EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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: Celgene Europe B.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	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 names	Idecabtagene vicleucel, Also: Anti-BCMA CART Cell Therapy - bluebird bio/Celgene; Anti-BCMA CART cells - bluebird bio/Celgene; bb-2121; ide-cel
International Non-Proprietary Name	Idecabtagene vicleucel
Tradename	Abecma
Orphan condition	Treatment of multiple myeloma
Sponsor's details:	Celgene Europe B.V. Winthontlaan 6n 3526 KV Utrecht Netherlands
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	
Transfer of sponsorship	Transfer from bluebird bio France to Celgene Europe Limited – EC decision of 13 October 2017
Transfer of sponsorship	Transfer from Celgene Europe Limited to Celgene Europe B.V. – EC decision of 9 November 2018
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Rune Kjeken / Olli Tenhunen
Applicant	Celgene Europe B.V.
Application submission	30 April 2020
Procedure start	21 May 2020
Procedure number	EMA/H/C/004662
Invented name	Abecma
Proposed therapeutic indication	Abecma 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. 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	24 June 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Karri Penttila / Maria Elisabeth Kalland
Sponsor's report submission	27 May 2020 and 18 November 2020
COMP discussion	15-17 June 2021
COMP opinion (adoption via written procedure)	30 June 2021

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2017 designation 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;
- 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.

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 (also called plasma cell myeloma) is a malignant neoplasm of plasma cells that clonally expand and accumulate in the bone marrow (BM) and/or extramedullary sites, leading to bone destruction, infections, renal insufficiency, and marrow failure (Dimopoulos et al, 2015). The disease is

often asymptomatic for a long period of time and therefore is often advanced at the time of diagnosis. MM is most frequently diagnosed among people >65 years of age and the median age at onset in Europe is 72 years. The incidence rates increase with age, particularly after the age of 40 years, and men are more likely to develop the disease than women. The aetiology is unknown with no established lifestyle, occupational or environmental risk factors.

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 a number of years. Common symptoms of MM include, but are not limited to, fatigue, persistent bone pain, pathologic fractures, spinal cord compression (from pathologic fracture), weakness, malaise, anaemia and/or bleeding, frequent infections (often pneumococcal), hypercalcemia, renal failure, and neuropathies.

The understanding of MM and its classification has not changed since the initial orphan designation.

The approved therapeutic indication "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" falls within the scope of the designated orphan condition "Treatment of multiple myeloma".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CAT/ CHMP on the basis of the submitted evidence including data from the pivotal single-arm, phase 2 study MM-001. Abecma received a conditional marketing authorisation (CMA). For a full discussion of the results and the justification of the CMA, please refer to the European Public Assessment Report of Abecma.

Chronically debilitating and/or life-threatening nature

Multiple myeloma 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. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures (Munshi, 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. However, even with optimal upfront therapy and advances in treatment, most MM patients progress or relapse, and further treatment is needed.

The condition therefore remains chronically debilitating and life-threatening in nature.

Number of people affected or at risk

The sponsor claims that the calculation of prevalence of MM was conducted using data collected from the Global Burden of Disease (GBD) study in 2017 by the Institute for Health Metrics and Evaluation (IHME), combined with Eurostat 2017 mortality rates and 2018 population counts for each country. It is unclear where the data on prevalence come from and if only 5 EU member states were included in this analysis. The sponsor suggested that in 2020, MM is estimated to affect 2.29 in 10,000 persons in

the EU, with point prevalence estimates ranging from 1.65 per 10,000 persons in France to 2.69 per 10,000 persons in Germany. The sponsor did not include any discussion of prevalence in the remaining 22 EU member states in addition to France, The Netherlands, Spain, Germany and Italy. It is also not clear whether the sponsor attempted to calculate complete or partial prevalence. In addition, the proposed estimate is considerably lower than other estimates previously accepted in recent designations for MM with a value of approximately 4 in 10,000. Therefore, the sponsor was asked to submit a re-calculation based on relevant epidemiological studies and registers for MM, taking into consideration various sources of incidence and providing a good justification of the assumed duration of the disease.

The point prevalence of MM has been recalculated as requested and 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 European Cancer Information System (ECIS). The sponsor used the standard formula P=I×D for indirectly establishing the prevalence of MM in the EU. The incidence of MM in the EU27 was 0.8 per 10,000 people according to ECIS (2020 data).

Since published data on the median overall survival (mOS) for the whole MM population is currently lacking, two factors should be taken into account when estimating the survival for all MM patients, namely eligibility for transplant and the international staging system (ISS) stage. 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 (Greipp, 2005; Cho, 2017; Kastritis, 2017; Usmani, 2018). MM patients with an ISS Stage I/II (60% to 70%) have a mOS of 6 to 7 years (Greipp, 2005; Cho, 2017; Kastritis, 2017; Usmani, 2018).

Based on these 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: 7 years (represents 60-70% of all MM patients)
- mOS for ISS stage III: 1-4 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.

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 of 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.

This estimate is higher than the estimates accepted in recent MM designations, where a prevalence of approximately 4 in 10,000 people in the EU was concluded. However, the COMP considered that the adjusted prevalence estimate reflects better the recent influences of the rapidly evolving therapeutic field and increasing survival of patients with MM, and was therefore agreed to be accepted.

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

The sponsor listed all authorised medicines used for the management of MM. Both the SmPC indications of authorised medicines as well as the treatment algorithms included in the treatment guidelines by ESMO and NCCN were referred to. Since the initial designation, 6 products were authorised for the treatment of MM, specifically Sarclisa (isatuximab), Empliciti (elotuzumab), Imnovid (pomalidomide), Darzalex (daratumumab), Blenrep (belantamab mafodotin), and Nexpovio (selinexor).

Elotuzumab (Elo), pomalidomide (Pom), ixazomib (Ixa), carfilzomib (Cfz) and panobinostat (Pano) are authorized in the EU for use as doublet or triplet therapy in combination with dexamethasone (Dex) and either lenalidomide (Len), Pom or bortezomib (Btz). Approvals of these medicinal products were based on registration studies in relapsed/refractory (r/r) MM patients who had received 1 to 3 or ≥ 2 prior regimens. These studies were not designed to address relapse after daratumumab (Dara) exposure and were not representative of the population targeted by ide-cel.

Daratumumab is authorized in the r/r MM setting in the EU as either monotherapy for the treatment of adult patients with r/r MM whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or in combination with Len and Dex, or Btz and Dex, for the treatment of adult patients with MM who have received at least one prior therapy. There is no standard of care for patients with MM who have relapsed after prior exposure to Dara. The latest ESMO clinical practice guidelines for diagnosis, treatment and follow-up of MM describe some of the recommended treatment options available for these patients (Moreau, Ann Oncol. 2017; 28(S4): iv52–61). However, the treatment algorithm for MM is evolving rapidly and the therapeutic field for the management of the condition is continually changing.

Isatuximab, which is another anti-CD38 directed antibody, received a marketing authorisation (MA) in May 2020 in combination with Pom and Dex for the treatment of r/r MM patients who have received at least two prior lines of therapy, including Len and a PI, and whose disease had progressed on the last therapy.

Currently, the two medicines belantamab mafotodin (Blenrep) and selinexor (Nexpovio) are indicated for the treatment of r/r MM patients who are triple- or quadruple-class refractory (i.e. refractory to IMiDs and PIs, and refractory or intolerant (or both) to an anti-CD38 directed antibody). These products are therefore considered relevant for the discussion on significant benefit because of the overlapping intended clinical setting.

Significant benefit

The sponsor performed a comparison of belantamab mafodotin (Blenrep), selinexor (Nexpovio) and ide-cel based on data from the three clinical studies DREAMM-2, STORM part 2 and MM-001.

The patient populations enrolled in DREAMM-2 and STORM were comparable to that enrolled in study MM-001 in several key features (e.g., number of previous regimens, extensive exposure and refractoriness to major anti-myeloma therapy [AMT] classes). Eligible patients in all these three clinical studies had been exposed to ≥ 3 prior AMT regimens including an IMiD, a PI, and an anti-CD38 antibody prior to enrolment. All three studies enrolled patient populations that had received a median

number of prior regimens of 6 to 8. In addition, as per the inclusion criteria, all patients in DREAMM-2 were triple-class refractory, meaning that they were refractory to an IMiD, a PI, and an anti-CD38 antibody. The patient population in STORM part 2 were even more heavily pre-treated and had received at least four prior regimens. All patients enrolled in this study were penta-refractory (defined as refractory to two IMiDs, two PIs, and one anti-CD38 antibody). In study MM--001, 89.1% and 84.4% of the enrolled patients were double refractory (refractory to an IMiD and a PI) or triple refractory, respectively, and 25.8% were penta-refractory. Thus, a comparison of efficacy using these three therapies is considered reasonable. A table overview has been provided outlining the reported outcomes of ide-cel for both the enrolled and infused patient populations in comparison to the data from the registration studies of belantamab mafotodin monotherapy and selinexor in combination with dexamethasone, for which phase 2 data in the relevant triple-class-exposed MM patient population are available (see table 1 below).

Table 1. Reported Efficacy Outcomes of Interest in MM 001, STORM Part 2, and DREAMM-2

Endpoint	Ide-cel (MM-001)		Selinexor/Dex STORM Part 2 mITT Population (N = 122)	Belantamab Mafodotin DREAMM-2 ITT Population (N = 97)
	Enrolled Population (N = 140)	Infused Population (N = 128)		
ORR, % (95% CI)	67 (59, 75)	73 (66, 81)	26 (19, 35)	31 (21, 43)
Median DoR, mo (95% CI)	10.6 (9.0, 11.3)	10.6 (9.0, 11.3)	4.4 (3.7, 10.8)	NE
Median PFS[a], mo (95% CI)	9.4 (6.7, 12.1)	8.6 (5.6, 11.3)	3.7 (3.0, 5.3)	2.9 (2.1, 3.7)
Median OS[a], mo (95% CI)	19.3 (17.9, NE)	18.2 (18.0, NE)	8.6 (6.2, 11.3)	9.9[b]

CI = confidence interval; DoR = duration of response; ITT = intent to treat; mITT = modified intent to treat; mo = month; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.
a Median PFS and OS were calculated from the date of infusion for the ide-cel-treated population and from the date of enrollment (ie, leukapheresis) for the enrolled population.
b Derived from published Kaplan-Meier curves, as medians are not reported in the publication.
Source: Chari, 2019; Lonial, 2020

The comparison between three single-arm studies is, technically, not very informative in terms of quantifying the effects observed. However, taking into consideration similar characteristics of the patient populations enrolled in these studies, and the fact that ide-cel seemed to perform significantly better than both belantamab mafodotin and selinexor in terms of higher overall response rate (ORR) and longer duration of response (DOR), the improved efficacy of this product is accepted. Therefore, the arguments of significant benefit over currently authorised methods of treatment for the target r/r MM population can be accepted based on improved efficacy.

In addition, the sponsor claims a significant benefit based on major contribution to patient care over other approved therapies, which require continuous dosing. Ide-cel is a one-time infusion with expected onset of acute on-target toxicities primarily occurring in the first weeks after infusion. Patients treated with ide-cel achieving a durable response can therefore expect a significant treatment-free interval and potential improvement in quality of life. According to the sponsor, this is supported by the assessments of the health-related quality of life (HRQoL) data derived from study MM-001.

Table 2. Baseline Mean Scores on the EORTC QLQ C30 and EORTC QLQ-MY20 Primary Domains of Interest for the PRO Analysis and Mean Scores for the General Population

Primary HRQoL Domains of Interest	Mean (SD)	
	Idecel Population	General Population[a]
EORTC QLQC30 fatigue subscale	39.3 (24.4)	29.5 (25.5)
EORTC QLQC30 pain subscale	39.9 (28.2)	23.5 (27.1)
EORTC QLQ-C30 physical functioning subscale	69.4 (25.2)	85.1 (18.9)
EORTC QLQ-C30 cognitive functioning subscale	82.4 (20.6)	84.8 (21.3)
EORTC QLQ-C30 global health/QoL subscale	60.7 (20.9)	66.1 (21.7)
EORTC QLQ-MY20 disease symptoms subscale[b]	32.5 (23.8)	No reference available
EORTC QLQ-MY20 side effects[b]	82.2 (14.8)	No reference available

EORTC QLQC30 = European Organization for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EORTC QLQ-MY20 = European Organization for Research and Treatment of Cancer – Quality of Life – Multiple Myeloma Module; HRQoL = health-related quality of life; idecel = idecabtagene vicleucel; PRO = patient-reported outcome; QoL = quality of life; SD = standard deviation.

[a] Reference: Nolte, 2019.

[b] Reference data are not available currently for the EORTC QLQ-MY20.

Note: Higher scores reflect better HRQoL for the functioning (ie, physical and cognitive) and global health subscales and more symptoms (ie, worse HRQoL) for the symptom subscales (ie, fatigue, pain, disease symptoms) and side effects.

Data cutoff date: 16 Oct 2019.

It is acknowledged that patients who achieve a durable response to ide-cel are expected to obtain a significant treatment-free interval that potentially might be accompanied with improvement in quality of life. However, the claim that ide-cel also offers a major contribution to patient care over other approved therapies is currently not considered supported by the available HRQoL data from the pivotal study MM-001. Hence, this argument cannot be used to further support significant benefit of ide-cel in MM.

The COMP concluded that Abecma is of significant benefit because of the improved efficacy. A higher proportion of clinically meaningful responses were observed in r/r MM patients treated with Abecma compared to patients treated with either Blenrep or Nexpovio. Furthermore, the observed responses were more durable. This is considered to constitute a clinically relevant advantage for adult patients with r/r MM who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 directed antibody.

4. COMP position adopted on 30 June 2021

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 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.