21 August 2023
EMA/OD/0000126657
EMADOC-1700519818-1030373
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Talvey (talquetamab)
Treatment of multiple myeloma
EU/3/21/2486

Sponsor: Janssen - Cilag International N.V.

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Un on

Table of contents

1. Product and administrative information 3

2. Grounds for the COMP opinion 4

3. Review of criteria for orphan designation at the time of marketing authorisation 4

Article 3(1)(a) of Regulation (EC) No 141/2000 4

Article 3(1)(b) of Regulation (EC) No 141/2000 6

4. COMP position adopted on 21 July 2023 26

1. Product and administrative information

Product	
Designated active substance	Talquetamab
Other name	Talquetamab
International Non-Proprietary Name	Talquetamab
Tradename	Talvey
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	15 July 2021
EC decision	20 August 2021
EC registration number	EU/3/21/2486
Post-designation procedural history	
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Armando Genazzani
Applicant	Janssen - Cilag International N.V.
Application submission	03 January 2023
Procedure start	25 January 2023
Procedure number	EMA/H/C/005864
Invented name	Talvey
Proposed therapeutic indication	TALVEY is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 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 Talvey can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/human/EPAR/Talvey
CHMP opinion	20 July 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Frauke Naumann-Winter / Karri Penttila
Sponsor's report submission	10 February 2023
COMP discussion and adoption of list of questions	15-17 May 2023
Oral explanation	12 July 2023

COMP opinion (adoption via written procedure)	21 July 2023

2. Grounds for the COMP opinion

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

- the intention to treat the condition with the medicinal product containing talquetamab was considered justified based on preclinical data showing that patients with relapsed or refractory multiple myeloma achieve 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 4.3 in 10,000 persons in the European Union, at the time the application was made.

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 talquetamab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with relapsed and penta-refractory multiple myeloma previously treated with selinexor and belantamab mafodotin achieved partial and stringent complete responses. 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 often advanced at the time of diagnosis (Rajkumar et al., 2014). MM is most frequently diagnosed among people older than 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 proposed therapeutic indication "TALVEY is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 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, see EPAR.

Chronically debilitating and/or life-threatening nature

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). 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).

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).

The sponsor has not identified any changes on the chronically debilitating or life-threatening nature of multiple myeloma since the original orphan designation was granted in August 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.

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/refractory (R/R) disease. The condition therefore remains chronically debilitating and life-threatening in nature.

Number of people affected or at risk

At time of initial orphan designation in 2021, the COMP concluded that the condition was estimated to be affecting approximately 4.3 in 10,000 persons in the European Union.

In the maintenance application, the sponsor referred to GLOBOCAN 5-year prevalence of 3.08 per 10,000. Furthermore, EU country registries (CancerMPact and NORDCAN) 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.

The sponsor also provided an indirect estimation of the prevalence based on incidence and survival. The incidence of multiple myeloma is consistently reported to be 0.8 per 10,000 people across the EU (ECIS 2020). However, median overall survival varies. To approximate the most comprehensive and up to date estimates of median overall survival, data from recent publications were used (Cho 2017, Greipp 2005, Kastritis 2017, Usmani 2018). Based on these data, the median OS for ISS Stage I/II patients, who represent 60% to 70% of all multiple myeloma patients, is approximately 7 years. For ISS Stage III patients, who represent 30% to 40% of all multiple myeloma patients, the median overall survival is approximately 1 to 4 years.

Using these estimates, the median overall survival for the entire multiple myeloma population is therefore estimated to be 5.8 years ([7 years*0.6) + (4 years*0.4)]. Using the formula P=I*D, the updated prevalence is estimated to be (0.8*5.8) = 4.64 per 10,000 persons in the EU. The sponsor considers that although this is higher than previously reported estimates, it likely reflects the recent increases in survival among this population due to therapeutic advances, and it is a conservative approach that utilizes recently published comprehensive data sources.

In relation to the indirect estimation for incidence multiplied with an approximated survival, the COMP considers whether the references above reflect the duration of survival according to recent advances in the therapeutic domain. Since improvements have been seen in the duration of survival probably also increasing the prevalence, the COMP considers that only sources beyond 2018 should be relevant for the estimation of survival and a more conservative approach should be followed.

The sponsor is invited to update the prevalence estimates by referring to updated literature challenging the duration of condition (up to 20 years in their own trial) and updating references on multiple myeloma epidemiology (e.g. Blimark 2022, Dyba 2021, Moore 2022).

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 presented below the medicinal products authorized in EU for the treatment of relapsed/refractory MM:

- Bortezomib: as a monotherapy, or in combination with pegylated liposomal doxorubicin or dexamethasone, is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for hematopoietic stem cell transplantation (Velcade EPAR 2021).
- Carfilzomib: in combination with daratumumab and dexamethasone, lenalidomide and dexamethasone, or dexamethasone alone after at least 1 prior therapy (Kyprolis EPAR 2022).
- Ixazomib: in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy (Ninlaro EPAR 2022).
- Lenalidomide: in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least 1 prior therapy (Revlimid EPAR 2022).

- Pomalidomide: in combination with bortezomib and dexamethasone for adult patients with multiple myeloma who have received at least 1 prior treatment regimen including lenalidomide, and in combination with dexamethasone in adult patients who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib (Imnovid EPAR 2022).
- Daratumumab: in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for patients who have received at least 1 prior therapy; in combination with pomalidomide and dexamethasone for patients who have received 1 prior therapy containing a PI and lenalidomide and were lenalidomide-refractory, or who have received at least 2 prior therapies that included lenalidomide and a PI and have demonstrated disease progression on or after the last therapy; or as a monotherapy for the treatment of relapsed and refractory multiple myeloma, for patients whose prior therapy included a PI and an IMiD (Darzalex EPAR 2022).
- Isatuximab: in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a PI and have demonstrated disease progression on the last therapy, and in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy (Sarclisa EPAR 2022).
- Panobinostat: in combination with bortezomib and dexamethasone, for adult patients who have received at least 2 prior regimens including bortezomib and an IMiD (Farydak EPAR 2022).
- Elotuzumab: in combination with lenalidomide and dexamethasone after at least 1 prior therapy, and in combination with pomalidomide and dexamethasone after at least 2 prior therapies including lenalidomide and a PI (Empliciti EPAR 2022).
- Belantamab mafodotin: monotherapy for the treatment of multiple myeloma in adult patients who have received at least 4 prior therapies and whose disease is refractory to at least 1 PI, 1 IMiD, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy (Blenrep EPAR 2022).
- Selinexor: in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy; in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, 2 IMiDs and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy (Nexpovio EPAR 2022).
- Melphalan flufenamide: in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 3 prior lines of therapies, whose disease is refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation (Pepaxti EPAR 2022).
- Teclistamab: as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy (Tecvayli EPAR 2022).

- Ide-cel: for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy (Abecma EPAR 2022).
- Cilta-cel: for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy (Carvykti EPAR 2022).

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 according to line of treatment:

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

Satisfactory methods for the target patient population

Talquetamab is indicated for patients who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression or did not respond to the last therapy. In this specific therapeutic area, ide-cel, cilta-cel and teclistamab are considered satisfactory methods as these medicines are approved for triple-class exposed r/r MM patients in fourth- or later lines.

Melphalan flufenamide is indicated for the treatment of adult patients with MM who have received at least 3 prior lines of therapies, whose disease is refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. Since the proposed indication for talquetamab is for triple exposed patients who are refractory to the last therapy and not refractory towards one of each class (PI, IMiD, and anti-CD38 mAb), considered that talquetamab includes a broader patient population, which is not covered by melphalan flufenamide.

The medicinal products belantamab and selinexor have more restricted therapeutic indications as compared to that for talquetamab. 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 talquetamab is approved for use in a less refractory patient population and already from fourth line of therapy. It is therefore considered that talquetamab does in principle include a broader patient population, which is not covered by belantamab and selinexor.

With regards to elotuzumab, an anti-SLAM7 mAb, it is authorized in combination with a class of products to which a significant part of the target patient population for talquetamab was largely refractory to, i.e. IMiDs (lenalidomide, pomalidomide), (Empliciti EPAR 2021). Furthermore, elotuzumab is neither recommended for triple-class refractory patients with r/r MM or for patients refractory to lenalidomide or proteasome-inhibitors according to the EHA-ESMO guideline (Dimopoulos et al., 2021).

Significant benefit

Significant benefit of talquetamab has to be evaluated over the satisfactory methods ide-cel, cilta-cel and teclistamab for the target patient population. The sponsor also proposed belantamab mafodotin and selinexor as satisfactory methods, however as discussed in the section above, these are not considered satisfactory methods from a regulatory perspective.

The justification for the significant benefit was based on an analysis of efficacy of talquetamab from Study 64407564MMY1001 based on prior therapies, including a subgroup analysis of the benefit of talquetamab in participants who had received prior T cell redirection therapy and also on an adjusted comparison of outcomes versus an external control arm using available individual participant-level data from Study 64407564MMY1001 and from the prospective observational studies LocoMMotion and MoMMent. Finally, the sponsor discussed the differentiation of talquetamab from teclistamab and from CAR-T therapies.

The sponsor received EMA protocol assistance dated 19 May 2022 with regards to the evidence needed to justify significant benefit of talquetamab over existing treatments used for the treatment of patients with r/r MM. The sponsor has used a similar approach as proposed during protocol assistance but did not comply with all the EMA recommendations. As set out during protocol assistance, the sponsor has conducted 2 types of efficacy analyses to establish the significant benefit of talquetamab compared with the existing therapies listed above. Additionally, the sponsor has more broadly compared talquetamab with teclistamab and available CAR-T therapies to demonstrate the significant benefit that talquetamab provides versus these agents.

The efficacy and safety of talquetamab monotherapy was evaluated in patients with r/r MM in a single-arm, open-label, multicentre study, MMY1001 (MonumenTAL-1). The study included patients who had previously received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. The study included patients who received prior T cell redirection therapy (N=51). Patients received talquetamab 0.4 mg/kg subcutaneously weekly, following two step-up doses (0.01 and 0.06 mg/kg) in the first week of therapy, or talquetamab 0.8 mg/kg subcutaneously biweekly (Q2W every 2 weeks), following three step-up doses (0.01, 0.06 and 0.3 mg/kg), until disease progression or unacceptable toxicity. The below results reported for Study 64407564MMY1001 are based on data from the clinical cut-off of 12 September 2022.

Of 143 patients treated with talquetamab 0.4 mg/kg weekly who were not exposed to prior Tcell redirection therapy, the median age was 67 (range: 46 to 86) years, 55% were male, 90% were White, and 8% were Black or African American. Patients had received a median of 5 (range: 2 to 13)

prior therapies, and 78% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-four percent (94%) of patients were refractory to their last therapy, and 74% were refractory to a PI, immunomodulatory agent, and anti-CD38 antibody. Of the 132 patients for whom baseline cytogenetic data were available, high-risk cytogenetic factors (presence of t (4:14), t (14:16), and/or del(17p)) were present in 31% of patients.

Of 145 patients treated with talquetamab 0.8 mg/kg biweekly (every 2 weeks) who were not exposed to prior Tcell redirection therapy, the median age was 67 (range: 38 to 84) years, 57% were male, 86% were White, and 6% were Black or African American. Patients had received a median of 5 (range: 2 to 17) prior therapies, and 79% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-four percent (94%) of patients were refractory to their last therapy, and 69% were refractory to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody. Of the 128 patients for whom baseline cytogenetic data were available, high-risk cytogenetic factors (presence of t (4:14), t (14:16), and/or del(17p)) were present in 29% of patients.

- *Benefit of talquetamab in study 64407564MMY1001 participants without prior T Cell redirection therapy*

Data presented here are based on the participants treated in Study 64407564MMY1001 at either the 0.4 mg/kg weekly SC RP2D (n=143) or the 0.8 mg/kg Q2W SC RP2D (n=145) who had no prior T-cell redirection therapy (Table 1). These participants were heavily pretreated and a high proportion had refractory disease. Participants treated at 0.4 mg/kg weekly SC and participants treated at 0.8 mg/kg Q2W SC who had no prior T-cell redirection therapy had a median of 5 (range: 2 to 13) and 5 (range: 2 to 17) prior therapies, respectively. In both groups, most participants (93.7% and 94.5%, respectively) were refractory to their last prior therapy. Among participants treated at 0.4 mg weekly SC, 74.1% were triple-class refractory (PI, IMiD, and anti-CD38 monoclonal antibody) and 29.4% were penta-refractory (at least 2 PIs, at least 2 IMiDs, and at least 1 anti-CD38 monoclonal antibody); among those treated at 0.8 mg/kg Q2W SC, 69.0% were triple-class refractory and 23.4% were penta-refractory.

Table 1. Prior Multiple Myeloma Therapy and Overall Response Rate; All Treated Analysis Set (Study 64407564MMY1001; RP2Ds Without Prior T Cell Redirection Therapy)

Agent Class	Prior Therapy Containing	0.4 mg/kg Weekly SC RP2D[a]				0.8 mg/kg Q2W SC RP2D[b]			
		No. Exposed Participants	ORR in Exposed Participants n (%)	No. Refractory Participants	ORR in Refractory Participants n (%)	No. Exposed Participants	ORR in Exposed Participants n (%)	No. Refractory Participants	ORR in Refractory Participants n (%)
IMiD	Pomalidomide	124	91 (73.4%)	108	77 (71.3%)	113	81 (71.7%)	98	69 (70.4%)
	Lenalidomide	142	106 (74.6%)	114	83 (72.8%)	144	105 (72.9%)	102	76 (74.5%)
	Thalidomide	72	54 (75.0%)	11	9 (81.8%)	62	43 (69.4%)	18	13 (72.2%)
PI	Bortezomib	138	103 (74.6%)	64	46 (71.9%)	142	104 (73.2%)	78	53 (67.9%)
	Carfilzomib	107	78 (72.9%)	88	62 (70.5%)	101	75 (74.3%)	72	51 (70.8%)
	Ixazomib	34	23 (67.6%)	24	16 (66.7%)	26	17 (65.4%)	20	13 (65.0%)
Anti-CD38 Ab	Daratumumab	140	103 (73.6%)	127	94 (74.0%)	144	105 (72.9%)	129	93 (72.1%)
	Isatuximab	12	10 (83.3%)	12	10 (83.3%)	15	8 (53.3%)	13	8 (61.5%)
Anti-SLAM7 Ab	Elotuzumab	14	7 (50.0%)	13	6 (46.2%)	31	22 (71.0%)	25	17 (68.0%)
HDAC Inhibitor	Panobinostat	3	1 (33.3%)	2	1 (50.0%)	4	2 (50.0%)	4	2 (50.0%)
Anti-BCMA ADC	Belantamab mafodotin	22	15 (68.2%)	18	12 (66.7%)	16	11 (68.8%)	13	9 (69.2%)
Nucleoside transporter	Selinexor	15	12 (80.0%)	13	10 (76.9%)	20	13 (65.0%)	14	9 (64.3%)
Alkylator	Melphalan flufenamide	2	2 (100.0%)	2	2 (100.0%)	3	2 (66.7%)	2	2 (100.0%)

Ab=antibody; ADC=antibody drug conjugate; BCMA= B-cell maturation antigen; 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.

[a] N=143; [b] N=145.

- *Benefit of talquetamab in study 64407564MMY1001 participants with prior T Cell redirection therapy*

Data are presented for the participants in Study 64407564MMY1001 who were treated at either of the talquetamab RP2Ds and who had previously received prior T cell redirection therapy (n=51).

The median age of these participants was 61.0 years (range: 38 to 78), and 7.8% were ≥75 years of age. More than half of the participants were male (60.8%), and most were White (92.2%). A majority

of participants had a baseline ECOG score of 1 (54.0%). Median time from initial diagnosis for these participants was 6.9 years (range: 1.7 to 19.6). The most common type of myeloma was light chain, in 47.1% of participants, and 31.4% of participants had 1 or more extramedullary plasmacytomas at baseline. Of 44 participants with baseline cytogenetic data reported, 40.9% had at least 1 high-risk abnormality, most frequently del(17p). Of 50 participants with baseline ISS data reported, 47.1% were ISS Stage I, 35.3% were Stage II, and 17.6% were ISS Stage III. These participants had received a median of 6 (range: 3 to 15) prior therapies; 60.8% of participants were refractory to their last prior therapy, 84.3% were triple-class refractory and 41.2% were penta-refractory.

Table 2 provides a summary of exposure and refractoriness to the prior therapies received by participants with prior T cell redirection therapy who received either of the talquetamab RP2Ds. This table also provides the ORRs from Study 64407564MMY1001 for those participants who were exposed to and whose disease was refractory to the prior therapies listed.

Table 2. Prior multiple myeloma therapy and ORR; all treated analysis set (Study 64407564MMY1001; RP2Ds with prior T cell redirection therapy)

		0.4 mg/kg Weekly SC RP2D or 0.8 mg/kg Q2W SC RP2Da			
Agent Class	**Prior Therapy Containing**	**No. Exposed Participants**	**ORR in Exposed Participants n (%)**	**No. Refractory Participants**	**ORR in Refractory Participants n (%)**
IMiD	Pomalidomide	45	28 (62.2%)	39	24 (61.5%)
	Lenalidomide	51	32 (62.7%)	43	27 (62.8%)
	Thalidomide	16	8 (50.0%)	5	2 (40.0%)
PI	Bortezomib	50	31 (62.0%)	36	23 (63.9%)
	Carfilzomib	41	23 (56.1%)	35	19 (54.3%)
	Ixazomib	10	5 (50.0%)	6	3 (50.0%)
Anti-CD38 Ab	Daratumumab	49	30 (61.2%)	48	30 (62.5%)
	Isatuximab	4	3 (75.0%)	4	3 (75.0%)
Anti-SLAM7 Ab	Elotuzumab	13	8 (61.5%)	13	8 (61.5%)
HDAC Inhibitor	Panobinostat	5	3 (60.0%)	4	2 (50.0%)
Anti-BCMA ADC	Belantamab mafodotin	6	5 (83.3%)	4	3 (75.0%)
Nucleoside transporter	Selinexor	7	3 (42.9%)	7	3 (42.9%)
Alkylator	Melphalan flufenamide	0	0	0	0
Bispecific antibody	Teclistamab	7	3 (42.9%)	7	3 (42.9%)
	Bispecific antibody not specified	11	5 (45.5%)	10	4 (40.0%)
CAR-T Therapy	Ide-cel	15	11 (73.3%)	3	1 (33.3%)[b]
	Cilta-cel	6	4 (66.7%)	0	0[b]
	CAR-T not specified	15	11 (73.3%)	2	2[b] (100.0%)

Ab=antibody; ADC=antibody drug conjugate; BCMA=B-cell maturation antigen; 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.
[a] N=51 ; [b]Refractory status was not uniformly collected on this study due to the variability in definition of refractoriness to a CART therapy.

The sponsor acknowledges that only a small number of participants were exposed and refractory to BCMA-targeted T-cell redirection therapies prior to receiving either of the talquetamab RP2Ds. This is likely due to the recent approval and the limited availability of these therapies at the time of the participants' enrolment in study 64407564MMY1001. ORR in this cohort (n=51) was 62.7% (95% CI:

48.1%, 75.9%) overall. ORRs were 44.4% among participants who received a prior bispecific antibody, and 72.2% among those who received prior CAR-T therapy (Table 2).

Among the 7 participants treated with talquetamab who previously received treatment with teclistamab, all of whom had teclistamab-refractory disease, the ORR was 42.9%. Responses were also documented in participants who received prior ide-cel treatment (ORR: 73.3%), including in 1 of 3 ide-cel-refractory participants (ORR: 33.3%), and in participants who received prior cilta-cel treatment (ORR: 66.7%). Since all 6 participants who received prior treatment with cilta-cel had disease progression >60 days following CAR-T cell infusion, none were considered to be refractory to this CAR-T therapy.

Overall, among responders who received either of the talquetamab RP2Ds and had previously been exposed to T-cell redirection therapy, median follow-up was 11.8 months (range: 4.4 to 25.4) and 84.4%, 59.4%, and 37.5% of responders had at least 6, 9, and 12 months of follow-up, respectively. The probability of responders remaining in response was 65.1% (95% CI: 45.8%, 78.9%) at 6 months, 57.1% (95% CI: 37.3%, 72.6%) at 9 months, and 57.1% (95% CI: 37.3%, 72.6%) at 12 months. As responses were maintained to the clinical cutoff for 18 of 32 responders (56.3%), DOR data were not yet mature (median DOR: 12.7 months [range: 3.7, not estimable]).

The COMP considered the talquetamab efficacy data in patients who received prior T-cell redirection therapy with ide-cel and cilta-cel of relevance for the discussion of significant benefit. However, the sponsor should provide updated response rate and duration of responses as achieved with treatment with talquetamab for all patients in the pivotal study, overall and separately for the subgroup with patients who were pre-treated with ide-cel and cilta-cel individually, and after all BCMA-targeting agents. In addition, the sponsor should provide a comparison of the baseline characteristics of patients included in the pivotal studies KarMMa for ide-cel and MMY2001 for cilta-cel, versus study 64407564MMY1001 for talquetamab. Finally, the sponsor should submit a matching-adjusted indirect comparisons, ideally by using individual patient data, of the efficacy outcomes between patients treated with ide-cel in KarMMa study and cilta-cel in MMY2001 study versus patients treated with talquetamab in Study 64407564MMY1001.

Comparison of Study 64407564MMY1001 Efficacy Data Using Real-World Evidence

In the absence of a direct comparator in Study 64407564MMY1001, an adjusted comparative analysis using the individual patient data from Study 64407564MMY1001 and from LocoMMotion and MoMMent, two prospective, observational studies of real-world physician's choice of treatment and associated outcomes in triple-class exposed patients with relapsed or refractory multiple myeloma has been provided by the sponsor. The objective of this analysis is to compare the efficacy results observed for talquetamab in Study 64407564MMY1001 to outcomes observed in similar patients treated with real-world treatment options, and to provide a contemporaneous standard of care context for Study 64407564MMY1001 data.

LocoMMotion: This study, initiated in 2019**,** is an ongoing, prospective, non-interventional study detailing the use of RWPC of treatment for r/r patients with MM who have received at least 3 prior therapies or were double refractory to a PI and an IMiD; received a PI, IMiD, and anti-CD38 monoclonal antibody, and have documented disease progression during or after their last treatment. The data are being collected prospectively across 76 sites in 10 countries. The primary endpoint is ORR as defined by IMWG response criteria and assessed by the Response Review Committee, which is composed of 3 leading hematologists in the field of multiple myeloma. The study has enrolled 248 participants between August 2019 and October 2020. Study enrollment has been completed, with the

last patient enrolled in October 2020. At the time of the clinical cutoff of 12 September 2022 for Study 64407564MMY1001, the study was ongoing. Follow up continued until study completion (defined as 2 years after last enrolled patient received first dose of treatment, ie, October 2022).

Earlier results reported from LocoMMotion (Mateos 2022) showed an ORR of 29.8% (95% CI: 24.2, 36.0), median PFS of 4.6 months (95% CI: 3.9, 5.6) and median OS of 12.4 months (95% CI: 10.3, not estimable). Moreover, 64.5% of LocoMMotion patients received a combination of 3 or more therapies. To further elaborate on the results from LocoMMotion, an additional study (MoMMent) was initiated.

MoMMent: MoMMent is a prospective, observational study of RWPC of treatment in patients with r/r MM. Enrollment into this study started in November 2021. The MoMMent study has 2 consecutive enrolment periods. Period 1 has a target enrollment of 50 participants who have received at least 3 prior therapies, including a PI, an IMiD, and an anti-CD38 monoclonal antibody, and has similar eligibility criteria to LocoMMotion. Period 1 enrolment has been designed with the primary goal of continuing the data collection initiated in LocoMMotion. Period 2 starts after completion of enrollment in Period 1 and will enroll participants who have received at least 3 prior therapies, including a PI, an IMiD, an anti-CD38 monoclonal antibody, and BCMA-targeted therapy. Although prior BCMA exposure is not an exclusion criterion in Period 1, the purpose of Period 2 is to enroll additional patients with prior BCMA-exposure to have total of 50 BCMA-exposed patients in the study. Study enrollment for Period 1 completed in July 2022 with at least 50 patients enrolled. Available data from Period 1 have been pooled with data from the LocoMMotion study and reported in aggregate to support the interpretation of results from Study 64407564MMY1001.

Pooled data from these two prospective observational studies was compared against Study 64407564MMY1001 data. The primary comparative analyses included all participants who received talquetamab at the 0.4 mg/kg weekly SC RP2D in Study 64407564MMY1001 (n=143) and all RWPC patients who met the inclusion criteria for Study 64407564MMY1001 (n=165). Additional comparative analyses included all participants who received talquetamab at the 0.8 mg/kg Q2W SC RP2D in Study 64407564MMY1001 (n=145) and all RWPC patients who met the inclusion criteria for Study 64407564MMY1001 (n=165) (criteria not further described, handling of missing data not described). The analyses were performed based on a prespecified statistical analysis plan. Results reported for Study 64407564MMY1001 are based on data from the clinical cutoff of 12 September 2022.

Very limited information is provided on the performance the prospective non-interventional trials (baseline characteristics, extent and handling of missing data), as well on the adjusted comparison of the pivotal study with the non-interventional studies (matching parameters, outcome of matching). Treatment received in the prospective non-interventional studies was however detailed in the CHMP report. The high rate of patients receiving doublet therapy or monotherapy in the non-interventional studies indicate that there were relevant differences in the populations form either the interventional and non-interventional studies. In addition, the non-interventional data provided do not inform on the outcomes of (BCMA-targeting/T-cell-redirecting agents) or how other authorised treatments perform after failure of these types of treatments.

The COMP considered that since the comparison to the observational non-interventional studies did not inform on outcomes after the three approved satisfactory methods ide-cel, cilta-cel and teclistamab or on the outcomes observed after failure of these agents, it is not considered relevant for the justification of the significant benefit.

Comparative Analysis Results for 0.4mg/kg weekly SC and 0.8 mg/kg Q2W SC

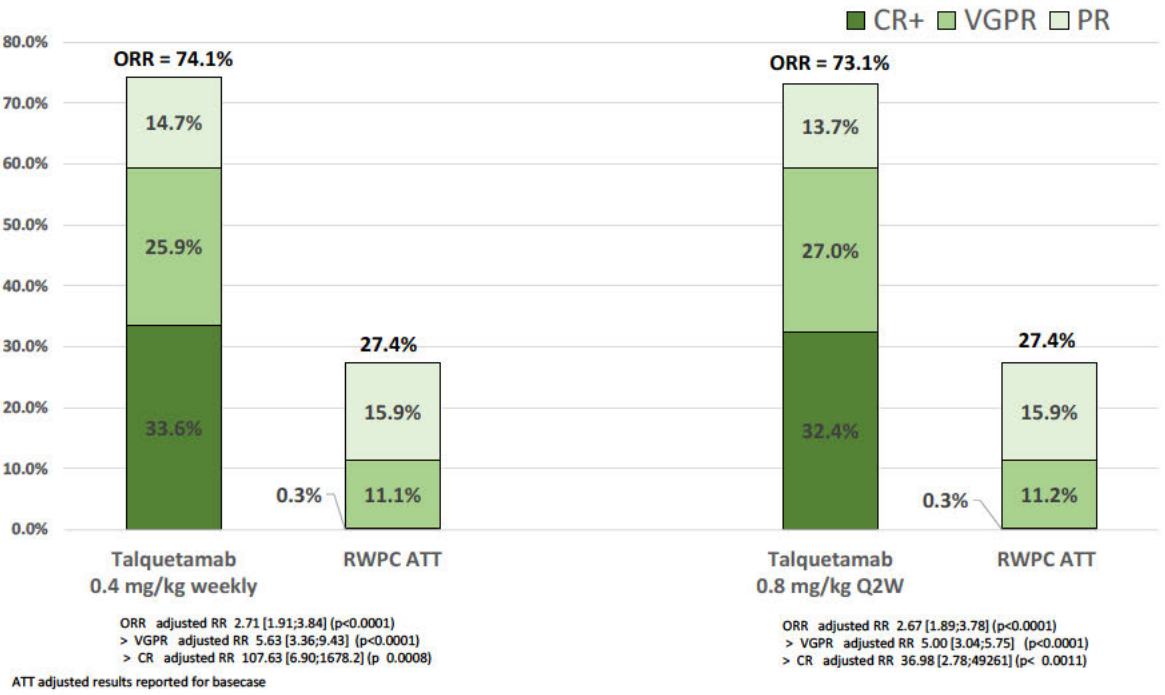
Participants receiving talquetamab at either RP2D (0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC) had superior outcomes compared with patients receiving other available treatments as measured by ORR, PFS, and OS. A propensity score weighted analysis using ATT weights was conducted to adjust for differences in baseline prognostic factors across Study 64407564MMY1001 and RWPC cohorts. After ATT adjustment, both cohorts were well balanced across all baseline prognostic factors, with all standardized mean differences <0.20. Results from the ATT analysis are summarized in Table 3.

Table 3 ATT-weighted results comparing talquetamab versus real-world physician's choice

Endpoints	**Talquetamab 0.4 mg/kg weekly SC N=143**	**RWPC N=165**	**Response Ratio/ Hazard ratio (95% CI)**	**Talquetamab 0.8 mg/kg Q2W SC N=145**	**RWPC N=165**	**Response Ratio/Hazard ratio (95% CI)**
ORR (%)	74.1%	27.4%	RR 2.71 (1.91, 3.84)	73.1%	27.4%	RR 2.67 (1.89, 3.78)
DOR (median months)	9.3	4.9	HR 0.70 (0.43, 1.14)	13.0	7.4	HR 0.47 (0.26, 0.84)
PFS (median months)	7.5	4.1	HR 0.54 (0.40, 0.72)	11.9	4.3	HR 0.44 (0.31, 0.62)
TTNT (median months)	9.0	4.7	HR 0.51 (0.38, 0.67)	11.3	4.7	HR 0.39 (0.28, 0.55)
OS (median months)	Not reached	11.1	HR 0.42 (0.28, 0.62)	20.1	11.8	HR 0.45 (0.28, 0.71)

ATT=average treatment effects on the treated; CI=confidence interval; DOR=duration of response; HR=hazard ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; Q2W=every 2 weeks; RR=response ratio; RWPC=real-world physician's choice; SC=subcutaneous; TTNT=time to next treatment.

Figure 1. ATT-weighted response rates comparing talquetamab 0.4mg/kg weekly SC and talquetamab



0.8 mg/kg Q2W SC treatment groups versus real-world physician's choice

ATT=average treatment effects on the treated; CR=complete response; ORR=overall response rate; PR=partial response; Q2W=every 2 weeks; RR=response ratio; RWPC=real-world physician's choice; VGPR=very good partial response.

The sponsor concluded that comparative analysis of efficacy results observed for talquetamab in Study 64407564MMY1001 versus the outcomes observed in patients treated with RWPC of treatment as captured in the LocoMMotion and MoMMent studies demonstrated that talquetamab at either RP2D (0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC) resulted in superior outcomes (ORR, CR or better rate, VGPR or better rate, PFS, TTNT, and OS) than RWPC of treatment in patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an IMiD, a PI, and an anti-CD38 antibody.

Differentiation from teclistamab

The sponsor argued that talquetamab provides an alternative mechanism of action that does not cause B cell depletion. In addition, hypogammaglobulinemia TEAEs and IVIg treatment were less frequent, and Grade 3 or 4 infections were less common with talquetamab treatment than with teclistamab treatment. Furthermore, talquetamab 0.8 mg/kg Q2W SC offers an alternative, more convenient treatment schedule than weekly subcutaneous injection of teclistamab which would be an advantage in this heavily treated population who would benefit from a reduction in the number of hospital visits.

The COMP considered that the different mechanism of action per se cannot justify the significant benefit. In addition, the argument regarding the major contribution to patient care cannot be accepted with no relevant data that could support it, especially in view of the concerns raised by CHMP regarding the length of follow-up and maturity of the biweekly dosing data. The sponsor should provide updated response rate and duration of responses as achieved with treatment with talquetamab for all patients in the pivotal study, overall and separately for the subgroup with patients who were pre-treated with

teclistamab individually, and after all BCMA-targeting agents. The sponsor should also provide an indirect comparison including the baseline characteristics of the patient populations included in the pivotal study MajesTEC-1 for teclistamab versus study 64407564MMY1001 for talquetamab. In addition, the sponsor should submit a matching-adjusted indirect comparisons using individual patient level data of the efficacy outcomes between patients treated with teclistamab in MajesTEC-1 study versus patients treated with talquetamab in Study 64407564MMY1001.

Differentiation from CAR-T therapies

The sponsor claimed that CAR-T therapies have limitations with regards to eligibility, safety, logistical, and accessibility considerations that may prevent them from being practical and clinically appropriate for all patients with heavily pretreated multiple myeloma. Talquetamab would confer a clinically relevant advantage in this respect and would provide a major contribution to the care of relapsed and refractory multiple myeloma. As an off-the-shelf product without a lengthy, complex manufacturing process, talquetamab would be readily available for administration, thereby offering a prompt therapeutic option for all triple-class exposed patients, including those who require urgent disease control and/or are not medically fit to receive CAR-T therapy.

The COMP acknowledged the sponsor's arguments and considered that they are relevant 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, the COMP considers that a positive conclusion on the product's (talquetamab) equivalence in terms of efficacy, safety and benefit/risk balance vis a vis the satisfactory methods ide-cel and cilta-cel cannot be drawn.

Overall conclusion COMP:

The COMP adopted a list of questions on the prevalence and on the significant benefit.

The COMP considered that the prevalence estimates should be updated by referring to updated literature challenging the duration of condition (up to 20 years in their own trial) and updating references on multiple myeloma epidemiology (eg. Blimark 2022, Dyba 2021, Moore 2022).

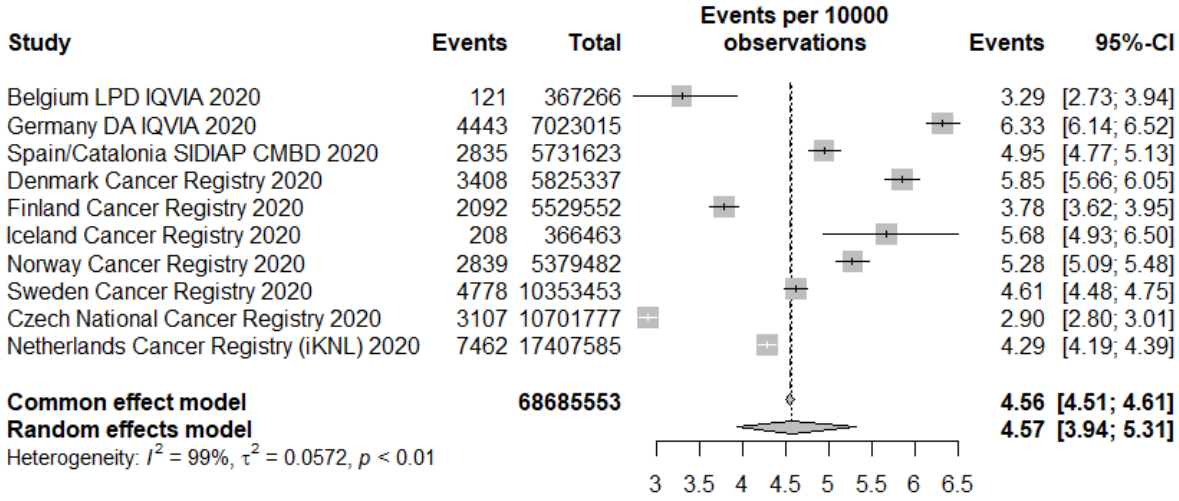
In addition, the claim of significant benefit of talquetamab over the authorised satisfactory methods, ide-cel (Abecma), cilta-cel (Carvykti) and teclistamab (Tecvayli), and for the indication (subject to change pending the final CHMP outcome) was not considered to be established by the COMP, based on the data presented by the sponsor. A list of questions on significant benefit aiming at clarifying the duration of responses as achieved with treatment with talquetamab for all patients in the pivotal study, overall and separately for the subgroup with patients who were pre-treated with ide-cel, cilta-cel and teclistamab individually, and after all BCMA-targeting agents. In addition, a comparison of the baseline characteristics of patients included in the pivotal studies was requested. Finally, matching-adjusted indirect comparisons of the efficacy outcomes between patients treated with ide-cel in KarMMa study, cilta-cel in MMY2001 study and teclistamab in MajesTEC-1 study versus patients treated with talquetamab in Study 64407564MMY1001 were also requested.

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

In the written response, and during an oral explanation before the Committee on 12 July 2023, the sponsor presented their responses to the COMP's list of questions. The sponsor reviewed the prevalence and selected a number of registries as well as referred to the primary care data base sources mentioned in the recently published DARWIN study. A final pooled, random effects estimate of 4.57 per 10,000 persons in 2020 was concluded upon.

The sponsor calculated the pooled complete prevalence of MM in the EU by conducting a meta-analysis of prevalence proportions across cohorts from primary care and cancer registries reporting complete prevalence in 2020 using the metaprop function from the meta-R package (Barendregt 2013; Balduzzi 2019). Meta-analysis forest plot pooling individual prevalence estimates from valid EU-27 data sources with complete prevalence in 2020 using common effects and random effects models is displayed in Figure 2.

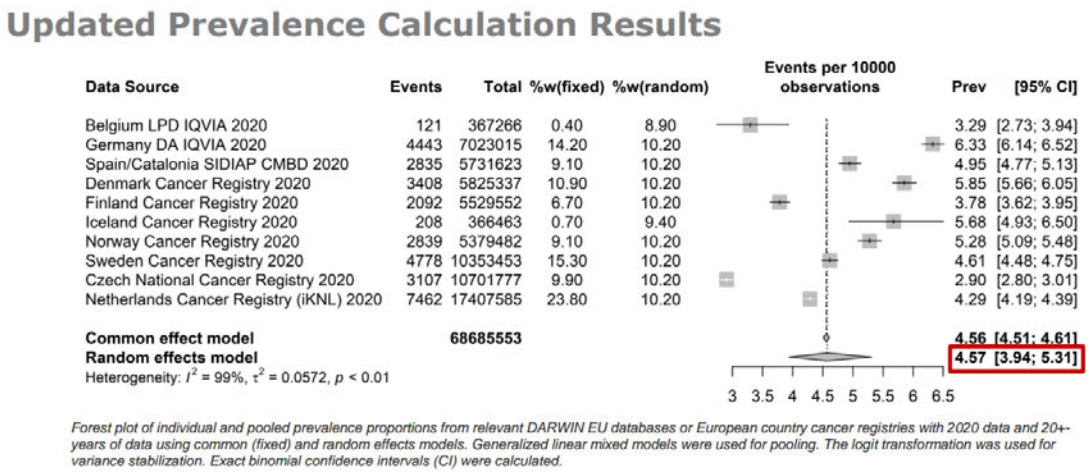
Figure 2. Meta-analysis Forest Plot Pooling Individual Prevalence Estimates From Valid EU-27 Data Sources With Complete Prevalence in 2020 Using Common Effects and Random Effects Models



EU=European Union; CI=confidence interval

Further to the COMP's request, the sponsor provided the results of an updated meta-analyses by keeping a similar selection but providing weight of the studies in the overall estimate (Figure 3).

Figure 3. Updated Meta-analysis Forest Plot Pooling Individual Prevalence Estimates From Valid EU-27 Data Sources With Complete Prevalence in 2020 Using Common Effects and Random Effects Models including weight of the studies



Forest plot of individual and pooled prevalence proportions from relevant DARWIN EU databases or European country cancer registries with 2020 data and 20+-years of data using common (fixed) and random effects models. Generalized linear mixed models were used for pooling. The logit transformation was used for variance stabilization. Exact binomial confidence intervals (CI) were calculated.

Overall response rate and duration of response, overall patient population in study 64407564MMY1001: Updated results (17 January 2023)

The sponsor submitted updated results from study 64407564MMY1001 (clinical cut-off of 17 January 2023), providing an additional 4 months of follow-up data since the efficacy update (clinical cut-off of 12 September 2022), that was included in the initial orphan maintenance report. A summary of the ORR and DOR is presented from the analysis of the RP2D populations of participants treated at 0.4 mg/kg weekly SC (n=143; 21 in Phase 1 and 122 in Cohort A of Phase 2 or 0.8 mg/kg Q2W SC (n=145; 36 in Phase 1 and 109 in Cohort C of Phase 2, in the ongoing, open-label, multicenter Phase 1/2 Study 64407564MMY1001 and who initiated treatment on or before 20 April 2022 (included in the All Treated Analysis Set).

For the 0.4 mg/kg Weekly SC participants with the additional >4 months of follow-up between the efficacy update and the updated clinical cut-off, the ORR (PR or better) remained stable as assessed by the IRC based on IMWG 2016 criteria of 74.1% (95% CI: 66.1%, 81.1%). This is consistent with the ORR reported in the primary CSR (72.7%) and efficacy update (74.1%). Most responses occurred rapidly and deepened over time, with a CR or better rate at the updated clinical cut-off of 33.6%.

For the 0.8 mg/kg Q2W SC participants with the additional >4 months of follow-up between the efficacy update and the updated clinical cut-off, 2 fewer responses were observed per IRC assessment, resulting in an ORR (PR or better) of 71.7% (95% CI: 63.7%, 78.9%) as assessed by the IRC based on IMWG 2016 criteria (Table 4). This ORR was greater than in the primary CSR (55.2%) and similar to the efficacy update (73.1%). Most responses occurred rapidly and deepened over time, with an improved CR or better rate at the updated clinical cutoff of 38.6%.

With the additional >4 months of follow-up at the updated clinical cut-off, median DOR for participants assigned to talquetamab 0.4 mg/kg weekly SC was 9.5 months (95% CI: 6.7, 13.3) overall. The percentages of participants estimated to be in response at 6, 9, and 12 months were consistent with the primary CSR. The median DOR for participants assigned to talquetamab 0.8 mg/kg Q2W SC was not mature, and 88.6% of responders had at least 9 months of follow-up.

Overall response rate and duration of response for participants who received prior teclistamab, ide-cel, cilta-cel, and all BCMA targeting agents in study 64407564MMY1001

The sponsor provided updated ORR and DOR results based on a more recent clinical cut-off of 17 January 2023, including a longer follow up from the previous analysis included in the initial orphan maintenance report. The updated data from Study 64407564MMY1001 are provided from participants treated with either RP2D (0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC) who were pre-treated with teclistamab, ide-cel, and cilta-cel individually. From the primary analysis, a total of 51 participants who initiated study drug on or before 20 April 2022 in either phase of the study and who were exposed to a T cell redirection therapy were included (Table 4).

To further substantiate these updated results, the sponsor has performed another analysis including an additional 19 participants from Study 64407564MMY1001 who were pretreated with a BCMA CAR T (including ide-cel and cilta-cel); BCMA bispecific (including teclistamab), and other BCMA-targeting agents (including belantamab mafodotin) and who were enrolled on or before 2 November 2022 and initiated treatment with 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC talquetamab after 20 April 2022 (clinical cut-off: 17 January 2023; n=70). These 19 participants were not included in the initial primary analysis due to insufficient follow-up (ie, participants were excluded in the analysis if they had <4 weeks of follow up from the primary analysis cut-off of 16 May 2022) (Table 5).

Table 4. Overall Response Rate and Duration of Response Rate Based on Independent Review Committee (IRC) Assessment; All Treated Analysis Set (Study 64407564MMY1001; RP2Ds With and Without Prior T cell Redirection Therapy; Enrolled on or Before 20 April 2022)

	Total RP2D					
	Ide-cel	Cilta-cel	All BCMA CAR-T Total[e]	Teclistamab	All BCMA Bispecific Total[e]	All BCMA Total[d]
Treated Subjects	15	6	34	7	16	86
Median Follow-up (months)	11.50	20.07	14.75	23.26	14.46	15.01
ORR in Exposed Participants n (%)	12 (80.0%)	4 (66.7%)	25 (73.5%)	3 (42.9%)	7 (43.8%)	55 (64.0%)
ORR in Refractory Participants n (%)	N/A[c]	N/A[c]	N/A[c]	3 (42.9%)	6 (40.0%)	30 (56.6%)
Duration of response[a,b]						
Number of events (%)	6 (50.0%)	2 (50.0%)	13 (52.0%)	2 (66.7%)	5 (71.4%)	26 (47.3%)
Number of censored (%)	6 (50.0%)	2 (50.0%)	12 (48.0%)	1 (33.3%)	2 (28.6%)	29 (52.7%)
Kaplan-Meier estimate (months)						
25th percentile (95% CI)	3.7 (1.7, 12.3)	2.4 (2.0, NE)	2.8 (1.7, 11.2)	1.7 (1.7, NE)	2.0 (1.7, 3.5)	3.5 (2.6, 6.3)
Median (95% CI)	11.9 (2.8, NE)	NE (2.0, NE)	11.9 (3.7, NE)	2.1 (1.7, NE)	3.5 (1.7, NE)	12.3 (6.3, NE)
75th percentile (95% CI)	NE (11.9, NE)	NE (2.0, NE)	NE (12.3, NE)	NE (1.7, NE)	NE (2.1, NE)	NE (NE, NE)
Range	(2, 15+)	(2, 15+)	(2, 19+)	(2, 22+)	(2, 22+)	(1, 22+)
6-month event-free rate % (95% CI)	64.8 (31.0, 85.2)	50.0 (5.8, 84.5)	63.5 (41.5, 79.1)	33.3 (0.9, 77.4)	42.9 (9.8, 73.4)	64.7 (50.3, 75.8)
9-month event-free rate % (95% CI)	64.8 (31.0, 85.2)	50.0 (5.8, 84.5)	59.3 (37.5, 75.7)	33.3 (0.9, 77.4)	28.6 (4.1, 61.2)	58.6 (44.1, 70.5)

Table 5. ORR and DOR rate based on independent review committee (IRC) Assessment; all treated analysis set (Study 64407564MMY1001; RP2Ds with and without prior T cell redirection therapy and enrolled on or before 2 Nov 2022)

	Total RP2D					
	Ide-cel	Cilta-cel	All BCMA CAR-T Total	Teclistamab	All BCMA Bispecific Total	All BCMA Total[d]
Treated Subjects	21	8	48	11	22	105
Median Follow-up (months)	10.64	16.85	11.10	7.85	13.40	13.93
ORR in Exposed Participants n (%)	17 (81.0%)	5 (62.5%)	35 (72.9%)	5 (45.5%)	11 (50.0%)	68 (64.8%)
ORR in Refractory Participants n (%)	N/Ac	N/Ac	N/Ac	5 (45.5%)	10 (47.6%)	37 (58.7%)
Duration of responsea,b						
Number of events (%)	7 (41.2%)	2 (40.0%)	14 (40.0%)	3 (60.0%)	6 (54.5%)	28 (41.2%)
Number of censored (%)	10 (58.8%)	3 (60.0%)	21 (60.0%)	2 (40.0%)	5 (45.5%)	40 (58.8%)
Kaplan-Meier estimate (months)						
25th percentile (95% CI)	3.7 (1.7, 12.3)	2.4 (2.0, NE)	2.8 (1.9, 11.2)	1.9 (1.7, NE)	2.0 (1.7, 6.5)	3.5 (2.6, 6.3)
Median (95% CI)	11.9 (3.7, NE)	NE (2.0, NE)	12.3 (4.8, NE)	2.1 (1.7, NE)	6.5 (1.9, NE)	12.3 (6.5, NE)
75th percentile (95% CI)	NE (11.9, NE)	NE (2.0, NE)	NE (12.3, NE)	NE (1.7, NE)	NE (3.5, NE)	NE (NE, NE)
Range	(2, 15+)	(1+, 15+)	(1+, 19+)	(2, 22+)	(2, 22+)	(1+, 22+)
6-month event-free rate % (95% CI)	64.8 (33.8, 84.1)	50.0 (5.8, 84.5)	66.7 (46.7, 80.6)	40.0 (5.2, 75.3)	53.0 (20.9, 77.3)	66.3 (53.0, 76.6)
9-month event-free rate % (95% CI)	64.8 (33.8, 84.1)	50.0 (5.8, 84.5)	62.5 (42.3, 77.4)	40.0 (5.2, 75.3)	39.8 (11.0, 68.0)	60.4 (46.8, 71.6)

Key: CI=confidence interval; N/A=not applicable; NE=not estimable; + =censored observation; RP2D=recommended Phase 2 dose; IRC=independent review committee; IMWG=international myeloma working group; PR=partial response

a Duration of response is calculated as the number of months from first documented response to progression or death due to any cause.
b Percentages are calculated using number of responders as denominator.
c Refractory status is not reported, as no end of treatment date can reliably be determined due to the potential ongoing propagation and activity of the modified T cells.
d Includes participants treated with BCMA CAR-T including ide-cel and cilta-cel; BCMA bispecific including teclistamab; and other BCMA-targeting agents including belantamab mafodotin. Some patients received more than 1 BCMA-targeted therapy.

Comparison of the baseline characteristics of patients included in the pivotal studies KarMMa for ide-cel, MMY2001 for cilta-cel and MajesTEC-1 study for teclistamab, versus study 64407564MMY1001 for talquetamab

As requested, the sponsor provided a comparison of the baseline characteristics of patients included in the pivotal studies KarMMa for ide-cel, MMY2001 for cilta-cel, and MajesTEC-1 study for teclistamab vs the participants of Study 64407564MMY1001 (Table 6). According to the sponsor the main baseline characteristics reported across the 4 studies showed no systematic differences between studies and no major imbalances.

Table 6. Comparison of baseline characteristics for talquetamab (study 64407564MMY1001, MonumenTAL-1), Teclistamab (MajesTEC-1), Ide-cel (KarMMa study), and Cilta-cel (Study MMY2001)

	Talquetamab 0.4 mg/kg Weekly SC	Talquetamab 0.8 mg/kg Q2W SC	Teclistamab[a]	Ide-cel[b]	Cilta-cel[c]
Number of Participants	143	145	165	140	113
Age (Years)					
Median (range)	67.0 (46, 86)	67 (38, 84)	64 (33, 84)	60.5 (33, 78)	62 (29, 78)
Sex					
Male	54.5%	57.2%	58.2%	58.6%	57.5%
Female	45.5%	42.8%	41.8%	41.4%	42.5%
Race					
White	89.5%	86.2%	81.2%	80.7%	73.5%
Black/ African American	8.4%	6.2%	12.7%	5.7%	15.0%
Not reported	1.4%	1.4%	2.4%	7.1%	9.0%
Other	0.7%	6.2%	3.6%	6.4%	2.7%
Refractory Status[d]					
Triple-refractory	74.1%	69%	77.6%	83.6%	88.5%
Penta-refractory	29.4%	23.4%	30.3%	26.4%	46.0%
Cytogenetic profile					
High	31.1%[e]	71.1%[f]	25.9%	32.9%	25.0%
Standard	68.9%[e]	28.9%[f]	74.1%	52.1%	62.0%
Unknown/not evaluable	-	-	-	15.0%	13.0%
ECOG status					
0	30.8%	38.6%	33.3%	42.9%	49.0%
1	60.1%	55.9%	66.1%	55.0%	51.0%
2	9.1%	5.5%	-	2.1%	-
3	-	-	0.6%	-	-
ISS stage					
I	43.4%	44.4%	52.5%	35.0%	55.0%
II	37.1%	31.3%	35.2%	39.3%	36.0%
III	19.6%	24.3%	12.3%	25.7%	9.0%
R-ISS stage					
I	20.3%	23.9%	27.6%	10.0%	-
II	69.6%	62.3%	64.1%	69.3%	-
III	10.1%	13.8%	8.3%	18.6%	-
Unknown	3.5%	-	-	2.1%	-
Stem Cell Transplant (SCT)					
Prior SCT for MM	79.0%	78.6%	81.8%	93.6%	-
Prior autologous SCT (%)	78.3%	78.6%	81.8%	-	88.0%

Table 6. Comparison of baseline characteristics for talquetamab (study 64407564MMY1001, MonumenTAL-1), Teclistamab (MajesTEC-1), Ide-cel (KarMMa study), and Cilta-cel (Study MMY2001)

	Talquetamab 0.4 mg/kg Weekly SC	Talquetamab 0.8 mg/kg Q2W SC	Teclistamab[a]	Ide-cel[b]	Cilta-cel[c]
Prior allogeneic SCT (%)	6.3%	1.4%	4.8%	-	7.0%
Presence of Extramedullary Disease					
Yes	23.1%	25.5%	17.0%	37.1%	NA[g]
No	76.9%	74.5%	83.0%	60.7%	NA[g]
Missing	-	-	-	2.1%	-
Number of Prior Lines of Therapy					
Median (Range)	5 (2, 13)	5 (2, 17)	5 (2, 14)	6 (3, 17)	5 (3, 18)
Mean	5.3	5.4	5.1	-	-
3	17.5%	20%	23.0%	11.4%	-
4	26.6%	25.5%	21.2%	14.3%	-
5	19.6%	11.7%	20.6%	16.4%	-
>5	35.7%	40.7%	32.1%	-	-
6	-	-	-	17.9%	-
7+	-	-	-	40.0%	-

ISS=International Staging System; PI=proteasome inhibitor; R-ISS=Revised International Staging System; tal=talquetamab

[a] MajesTEC-1 study (TECVAYLI EPAR 2022); [b] KarMMa study (ABECMA EPAR 2021); [c] CARTITUDE-1 study (CARVYKTI SmPC 2023); [d] Triple-refractory to 2 IMiDs and 1 PI, or 2 PIs and 1 IMiD or ≥1 PI, ≥1 IMiD, and 1 anti-CD38 monoclonal antibody; penta-refractory to at least 2 IMiDs, at least 2 PIs, and an anti-CD38 monoclonal antibody. [e] N=132; [f] N=128; [g] Plasmacytomas were not assessed until prior to lymphodepletion.

Matching-adjusted indirect comparisons, of the efficacy outcomes between patients treated with ide-cel in KarMMa study, cilta-cel in MMY2001 study and teclistamab in MajesTEC-1 study versus patients treated with talquetamab in Study 64407564MMY1001

The sponsor performed MAICs as it was requested (data not shown).

COMP discussion

The sponsor has provided additional data to further substantiate the prevalence estimate. The validity to meta-analyse prevalence estimates derived from either cohorts from primary care or a selection of cancer registries in order to establish a pan-EU prevalence estimate was questioned by the COMP based on methodological reasoning. First, characteristics of the data sources differ substantially which may question their suitability for joint analysis. Second, different criteria for selecting sources for meta-analysis do not allow to conclude on a European estimate of prevalence due to the lack of geographic representativity and lack of adequate reflection of the different size of the different member states. In addition, as seen in the figure above, prevalence estimates from the different sources varying from 2.9 to 6.3 in 10.000 with narrow confidence limits, suggest true heterogeneity of prevalence, thereby precluding fixed effect meta-analysis which assumes a common underlying prevalence. Third, the random effects model assumes different underlying prevalences and provides an estimate of the average of these prevalences but not an estimate of the EU-wide prevalence.

Recently, the COMP accepted a prevalence estimate based on an indirect calculation of incidence times duration. A disease duration of 5.8 years was used (Greipp 2005; Cho 2017; Kastritis 2017; Usmani 2018). Based on these assumptions, 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 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. While this indirect way of estimating prevalence has also methodological limitations, it 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 discussion of the more recent data.

Furthermore, the sponsor further justified the claim for significant benefit of talquetamab over ide-cel (Abecma), cilta-cel (Carvykti) and teclistamab (Tecvayli), for the target multiple myeloma population as requested.

Updated data on response (ORR, VGPR, (s)CR, PR) are provided for all patients receiving the RP2D. Updated results are overall similar and subgroup analyses demonstrate consistent results in both cohorts. DOR data are also in line with previous results and indicate continued benefit in responding patients (data not mature especially for the biweekly schedule (73% censored patients), however).

The ORR among participants who had prior CAR-T therapy was higher among participants treated with talquetamab in Study 64407564MMY1001 than among participants treated with teclistamab in MajesTEC-1 (73.5% versus 45.5%, respectively) and no participant in the MajesTEC-1 had received prior bi-specific antibodies. The ORR for participants who were previously exposed to any (not necessarily specified) BCMA-targeting agent was 64.0%.

Talquetamab elicits high and durable (still ongoing in recent cut-off date) responses in patients with prior BCMA-targeted therapies, including bispecific antibodies and CAR-T therapy (i.e., teclistamab, ide-cel, and cilta-cel). Additionally, talquetamab would provide the first GPRC5D-targeted therapy to patients who have exhausted all other treatment options.

The COMP also agreed with the sponsor that there are no major differences in terms of the baseline characteristics of patients included in the pivotal studies KarMMa for ide-cel, MMY2001 for cilta-cel, and MajesTEC-1 study for teclistamab vs the participants of Study 64407564MMY1001.

Finally, the sponsor performed MAICs but not using IPD data as asked for. Very little information is given on the methodology of the MAICs and the quality of the comparisons cannot be judged (e.g. no ESS given). Results for the efficacy endpoints ORR, DOR, PFS, and OS are provided in both tables and figures. Talquetamab appears sometimes better and sometimes worse in this indirect comparison, but the results cannot be adequately assessed in view of the lack of reported details. Since the durable responses elicited among patients across several BCMA targeting agents (CAR-T, bispecific and AbDC) are considered sufficient for the justification of significant benefit, the MAICs are no longer needed.

COMP conclusion:

In conclusion, the COMP agreed on a prevalence of 4.6 in 10.000 persons. In addition the significant benefit of talquetamab over the authorized Tecvayli, Abecma and Carvykti is considered to be established based on improved and durable responses with Talvey in patients with relapsed and

refractory multiple myeloma, who have been pretreated with the authorised medicinal products (Tecvayli, Abecma and Carvykti) and who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

4. COMP position adopted on 21 July 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of multiple myeloma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 4.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening due to development of hypercalcemia, renal insufficiency, anaemia, bone lesions, and reduced life expectancy;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Talvey, the assumption that Talvey may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical study data that demonstrated improved and durable responses with Talvey in patients with relapsed and refractory multiple myeloma, who have been pretreated with the authorised medicinal products (Tecvayli, Abecma and Carvykti) and who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.
- The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:
- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Talvey, talquetamab for treatment of multiple myeloma (EU/3/21/2486) is not removed from the Community Register of Orphan Medicinal Products.