7 December 2023
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Elrexfio (elranatamab)
Treatment of multiple myeloma
EU/3/21/2471

Sponsor: Pfizer Europe MA 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(s)	Humanised IgG2k Fc-modified bispecific monoclonal antibody against CD3 and BCMA
Other name(s)	-
International Non-Proprietary Name	Elranatamab
Tradename	Elrexfio
Orphan condition	Treatment of multiple myeloma
Sponsor's details:	Pfizer Europe MA EEIG Boulevard De La Plaine 17 Elsene 1050 Brussels Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pfizer Europe MA EEIG
COMP opinion	17 June 2021
EC decision	19 July 2021
EC registration number	EU/3/21/2471
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Jan Mueller-Berghaus / Johanna Lähteenvuo
Applicant	Pfizer Europe MA EEIG
Application submission	4 January 2023
Procedure start	26 January 2023
Procedure number	EMA/H/C/005908
Invented name	Elrexfio
Proposed therapeutic indication	ELREXFIO is indicated as monotherapy 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 can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Elrexfio
CHMP opinion	12 October 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Maria Elisabeth Kalland / Karri Penttila
Sponsor's report submission	20 July 2023
COMP discussion Adoption of list of issues via written procedure	3-5 October 2023 11 October 2023
Sponsor's removal request	25 October 2023

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2021 was based on the following grounds:

"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 humanised IgG2k Fc-modified bispecific monoclonal antibody against CD3 and BCMA was considered justified based on preliminary clinical data showing that advanced patients with relapsed or refractory multiple myeloma achieved partial or complete responses;
- the condition is chronically debilitating and life-threatening due to the development of hypercalcaemia, renal insufficiency, anaemia and bone lesions;
- the condition was estimated to be affecting approximately 4.1 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 Humanised IgG2k Fc-modified bispecific monoclonal antibody against CD3 and BCMA will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that heavily pre-treated patients with relapsed/refractory multiple myeloma who failed several lines of currently approved therapies achieved partial and stringent 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 cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing humanised IgG2k Fc-modified bispecific monoclonal antibody against CD3 and BCMA 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 called plasma cell myeloma) is a malignant neoplasm of plasma cells that clonally expand and accumulate in the bone marrow 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 often advanced at the time of diagnosis (Rajkumar et al., 2014). 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 with a ratio of around 3:2. 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.

The proposed therapeutic indication "*ELREXFIO is indicated as monotherapy 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*" 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 CHMP.

Chronically debilitating and/or life-threatening nature

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, but are not limited to, pathologic fractures, spinal cord compression (from pathologic fracture), weakness, malaise, anaemia and/or bleeding, hypercalcemia, renal insufficiency/failure, 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).

Multiple myeloma is estimated to represent 1.32% of all cancers in the EU-27, with an estimated incidence of 35800 cases in 2020 (Dyba 2021). In 2020, there has been approximately 35,842 new cases of MM, and 23,275 deaths due to this disease in European Union (EU), according to the European Cancer Information System (ECIS 2021). Multiple myeloma remains a life-threatening and chronic, debilitating condition. Despite multiple therapeutic options, multiple myeloma often recurs and remains incurable. All patients with this disease eventually relapse and become refractory to existing treatments. With each successive relapse, symptoms return, quality of life worsens, and both the chance of responding and duration of response typically decrease. Survival after diagnosis differs by age, with a recent global review reporting median relative survival among patients diagnosed at less than 65 years ranging from 50% to over 60 % among patients diagnosed at 65 years and older (Turesson 2018).

The sponsor has not identified any changes on the chronically debilitating or life-threatening nature of MM since the orphan designation was granted in July 2021, although five new therapies (two CAR-T cell products, melphalan flufenamide, teclistamab, and talquetamab) have been authorised in the EU since then for the treatment of MM patients who are triple-class exposed or triple- or higher-class

refractory. The COMP has previously acknowledged 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 due to the poor survival of patients with relapsed and refractory (RR) disease. This view is maintained by the COMP.

Number of people affected or at risk

The sponsor proposed a prevalence estimate for MM of less than 4.96 per 10,000 people in the EU.

The sponsor derived the prevalence estimate indirectly through data on disease incidence and duration (i.e., overall survival) using the standard formula P (point prevalence) = I (incidence) x D (mean duration) under the assumptions of stable incidence and duration of the condition.

Data on the number of incident cases, crude incidence rates, and age-standardized rates (age standard is Europe) for 2020 were derived from the interactive web-based European Cancer Information System (ECIS) database (Ferlay J, Ervik M, Lam F, et al., 2020). Across the 27 EU member states (EU27), the crude incidence as reported by ECIS is 0.80 per 10,000 person-years in 2020, while the age standardized incidence is 0.75 per 10,000 person-years.

The mean overall survival (OS) ranged from 3.26 to 5.06 years in six studies that reported median OS in an unselected sample of MM patients (Félix J, Aragão F, Almeida J, et al, 2013; Gregersen H, Vangsted AJ, Abildgaard N, et al. 2017; Oortgiesen B, van Roon EN, Joosten P, et al.2017; Blimark C, Turesson I, Genell A, et al., 2018; Mair M, Straka C, Buratti T, et al.,2020). Table 1 summarises the median OS reported for patients with MM from these six European studies.

Table 1. Median Overall Survival Reported from Studies Based in Europe

Reference	Geography	Study Years	Median Overall Survival
Blimark 2018	Sweden	2008-2015	3.50 years
Felix 2013	Review of Trials	Published 1970-2011	3.26 years
Gregersen 2017	Denmark	2005-2012	3.3 (IQR 1.0, 6.5) years
Hajek 2018	Czechia	2007-2014	4.2 years
Mair 2020	Italy	1998-2017	5.06 years
Oortgiesen 2017	Netherlands	2005-2014	3.33 years

Abbreviations: NR = not reported; py = person-years

Complete prevalence was estimated based on crude incidence rates reported by ECIS, country population size, and the lowest and highest median OS found in the literature, as well as a higher median OS of 6.2 years reported among adult patients in the US with newly diagnosed MM as a sensitivity analyses considering the increasing survival of patients with MM (Fonseca R, Abouzaid S, Bonafede M, et al, 2017). The estimated complete prevalence of MM is provided in Table 2. The complete prevalence, as calculated based on country-specific incidence rates and population size, and the most conservative median OS of 6.2 years, was 4.96 per 10,000 persons.

The prevalence of MM in Europe as reported in the published literature ranged from 1.8 to 3.9 per 10,000 people (Ocias LF, Larsen TS, Vestergaard H, et al., 2016; Polsinelli B, Tsigkos S, Naumann-Winter F, et al. , 2017; Cowan AJ, Allen C, Barac A, et al., 2018) .

Table 2. Incidence of MM in the EU and Other Selected Countries in 2020

	2021	Incidence	Prevalence per 10,000		
Country	**Population [a]**	**/10,000 py [b]**	**mOS=3.26y [c]**	**mOS=5.06y [d]**	**mOS=6.2y [e]**
EU-27	443,678,000	0.80	2.61	4.05	4.96

Across the EU27, the crude and age standardized incidence as reported by ECIS is 0.80 and 0.75 per 10,000 persons in 2020, respectively. Complete prevalence, as calculated based on country-specific incidence rates and population size, and a median OS of 6.2 years, is 4.96 per 10,000 person years.

At the time of the orphan designation in 2021, the sponsor presented the same prevalence calculation and final estimate for MM. The COMP then noted that using the highest median OS of 5.06 years found in the literature, the prevalence estimate will be 4.05 in 10,000 people and concluded that the condition was estimated to be affecting approximately 4.1 in 10,000 people in the EU.

During the most recent orphan maintenance procedures for the multiple myeloma products Talvay and Carvykti in August 2023 and June 2022 respectively, the COMP accepted a prevalence estimate of 4.6 per 10,000 persons. While the same incidence figure and source was used as in this application (ECIS 2020, 0.8), the estimate of median OS were based on publications by 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.

Considering the above, the COMP accepted a prevalence estimate for MM of 4.6 in 10,000 persons in the EU based on ECIS data for the crude incidence and an estimated disease duration for the whole MM population of 5.8 years, which is largely in line with those accepted in recent MM designations and maintenance procedures assessed for this condition during the last years.

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 the treatment of MM. Central marketing authorisations include the following classes:

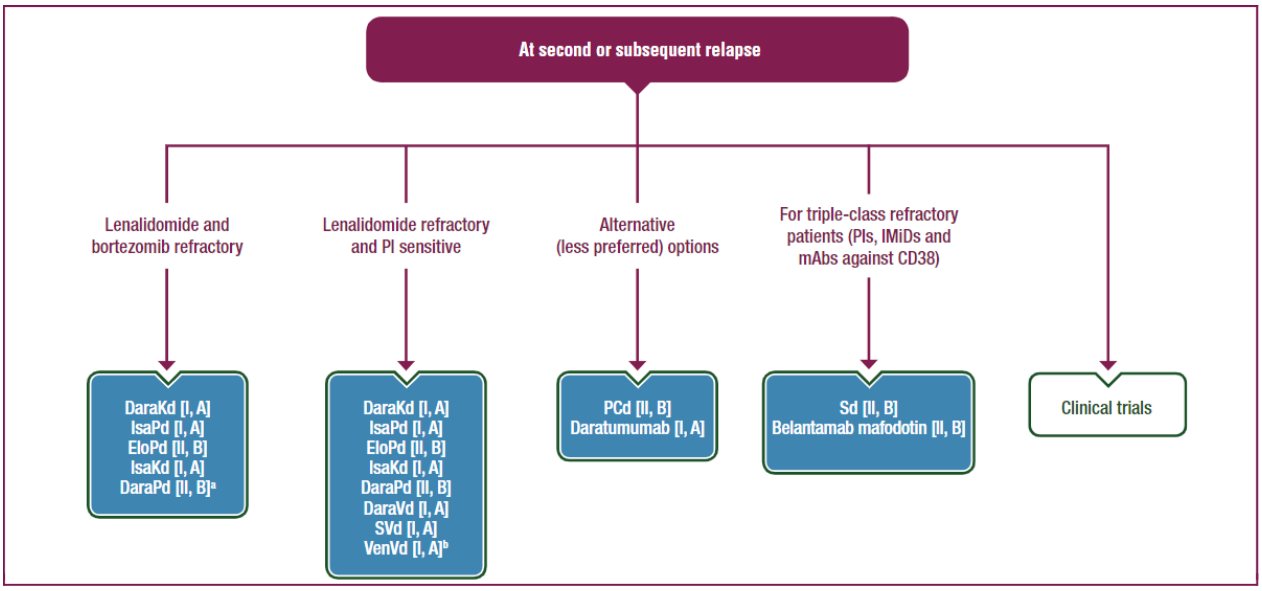
- Doxorubicin liposomal (Zolsketil pegylated liposomal; Celdoxome pegylated liposomal).
- Dexamethasone (Neofordex, generics).

- Immunomodulating agents: Pomalidomide (Imnovid), Lenalidomide (Revlimid and generics), Thalidomide (generics).
- Proteasome inhibitors: Carfilzomib (Kyprolis), Bortezomib (Velcade and generics), Ixazomib (Ninlaro).
- Antibodies against CD38: Daratumumab (Darzalex), Isatuximab-irfc (Sarclisa).
- SLAMF7-directed immunostimulatory antibody: Elotuzumab (Empliciti).
- Histone Deacetylase (HDAC) Inhibitors: Panobinostat (Farydak).
- Nuclear export inhibitor: Selinexor (Nexpovio).
- Antibody-drug conjugates: Belantamab Mafodotin (Blenrep).
- Peptide conjugated alkylating drug: Melphalan flufenamide (Pepaxti).
- BCMA CAR-T treatment: idecabtagene vicleucel (hereinafter referred to as ide-cel, Abecma) and ciltacabtagene autoleucel (hereinafter referred to as cilta-cel, Carvykti).
- BCMA/CD3 bispecific antibody: Teclistamab (Tecvayli).
- GPRC5D/CD3 (novel multiple myeloma target) bispecific antibody: Talquetamab (Talvey).

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

The 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 RRMM patients in the third- and later lines settings (Dimopoulos et al., 2021; Figure 1). 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 RR 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.

Figure 1. Recommendations for MM patients who receive a third or subsequent line of therapy



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, ortezomib/dexamethasone; Ven, venetoclax.
a Only phase IB data are published for DaraPd. Publication of phase III data are expected in 2021.
b For patients with t(11;14) or high BCL2 levels.

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 RRMM setting in the EU:

- 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**: talquetamab, teclistamab, melphalan flufenamide, ide-cel, and cilta-cel.
- Fifth- and later lines: belantamab and selinexor.

Satisfactory methods for the target patient population

The sponsor's product elranatamab is intended to treat triple-class exposed (to a proteasome inhibitor [PI], an immunomodulatory drug [IMiD], and an anti-CD38 monoclonal antibody [mAb]) patients with RRMM who have received at least three prior therapies and have demonstrated disease progression on the last therapy. Considering the target patient population for elranatamab, products in the following classes are not considered relevant satisfactory methods: proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies (please see above product class list). Furthermore, melphalan flufenamide is not considered a satisfactory method for the intended patient population, as it has a more restricted therapeutic indication and only target RRMM patients who are at least triple-class refractory. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation. Elranatamab does not have this restriction in the indication wording (4.1 of SmPC).

Elotuzumab (Empliciti), which is a SLAM7-directed immunostimulatory mAb and panobinostat (Farydak), a pan histone deacetylase (HDAC) inhibitor, are both authorised in combination with classes

of products to which a significant part of the target patient population for elranatamab was largely refractory to, i.e. IMiDs (lenalidomide, pomalidomide) (Empliciti EPAR – Product information 2023) and PI (bortezomib) (Farydak EPAR – Pruduct Information 2023).

Medicinal products that are authorised in the fifth- and later lines setting are also not considered satisfactory methods for the intended patient population, as they have a more restricted therapeutic indication. It is therefore considered that elranatamab does in principle include a broader patient population, which is not entirely covered by belantamab mafodotin (Blenrep) and selinexor (Nexpovio).

In conclusion, only talquetamab, teclistamab, ide-cel, and cilta-cel are considered satisfactory methods and hence relevant for a discussion on the significant benefit of elrantamab (Elrexfio) in MM.

Significant benefit

The sponsor received protocol assistance from EMA on 22-Apr-2022 regarding the evidence needed to demonstrate significant benefit of elranatamab over existing methods used for the treatment of RRMM (Case No.: EMA/SA/0000082372). The following main concerns was raised by the COMP on the proposed matching-adjusted indirect comparisons (MAICs) and further contextualisation with four real-word data sources:

- Possible differences in the prior treatment history or differences in reporting on outcomes and/or relevant prognostic markers or on different subgroups.
- Indirect comparisons typically require compelling/convincing treatment effect size differences to establish significant benefit based on efficacy.
- Indirect comparison may be challenging especially against CAR-T cell products.
- It is also regarded as critical that the cohorts with prior treatment including BCMA-targeted agents (CAR-T cells, ADC) enrol enough patients to be informative.
- The suggested real-world data programme was not supported because of the methodological uncertainties (defining triple-class refractory patients retrospectively, response assessment, [information on duration of response frequently not available] and the proposed sources, especially from the US). Best ORR is also not considered a validated endpoint for comparison with the pivotal trial data from the proposed product.

Elrantamab is a bispecific B-cell maturation antigen (BCMA)-directed T-cell engaging antibody that binds BCMA on plasma cells (plasmablasts) and myeloma cells and CD3-epsilon on T cells. Binding of elrantamab to BCMA on tumour cells and CD3 expressed on T cells is independent of native T cell receptor (TCR) specificity and antigen-presentation on major histocompatibility complex (MHC) class 1 molecules. Activation of T cells through binding of elrantamab thus leads to release of proinflammatory cytokines and ultimately lysis of MM cells.

The claim of significant benefit is based on the results from an open-label, multicenter, non-randomised phase 2 study C1071003 (also known as MagnetisMM-3) which is used to obtain the pivotal evidence for elranatamab monotherapy in participants with MM who have relapsed or are refractory to at least one PI, one IMiD and one anti-CD38 antibody. The study included 123 patients naïve to prior BCMA-directed therapy (pivotal Cohort A) and 64 patients with prior exposure to BCMA-directed antibody drug conjugate (ADC) or chimeric antigen receptor (CAR) T cell therapy (supportive Cohort B). Patients had measurable disease by international myeloma working group (IMWG) criteria at enrolment. The study included patients with an ECOG score of ≤2, adequate baseline bone marrow (absolute neutrophil count ≥1.0 × 10^9/L, platelet count ≥25 x 10^9/L, haemoglobin level ≥8 g/dL),

renal (CrCL ≥30 mL/min), and hepatic (AST and ALT ≤2.5 x ULN, total bilirubin ≤2 x ULN) function, and left-ventricular ejection fraction ≥40%. Patients with smouldering MM, active plasma cell leukaemia, amyloidosis, POEMS syndrome, stem cell transplant within 12 weeks prior to enrolment and active infections were excluded from the study. As of the updated data cut-off (DCO) date of 16-Apr-2023, the median (range) follow-up was 15.90 months (0.23, 26.18) for Cohort A and 9.89 months (0.30, 18.40) for Cohort B. Among responders, the median (range) follow-up from initial response was 15.21 (2.40, 24.21) months for Cohort A and 13.42 (2.43, 16.95) months for Cohort B.

Patients received subcutaneous (SC) administration of elrantamab at two step-up priming doses of 12 mg on Day 1 and 32 mg on Day 4 of treatment, followed by the first full treatment dose of 76 mg on Day 8 of treatment. Thereafter, patients received 76 mg once weekly. After 24 weeks, in patients who achieved an IMWG response category of partial response (PR) or better with responses persisting for at least 2 months, the dosing interval was changed from every week to every 2 weeks.

The primary endpoint was overall response rate (ORR) as assessed by a blinded independent review committee (BICR) per the International Myeloma Working Group (IMWG) in Cohort A and Cohort B. Objective response is defined as having a best overall response (BOR) of confirmed stringent complete response (sCR), complete response (CR), very good PR (VGPR) or PR per IMWG criteria, from the date of first dose until confirmed progressive disease (PD), death or start of new anticancer therapy, whichever occurs first. Secondary endpoints (by BICR and Investigator per IMWG) in Cohort A and Cohort B included ORR by baseline extramedullary disease (EMD) status for Cohort A (key secondary), ORR by investigator, complete response rate (CRR), duration of response (DOR), duration of complete response (DOCR), time to response (TTR), progression-free survival (PFS), OS, and minimal residual disease (MRD) negativity rate (assessed by central lab) per IMWG sequencing criteria.

Significant benefit of elranatamab over the approved CAR-T cell products

The claim of a significant benefit of elranatamab vis a vis the two approved CAR-T cell products ide-cel and cilta-cel is based on two different grounds: 1) a clinically relevant advantage due to a clinically meaningful benefit in patients who have already received the two approved CAR-T cell products and 2) major contribution to patient care by being readily available as an off-the-shelf immunotherapy when needed to patients with a highly aggressive and rapidly progressing disease.

Clinically relevant advantage of elranatamab vis a vis ide-cel and cilta-cel

The sponsor claimed that elranatamab provides a clinically meaningful benefit for patients who have previously been treated with BCMA-directed CAR-T cell products, which qualifies for a clinically relevant advantages based on provision stated in the commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03).

In support of this claim, the sponsor presented efficacy data from an analysis of a subpopulation of Cohort B of their phase 2 licensing study C1071003, i.e., in triple-class exposed patients who have also been previously treated with a BCMA-directed CAR-T cell product (n=21). From the sponsors document it appears as if these patients have been previously treated with both authorised and investigational CAR-T cell products but the name of the products that have been used have not been specified by the sponsor.

Among patients in the subpopulation of Cohort B who have also been previously treated with a BCMA-directed CAR-T cell product (n=21), the ORR (sCR+CR+VGPR+PR) was **42.9%** (95%CI: 21.8, 66.0), all of which were observed to be VGPR or better (sCR+CR+VGPR) (Table 3).

Table 3. Summary of Best Overall Response by BICR (Cohort B) (Protocol C1071003)

	Cohort B (N=46) Prior ADC	Cohort B (N=21) Prior CAR-T
Best Overall Response, n (%)		
Stringent Complete Response (sCR)	0	0
Complete response (CR)	4 (8.7%)	3 (14.3%)
Very Good Partial Response (VGPR)	8 (17.4%)	6 (28.6%)
Partial response (PR)	1 (2.2%)	0
Minimal Response (MR)	0	0
Stable disease (SD)	14 (30.4%)	4 (19.0%)
Progressive disease (PD)	14 (30.4%)	6 (28.6%)
Objective Response (sCR+CR+VGPR+PR) 95%CI [1]	13 (28.3%) 16.0, 43.5	9 (42.9%) 21.8, 66.0
Complete Response (sCR+CR) 95%CI [1]	4 (8.7%) 2.4, 20.8	3 (14.3%) 3.0, 36.3
VGPR or Better (sCR+CR+VGPR) 95%CI [1]	12 (26.1%) 14.3, 41.1	9 (42.9%) 21.8, 66.0

[1] 95% CIs using the Clopper-Pearson method. PFIZER CONFIDENTIAL SDTM Creation: 31MAY2023 (07:32) Source Data: adrsb Table Generation: 12JUN2023 (23:51) (Data cutoff date : 16Apr2023 Database snapshot date : 05May2023)
Output File: ./IA/C1071003_EU_FU_MAA_eff/adrs_borc_s001_bicr_cart [1] Clopper-Pearson method used

The COMP acknowledged the results in this subpopulation but did not consider the data sufficient to support the claim of a clinically relevant advantage over ide-cel and cilta-cel as it was not clear which CAR-T cell products the patients actually received prior to treatment with elranatamab, and the number of patients in this sub-population of Cohort B was very limited. The sponsor should therefore specify the efficacy data (best responses and duration of the responses) as achieved with elranatamab for those patients in Cohort B of study C1071003 who were pre-treated with each of the approved CAR-T cell products, specifically Carvykti (cilta-cel) and Abecma (ide-cel). The efficacy results should be presented for each product separately and based on the latest available study data cut-off (DCO). In addition, the sponsor may also consider doing such a specific efficacy sub-group analysis for patients who received prior therapy with teclistamab and talquetamab before study entry in case such data is available.

Major contribution to patient care of elranatamab vis a vis ide-cel and cilta-cel

To establish a major contribution to patient care, at least comparable efficacy, safety, and benefit/risk balance with the authorised satisfactory methods needs to be demonstrated. The sponsor presented a side-by-side comparison and concluded that elranatamab demonstrated to be effective in a similar range as cilta-cel and ide-cel in patients with similar baseline characteristics (Table 4).

Table 4. Efficacy Results Comparison Elranatamab vs. Ide-cel, and Cilta-cel.

Parameters	ide-cel KarMMa	cilta-cel CARTITUDE-1	elranatamab Cohort A C1071003
N	140 (All Leukapheresed)	113 (All Leukapheresed)	123
ORR n (%) 95% CI:	67.1% (59.4, 74.9)	84.1% (76.0, 90.3)	61.0% (51.8, 69.6)
CR	30%	-	20.3%
sCR	69%	70.8%	15.4%
VGPR	48.6%	10.6%	20.3%
MRD-negative status	Based on treated (N=128) 25%*	49.6%**	Based on N=29 89.7%***
Median DOR (months) 95% CI	10.6 (8.0, 11.4)	21.8 (21.8, NE)	Not yet reached (NE, NE) FU 15.90 months

Source Abecma SmPC 2023 ; Carvykti SmPC 2023. Elranatamab SmPC cut-off 16 April 2023
* 10^{-5} testing threshold. MRD-negative status and ≥ CR ** Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR. *** MRD-negativity rate only MRD assessments (10^{-5} testing threshold) in patients achieving CR or sCR and evaluable for MRD.

The COMP did not consider that the side-by-side comparison presented by the sponsor allowed a conclusion on comparable efficacy of elranatamab vis a vis the approved CAR-T cell products, especially cilta-cel. Of note, the CHMP concluded in their assessment report that "*With the limits of naïve indirect comparisons in a heterogeneous condition such as MM, the ORR of 61% (51.8, 69.6) is:*

- *comparable to teclistamab – ORR 63% (95%CI: 55.2, 70.4) and CAR T product idecabtagene vicleucel (Abecma) – ORR 67.1% (95%CI: 59.4, 74.9) in the ITT population.*
- ***Possibly inferior** to CAR-T product ciltacaptagene autoleucel (Carvykti) – ORR 84.1% (95%CI: 76, 90.3)*."

In addition, the sponsor pointed out that the safety profile of elranatamab is manageable and predictable for a BCMA-directed therapy as compared to CAR-T cell products. In specific the sponsor argued that lower incidences and severity of cytokine release syndrome (CRS), Immune effector cell-associated neurotoxicity syndrome (ICANS) and other neurologic adverse events (AEs), and infections have been observed in participants treated with elranatamab compared to the reported rates in participants receiving CAR-T cell therapies, although there are limitations to cross-study safety comparisons, including differences in follow-up time. The COMP deemed the experience and safety data available to date for elranatamab in patients with RRMM limited as compared to those reported for the authorised CAR-T cell products. Furthermore, a comprehensive safety comparison of the individual safety profiles was not conducted. An argument of a better safety profile of elranatamab in comparison to the approved CAR-T cell therapies cannot therefore be concluded on at present stage.

Furthermore, while emphasising the comparable overall benefit/risk balance of elranatamab and BCMA-directed CAR-T cell products, the sponsor mentioned the following additional arguments to stress the clinically meaningful benefit of elranatamab for patients with RRMM:

- Ready to use therapy and administered in oncology hospital versus waiting for manufacturer and administered in specialized centres with limited access for patients. In contrast, elrantamab will be available to as large as possible part of the European population.
- A portion of patients who undergo leukapheresis do not receive CAR-T cell therapy (CARVYKTI 14%; ABECMA 8%), whereas all subjects receive elranatamab SC therapy.
- No requirement for bridging or pre-treatment therapy which is associated with a risk of serious adverse reactions.
- No delay in administration of the targeted treatment with no risk of progression associated to the time from initial leukapheresis to infusion as reported in the SmPCs of the CAR-T cell products (ABECMA SmPC 2023, Carvykty SmPC 2023):
    - Carvykti: 47 days (range: 41 to 167 days)
    - Abecma: 40 days (range: 33 to 79 days)

The COMP acknowledged these arguments but did not further discuss them due to uncertainty regarding comparable efficacy of elranatamab with the approved CAR-T cell products, especially cilta-cel. Furthermore, the COMP noted the lack of more sophisticated indirect efficacy comparisons, such as matched-adjusted-indirect comparisons (MAICs) of elrantamab versus the approved CAR-T cell products.

Significant benefit of elranatamab over teclistamab

The sponsor claimed significant benefit of elranatamab over teclistamab based on a major contribution to patient care for patients with RRMM in the fourth- and later lines setting.

Major contribution to patient care of elranatamab vis a vis teclistamab

The sponsor presented a side-by-side comparison and concluded that elranatamab have comparable efficacy to teclistamab (Table 5) while patients in the pivotal study C1071003 with elranatamab were considered to have a slightly worse prognosis as compared to those included in the pivotal study MajesTEC-1 for teclistamab (Table 6), i.e. the population treated with elranatamab had a higher proportion of patients ≥75 years, higher proportion of patients with stage III disease and higher proportion of patients with triple- and penta-class refractory disease.

Table 5. Efficacy Results Comparison Elrantamab versus Teclistamab

Parameters	**Teclistmab** **MajesTEC-1**	**Elrantamab** **C1071003 study cohort A**
Median Follow-up	14.1 months	15.90 months
ORR by BICR	63.0% 95% CI: 55.2%, 70.4%	61.0% 95% CI: 51.8%, 69.6%
sCR	32.7%	15.4%
CR	6.7%	20.3%
VGPR	19.4%	20.3%
PR	4.2%	4.9%
Median DOR (months)	18.4 (14.9, NE)	Not yet reached (NE, NE)
Time to First Response (months)	1.2 (0.2; 5.5)	1.22 (0.9, 7.4)

Source Tecvayli SmPC 2023 and elranatamab SmPC cut-off date 16 April 2023 Annex 3.

Table 6. Clinical Significant Patients Characteristics Teclistamab versus Elranatamab

Parameter	MajesTEC-1 study	C1071003 study Cohort A
Median age:	64 (33 to 84) years 15% were ≥75 years old	68 (36 to 89) years 19.5% were ≥75 years old
ECOG score 2:	none	5.7%
Median time since initial diagnosis of plasma cell MM	6.5 years (range: 1.1 to 24.1)	72.9 months
R-ISS I*	ISS III: 52%	22.8%
R-ISS II*	ISS II: 35%	55.3%
R-ISS III*	ISS III 12%	15.4%
Extramedullary disease	17%***	31.7%**
High-risk cytogenetics [t(4;14), t(14;16), or del(17p)]	25.9%	25.2%
Prior autologous stem cell transplantation	82%	68.3%
Prior allogenic transplantation	4.8%	5.7%
Median prior lines of anticancer therapy (N)	Median 5 (Range: 2-14)	Median 5 (Range: 2 to 22)

Source: Tecvayli SmPC,2023, elranatamab see Table 21 Table 22. *Revised International Staging System (R-ISS) (Palumbo, 2015). This new R-ISS staging system, using additional information including CG-profile and serum LDH, separates in real-life setting more profoundly patients with poor prognosis than the old ISS staging (Kurki S., Tamminen K, et al). Teclistamab MajesTEC-1 study used old ISS. ** Extramedullary disease definition: presence of any plasmacytoma (extramedullary and/or paramedullary) with a soft-tissue component. ***includes soft-tissue plasmacytoma not associated with bone

Additional arguments given by the sponsor to further support their claim for a major contribution to patient care of elranatamab over teclistamab were as follows:

- Offering the possibility of flat dosing as opposite to dose calculated by weight which may contribute to less medication errors in real world settings.
- Offering a more patient-centric dosing schedule with the ability to transition to every two-week schedule after at least 24 weeks in patients who achieve a response.
- Lowering the incidence and severity of CRS and the number of patients with multiple CRS.

The COMP noted that these data are not considered sufficient to establish a significant difference in the patient populations, to conclude on an improved safety profile or a decrease in patient burden after treatment with elranatamab versus teclistamab. The claim of significant benefit based on a major contribution to patient care compared to teclistamab could therefore not be concluded on by the COMP.

Significant benefit of elranatamab over talquetamab

No data was submitted to support significant benefit of elranatamab over Talvey (talquetamab), which was granted a conditional marketing authorisation in the EU in August 2023.

Overall conclusion

In conclusion, the COMP considered that the claim of significant benefit of elranatamab over the authorised medicinal products Talvey (talquetamab), Tecvayli (teclistamab), Abecma (ide-cel) and

Carvykti (cilta-cel) is not established based on the data presented. The sponsor should therefore provide additional data to support their claim of significant benefit for elranatamab over these four products in adult patients with RRMM in the fourth- and later lines setting. Conductance of methodologically sound indirect comparisons, including thorough comparison of the baseline characteristics of the studied patient populations, to the authorised satisfactory methods could be useful to establish a significant benefit. The committee adopted a question on significant benefit.

4. COMP list of issues

- Significant benefit

The claim of significant benefit of Elrexfio (elranatamab) over the authorised satisfactory methods Talvey (talquetamab), Tecvayli (teclistamab), Abecma (ide-cel), and Carvykti (cilta-cel) for the target patient population is not considered established based on the data presented. The sponsor should therefore further support the claim of significant benefit of elranatamab over these four medicinal products in adult patients with RRMM in the fourth- and later lines setting based on relevant data.