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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Abecma (idecabtagene vicleucel)
Treatment of multiple myeloma
EU/3/17/1863

Sponsor: Bristol-Myers Squibb Pharma EEIG

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	Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains
Other name	--
International Non-Proprietary Name	Idecabtagene vicleucel
Tradename	Abecma
Orphan condition	Treatment of multiple myeloma
Sponsor's details:	Bristol-Myers Squibb Pharma EEIG Blanchardstown Corporate Park 2 Plaza 254 Dublin 15 D15 T867 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	bluebird bio France
COMP opinion	15 March 2017
EC decision	20 April 2017
EC registration number	EU/3/17/1863
Post-designation procedural history	
Transfers of sponsorship	Transfer from bluebird bio France to Celgene Europe Limited – EC decision of 13 October 2017 Transfer from Celgene Europe Limited to Celgene Europe B.V. – EC decision of 9 November 2018 Transfer from Celgene Europe B.V. to Bristol-Myers Squibb Pharma EEIG – EC decision of 26 November 2021
COMP opinion on review of orphan designation at the time of marketing authorisation	30 June 2021
Type II variation procedural history	
Rapporteur / Co-rapporteur	Rune Kjeken / Heli Suila
Applicant	Bristol-Myers Squibb Pharma EEIG
Application submission	6 March 2023
Procedure start	25 March 2023
Procedure number	EMEA/H/C/004662/II/0031
Invented name	Abecma

Therapeutic indication extension	Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy. Further information on Abecma can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/abecma
CHMP opinion	25 January 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Maria Elisabeth Kalland / Karri Penttila
Sponsor's report submission	29 March 2023
COMP discussion	16-18 January 2024
COMP opinion (adoption via written procedure)	29 January 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 designation in 2017 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains was considered justified based on data showing that patients with relapsed refractory multiple myeloma achieve partial or complete responses;
- the condition is chronically debilitating and life threatening due to the poor survival of patients with relapsed or refractory disease;
- the condition was estimated to be affecting approximately 3.6 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with relapsed refractory multiple myeloma achieve partial and stringent complete responses. This compared favourably with a long list of authorised products to which these patients were not responding anymore. 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 T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains as an orphan medicinal product for the orphan indication: treatment of multiple myeloma.

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

The COMP opinion on the initial review of the orphan medicinal product designation in 2021 was based on the following grounds:

- 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 the development of hypercalcaemia, renal insufficiency, anaemia and bone lesions;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Abecma may be of potential significant benefit to those affected by the orphan condition still holds;
- the sponsor has provided clinical data that demonstrated efficacy of Abecma in heavily pre-treated multiple myeloma patients who had relapsed or were refractory to several classes of products after at least three prior therapies (including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody), and whose disease had progressed on the last therapy. These patients achieved a higher proportion of clinically meaningful responses than patients treated with either Blenrep or Nexpovio, and the observed responses were more durable. The Committee considers that this constitutes a clinically relevant advantage.

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 Abecma, autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains, idecabtagene vicleucel, for treatment of multiple myeloma (EU/3/17/1863) 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 called plasma cell myeloma) is a malignant neoplasm of plasma cells that clonally expand and accumulate in the bone marrow and/or at extramedullary sites, which may lead to skeletal destruction, infections, renal insufficiency, and bone marrow failure (Dimopoulos et al., 2015). The disease is often asymptomatic for a long period of time and often advanced at the time of diagnosis (Rajkumar et al., 2014).

MM 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). In Europe, the median age at onset of MM is 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 aetiology is unknown with no established lifestyle, occupational or environmental risk factors.

The extension of the therapeutic indication "Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor (PI) 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 is confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The clinical course of MM can be highly variable due to the heterogeneity of the disease with some patients progressing rapidly despite treatment and others remaining stable without therapy for several years. Common symptoms of MM include, but are not limited to, fatigue, persistent bone pain, especially in the lower back or thorax, pathologic fractures, spinal cord compression (from pathologic fracture), weakness, malaise, anaemia and/or bleeding, frequent- and opportunistic infections (often pneumococcal), 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).

Survival after diagnosis differs by age, with a recent global review reporting median survival among patients diagnosed at less than 65 years ranging from <2.75 to 5.42 years, and among patients diagnosed at 65 years and older ranging from 2.17 to 2.67 years (Turesson 2018). In a study based on data collected from existing medical records from multiple centres, patients with relapsed MM, who had

received at least three prior lines of therapy, were refractory to both an immunomodulatory agent (IMiD; lenalidomide or pomalidomide) and a proteasome inhibitor (PI; bortezomib or carfilzomib), and had been exposed to an alkylating agent, median overall survival (OS) was reported to be 13.0 months and median progression free survival (PFS) was 5.0 months (Kumar, 2017).

The sponsor has not identified any substantial changes on the chronically debilitating or life-threatening nature of MM since the orphan designation was granted in 2017 and the criteria was reviewed and considered maintained at the time of the conditional marketing authorisation (CMA) in 2021. The increase in survival for patients with MM has been driven by the availability of newer therapies and novel combination approaches, as well as by improved supportive therapies (NCCN guidelines, version 5.2022). However, even with optimal upfront therapy, most MM patients progress or relapse, and need further treatment. The increasing use of triplet and quadruplet combination regimens in earlier lines of therapy, many of which include an anti-CD38 mAb, limit therapeutic options in the relapsed/refractory setting and underscore the need for medicines with a novel mechanism of action.

The COMP has previously acknowledged that MM 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. The condition therefore remains chronically debilitating and life-threatening in nature.

Number of people affected or at risk

At time of the initial marketing authorisation in 2021, the COMP concluded that the condition was estimated to be affecting approximately 4.6 in 10,000 persons in the European Union (EU).

In this maintenance application, the point prevalence of MM was estimated to be affecting a range of between 3.68 to 4.88 per 10,000 people in the EU. The revised estimate was based on a sensitivity analysis conducted to address the uncertainty around the calculation and by use of data from the interactive web-based European Cancer Information System (ECIS) database.

The sponsor used the standard formula P (point prevalence) =I (incidence) ×D (mean duration) for indirectly establishing the prevalence of MM in the EU, under the assumptions of stable incidence and duration of the condition. The crude incidence of MM in the 27 EU member states (EU27) was 0.8 per 10,000 people according to ECIS (2020 data).

Two factors should be considered when estimating the survival for all MM patients, namely eligibility for transplant and the international staging system (ISS) stage. However, published data on median overall survival (mOS) for the whole MM population are limited and should be interpreted with caution.

The mOS for post-transplant maintenance MM patients has been reported to be approximately 7 years (Sengsayadeth et al., 2017). A study of 381 patients with newly diagnosed MM (NDMM) found that 30% of the study population were transplant ineligible, and these patients had a mOS of approximately 3.5 years (Jimenez-Zepeda et al., 2016).

A large proportion (30% to 40%) of MM patients are ISS Stage III and these patients have a reported mOS of 2 to 3 years, while MM patients with an ISS Stage I/II (60% to 70%) have a mOS of 6 to 7 years (Greipp et al., 2005; Cho et al., 2017; Kastritis et al., 2017; Usmani et al., 2018).

Based on this data, the sponsor performed a sensitivity analysis to calculate the mOS for all patients with MM with the following assumptions:

- mOS for ISS stage I/II: 6 to 7 years (represents 60-70% of all MM patients)
- mOS for ISS stage III: 2-3 years (represents 30-40% of all MM patients)

As variables in the sensitivity analysis, the sponsor used both the 30/70% or the 40/60% distribution, and a mOS of 1 to 4 years for the stage III group of patients. According to the sponsor, the proposed stage distribution was supported by published literature (single and multicentre studies) and 30% can be regarded as conservative starting point for the prevalence calculation.

Table 1. Sensitivity analysis of the prevalence of MM in the EU, varying the mOS for ISS stage III patients and the distribution of ISS stage I/II and stage III patients (60%/40% or 70%/30%)

Distribution of ISS Stage I/II and III patients	**Stage III mOS**			
	4 years	**3 years**	**2 years**	**1 years**
Stage I/II: 60% Stage III: 40%	4.64	4.32	4.00	3.68
Stage I/II: 70% Stage III: 30%	4.88	4.64	4.40	4.16

Prevalence was calculated using the equation P = I × D, where I was 0.8 per 10,000 people and D was a weighted mOS of ISS Stage III NDMM patients (which varied from 1 to 4 years) and ISS Stage I/II NDMM patients (fixed at 7 years).
Prevalence is reported per 10,000 people.
Source: Greipp, 2005**Error! Bookmark not defined.**; Cho, 2017**Error! Bookmark not defined.**; Kastritis, 2017**Error! Bookmark not defined.**; Usmani, 2018**Error! Bookmark not defined.**.

Based on the mOS assumptions for patients with ISS stage I/II and III made in the sensitive analysis, a mOS for the whole MM population of 4.6 to 6.1 years was estimated, which resulted in a prevalence estimate within the range of 3.68 to 4.88 per 10,000 people. Based on these numbers, the sponsor calculated the mOS for the whole MM population to be 5.8 years ([7 years×0.6] + [4 years×0.4]). The prevalence was then indirectly estimated (P=IxD [0.8 × 5.8]) to 4.64 per 10,000 persons in the EU.

The COMP agreed with the calculation of the prevalence for MM and concluded that the condition is affecting approximately 4.6 in 10,000 persons 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

Table 2. Products centrally authorized in the EU since 2004 or currently under review by the EMA for the treatment of relapsed/refractory MM

Drug Brand Name (Generic Name)/ Class	**Date of Authorization**	**Indication**	**SB applicable**
Tecvayli (teclistamab)	23-Aug-2022	As monotherapy for the treatment of adult patients with RRMM, who have received at least 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.	NO
Talvey (talquetamab)	21- Aug-2023	As monotherapy for the treatment of adult patients with RRMM, who have received at least 3 prior therapies, including an immunomodulatory agent, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy"	NO
Pepaxti (melphalan flufenamide)	17-Aug-2022	In combination with Dex, 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 immunomodulatory agent, 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 progression should be at least 3 years from transplantation	NO
Carvykti (ciltacabtagene autoleucel)	25-May-2022	Treatment of adult patients with RRMM, who have received at least 3 prior therapies, including an immunomodulatory agent, a PI and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy	NO
Nexpovio (selinexor)/	18-Jul-2022	In combination with Btz and Dex for the treatment of adult patients with MM who have received at least 1 prior therapy	NO

	26-Mar-2021	In combination with Dex, 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 immunomodulatory agents, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy	
Blenrep (belantamab mafotodin)/	26-Aug-2020	As monotherapy for the treatment of MM 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	NO
Sarclisa (isatuximab)/	15-Apr-2021	In combination with Cfz and Dex, for the treatment of adult patients with MM who have received at least 1 prior therapy	YES
	30-May-2020	In combination with Pom and Dex, for the treatment of adult patients with RRMM who have received at least 2 prior therapies including Len and a PI and have demonstrated disease progression on the last therapy	
Empliciti (elotuzumab)/	02-Aug-2019	In combination with Pom and Dex for the treatment of adult patients with RRMM who have received at least 2 prior therapies including Len and a PI and have demonstrated disease progression on the last therapy	YES
	11-May-2016	In combination with Len and Dex for the treatment of MM in adult patients who have received at least1 prior therapy	
Imnovid (pomalidomide)/	29-Mar-2019	In combination with Btz and Dex for the treatment of adult patients with Mm who have received at least 1 prior treatment regimen including Len	YES
	05-Aug-2013	In combination with Dex for the treatment of adult patients with RRMM who have received at least 2 prior treatment regimens, including both Len and Btz, and have demonstrated disease progression on the last therapy	
Darzalex (daratumumab)/	21-Jun-2021	in combination with Pom and Dex for the treatment of adult patients with MM who have received 1 prior therapy containing a PI and Len and were Len refractory, or who have received at least 2 prior therapies that included Len and a PI and have demonstrated disease progression on or after the last therapy	YES
	28-Feb-2017	In combination with Len and Dex, or Btz and Dex, for the treatment of adult patients with MM who have received at least 1 prior therapy	

	20-May-2016	As monotherapy, for the treatment of adult patients with RRMM, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated disease progression on the last therapy	
Ninlaro (ixazomib)/	21-Nov-2016	In combination with Len and Dex for the treatment of adult patients with MM who have received at least 1 prior therapy	NO
Kyprolis (carfilzomib)/	17-Dec-2020	In combination with Dara and Dex is indicated for the treatment of adult patients with MM who have received at least 1 prior therapy	NO
	19-Nov-2015	In combination with either Len and Dex or with Dex alone for the treatment of adult patients with MM who have received at least 1 prior therapy	
Farydak (panobinostat)/	28-Aug-2015	In combination with Btz and Dex, for the treatment of adult patients with relapsed and/or refractory MM who have received **at least 2 prior regimens, including Btz and an immunomodulatory agent**	YES
Caelyx (doxorubicin HCl liposome)/	14-Dec-2007	In combination with Btz 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
Revlimid (lenalidomide)/	14-Jun-2007	In combination with Dex for the treatment of MM in adult patients who have received at least 1 prior therapy	NO
Velcade (bortezomib)	26-Apr-2004	As monotherapy or in combination with pegylated liposomal doxorubicin or Dex for the treatment of adult patients with progressive MM who have received at least 1 prior therapy and who have undergone or are unsuitable for hematopoietic stem cell transplantation	NO

Note: Table does not include older chemotherapy drugs (e.g., melphalan, prednisone, vincristine) used to treat MM.
Source: EMA, 2023

In addition to the products included in the table above, elranatamab (Elrexfio) has been recently approved and it is indicated as monotherapy for the treatment of adult patients with relapsed and refractory MM, who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

The European Haematology 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 et al., 2021). 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 suitable 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 continuously changing. Currently, the following agents are specifically authorised in the r/r MM setting in the EU according to line of treatment:

- Second- and later lines: bortezomib, carfilzomib, ixazomib, lenalidomide, pomalidomide, daratumumab, isatuximab, elotuzumab and selinexor.
- **Third- and later lines**: pomalidomide, daratumumab, isatuximab, elotuzumab, and panobinostat.
- Fourth- and later lines: ide-cel, cilta-cel, melphalan flufenamide, teclistamab, talquetamab, and elranatamab.
- Fifth- and later lines: belantamab and selinexor.

Satisfactory methods for the target patient population

The indication of Abecma (idecabtagene vicleucel; hereinafter referred to as ide-cel) is extended to include treatment of adult patients with relapsed and refractory MM who have received at least two prior therapies, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. In this disease setting, the approved combinations of isatuximab (Sarclisa; anti-CD38 mAb) plus pomalidomide and dexamethasone (IsaPd), elotuzumab (Empliciti) plus pomalidomide and dexamethasone (EPd), and daratumumab (Darzalex; anti-CD38 mAb) plus pomalidomide and dexamethasone (DPd) can be used for treatment of patients who have received at least two prior therapies including lenalidomide (Len) and a PI. Furthermore, selinexor (Nexpovio) and panobinostat (Farydak) are authorised in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received at least one- (SVd) or two prior lines of therapy (PanoVd), respectively.

The medicinal products cilta-cel (Carvykti), melphalan flufenamide (Pepaxti), talquetamab (Talvey), teclistamab (Tecvayli), elranatamab (Elrexfio), and belantamab mafodotin (Blenrep)have more restricted therapeutic indications as compared to the indication extension for ide-cel. These agents are approved as fourth- or fifth- and later lines of therapy in more refractory MM patients being either triple-class exposed or triple-class refractory (to a PI, an IMiD, and an anti-CD38 mAb) for melphalan flufenamide and belantamab, while ide-cel is approved for use in a less refractory patient population and already from third line of therapy. It is therefore considered that ide-cel, does in principle include a broader patient population, which is not covered by cilta-cel, melphalan flufenamide, talquetamab, teclistamab, elranatamab, and belantamab.

In conclusion, the approved regimens with selinexor (SVd), panobinostat (PanoVd), isatuximab (IPd), elotuzumab (EPd), and daratumumab (DPd) are all considered to be satisfactory methods relevant for a discussion on the significant benefit of ide-cel in the target MM population as their indications are covering the indication extension proposed for ide-cel, although they do not include the requirement of prior exposure to an anti-CD38 mAb which is mandated for ide-cel.

Significant benefit

The sponsor did not seek any protocol assistance from EMA to get advice on a proper approach for collecting the evidence needed to justify significant benefit of ide-cel over authorised satisfactory methods of treatment for the target patient population of this extension of indication.

The sponsor argued that ide-cel will be of significant benefit based on a clinically relevant advantage in terms of the clinical efficacy observed in the pivotal study MM-003 and provide a major contribution to patient care compared to existing methods of treatment for patients with RRMM who have received at least two prior therapies.

Abecma is a chimeric antigen receptor (CAR)-positive T cell therapy targeting B-cell maturation antigen (BCMA), which is expressed on the surface of normal and malignant plasma cells. The CAR construct includes an anti-BCMA scFv-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T cell activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of Abecma results in CAR-positive T cell proliferation, cytokine secretion and subsequent cytolytic killing of BCMA-expressing cells.

The claim of significant benefit is based on the results from an ongoing, open-label, multicentre, randomized, controlled phase 3 study BB2121-MM-003 (MM-003, also called KarMMa-3) designed to evaluate the efficacy and safety of ide-cel, versus pre-specified standard anti-myeloma regimens (i.e., DPd, daratumumab, bortezomib and dexamethasone [DVd], ixazomib, lenalidomide and dexamethasone [IRd], carfilzomib and dexamethasone [Kd], or EPd) in patients with RRMM who had received 2 to 4 prior therapies, including daratumumab, an IMiD, and PI and had documented disease progression during or within 60 days after the last therapy.

The study included patients who achieved a response (minimal response or better) to at least 1 prior treatment regimen and had ECOG performance status of 0 or 1.

Patients enrolled were randomized 2:1 to arm A (lymphodepleting chemotherapy (LDC) followed by ide-cel infusion; n=254) or arm B (standard regimens: DPd, DVd, IRd, Kd, or EPd; n=132) and stratified by age (<65 years vs. ≥65 years), number of prior anti-myeloma regimens (2 vs. 3 or 4 prior therapies) and high-risk cytogenetic abnormalities (presence vs. absence or unknown presence of t(4;14) or t(14;16) or del 17p). Patients receiving standard regimens were allowed to receive ide-cel upon confirmed disease progression.

Patients randomised to ide-cel were to receive lymphodepleting chemotherapy consisting of cyclophosphamide (300 mg/m2 IV infusion daily for 3 days) and fludarabine (30 mg/m^2 IV infusion daily for 3 days) starting 5 days prior to the target infusion date of (ide-cel. Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd anticancer therapy for disease control (bridging therapy) was permitted between apheresis and until 14 days before the start of lymphodepleting chemotherapy.

The primary efficacy endpoint was progression free survival (PFS) according to the IMWG Uniform Response Criteria for MM as determined by an Independent Review Committee (IRC). Key secondary endpoints were overall response rate (ORR) per IRC and OS, which were tested in a hierarchical order from PFS to ORR and then to OS to control type I error rate. Other secondary endpoints included complete response (CR) rate, time to response (TTR), duration of response (DoR), event-free survival (EFS), PFS after next line of therapy (PFS2), time to next anti-myeloma treatment, minimal residual disease (MRD) negativity rate and patient reported outcome (PRO). The enrolled (intent to treat [ITT]) population was defined as the primary analysis population. At a pre-specified interim analysis at 80% information fraction with a median follow up time of 18.6 months, Abecma demonstrated a statistically significant improvement in PFS compared to the standard regimens arm; HR = 0.493 (95% CI: 0.38, 0.65, two-sided p-value < 0.0001). As of the updated data cut-off (DCO) date of 28 April 2023, the median PFS was 13.8 months (95% CI: 11.8, 16.1) for patients receiving ide-cel versus 4.4 months (95% CI: 3.4, 5.8) for patients receiving standard regimens.

- **Significant benefit of idecabtagene vicleucel (ide-cel) over daratumumab in combination with pomalidomide and dexamethasone (DPd)**

The data supporting the licencing of the combination regimen with daratumumab (DPd) in the third- and later lines setting was obtained from a study called APOLLO. APOLLO was a randomised, open-label, phase 3 study comparing DPd versus Pd in patients with RRMM who had received at least one previous line of therapy, including Len and a PI, had a partial response (PR) or better to one or more previous lines of anti-myeloma therapy (AMT), and were refractory to Len if only one previous line of therapy was received (Dimopoulos et al., 2021).

A total of 304 patients were randomly assigned 1:1 to the DPd group (n=151) or Pd group (n=153). All patients received oral treatment with pomalidomide (Pom; 4 mg, once daily on days 1–21) and dexamethasone (40 mg once daily on days 1, 8, 15, and 22; 20 mg for those aged 75 years or older) at each 28-day cycle. The DPd group received daratumumab (Dara; 1800 mg subcutaneously or 16 mg/kg intravenously) weekly during cycles 1 and 2, every 2 weeks during cycles 3–6, and every 4 weeks thereafter until disease progression or unacceptable toxicity.

The median age was 67 years and the median time since the initial diagnosis of MM was 4.4 years. Patients had received a median of 2 previous lines of therapy with approximately 11% of patients receiving one prior line of therapy. In total, 80% of patients were refractory to Len, 48% of patients were refractory to a PI, and 42.4% of patients were refractory to both PI and IMiD. For patients who received only one prior line of therapy, all were refractory to Len and 32.4% of patients were double-class refractory to both a PI and an IMiD. No patients had received prior anti-CD38 therapy.

At a median follow-up of 16.9 months, median PFS was 12.4 months (95% CI: 8.3, 19.3) in the DPd group and 6.9 months (95% CI: 5.5, 9.3) in the Pd group (HR 0.63 [95% CI: 0.47, 0.85], two-sided p=0.0018. DPd showed a statistically significant improvement in ORR compared with the Pd group (68.9% vs. 46.4%). The stratified CMH estimate of odds ratio was 2.68 (95% CI: 1.65, 4.35) and 2-sided p<0.0001. The median DoR had not been reached in the DPd group (range: 1 to 34.9+ months) and was 15.9 months (range: 1+ to 24.8) in the Pd group. DPd also showed a statistically significant higher rate of CR (sCR and CR) or better compared with the Pd group (24.5% vs. 3.9%; stratified CMH odds ratio=8.24 (95% CI: 3.35, 20.26), p<0.0001.

Comparison of daratumumab registrational data and ide-cel data

Given the differences in baseline patient disease characteristics, efficacy results from study MM-003 cannot be directly compared with those from APOLLO. First, patients treated in study MM-003 had a median of 3 prior regimens compared with 2 prior regimens in APOLLO. Second, a greater proportion of patients treated in study MM-003 were exposed to various prior therapies compared with the APOLLO DPd arm (anti-CD38 mAb: 100% vs. 0%, Pom: 55% vs. 0%, ASCT: 84.3% vs. 60%, respectively). Patients were excluded from APOLLO if they had previous therapy with any anti-CD38 mAb. No patient in the DPd arm was therefore previously treated with Dara, whereas 95% of patients in study MM-003 were refractory to prior anti-CD38 therapy, which constitute a patient population known to be particularly difficult to treat. Despite these differences, the sponsor claimed that the median PFS (13.8 vs. 12.4 months) compared favourably for ide-cel versus DPd. Additionally, it was argued that patients who received ide-cel in MM-003 had a better response rate relative to that of patients who received DPd in APOLLO (ORR: 71.3% vs. 68.9%; CR rate: 43.7% vs. 24.5%).

Direct comparison of DPd versus ide-cel in study-MM-003 (sub-group analysis)

DPd was one of the standard regimens used as comparator in the control arm B of study MM-003. A subgroup analysis of the primary endpoint was conducted per regimen included in the comparator arm. Table 3 summarises the results for the ide-cel arm versus those who received DPd in arm B. According to the sponsor, the baseline characteristics were balanced between patients in Arm A (ide-cel arm) and the subgroup of patients treated with DPd in Arm B of study MM-003.

Table 3. Summary of PFS per IRC for Ide-cel and DPd in MM-003 (28-Apr-2023 Data cut-off)

	Ide-cel **(N=254)**	**DPd** **(N=43)**
Progressed/died n(%) Censored n (%)	184 (72.4) 70 (27.6)	34 (79.1) 9 (20.9)
Median PFS, mo (95 CI)	13.8 (11.8, 16.1)	8.5 (3.7, 14.6)
Event-free Rate 6-month 12-month	 72.7 (2.8) 55.1 (3.2)	 54.2 (8.2) 45.6 (8.3)

The sponsor concluded that although cross-study comparisons should be interpreted with caution, the outcomes observed among patients treated with ide-cel were favourable or equivalent in comparison to the data from the registrational study for Dara. Moreover, when directly comparing Dara outcomes to ide-cel outcomes in study MM-003, a clinically relevant advantage was demonstrated.

The clinical data derived from the pivotal, comparative study MM-003 demonstrate the capacity of ide-cel to prolong PFS and are considered sufficient to support the basis of significant benefit based on a clinically relevant advantage in terms of improved efficacy in comparison to the authorised regimen with daratumumab (DPd) for adult patients with RRMM who have received at least two prior therapies.

- **Significant benefit of idecabtagene vicleucel (ide-cel) over elotuzumab in combination with pomalidomide and dexamethasone (EPd)**

The data supporting the licensing of the combination regimen with elotuzumab (EPd) in the third- and later lines setting was obtained from a study called ELOQUENT-3. ELOQUENT-03 was a randomised, open-label, phase 2 study comparing EPd versus Pd in patients with RRMM who had received at least 2 prior therapies, including Len and a PI, and had demonstrated disease progression on the last therapy (Dimopoulos et al., 2018).

A total of 117 patients were randomized 1:1 to the EPd arm (n=60) or Pd arm (N=57). Patients in the EPd arm received 10 mg/kg elotuzumab (Elo) IV on Days 1, 8, 15, and 22 during Cycle 1 and 2 and 20 mg/kg Elo IV on Day 1 of each cycle thereafter. Patients in both the EPd arm and the Pd arm received Pom (4 mg Days 1 to 21 of each cycle). Patients received dexamethasone (40 mg for patients ≤75 years or 20 mg for patients > 75 years), per week, except on the days of Elo administration, when patients in the EPd arm received dexamethasone both per oral (PO) (28 mg for patients ≤ 75 years or 8 mg for patients > 75 years) and IV (8 mg). Treatment was continued until disease progression, development of unacceptable toxicities, or withdrawal of consent.

The baseline treatment characteristics were generally well-balanced between treatment arms. The median age was 69 and 66 years in the EPd and Pd arms, respectively. The median number of prior AMTs was 3 (range: 2-8), with 40% and 37% of patients in the EPd and Pd arms receiving ≥4 prior

AMTs, respectively. Patients were required to be either refractory or relapsed and refractory to a PI and Len at study entry. In all, 68% of patients in the EPd arm and 72% in the Pd arm had MM that was refractory to both Len and a PI. Patients were predominantly Dara-naïve.

After a minimum follow-up of 9.1 months, the median PFS was 10.3 months (95% CI: 6.5, NE) in the EPd arm and 4.7 months (95% CI: 2.8, 7.6) in the Pd arm. The ORR was 58% (95% CI: 45, 71) in the EPd arm compared with 25% (95% CI: 14, 38) in the Pd arm. A total of 8% of patients in EPd arm and 2% of patients in the Pd arm achieved CR or better. The very good PR (VGPR) or better rate was 20% in EPd arm and 9% in the Pd arm. The median DoR was not reached (95% CI: 8.3, NE) in the EPd arm and was 8.3 months (95% CI: 4.6, NE) in the Pd arm.

A non-prespecified analysis was conducted after a minimum follow-up of 18.3 months to provide a descriptive assessment of OS with EPd and Pd (Dimopoulos et al., 2019). Median OS in this analysis was not reached (95% CI: 24.9, NE) with EPd and was 17.4 months (95% CI: 13.8, NE) with Pd.

Comparison of elotuzumab registrational data and ide-cel data

Both studies included patients who had received a median of 3 prior regimens and the proportions of patients who were refractory to both Len and a PI were similar between studies (68% in EPd arm vs. 66.5% in idel-arm). However, in study MM-003, the majority of patients were triple-class refractory to therapy they were required to have been exposed to. In total, 64.6% of patients in the ide-cel arm were refractory to an IMiD, a PI, and an anti-CD38 mAb. With regards to refractoriness to Dara, in the ide-cel arm, 68.9% of patients were refractory to Dara received as part of their last prior anti-myeloma regimen and 26.4% were refractory to Dara as part of an earlier anti-myeloma regimen. To the opposite, in ELOQUENT-3, only one patient had received Dara in the EPd arm. The sponsor stressed that these comparisons underscore the significant differences in prior therapy exposure between the study populations in the two clinical studies, MM-003 and ELOQUENT-3.

Although the MM-003 population was more exposed, refractory, and at higher risk, the median PFS results compared favourably for ide-cel relative to EPd (13.8 months vs. 10.3 months). Both ORR and CR in patients who received ide-cel were higher than those reported in patients treated with EPd (ORR: 71.3% vs. 58%; and CR rate: 43.7% vs. 8%, respectively).

Direct comparison of EPd versus ide-cel in study-MM-003 (sub-group analysis)

EPd was one of the standard regimens used as comparator in the control arm B of study MM-003. A subgroup analysis of the primary endpoint was conducted per regimen included in the comparator arm. Table 4 summarizes the results for the ide-cel arm versus those who received EPd in arm B. According to the sponsor, the baseline characteristics were balanced between patients in Arm A (ide-cel arm) and the subgroup of patients treated with EPd in Arm B of study MM-003.

Table 4. Summary of PFS per IRC for Ide-cel and EPd in MM-003 (28-Apr-2023 Data Cutoff)

	Ide-cel **(N=254)**	**EPd** **(N=30)**
Progressed/died n(%) Censored n (%)	184 (72.4) 70 (27.6)	27 (90.0) 3 (10.0)
Median PFS, mo (95 CI)	13.8 (11.8, 16.1)	2.9 (2.0, 4.7)
Event-free Rate 6-month 12-month	 72.7 (2.8) 55.1 (3.2)	 20.7 (7.5) 10.3 (5.7)

The sponsor concluded that although cross-study comparisons should be interpreted with caution given limitations in available data and varying definitions used for study data, the outcomes among patients treated with ide-cel in study MM-003 compared favourably relative to those reported among patients treated with EPd in the registrational study ELOQUENT-3, with a better median PFS and more frequent and deeper responses for ide-cel relative to EPd. Moreover, when directly comparing Elo outcomes to ide-cel outcomes in study MM-003, a clinically relevant advantage was demonstrated.

The clinical data derived from the pivotal, comparative study MM-003 demonstrate the capacity of ide-cel to prolong PFS and are considered sufficient to support the basis of significant benefit based on a clinically relevant advantage in terms of improved efficacy in comparison to the authorised regimen with elotuzumab (EPd) for adult patients with RRMM who have received at least two prior therapies. This was also supported by the descriptive side-by-side comparison which indicated a longer PFS associated with a numerically higher ORR and CR rate in patients with RRMM who were treated with ide-cel in study MM-003 as compared to that achieved with the combination regimen with elotuzumab (EPd) in a less heavily pre-treated and refractory MM populations from its pivotal study ELOQUENT-03.

- **Significant benefit of idecabtagene vicleucel (ide-cel) over isatuximab in combination with pomalidomide and dexamethasone (IPd)**

The data supporting the licencing of the combination regimen with isatuximab (IPd) in the third- and later lines setting was obtained from a study called ICARIA. The ICARIA-MM study was a randomised, open-label, multicenter, phase 3 study comparing IPd with Pd in patients with RRMM who received two or more prior lines of therapy including Len and a PI. Only one patient in the IPd arm was previously treated with Dara (Attal et al., 2019).

A total of 307 patients were randomized 1:1 to receive either IPd (n=154) or Pd (n=153) in 28-day cycles. All patients received 4 mg of Pom on Days 1 to 21 and 40 mg of dexamethasone once weekly (i.e., Days 1, 8, 15, and 22). Patients in the IPd arm received isatuximab (Isa) at a dose of 10 mg/kg IV once weekly (i.e., Days 1, 8, 15, and 22) during the first cycle and on Days 1 and 15 thereafter. Treatment was given until PD or unacceptable adverse events (AEs).

In the ITT population, the median age was 67 years and the median number of prior AMTs was 3 across both treatment arms. The time since initial diagnosis was 4.46 and 4.09 years, with 54% and 59% of patients having had prior ASCT in the IPd and Pd arms, respectively.

The median follow-up time was 11.6 months, with a median PFS of 11.53 months in the IPd arm and 6.47 months in the Pd arm. The ORR was 60% in the IPd arm and 35% in the Pd arm, with 4.5% and 2.0% achieving either CR/stringent CR (sCR). Median OS was not reached in either treatment arm.

Median TTR (PR or better) was 35 days in the IPd arm compared to 58 days in the Pd arm. Median DoR was 13.3 months in the IPd arm and 11.1 months in the Pd arm.

Comparison of isatuximab registrational data and ide-cel data

Both studies included patients who had received a median of 3 prior regimens and the proportions of patients who were refractory to both Len and a PI were similar between studies (72% of patients in the IPd arm vs. 66.5% in ide-cel arm). Nevertheless, 64.6% of patients in the ide-cel arm of study MM-003 were also refractory to an IMiD, a PI and an anti-CD38 mAb. In addition, 95% of patients in MM-003 were refractory to prior anti-CD38 therapy. In ICARIA-MM, only one patient in the IPd arm was previously treated with Dara. Despite the differences in patient populations, the sponsor claimed that median PFS compared favourably for ide-cel versus IPd (13.8 vs. 11.5 months). Additionally, patients who received ide-cel in MM-003 had a better response rate relative to that of patients who received IPd in the ICARIA-MM study (ORR: 71.3% vs. 60%; CR rate: 43.7% vs. 4.5%).

The sponsor concluded that although cross-study comparisons should be interpreted with caution given limitations in available data and varying definitions used for study data, the outcomes among patients treated with ide-cel in study MM-003, including more frequent and deeper responses, were favourable relative to those reported among patients treated with IPd in the registrational study ICARIA-MM, which enrolled a less heavily pre-treated and refractory MM population with almost no prior exposure to anti-CD38 therapy.

The descriptive side-by-side comparison indicated a longer PFS associated with a numerically higher ORR and CR rate in patients with RRMM who were treated with ide-cel in study MM-003 as compared to that achieved with the combination regimen with isatuximab (IPd) in a less heavily pre-treated and refractory MM populations from its pivotal study ICARIA-MM. These efficacy results provide sufficient evidence to support the claim of a clinically relevant advantage based on improved efficacy with ide-cel compared to that obtained with isatuximab (IPd).

- **Significant benefit of idecabtagene vicleucel (ide-cel) over panobinostat in combination with bortezomib and dexamethasone (PanoVd)**

The sponsor presented a comparison of PanoVd registrational data (PANORAMA-1 study) and ide-cel data (study MM-003).

The data supporting the licencing of panobinostat in combination with bortezomib and dexamethasone (PanoVd) in the third- and later lines setting was obtained from the PANORAMA-1 study. This was a multicenter, randomised, double-blind, placebo-controlled, phase 3 study comparing PanoVd versus Vd in patients with relapsed MM who had received one to three prior lines of therapies (San-Miguel et al., 2014). Patients with primary refractory or bortezomib-refractory disease, or who had received previous histone deacetylase inhibitor therapy were excluded from the study. Based on the benefit-risk evaluation by the EMA, panobinostat was approved in a subgroup of patients with relapsed/refractory MM who have received at least two prior regimens, including bortezomib and an IMiD (Farydak EPAR, 2015).

A total of 768 patients were randomized 1:1 to either PanoVd (n=387) or Vd (n=381) in PANORAMA-1 (San-Miguel et al., 2014; San-Miguel et al., 2016). Patients received 21-day cycles of placebo or Pano (20 mg PO on Days 1, 3, 5, 8, 10 and 12), both in combination with bortezomib (1.3 mg/m^2 IV on Days 1, 4, 8, and 11) and dexamethasone (20 mg PO on Days 1, 2, 4, 5, 8, 9, 11, and 12).

The median age was 63 years for patients enrolled across both treatment arms. Nearly half of the patients received at least two prior AMTs, and 17% in the PanoVd arm and 20% in the Vd arm received three prior AMTs. Patients were predominantly Dara-naïve. At a median follow up time of 6.5 months

in the PanoVd arm and 5.6 months in the Vd arm, the median PFS was significantly longer for those patients who were treated with PanoVd (12 months [95% CI: 10.3, 12.9]) than with Vd (8.1 months [95% CI: 7.56, 9.23]). The ORR was similar between the two treatment arms (60.7% for PanoVd vs. 54.6% for Vd). However, the CR rate was slightly higher in the PanoVd arm (11%) compared with the Vd arm (6%). The median TTR was 1.5 months for PanoVd patients and 2 months for Vd patients. The median DoR was 13.1 months (95% CI: 11.76, 14.92) and 10.9 months (95% CI: 9.23, 11.76), respectively (San-Miguel et al., 2014). The median OS was 40.3 months (95% CI: 35.0, 44.8) for PanoVd and 35.8 months (95% CI: 29.0, 40.6) for Vd (San-Miguel et al., 2016).

In patients who had received at least two prior regimens including bortezomib and an IMiD agent, median PFS was 12.5 months (95% CI: 7.3, 14.0) for PanoVd and 4.7 months (95% CI: 3.7, 6.1) for Vd with a HR of 0.47 (95% CI: 0.31, 0.72). The ORR was 58.9 % for PanoVd versus 39.2% for Vd. The median DoR was 11.99 months (95% CI: 9.69, 13.37) for PanoVd and 6.97 months (95% CI: 4.86, 13.40) for Vd (Richardson et al., 2016). Finally, median OS was reported to 25.5 months (95% CI: 19.6, 34.3) for PanoVd (n=73) and 19.5 months (95% CI: 14.1, 32.5) for Vd (n=74) (San-Miguel et al., 2016).

Comparison of panobinostat registrational data and ide-cel data

Several factors make a direct comparison between study MM-003 and PANORAMA-1 difficult. The patient population in MM-003 was more heavily pre-treated than in PANORAMA. All patients enrolled in study MM-003 had received at least 2 prior regimens with a median of 3 prior lines compared with patients in PANORAMA-1 who had received a maximum of 3 prior lines with < 20% having 3 prior lines. In addition, all patients in study MM-003 had prior PI exposure and 74.4% were PI-refractory whereas in PANORAMA-1 only 44.4% patient had prior bortezomib exposure and 0% were bortezomib -refractory as those patients were excluded from the study. Moreover, PANORAMA-1 likely had very few anti-CD38 antibody-exposed patients, since these agents were not approved when the study was conducted, whereas 95% of patients in study MM-003 were refractory to prior anti-CD38 therapy, a population known to be particularly difficult to treat. Despite these differences, the sponsor claimed that the median PFS compares favourably for ide-cel versus PanoVd (13.8 vs. 12.0 months). Additionally, patients who received ide-cel had a better response rate relative to that observed for patients who received PanoVd in PANORAMA-1 (ORR: 71.3% vs. 60.7%; CR rate: 43.7% versus 11%).

The sponsor concluded that although cross-study comparisons should be interpreted with caution and despite the differences in study populations, the outcomes observed among patients treated with ide-cel were favourable in comparison to the data from the registrational study for panobinostat.

The descriptive side-by-side comparison indicated a slightly longer PFS associated with a numerically higher ORR and CR rate in patients with RRMM who were treated with ide-cel in study MM-003 as compared to that achieved with the combination regimen with panobinostat (PanoVd) in a less heavily pre-treated and refractory MM populations from its pivotal study PANORAMA-1. These efficacy results provide sufficient evidence to support the claim of a clinically relevant advantage based on improved efficacy with ide-cel compared to that obtained with panobinostat (PanoVd).

- **Significant benefit of idecabtagene vicleucel (ide-cel) over selinexor in combination with bortezomib and dexamethasone (SVd)**

The data supporting the licencing of selinexor in combination with bortezomib and dexamethasone (SVd) in the second- and later lines setting was obtained from a study called BOSTON. This was a randomised, open-label, multicenter, phase 3 study comparing weekly treatment with selinexor, bortezomib, and dexamethasone (SVd) versus standard bortezomib and dexamethasone (Vd) in adult

patients with MM who had previously been treated with one to three lines of therapy, including PIs (Grosicki et al., 2020).

A total of 402 patients were randomly allocated 1:1 to receive selinexor (100 mg once per week), bortezomib (1.3 mg/m² once per week), and dexamethasone (20 mg twice per week), or bortezomib (1.3 mg/m² twice per week for the first 24 weeks and once per week thereafter) and dexamethasone (20 mg four times per week for the first 24 weeks and twice per week thereafter).

Baseline demographic, disease, and clinical characteristics were balanced across the two treatment groups. Median age was 67 years (IQR 59-73). Median time since initial diagnosis of MM was 3.7 years (range: 2.3-5.5). High-risk cytogenetic abnormalities were present in 192 patients (48%). Median number of previous regimens was 2, 75 patients (19%) had received three previous lines of therapy, and 139 patients (35%) had undergone SCT. Previous therapies included lenalidomide (154 patients [38%]) and PIs (307 patients [76%]), including bortezomib (279 patients [69%]).

After a median follow-up period of 13.2 months (IQR 6.2-19.8) for the SVd group and 16.5 months (9.4-19.8) for the Vd group, median PFS was significantly longer in the SVd group (13.93 months [95% CI: 11.73, not evaluable]) than in the Vd group (9.46 months [95% CI: 8.11-10.78]) with a HR of 0.70 (95% CI: 0.53, 0.93; p=0.0075). ORR was significantly higher in the SVd group (76.4% [95% CI: 69.8, 82.2]) than in the Vd group (62.3% [95% CI: 55.3, 68.9]) with an odds ratio (OR) of 1.96 (95% CI: 1.3, 3.1; p=0.0012). Median DoR was longer with SVd than with Vd (20.3 months [95% CI: 12.5, not evaluable] vs. 12.9 months [95% CI: 9.3, 15.8]) with a HR of 0.81 (95% CI: 0.56, 1.17; p=0.1364).

Comparison of selinexor registrational data and ide-cel data

The baseline patient disease characteristics in BOSTON were different than those in study MM-003 in several important ways that precluded a direct comparison of efficacy. Overall, 35% of the patients in BOSTON had undergone SCT versus 85% in study MM-003. Median number of prior therapies was 2 in BOSTON compared to 3 in MM-003. Patients in BOSTON who had previously received PIs (alone or as part of a combination treatment) were required to have had at least a PR to the therapy and at least a 6-month interval since their last PI therapy, while most of the patients (74.4%) in study MM-003 were refractory to a PI. Moreover, BOSTON patients had a limited prior exposure to an anti-CD38 therapy (4.2%). The patient population in study MM-003 was therefore more heavily pre-treated than that included in the BOSTON study. Despite these differences, the sponsor claimed that the median PFS (13.8 vs. 13.9 months) and ORR (71.3% vs. 76.4%) were similar for ide-cel and SVd, whereas the reported CR rates compared favourably for ide cel versus SVd (43.7% vs. 7%).

The sponsor argued that ide-cel showed clinical benefits with deeper responses in study MM-003 in a more exposed and refractory MM population, which compared favourably to selinexor, and concluded that the outcomes observed among patients treated with ide-cel in study MM-003 were favourable in comparison to the data from the registrational study for selinexor.

The descriptive side-by-side comparison indicated that a higher proportion of RRMM patients treated with ide-cel achieved deeper responses in terms of CR rate in study MM-003 as compared to that achieved in a less heavily pre-treated and refractory MM populations with the combination regimen with selinexor (SVd) from its pivotal study BOSTON. This is considered sufficient evidence to support the claim of a clinically relevant advantage based on improved efficacy with ide-cel compared to that obtained with selinexor (SVd).

- **Significant benefit based on a major contribution to patient care**

The sponsor also claimed that ide-cel offers a significant benefit by providing a major contribution to patient care by being a one-time infusion for patients with RRMM who achieve a durable response to treatment, whereas the satisfactory methods of treatment are administered on a continuous dosing schedule until progression or unacceptable toxicity.

The sponsor argued that administration of ide-cel as a single infusion in study MM-003 demonstrated statistically significant and clinically meaningful improvements in terms of PFS and ORR, with a long-term benefit as illustrated by the numerical advantage in PFS2. Nevertheless, as patients randomised to the standard regimens arm were allowed to cross-over to the ide-cel arm after IRC confirmation of disease progression, the OS data were confounded since most of the patients in the study received ide-cel infusion. Multiple analyses correcting for cross-over were conducted post-hoc and resulted in consistent trend of OS benefit in favour of ide-cel. They further claimed that a major contribution to patient care for RRMM patients in third- and later lines of therapy was supported by meaningful improvements in quality of life (QoL) based on patient reported outcomes (PRO) data from study MM-003, in which secondary endpoints were included in the assessment of patient outcomes using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30). Of the questionnaire responders (n=211 for ide-cel; n=108 for standard regimens), when comparing least square (LS) mean changes from baseline to month 25 using constrained longitudinal data analyses, the overall LS mean change scores favoured ide-cel-treated patients compared to patients treated with the selected standard regimens, including global health status, QoL (6.17; 95% CI: 3.35, 8.99), fatigue (6.24; 95% CI: 9.52, 2.96), pain (5.68; 95% CI: 9.36, 1.99), and physical functioning (4.32, 95% CI: 1.66, 6.98).

The COMP considered that while the PRO data from study MM-003 could indicate a clinically relevant improvement in QoL after treatment with ide-cel over the standard regimens, the open-label design reduced the reliability and consequently the interpretability of the data presented. The arguments provided by the sponsor for a major contribution to patient care of ide-cel are consequently not considered sufficiently substantiated and cannot be accepted based on the data provided.

Overall conclusion

In conclusion, the COMP considered that the claim of significant benefit of Abecma (ide-cel) over the authorised regimens with the medicinal products Darzalex (daratumumab), Sarclisa (isatuximab), Empliciti (elotuzumab), Farydak (panobinostat), and Nexpovio (selinexor) is established based on the data presented.

4. COMP position adopted on 29 January 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 Abecma, the assumption that Abecma 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 after treatment with Abecma as compared to the authorised regimens with daratumumab (DPd) and elotuzumab (EPd), and sustained and deeper responses compared to the combination regimens with isatuximab (IPd), panobinostat (PanoVd), and selinexor (SVd), in adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including an immunomodulatory agent, a proteasome inhibitor 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 Abecma, autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains, idecabtagene vicleucel for treatment of multiple myeloma (EU/3/17/1863) is not removed from the Community Register of Orphan Medicinal Products.