to the other endpoints, reflecting low observed number of events within sub-populations. The presented OS results therefore need to be interpreted with caution, due to the wide CI around the HR point estimates, induced by the low sample size as well as the low number of events by subgroup.

The sponsor concluded that the outcomes in triple-exposed r/r MM patients are consistently in favour of cilta-cel versus ide-cel across all efficacy endpoints and sub-populations that were investigated. It is agreed that the reported efficacy results for the unanchored MAIC indicate that r/r MM patients in the fourth- and later lines setting treated with cilta-cel seemed to have superior outcomes compared to patients treated with ide-cel in the pivotal study KarMMa, with substantially higher as well as deeper response rates and extended survival without disease progression for cilta-cel.

However, the sponsor did not provide any table overview comparing all the baseline characteristics for the studied patient populations from the two clinical studies. This information is necessary to be able to decide whether the two populations are comparable. In addition, a secondary analysis using a similar comparison including all enrolled patients from CARTITUDE-1 versus the same patient population as mentioned for KarMMa was not conducted, although the outcomes for the enrolled patient population in KarMMa have been reported in the approved SmPC and are also accessible in the published EPAR for Abecma. The sponsor should therefore provide these data to further support the claim for significant benefit. In addition, the very high OR value >100 reported for the observed and adjusted ORR between the cilta-cel and ide-cel groups must be further clarified as it does not seem to be a very reliable estimate, and the cause of this extreme outcome is not further explained. The sponsor should therefore also present the unadjusted results along with adjusted results to expose the impact of the conducted adjustments.

# 4. COMP list of issues

**Prevalence**

The sponsor appears to have provided a prevalence which is an underestimate of the situation in Europe. The sponsor is invited to revise the prevalence using recent data sources which reflect more adequately median survival.

**Significant Benefit**

The sponsor is requested to further elaborate on comparing all the baseline characteristics for the studied patient populations from the two clinical studies. In addition, a secondary analysis using a similar comparison including all enrolled patients from CARTITUDE-1 versus the same patient population as mentioned for KarMMa was not conducted. The sponsor should therefore provide this data to further support the claim for significant benefit. In addition, the very high OR value >100 reported for the observed and adjusted ORR between the cilta-cel and ide-cel groups must be further clarified as it does not seem to be a reliable estimate, and the cause of this extreme outcome should be further explained. The sponsor should therefore also present the unadjusted results along with adjusted results to reveal the impact of the conducted adjustments.

**Comments on sponsor's response to the COMP list of issues**

The sponsor provided a written response and presented at an oral explanation.

Concerning the response about the MM prevalence, the sponsor revised the calculation using data sources as recommended by the COMP, including ECIS incidence data for 2020, Eurostat mortality rates (Eurostat 2020), and recent publications on OS for MM patients by stage (Greipp 2005; Cho 2017; Kastritis 2017; Usmani 2018) to account for varying estimates across data sources and observed increases in the assumed duration of the disease.

The incidence of MM is consistently reported to be 0.8 per 10,000 people across the EU (ECIS; 2020 data). However, median OS varies. To approximate the most comprehensive and up to date estimates of median OS, the sponsor utilised data from recent publications (Greipp 2005; Cho 2017; Kastritis 2017; Usmani 2018). Based on these data, the median OS for International Staging System (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 median OS is approximately 1-4 years.

Using these estimates, the median OS for the entire MM population was estimated to be 5.8 years ([7 years*0.6) + (4 years*0.4)]. Using the standard formula P=I*D, the updated prevalence was estimated to be (0.8*5.8) = 4.64 per 10,000 persons. Although this is higher than the estimates reported in the initial application, it likely reflects the recent increases in survival among patients with MM due to therapeutic advances, and it is a conservative approach that utilises recently published comprehensive data sources. The sponsor therefore concluded on a revised prevalence estimate for MM of **4.64 per 10,000** persons in the EU based on a higher median OS of **5.8 years** for the whole patient population. The proposed estimate and assumptions are in line with those accepted in recent designations for MM and is identical to the orphan maintenance procedure for Abecma. The revised prevalence calculation proposed by the sponsor was accepted.

In response to the question on significant benefit, the sponsor provided a table overview of the distribution of clinically important prognostic factors which were commonly reported in the infused and enrolled populations from CARTITUDE-1 and KarMMa as requested (Table 4). In addition, a secondary analysis using a similar unanchored MAIC approach for the enrolled patient populations from CARTITUDE-1 and KarMMa was conducted.

**Table 4.** Baseline Characteristics of the Infused/Enrolled Populations from CARTITUDE-1 and KarMMa

| | Infused Population | | Enrolled Population | |
|---|---|---|---|---|
| | **Cilta-cel (CARTITUDE-1)** | **Ide-cel (KarMMa)** | **Cilta-cel (CARTITUDE-1)** | **Ide-cel (KarMMa)** |
| **N patients** | 97 | 128 | 113 | 140 |
| **Refractory status (%)** | | | | |
| Non-triple-refractory | 12% | 16% | 12% | 16% |
| Triple or quad-refractory | 45% | 58% | 42% | 58% |
| Penta-refractory | 42% | 26% | 46% | 26% |
| **High cytogenetic risk (%)** | 24% | 35% | 25% | 33% |
| **R-ISS stage (%)** | | | | |
| Stage I | 34% | 11% | 34% | 10% |
| Stage II | 59% | 72% | 59% | 71% |
| Stage III | 7% | 17% | 7% | 19% |
| **Patients with plasmacytomas (%)** | 20% | 39% | 19% | 38% |
| **Median number of prior lines of treatment** | 6 | 6 | 5 | 6 |
| **Median time since diagnosis (years)** | 6 | 6 | 6 | 6 |
| **Median age (years)** | 61 | 60.5 | 62 | 60.5 |
| **Male (%)** | 59% | 59% | 58% | 59% |
| **Prior autologous HCT (%)** | 90% | 94% | 88% | 94% |
| **ECOG Score** | | | | |
| 0 | 40% | 45% | 49% | 43% |
| 1-2 | 60% | 55% | 51% | 57% |

ECOG=Eastern Cooperative Oncology Group; HCT=hematopoietic cell transplantation; N=number; R-ISS=Revised International Staging System.

The sponsor concluded that the study populations are very similar, with only minor differences between the patient populations in the two clinical studies. Specifically, the infused and enrolled populations in KarMMa included slightly more patients with high cytogenetic risk, Revised ISS (R-ISS) stage II/III, and plasmacytomas than CARTITUDE-1, and CARTITUDE-1 included slightly more penta-refractory patients than KarMMA. However, these differences were quite minor and the infused and enrolled patients from both studies were considered "functionally high-risk" since all were heavily pre-treated and had a similarly high median number of prior lines of therapy. The other commonly reported baseline characteristics were more balanced across both studies. The observed imbalances for these risk factors were adjusted for in the MAIC conducted in the infused populations (as presented in the initial orphan maintenance report for cilta-cel) and in the enrolled populations.

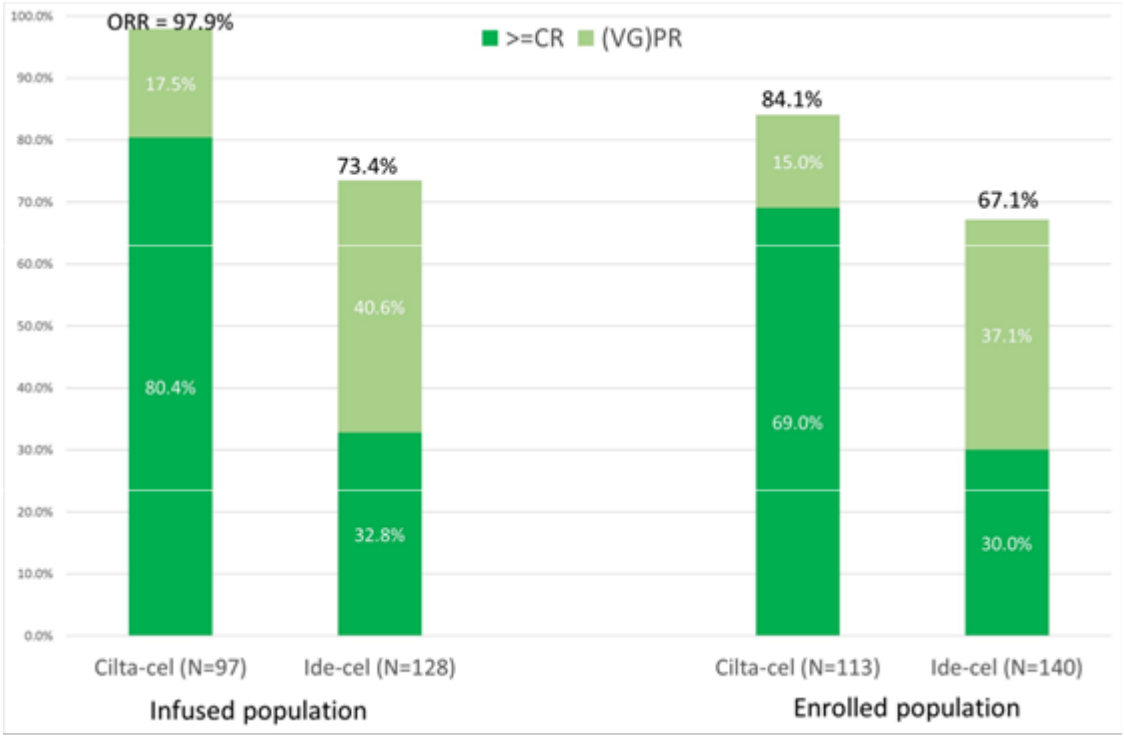
***MAIC in the infused and enrolled populations from CARTITUDE-1 and KarMMa***

According to the sponsor, the comparative analyses on the enrolled populations confirmed the results of the analyses on the infused populations, with the outcomes being consistently in favour of cilta-cel.

The sponsor noted following their analysis that the response rates were substantially higher for cilta-cel versus ide-cel for both ORR and ≥CR. The results presented demonstrated, after MAIC-based adjustment for imbalances between study populations on clinically important prognostic factors, that the odds of responding to treatment were significantly higher for patients treated with cilta-cel than for patients treated with ide-cel (with all lower limits of the confidence intervals [CIs] above 1) for both

populations. In terms of response ratios, patients were 1.36-fold and 1.28-fold more likely to respond when treated with cilta-cel versus ide-cel for the infused and the enrolled populations, respectively. Similarly, patients were 2.23-fold and 1.96-fold more likely to achieve a ≥CR when treated with cilta-cel versus ide-cel for the infused and the enrolled populations, respectively.

**Figure 3.** Observed Response Rates (per IRC) Based on Published Results.




CR=complete response; IRC=Independent Review Committee; ORR=overall response rate; VGPR=very good partial response.

The results of the unadjusted and adjusted comparisons of PFS based on the MAIC approach, with hazard ratios (HRs) adjusted for differences in refractory status, cytogenetic risk, R-ISS stage, and presence of plasmacytomas, are presented in Table 5.

**Table 5.** Median PFS by Treatment, and HR for Cilta-cel vs. Ide-cel (Infused and Enrolled Populations)

| | **Median PFS (95% CI)** | | **Hazard Ratio (95% CI) for Cilta-cel vs Comparator** | | | |
|---|---|---|---|---|---|---|
| | | | **Unadjusted** | | **Adjusted** | |
| | **Infused Population** | **Enrolled Population** | **Infused Population** | **Enrolled Population** | **Infused Population** | **Enrolled Population** |
| Cilta-cel | 22.8 (22.8; NE)[a] | 24.3 (19.8; NE)[a] | - | - | - | - |
| Ide-cel | 8.8 (5.6; 11.6) | 8.0 (6.8; 12.0) | 0.23 (0.15; 0.36) | 0.35 (0.24; 0.50) | 0.33 (0.20; 0.54) | 0.53 (0.34; 0.82) |

CI=confidence interval; PFS=progression-free survival.
[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 adjusted HRs showed significantly better PFS outcomes (with all upper CIs below 1) for cilta-cel versus ide-cel for both the infused and enrolled populations. A reduction in the risk of progression or death of 67% and 47% is seen for the infused and the enrolled populations, respectively, when treated with cilta-cel versus ide-cel. The sponsor concluded that these results showed that the improvement in PFS for cilta-cel versus ide-cel is statistically significant and clinically relevant for both populations.

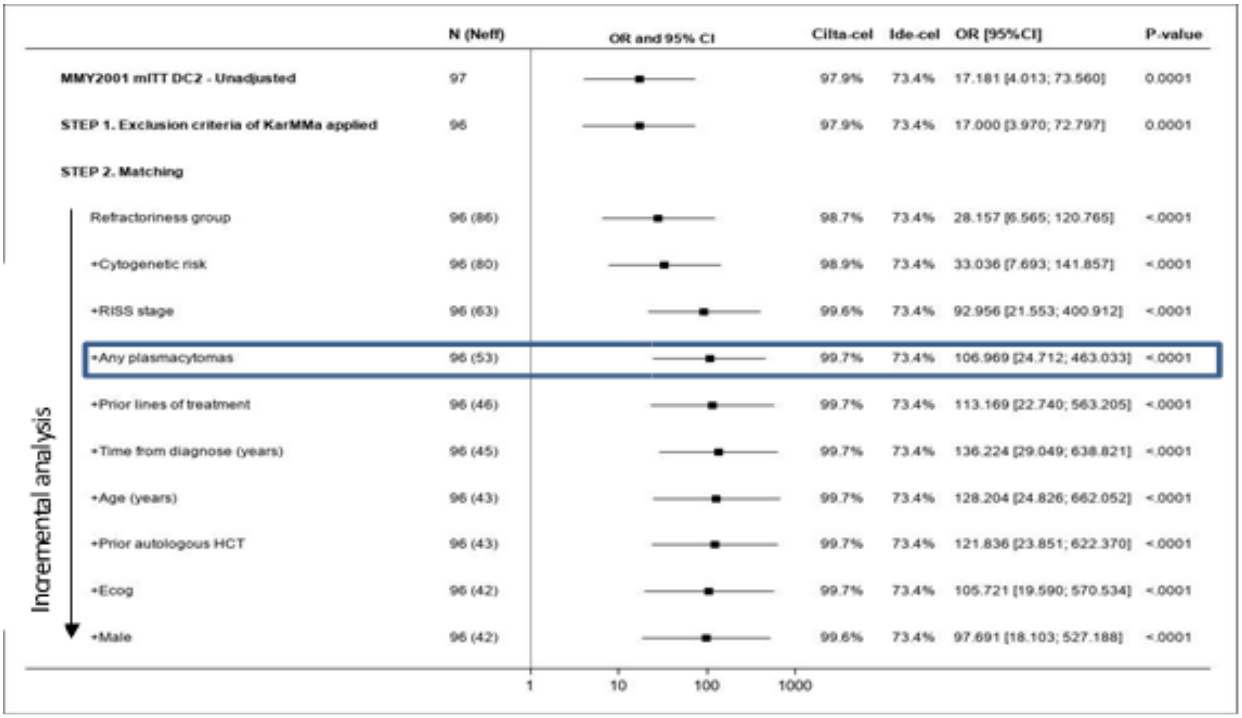
***Discussion on the high odds ratio reported for ORR between cilta-cel and ide-cel***

The sponsor explained upon request that a high absolute value for an odds ratio (OR), as was the case for the OR reported for the adjusted ORR among patients infused with cilta-cel versus ide-cel, can be observed when a proportion of interest comes close to the boundary of a probability (0 or 1).

The ORR for patients treated with cilta-cel after MAIC-based adjustment changed from 97.9% to 99.7%, which corresponds to an odds (defined as the ratio between the percentage of responders and non-responders) of 99.7/0.03. The ORR of 73.4% for ide-cel corresponds to an odds of 73.4/26.6. The OR is the ratio of the odds of a response versus non-response for both treatments. As the odds for cilta-cel is close to 100% (and, therefore, high), the reported value for OR is high. Since the absolute values of an OR are difficult to interpret, the sponsor also reported the results of the relative response rates, calculated as a ratio of response rates (i.e., relative risk [RR]).

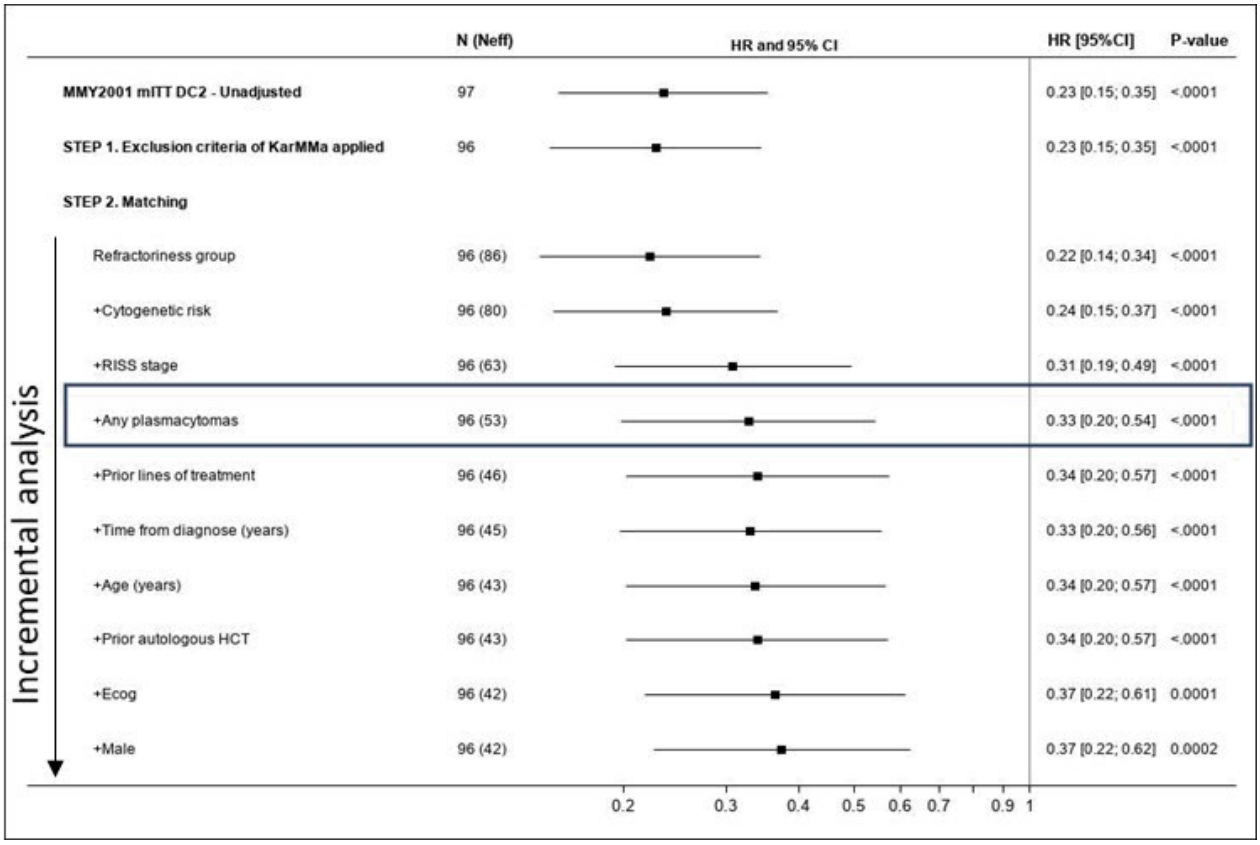
As requested, the sponsor presented the incremental impact on the reported values of both ORs and RRs when the ORR observed in the infused populations were adjusted for after applying the exclusion criteria of KarMMa to CARTITUDE-1 and based on selected prognostic factors that were identified as clinically important for the MM population (as mentioned above). The relative effects on the ORs after the adjustment and matching steps applied are presented in Figure 4. The trend of adjustment noticed for the OR and RR was the same. However, the adjustment for OR seems to be more pronounced due to the properties of this ratio, as explained above. All estimates for OR and RR were consistently above 1, indicating better response rates for patients treated with cilta-cel in comparison with ide-cel across all sensitivity analyses adjusted for all available important risk factors recorded at baseline.

**Figure 4.** Odds ratio for ORR for Cilta-cel versus Ide-cel (Infused Population)



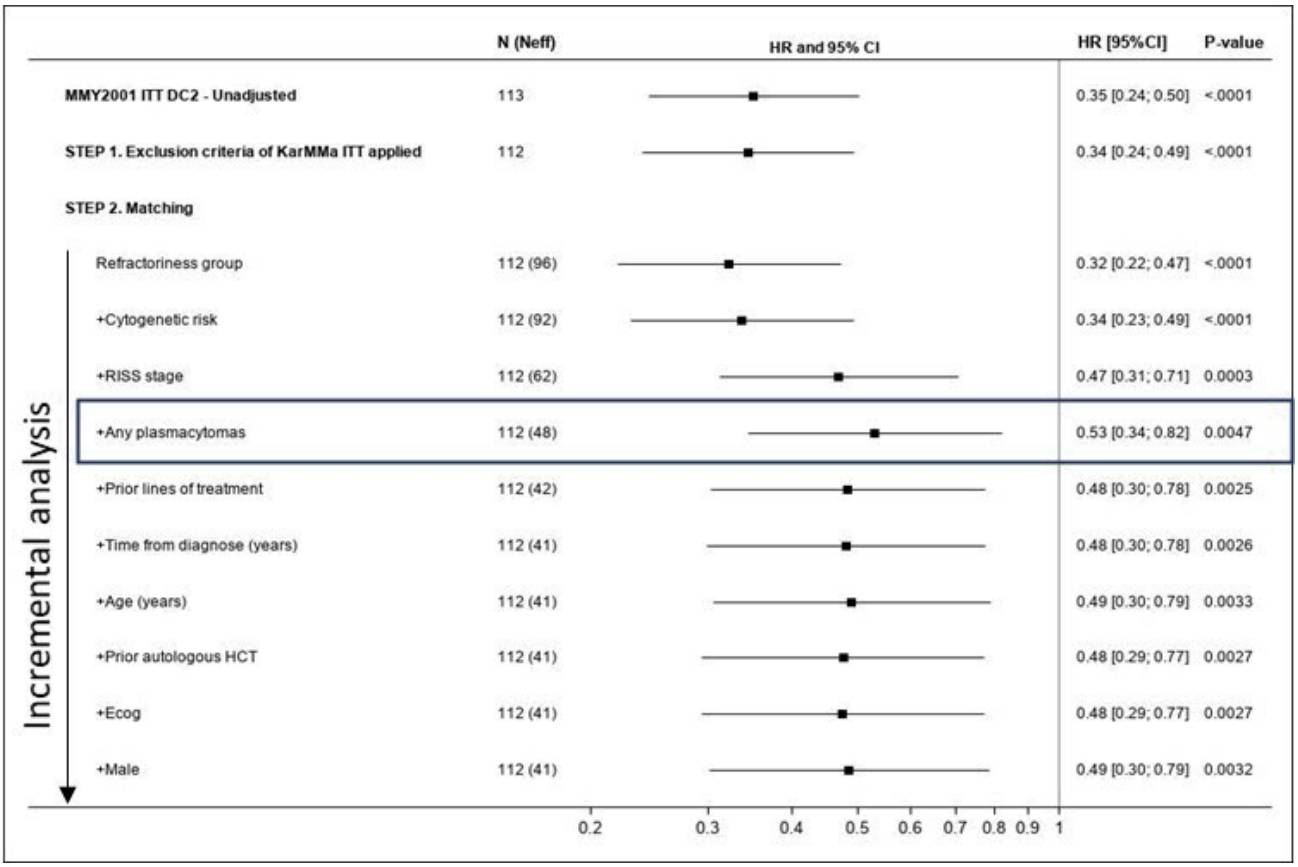
The sponsor also showed the incremental impact on PFS when adjusting for imbalances in baseline characteristics for the infused and enrolled populations. While this adjustment process for the ORR has little impact on the comparison between studies, the cumulative adjustment process for PFS has a substantial impact. The figures presented illustrated that the adjustment for R-ISS stage has the biggest impact on the HR, shifting it from 0.23 to 0.31 in the infused populations, and from 0.35 to 0.47 in the enrolled populations (Figure 5 and Figure 6). This demonstrated that the comparative analyses considering and adjusting for the higher proportion of stage III patients in KarMMa as advanced disease was associated with worse outcomes.

**Figure 5.** Hazards ratio for PFS for Cilta-cel versus Ide-cel (Infused population)




The base case, which was presented before, additionally adjusted for the percentage of patients with plasmacytomas. The additional impact of adjusting for other baseline characteristics was limited. The same pattern was observed for the analyses on both the infused and enrolled populations. The relative treatment effect for cilta-cel versus ide-cel was consistently in favour of cilta-cel across all sensitivity analyses conducted, with point estimates and upper CIs below 1, illustrating statistically significant improved outcomes for cilta-cel.

**Figure 6.** Hazards ratio for PFS for Cilta-cel versus Ide-cel (Enrolled population)




The submitted table overview comparing the distribution of clinically important prognostic factors identified a priori for the infused and enrolled populations from CARTITUDE-1 and KarMMa revealed that the patient populations from these two clinical studies were similar. However, the infused and enrolled populations in KarMMa included more patients with high cytogenetic risk, R-ISS stage II/III, and plasmacytomas than CARTITUDE-1, and CARTITUDE-1 included more penta-refractory patients than KarMMA. It should be noted that the observed imbalances for these risk factors were adjusted for in the unanchored MAIC approach conducted for both the infused and enrolled populations. However, this has led to a reduction of the effective sample size in the MAIC approach as compared to the actual sample size.

The reported efficacy results for the MAIC after adjusting for differences of important prognostic baseline factors between the study populations indicated that patients with r/r MM in the fourth- and later lines setting treated with cilta-cel in CARTITUDE-1 have superior efficacy outcomes compared to patients treated with ide-cel in the pivotal study KarMMa. Specifically, higher, deeper response rates and prolonged PFS were observed for cilta-cel versus ide-cel in triple-exposed patients with r/r MM.

The COMP noted that the sponsor had satisfactorily explained the reason for the large OR value >100 reported for the adjusted ORR between patients treated with cilta-cel versus ide-cel, which appear to be caused by the high ORR for the cilta-cel treated group that approached the boundary of a probability of 1. It was therefore emphasised that the results of the relative response rates reported as RRs were more reliable for the interpretation of the MAIC.

The efficacy data from CARTITUDE-1 combined with the presented outcomes of the unanchored MAIC approach provide adequate evidence to support the claim for significant benefit of cilta-cel based on

better efficacy in terms of higher and deeper response rates compared to ide-cel in triple-exposed patients with r/r MM.

The COMP concluded that it could recommend maintaining the orphan designation.

# 5. COMP position adopted on 13 April 2022

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.