23 August 2022
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Tecvayli (teclistamab)
Treatment of multiple myeloma
EU/3/20/2331
Sponsor: Janssen-Cilag International N.V.

Note

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

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1. Product and administrative information

Product	
Designated active substance	Teclistamab
Other name(s)	--
International Non-Proprietary Name	Teclistamab
Tradename	Tecvayli
Orphan condition	Treatment of multiple myeloma
Sponsor's details:	Janssen-Cilag International N.V. Turnhoutseweg 30 2340 Beerse Antwerp Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Janssen-Cilag International N.V.
COMP opinion	10 September 2020
EC decision	19 October 2020
EC registration number	EU/3/20/2331
Marketing authorisation	
Rapporteur / Co-rapporteur	Johanna Lähteenvuo / Armando Genazzani
Applicant	Janssen-Cilag International N.V.
Application submission	31 January 2022
Procedure start	17 February 2022
Procedure number	EMA/H/C/005865
Invented name	Tecvayli
Proposed therapeutic indication	Tecvayli 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 on Tecvayli can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/tecvayli
CHMP opinion	21 July 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Maria Elisabeth Kalland / Karri Penttila
Sponsor's report submission	23 February 2022
COMP discussion and adoption of list of questions	14-16 June 2022
Oral explanation	12 July 2022
Sponsor's removal request	14 July 2022

2. Grounds for the COMP opinion

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

- the intention to treat the condition with the medicinal product containing teclistamab was considered justified based on preliminary clinical observations showing responses in heavily pretreated relapsed/refractory patients;
- the condition is chronically debilitating and life-threatening in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions;
- the condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made.
- 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 teclistamab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that support higher response rates in last line multiple myeloma patients compared to the expectations with the currently authorised products. 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 (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. 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 (Shah and Besa, 2018).

The approved therapeutic indication "*Teclistamab 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" 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

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 et al., 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 due to decreased production of antibodies, cytopenias (especially anaemia, but also thrombocytopenia, and neutropenia), renal failure due to the protein overload, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures (Munshi et al., 2012).

Substantial progress has been made during the last decade in improving the overall survival (OS) of patients with MM through the development and availability of new approved treatment options. Still, even with optimal upfront therapy and advances in treatment, most MM patients progress or relapse, and further treatment is needed.

The sponsor has not identified any changes in the seriousness of MM since the orphan designation was granted in 2020. 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 r/r disease. The seriousness of MM earlier accepted by the COMP remains acceptable for this procedure.

Number of people affected or at risk

At time of initial orphan designation in 2020, the COMP concluded that the condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union.

The sponsor performed an updated comprehensive search to determine the prevalence of MM in the EU, including publications from population-based cancer registry databases. Prevalence estimates (both limited-duration prevalence and complete prevalence) reported by population-based registries (i.e., direct method) were found in published reports by the International Agency for Research on Cancer (IARC)'s GLOBOCAN surveillance project (2020 data) and the Association of the Nordic Cancer Registries (NORDCAN; 2020 data). Furthermore, the sponsor reported relevant MM prevalence data from the CancerMPact® project, comprising data from the 4 most populous EU countries, specifically Germany, France, Italy, and Spain (including the Robert Koch Institute, ITACAN, InVS in France, and IARC), which represent 58% of the EU population (2020 data). Additionally, the sponsor considered the latest available MM incidence figure according to the European Cancer Information System (ECIS; 2020 data).

According to NORDCAN (2020), the complete prevalence can be calculated for these countries because the full history of MM can be determined from population-based registries. The complete prevalence of MM ranged from 3.21 per 10,000 persons in Finland to 4.19 per 10,000 in Denmark, with an average of 3.68 per 10,000 across the 3 countries. GLOBOCAN provides a 5-year prevalence of 3.08 per

10,000. EU country registries provide slightly higher 10-year and total prevalence estimates, with an average 10-year prevalence in 4 of the most populous EU countries of 3.52 per 10,000 and an average total prevalence in the 3 Nordic EU countries of 3.68 per 10,000. However, when estimating prevalence using the most contemporary and conservative European incidence and survival data, the prevalence of multiple myeloma is 4.34 per 10,000 persons. Prevalence estimates will vary from this value according to age group and treatment line. The sponsor considered that 4.34 per 10,000 persons is the most contemporary, conservative estimate of the prevalence of MM in the EU. This estimate was derived from the following source data:

The estimated crude incidence for the 27 EU member states (EU27) was reported to be 0.80 per 10,000 persons in 2020 (ECIS 2020). The sponsor noted that males have a higher estimated crude incidence of MM than females in the EU27 with 0.92 versus 0.69 per 10,000 persons, respectively.

The reported survival differed by both age at MM diagnosis and the line of treatment received. A recent global review reported that the median survival among patients diagnosed at less than 65 years varied from <2.75 to 5.42 years and the median survival among patients diagnosed at 65 years and older ranged from 2.17 to 2.67 years (Turesson et al., 2018). The sponsor then chose the highest median survival duration of 5.42 years reported in this review for their final prevalence calculation. However, this estimate was based on the survival duration reported among MM patients aged 65 years or younger who were diagnosed between 2001-2006 at the Mayo Clinic in the US (Kumar et. al., 2008), and is therefore considered to be outdated.

According to the sponsor, a conservative prevalence estimate for MM is proposed which considered the highest median survival duration of 5.42 years among patients aged less than 65 years together with the most recent ECIS crude incidence data for MM from 2020 of 0.8. This resulted in an estimated prevalence of **4.34** per 10,000 persons in the EU (0.80 per 10,000 * 5.42 years = 4.34 per 10,000).

Previously COMP accepted higher disease duration of 5.8 years which is derived from the following publications (Greipp 2005; Cho 2017; Kastritis 2017; Usmani 2018). Based on these data, the median OS for International Staging System (ISS) stage I/II patients, who represent 60-70% of all MM patients, is approximately 7 years. For ISS stage III patients, who represent 30-40% of all MM patients, the median OS is approximately 1-4 years, i.e. using a 7-year mOS for ISS stage I/II, representing 60% of the population and 4-year mOS for ISS stage III, representing 40%.

Combining this updated and slightly higher OS estimate in MM together with the ECIS 2020 incidence data of MM of 0.8, the estimated prevalence results in **4.6** per 10,000 persons, i.e. (0.8*5.8) = 4.64 per 10,000 persons. This estimate was accepted by the COMP for the recent orphan maintenance designations of Abecma and Carvykti and is also relevant and preferable for this procedure, based on the above outlined recent data.

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

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

Existing methods

There are several medicinal products authorised in the European Community for treatment of MM. Central marketing authorisations (MAs) include daratumumab (Darzalex), carfilzomib (Kyprolis), bortezomib (Velcade and generics), doxorubicin (Caelyx), interferon-α-2b (IntronA/ Alfatronol),

lenalidomide (Revlimid and generics), thalidomide (generics), panobinostat (Farydak), elotuzumab (Empliciti), ixazomib (Ninlaro), pomalidomide (Imnovid), dexamethasone (generics), isatuximab (Sarclisa), belantamab mafodotin (Blenrep), selinexor (Nexpovio) and the two recently approved CAR-T cell products idecabtagene vicleucel (hereinafter referred to as ide-cel, Abecma; CMA in August 2021) and ciltacabtagene autoleucel (hereinafter referred to as cilta-cel, Carvykti; CMA May 2022). In addition, several products are authorised at the national level for the 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 r/r disease) and are often used in combination.

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

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

Satisfactory methods for the target patient population

Teclistamab is indicated for triple-class exposed (to a proteasome inhibitor [PI], an immunomodulatory drug [IMiD], and an anti-CD38 monoclonal antibody [mAb]) patients with r/r MM who have received at least 3 prior lines of therapy and have demonstrated disease progression on the last therapy. In this specific therapeutic area, ide-cel and cilta-cel are considered satisfactory methods as these medicines are approved for triple-class exposed r/r MM patients in fourth- or later lines.

The medicinal products belantamab and selinexor have more restricted therapeutic indications as compared to that for teclistamab. These agents are approved as fifth- and later lines of therapy in more refractory MM patients being either triple-class refractory (to a PI, an IMiD, and an anti-CD38 mAb) for belantamab or penta-class refractory (to 2 PIs, 2 IMiDs, and 1 anti-CD38 mAb) for selinexor, while teclistamab is approved for use in a less refractory patient population and already from fourth line of therapy. It is therefore considered that teclistamab does in principle include a broader patient population, which is not covered by belantamab and selinexor.

With regards to elotuzumab, which is an anti-SLAM7 mAb, it is pointed out that its use is authorized in combination with a class of products to which a significant part of the target patient population for teclistamab was largely refractory to, i.e. IMiDs (lenalidomide, pomalidomide), (Empliciti EPAR 2021).

Furthermore, elotuzumab is not recommended for triple-class refractory patients with r/r MM according to the EHA-ESMO guideline (Dimopoulos et al., 2021).

Foresighted the sponsor also considered the product melphalan flufenamide (Pepaxti) with an expected indication in r/r MM as satisfactory method. However, the notification of MA for melphalan flufenamide has not been published in the Official Journal of the European Union at the time of the re-evaluation of the designation criteria of teclistamab for the treatment of MM. Melphalan flufenamide is therefore not considered a satisfactory method.

Significant benefit

The sponsor argued that teclistamab will be of significant benefit based on a clinically relevant advantage in terms of the clinical efficacy observed in the pivotal study MajesTEC-1 and provide a major contribution to patient care compared to existing methods of treatment for the target patient population. As explained in the previous section, significant benefit of teclistamab has to be evaluated over the two satisfactory methods ide-cel and cilta-cel for the target patient population. The sponsor also proposed belantamab, selinexor, elotuzumab, and melphalan flufenamide as satisfactory methods, however this view is not supported (please see the section on *Existing methods* above).

The sponsor received EMA protocol assistance dated 11-Nov-2021 with regards to the evidence needed to justify significant benefit of teclistamab over existing treatments used for the treatment of patients with r/r MM. Since the treatment landscape in MM are changing rapidly, the sponsor was reminded by the EMA that that the most recent therapeutic options for the intended patient population will need to be evaluated for demonstrating significant benefit at the time of MA to maintain the orphan medicinal product status. The sponsor confirmed that they have used the same approach as described during the protocol assistance and, where applicable, complied with the EMA recommendations (Case No. EMA/SA/0000069104).

The sponsor has conducted 2 types of efficacy analyses to establish significant benefit of teclistamab compared with their proposed selection of satisfactory methods for patients with relapsed and refractory MM (Analysis 1 and Analysis 2). Additionally, the sponsor has more broadly compared teclistamab with available CAR-T cell therapies to demonstrate that teclistamab provides a significant benefit versus this class of products. In line with the above discussion on satisfactory methods for the purpose of this procedure, only parts of the provided analyses are of relevance and will be reflected below accordingly.

The primary data supporting the efficacy and safety of teclistamab in MM in the CMA application were obtained from the ongoing, open-label, multicentre, single-arm phase 1/2 study 64007957MMY1001 (also called MajesTEC-1). The study was designed to evaluate safety, tolerability, PK, and efficacy of teclistamab monotherapy (1.5 mg/kg subcutaneous [SC] administered weekly with the first treatment dose preceded by step-up doses of 0.06 and 0.3 mg/kg) in adult patients with r/r MM. The study was conducted in 3 parts, which constituted the dose escalation (Part 1) to identify the recommended phase 2 dose(s) [RP2D(s)], dose expansion to evaluate the tolerability of the proposed RP2Ds (Part 2), and phase 2 dose expansion to further study teclistamab SC at the RP2D in cohorts of patients with r/r MM who had previously received at least 3 prior lines of therapy and were triple class exposed (Part 3). The pivotal population with regards to efficacy were patients treated at the RP2D in the phase 1 part and patients treated in Cohort A in the phase 2 (n=165), part 3 of the study, with previous exposure to at least one PI, one IMiD, and one anti-CD38 mAb. Efficacy data especially supporting the efficacy in patients who had received previous BCMA-targeting treatment was provided from Cohort C.

The primary efficacy endpoint for the phase 2 part 3 of the study was overall response rate (ORR), defined as the proportion of patients who achieved a partial response (PR) or better (i.e., stringent complete response [sCR] + complete response [CR] + very good PR [VGPR] + PR) according to the International Myeloma Working Group (IMWG) response criteria (Kumar et al., 2016) as assessed by an independent review committee (IRC). Secondary efficacy endpoints included duration of response (DOR), rates of VGPR or better/CR or better/sCR, minimal residual disease (MRD) negativity rate (as defined by the IMWG criteria), time to response (TTR), progression-free survival (PFS), and OS.

Analysis 1: Efficacy of teclistamab from MajesTEC-1 based on prior therapies

The aim of the first analysis was to demonstrate that teclistamab provided efficacy for patients who are refractory to previous treatments.

The data that were presented represented the respective efficacy analysis sets for the 2 populations from the pivotal study MajesTEC-1 that received the RP2D, i.e. including Phase 1 subjects treated at the RP2D (n= 40) and Phase 2 subjects treated in Cohort A (n= 110), as well as subjects from an additional Cohort C (n = 25). The pivotal RP2D cohorts (n =150) included subjects who had previously received pomalidomide, lenalidomide, bortezomib, carfilzomib, ixazomib, daratumumab, isatuximab, elotuzumab, panobinostat, selinexor, and melphalan flufenamide. Importantly, in the exploratory Cohort C of the MajesTEC-1 study, patients were enrolled with prior BCMA-targeted therapies, including those who had previously received the CAR-T cell therapies ide-cel and cilta-cel.

The median age of the patients who received the RP2D of teclistamab in the MajesTEC-1 study was 64.5 years (range: 33 to 84) and 15.3% (23/150) of subjects were ≥75 years of age. Most subjects were males (58.7%; 88/150) and White (89.3%; 134/150). All subjects had an ECOG performance score of 0 (35.3%; 53/150) and 1 (64.7%; 97/150). The study population was both heavily pretreated with a median of 5 prior lines of therapy (range: 2 to 14) for the pivotal RP2D cohorts, and a median of 6 prior lines (range: 3 to 13) for Cohort C, and highly refractory. Of the patients in the pivotal RP2D cohorts, 89.3% (134/150) were refractory to their last line of prior therapy, 77.3% (116/150) were triple-class refractory and 29.3% (44/150) were penta-class refractory. Of the patients in Cohort C, 80.0% (20/25) were refractory to their last line of prior therapy, 84.0% (21/25) were triple-class refractory, and 32.0% (8/25) were penta-class refractory.

Table 2 provides a summary of exposure and refractoriness to the prior therapies received by subjects included in the pivotal RP2D Efficacy Analysis Set (EAS) and the EAS of the exploratory Cohort C for the MajesTEC-1 study. Within this table, the sponsor has also reported the ORRs from the MajesTEC-1 study for those subjects who were exposed to and whose disease was refractory to the prior therapies listed.

Table 1. Prior Multiple Myeloma Therapy and Overall Response Rate: MajesTEC-1 Study (Efficacy Analysis Set)

Agent Class	Prior Therapy Containing:	Study population	Exposed to (n)	ORR in Exposed Patients n (%)	Refractory to (n)	ORR in Refractory Patients n (%)
	09 November 2021 cutoff					
IMiD	Pomalidomide	Pivotal	124	74 (59.7%)	114	70 (61.4%)
	Lenalidomide	Pivotal	146	90 (61.6%)	121	75 (62.0%)
PI	Bortezomib	Pivotal	147	91 (61.9%)	75	45 (60.0%)
	Carfilzomib	Pivotal	108	66 (61.1%)	85	55 (64.7%)
	Ixazomib	Pivotal	35	22 (62.9%)	28	18 (64.3%)
Anti-CD38 Ab	Daratumumab	Pivotal	137	86 (62.8%)	122	78 (63.9%)
	Isatuximab	Pivotal	21	13 (61.9%)	21	13 (61.9%)
Anti-SLAM7 Ab	Elotuzumab	Pivotal	14	10 (71.4%)	14	10 (71.4%)
HDAC Inhibitor	Panobinostat	Pivotal	7	5 (71.4%)	6	4 (66.7%)
Nucleoside transporter	Selinexor	Pivotal	6	3 (50.0%)	4	1 (25.0%)
Alkylator	Melphalan flufenamide	Pivotal	1	0	1	0
	07 September 2021 cutoff					
ADC	Belantamab mafodotin	Cohort C	15	6 (40.0%)	11	6 (54.5%)
CAR-T	Ide-cel	Cohort C	8	4 (50.0%)	2*	1 (50.0%)
CAR-T	Cilta-cel	Cohort C	2	0	1*	0

Ab=antibody; ADC=antibody drug conjugate; CAR-T=chimeric antigen receptor T cell; HDAC=histone deacetylase inhibitor; IMiD=immunomodulatory agent; ORR=overall response rate; PI=proteasome inhibitor; RP2D=recommended Phase 2 dose. Pivotal RP2D efficacy analysis set=Phase 1 RP2D and Cohort A pooled, n=150. Cohort C efficacy analysis set, n=25.
* All subjects who received CAR-T therapy had disease progression prior to next line of therapy.

The sponsor has prepared a separate subset analysis for the entire exploratory Cohort C, including not only the CAR-T cell therapies ide-cel and cilta-cel but also the BCMA-targeting antibody drug conjugate belantamab. The sponsor pooled the data from Cohort C to support their claim of teclistamab providing a benefit for patients with prior therapy targeting BCMA, including ADC and CAR-T cell products. However, for the purpose of evaluating significant benefit within this procedure, only data from a subset of this exploratory Cohort C is of relevance, i.e., patients previously treated with the two approved CAR-T cell products for MM (ide-cel and cilta-cel). Nevertheless, for sake of completeness and for providing a comprehensive overview of the pivotal licensing study (MajesTEC-1), the whole Table 1 is included in this report.

The sponsor concluded that preliminary response data from Cohort C suggested that teclistamab may provide benefit for patients with prior CAR-T cell therapy. The ORR in patients previously treated with CAR-T cell therapy was reported to be 45.5% (5/11; including 8 patients who had received prior treatment with ide-cel, 2 patients who had received cilta-cel, and 1 patient for whom the exact CAR-T cell therapy was not specified and whose response data is therefore not reflected in Table 1). The DOR

in patient who had received CAR-T cell therapies was not separately reported. Of note, the two patients who had previously received cilta-cel did not obtain an ORR in response to teclistamab.

The COMP considered the teclistamab efficacy data from the subset of patients in Cohort C who received prior CAR-T cell therapy with ide-cel and cilta-cel of great relevance for the discussion of significant benefit. The sponsor should therefore provide an updated sub-analysis of all efficacy parameters measured and available to date for patients previously receiving ide-cel and cilta-cel.

Analysis 2: Comparative analysis of efficacy for teclistamab versus other novel therapies based on matching-adjusted indirect comparisons

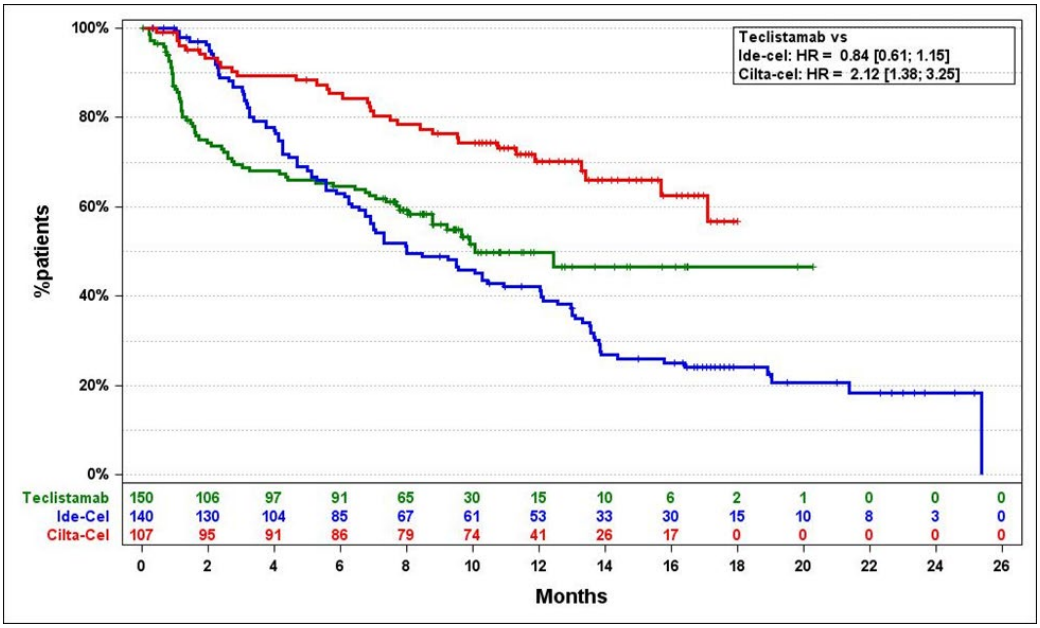
The sponsor acknowledged that interpretation of the results for Analysis 1 for ide-cel and cilta-cel is limited by the small numbers of subjects exposed and whose disease was refractory to these agents prior to enrollment in MajesTEC-1. Hence, the sponsor has undertaken further analyses of the efficacy of these newer agents relative to teclistamab using a matching-adjusted indirect comparisons (MAIC) approach (Analysis 2). The sponsor has conducted MAICs of the outcomes between subjects treated with ide-cel (Abecma) in KarMMa and cilta-cel (Carvykti) in CARTITUDE-1 versus subjects treated with teclistamab in the pivotal RP2D EAS for MajesTEC-1 (n=150). The MAIC analyses of teclistamab versus ide-cel, as described in the sponsor's initial maintenance report based on an earlier data-cut (November 2021) from the MajesTEC-1 study, favored ide-cel with statistical significance on ORR and OS, and were numerically in favor of ide-cel for CR or better rate and PFS. However, DOR was significantly longer with teclistamab compared to ide-cel. Comparisons of teclistamab versus cilta-cel, based on the November 2021 data cut-off, generally favored cilta-cel, with statistical significance for ORR, CR or better rate, PFS and OS. For DOR, results were numerically in favor of teclistamab. The sponsor concluded that the reported results suggested that the efficacy of teclistamab is not significantly better as compared to ide-cel and cilta-cel and hence cannot be used in support of establishing significant benefit of teclistamab over these two therapies.

Table 2. Observed and Adjusted Response Rates, by Treatment (Teclistamab and CAR-T Comparators)

a. ORR	**Observed Response**	**Adjusted Comparisons**		
		Teclistamab Adjusted[a]	**Odds Ratio (CI)[b]**	**Response Ratio (CI)[c]**
Teclistamab	62.7%	-	-	-
Ide-cel	67.1%	45.0%	0.40* (0.23; 0.71)	0.67* (0.51; 0.88)
Cilta-cel	83.2%	58.7%	0.29* (0.15; 0.55)	0.71* (0.59; 0.85)
b. CR or better rate	**Observed Response**	**Adjusted Comparisons**		
		Teclistamab Adjusted[a]	**Odds Ratio (CI)[b]**	**Response Ratio (CI)[c]**
Teclistamab	32.0%	-	-	-
Ide-cel	28.6%	18.8%	0.58 (0.32; 1.03)	0.66 (0.42; 1.03)
Cilta-cel	57.9%	28.7%	0.29* (0.17; 0.51)	0.49* (0.35; 0.69)

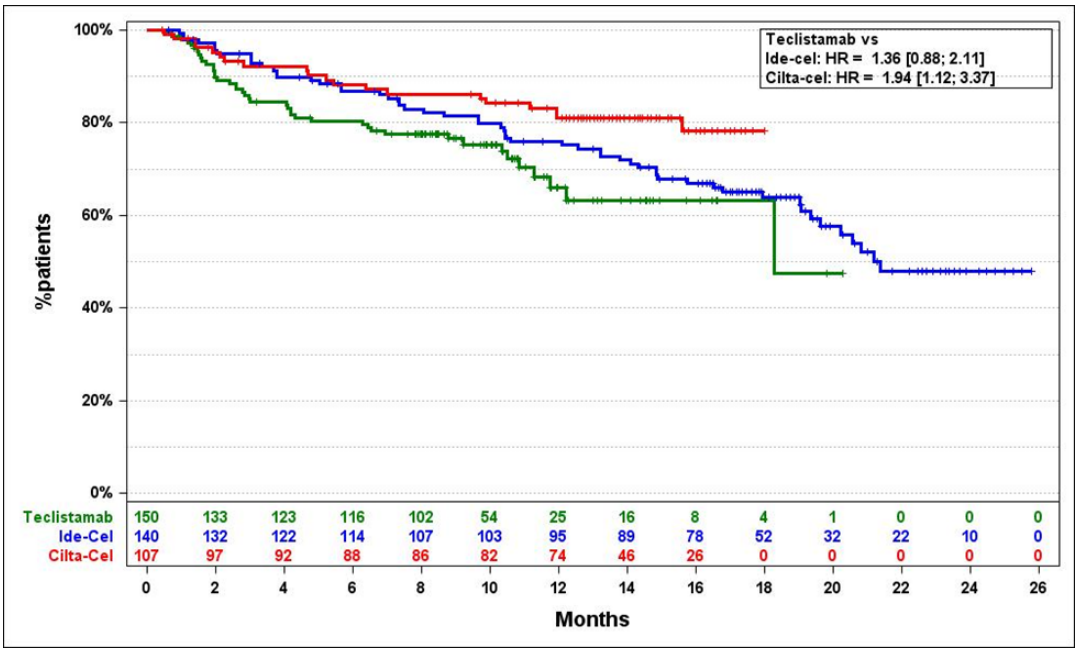
CAR-T=chimeric antigen receptor T-cell; CI=confidence interval; cilta-cel=ciltacabtagene autoleucel; CR=complete response; ide-cel=idecabtagene vicleucel; ORR=overall response rate
[a] 'Teclistamab adjusted' is the estimated response rate for teclistamab, after matching population to the comparator.
[b, c] Odds ratio and response ratio are estimated from the same weighted multivariable logistic regression model.
* indicates 95% CI not overlapping 1 (statistical significance p<0.05).

Figure 1. Observed Kaplan-Meier Plots of PFS for Teclistamab and CAR-T Comparator Treatments



CAR-T=chimeric antigen receptor T-cell; cilta-cel=ciltacabtagene autoleucel; HR=hazard ratio; ide-cel=idecabtagene vicleucel; PFS=progression-free survival
Munshi 2021; Berdeja 2021; Costa 2021

Figure 2. Observed Kaplan-Meier Plots of OS for Teclistamab and CAR-T Comparator Treatments



CAR-T=chimeric antigen receptor T-cell; cilta-cel=ciltacabtagene autoleucel; HR=hazard ratio; ide-cel=idecabtagene vicleucel; OS=overall survival Munshi 2021; Berdeja 2021; Costa 2021

The interpretation of the results needs to take into account that the matching of the MajesTEC-1 population versus the populations of the comparator studies reduced the effective sample size of the study, which may have limited the power for observed differences in outcomes between studies to reach statistically significant differences between studies.

The sponsor therefore proposed to base significant benefit for teclistamab versus the two approved CAR-T cell comparators on major contribution to patient care. This is discussed in the following section.

Differentiation from CAR-T cell therapies

The sponsor pointed out that teclistamab will provide a major contribution to patient care as compared to the authorized CAR-T cell therapies ide-cel and cilta-cel, as these have limitations with regards to patient eligibility, safety, logistical, and accessibility considerations that may prevent them from being practical and clinically appropriate for all patients with heavily pretreated MM. According to the sponsor, teclistamab confers a clinically relevant advantage in this respect and will provide a major contribution to patient care as the most efficacious, off-the-shelf treatment option without compromising on efficacy for all triple-class exposed patients with r/r MM, including those who are unable to receive CAR-T cell therapy.

The sponsor's arguments are acknowledged and supported from a clinical perspective. However, from a regulatory perspective within the remits of this procedure it is reminded that a (minimal) prerequisite for the claim of major contribution to patient care is the demonstration of the product's equivalence in terms of efficacy, safety and benefit/risk balance as compared with relevant authorized medicinal products for the target patient population, i.e., in this case ide-cel and cilta-cel. Reference is made to the "*Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products*":

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN

Based on the data provided by the sponsor, a positive conclusion on the product's (teclistamab) equivalence in terms of efficacy, safety and benefit/risk balance vis a vis the satisfactory methods ide-cel and cilta-cel cannot be drawn.

Conclusion

In conclusion, significant benefit of teclistamab over the authorized CAR-T cell therapies ide-cel and cilta-cel is not considered to be established based on the data presented. The COMP therefore adopted a question on significant benefit.

4. COMP list of issues

- **Significant benefit**

Significant benefit of teclistamab over the authorised medicinal products Abecma (ide-cel) and Carvykti (cilta-cel) is not considered established, based on the data presented. The sponsor should therefore further justify the claim of significant benefit of teclistamab over these two medicinal products in the fourth- and later lines setting for the target patient population.