Talquetamab (Talvey®) for the treatment of adult patients with relapsed and refractory multiple myeloma (MM)

General information [1]

Drug description

The active substance of Talvey® is talquetamab, a bispecific antibody that targets the CD3 receptor expressed on the surface of T cells and GPRC5D which is expressed on the surface of plasma cells, including malignant MM cells.

Indication

Talquetamab (Talvey®, JNJ-64407564) is indicated as monotherapy for the treatment of adult patients with relapsed and refractory MM, 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.

Incidence [2]

In Austria, in 2020, a total of 521 patients were newly diagnosed with MM.
The age- standardised incidence rate[1] was 7.3 per 100,000 men and 4.3 in 100,000 women.

Current treatment [3]

For the treatment of MM (third-line and beyond), Onkopedia recommends the following:

- The choice of therapy in patients with relapsed or refractory disease after second-line therapy depends on the patient´s aims and, essentially, on the patient´s experiences with prior therapies.
- Recent data, regarding patients who received at least 2 lines of therapy, can be summarised as follows:
  - Repetition of second-line therapy in patients with long, deep remission and good tolerability.
  - New double- or triple combinations of second-line therapy agents.
  - Additional options:
    - Panobinostat, combined with bortezomib/dexamethasone (as compared to bortezomib/dexamethasone) leads to prolongation of PFS, but not of OS.
    - Pomalidomide combined with low-dosed dexamethasone (as compared with high-dosed dexamethasone) lead to a prolonged PFS and OS and increases the remission rate. The additional combination with cyclophosphamide increases the response rate, but also the haematological toxicity.
    - With daratumumab monotherapy, 30% of heavily pretreated patients achieve at least partial remission and a median PFS of 4 months.
    - Cytostatic agents: Efficient "classical" cytostatic agents are bendamustine, cyclophosphamide, doxorubicin and melphalan, each as monotherapy or as combination therapy. This also includes therapy regimens such as DCEP or DT-PACE that are partially administered by continuous infusion.

Regulatory status

EMA [1]	FDA
Approval status for this indication: On 20 July 2023, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Talvey®. The full indication is: ❖ Talvey® is indicated as monotherapy for the treatment of adult patients with relapsed and refractory MM, 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. **Other indications**: none	**Approval status for this indication**: not approved In December 2022, a biologics license application has been submitted to the FDA for talquetamab for the treatment of patients with relapsed or refractory MM [4]. On 9 September 2023, the FDA approved Talvey® for the treatment of adult patients with relapsed or refractory MM who have received at least **four** prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. This indication is approved under accelerated approval based on response rate and durability of response [5]. **Other indications**: none

[1] European Standard Population 2013.

✓ **Orphan status** ✓ **Medicine received a conditional marketing authorisation**[2] ✓ **Medicine is under additional monitoring**	

Manufacturer

Talvey® is manufactured by Janssen-Cilag International N.V.

Costs [6]

1.5 ml Talvey® solution for injection 2 mg/ml = € 380.77 (ex-factory price)
1 ml Talvey® solution for injection 40 mg/ml = € 5,076.92 (ex-factory price)

Pre-treatment [7]

- following pre-treatment medicinal products must be administered 1 to 3 hours before each dose of Talvey® during the step-up phase to reduce the risk of cytokine release syndrome (CRS):
  - Corticosteroid (oral or intravenous dexamethasone 16 mg or equivalent)
  - Antihistamine (oral or intravenous diphenhydramine 50 mg or equivalent)
  - Antipyretics (oral or intravenous paracetamol 650 mg to 1 000 mg or equivalent)
- Pre-treatment medicinal products should be administered prior to subsequent doses for patients who repeat doses within the Talvey® step-up phase due to dose delays or for patients who experienced CRS.
- Prevention of infection

  Prior to starting treatment with Talvey®, prophylaxis should be considered for the prevention of infections, per local institutional guidelines.

Special warnings and precautions for use [7]

- **Traceability**
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- **CRS**
  - CRS, including life-threatening or fatal reactions, may occur in patients receiving Talvey®.
  - Clinical signs and symptoms of CRS may include but are not limited to pyrexia, hypotension, chills, hypoxia, headache, tachycardia and elevated transaminases.
  - Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation.
  - Talvey® therapy should be initiated with step-up phase dosing and pre-treatment medicinal products (corticosteroids, antihistamine, and antipyretics) should be administered prior to each dose of Talvey® during the step-up phase to reduce the risk of CRS. Patients should be monitored following administration accordingly. In patients who experience CRS following their previous dose, pre-treatment medicinal products should be administered prior to the next Talvey® dose.
  - Subjects who experienced Grade 3 or higher CRS with any previous T cell redirection therapy were excluded from clinical studies. It cannot be excluded that prior severe CRS with chimeric antigen receptor (CAR) T-cell therapy or other T-cell engagers might impact on the safety of Talvey®. The potential benefits of treatment should be carefully weighed against the risk of neurologic events, and heightened caution should be exercised when administering Talvey® to these patients.
  - Patients should be counselled to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, patients should be immediately evaluated for hospitalisation and treatment with supportive care, tocilizumab and/or corticosteroids, should be instituted based on severity. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor, should be avoided during CRS. Talvey® should be withheld until CRS resolves.
- **Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS)**
  - Serious or life-threatening neurologic toxicities, including ICANS have occurred following treatment with Talvey®.

[2] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks, and the applicant should be in a position to provide the comprehensive clinical data in the future.

- ICANS, including fatal reactions, have occurred following treatment with Talvey®. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia. Patients should be monitored for signs and symptoms of neurologic toxicities and treated promptly. Patients should be counselled to seek medical attention should signs or symptoms of neurologic toxicities including ICANS occur. At the first sign of neurologic toxicities including ICANS, the patient should be immediately evaluated, and supportive care should be provided based on severity. Patients who experience Grade 2 or higher ICANS should be instructed to remain within proximity of a healthcare facility and monitored for signs and symptoms for 48 hours following the next dose of Talvey®.
- For ICANS and other neurologic toxicities, Talvey® should be withheld or discontinued based on severity and management recommendations should be followed as indicated in Product Information.
- There are no data on use of talquetamab in patients with CNS involvement of myeloma or other clinically relevant CNS pathologies as a result of their exclusion from the study due to the potential risk of ICANS.
- Due to the potential for ICANS, patients should be instructed to avoid driving or operating machines during the step-up phase and for 48 hours after completion of the step-up phase, and in the event of new onset of any neurological symptoms, until symptoms resolve.
- Management of neurologic toxicities
    - At the first sign of neurologic toxicity, including ICANS, neurology evaluation should be considered. Other causes of neurologic symptoms should be ruled out. Talvey® should be withheld until adverse reaction resolves.
    - Intensive care and supportive therapy should be provided for severe or life-threatening neurologic toxicities.

❖ **Oral toxicity**

- Oral toxicities, including dysgeusia, dry mouth, dysphagia, and stomatitis occur very commonly following treatment with Talvey®.
- Patients should be monitored for signs and symptoms of oral toxicity. Patients should be counselled to seek medical attention should signs or symptoms of oral toxicity occur, and supportive care should be provided. Supportive care may include saliva stimulating agents, steroid mouth wash, or consultation with a nutritionist.
- Talvey® should be interrupted or less frequent dosing should be considered.
- Over time, notable weight loss may occur. Weight change should be monitored regularly during therapy. Clinically significant weight loss should be further evaluated. Talvey® should be interrupted or less frequent dosing should be considered.

❖ **Serious infections**

- Serious infections, including life-threatening or fatal infections, have been reported in patients receiving Talvey®. Patients should be monitored for signs and symptoms of infection prior to and during treatment with Talvey® and treated appropriately. Prophylactic antimicrobials should be administered according to local guidelines.
- Talvey® should not be administered in patients with active serious infection. Talvey® should be withheld as indicated. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur.

❖ **Hypogammaglobulinaemia**

- Hypogammaglobulinaemia has been reported in patients receiving Talvey®.
- Immunoglobulin levels should be monitored during treatment with Talvey®. Intravenous or subcutaneous immunoglobulin therapy was used to treat hypogammaglobulinaemia patients. Patients should be treated according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement.

❖ **Cytopenias**

- Treatment-emergent Grade 3 or 4 neutropenia, febrile neutropenia and thrombocytopenia have been observed in patients who received Talvey®.
- A majority of cytopenias occurred during the first 8 to 10 weeks. Complete blood counts should be monitored at baseline and periodically during treatment. Supportive care should be provided per local institutional guidelines.
- Patients with neutropenia should be monitored for signs of infection.
- Talvey® should be withheld as warranted.

❖ **Skin reactions**

- Talvey® can cause skin reactions including rash, maculo-papular rash, erythema, erythematous rash, as well as nail disorders. Skin reactions including rash progression should be monitored for early intervention and treatment with corticosteroids.

- For Grade 3 or higher, or worsening Grade 1 or 2 rashes, oral steroids should also be administered. For non-rash skin reactions dose modification may be considered.
- For skin reactions and nail disorders, Talvey® should be withheld based on severity and institutional guidelines should be followed.

❖ **Vaccines**
- Immune response to vaccines may be reduced when taking Talvey®. The safety of immunisation with live viral vaccines during or following Talvey® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 4 weeks prior to the start of treatment, during treatment, and at least 4 weeks after treatment. For unexpected exposure during pregnancy, see Product Information.

❖ **Women of child-bearing potential/contraception**
- Pregnancy status of females of child-bearing potential should be verified prior to initiating treatment with Talvey®. Females of reproductive potential should use effective contraception during treatment and for 3 months after the last dose of Talvey®.

❖ **Excipients**
- This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

Study characteristics [8-11]

Trial name	*n*	Intervention (I), n=102	Comparator (C), n=130	PE	Median follow-up (I vs. C)	Characteristics	Biomarker	Funding	Publication(s)
MonumentTAL-1 NCT03399799	232	talquetamab IV (0.5 - 3.38 µg/kg weekly or every other week or 5 - 180 µg/ kg weekly with or without step-up doses)	talquetamab subcutaneously (5 -405 µg/kg weekly, 800 µg/kg weekly or every other week, 1200 µg/kg every other week, or 1600 µg/kg monthly, with step-up doses)	frequency and type of dose-limiting toxic effects[3], AEs, and laboratory abnormalities	4.0 vs. 4.2 months	**ongoing**[4], open-label, multicentre, phase 1 study[5]	GPRC5D	Janssen Research and Development	MonumenTAL-1 trial [10]

Inclusion criteria[6]	Exclusion criteria	Patient characteristics at baseline (I vs. C)
❖ Patients ≥18 years of age with documented initial diagnosis of MM according to IMWG diagnostic criteria. ❖ Measurable MM that is relapsed or refractory to established therapies with known clinical benefit in relapsed/refractory MM or determined to be intolerant of those established MM therapies, and a candidate for JNJ-64407564 treatment, in the opinion of the treating physician. ❖ Prior lines of therapy must include a proteasome inhibitor and an	❖ Prior Grade 3 CRS related to any T cell redirection or any prior GPRC5D targeting therapy. ❖ Prior antitumor therapy[7]. ❖ Vaccinated with live, attenuated vaccine within 4 weeks or as recommended by the product manufacturer prior to the first dose, during treatment, or within 100 days of the last dose of JNJ-64407564. ❖ Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less except for alopecia or peripheral neuropathy. ❖ Received a cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14-day period before the first dose of study drug.	❖ Median age: 65 vs. 64 years ❖ Male sex: 56% vs. 58% ❖ Median time since diagnosis: 6.6 vs. 6.1 years ❖ ≥1 Extramedullary plasmacytoma: 15% vs. 32% ❖ ≥60% Plasma cells in bone marrow: 22% vs. 17% ❖ International Staging System class: • I: 33% vs. 35% • II: 43% vs. 45% • III: 24% vs. 19% ❖ High-risk cytogenetic abnormalities: 16% vs. 16% ❖ Median no. of lines of previous therapy: 6 vs. 6 ❖ Previous stem-cell transplantation: 85% vs. 85% ❖ Previous therapy exposure:

[3] Only in part 1, the dose-escalation phase.
[4] The MonumenTAL-1 trial is currently ongoing; estimated study completion date is 03/2025.
[5] Composed of a dose-escalation phase (part 1) and a dose-expansion phase (part 2).
[6] For detailed in- and exclusion criteria, please see study protocol.
[7] Targeted therapy, epigenetic therapy, or treatment with an investigational drug or an invasive investigational medical device within 21 days or at least 5 half-lives, whichever is less. Monoclonal antibody treatment for MM within 21 days. Cytotoxic therapy within 21 days. Proteasome inhibitor therapy within 14 days. Immunomodulatory agent therapy within 7 days. Radiotherapy within 21 days.

immunomodulatory drug in any order during the course of treatment. ❖ ECOG PS of 0 or 1. ❖ Clinical laboratory values at screening: please see study protocol. ❖ Women of childbearing potential must have a negative pregnancy test at screening. ❖ Women of childbearing potential and fertile men who are sexually active must agree to use a highly effective method of contraception during the study and for 100 days after the last dose of study drug.	❖ Previously received an ASCT; received an ASCT ≤12 weeks before the first dose of study drug. ❖ Documented history of CNS involvement or exhibits clinical signs of meningeal involvement of MM. ❖ Known to be seropositive for human immunodeficiency virus or acquired immune deficiency syndrome. ❖ Hepatitis B infection as defined according to the ASCO guidelines. ❖ Active Hepatitis C infection as measured by positive HCV-RNA testing. ❖ Pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation. ❖ Known allergies, hypersensitivity, or intolerance to JNJ-64407564 or its excipients. ❖ Any serious underlying medical condition[8]. ❖ Pregnant or breast-feeding women. ❖ Major surgery within 2 weeks of the first dose.	• Triple-class exposure: 99% vs. 99% • Penta-drug exposure: 77% vs. 77% ❖ Refractory status: • Immunomodulatory drug: 96% vs. 93% • Proteasome inhibitor: 90% vs. 82% • Anti-CD38 monoclonal antibody: 95% vs. 92% • Triple-class refractory: 85% vs. 75% • Penta-drug refractory: 35% vs. 25% • Refractory to last line of therapy: 89% vs. 85%

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Patients who received talquetamab at the 405-µg dose level:</u> Response: 70% (95% CI, 51-85) Good PR or better: 57% CR or better: 23% Median time to response: 0.9 months (range, 0.2-3.8) Median time to a CR or better: 9.3 months (range, 1.7-17.1) Median duration of response: 10.2 months (95% CI, 3.0-NR) Response in patients with triple-class–refractory disease: 65% Response in patients with a penta-drug–refractory disease: 83% **<u>Patients who received talquetamab at the 800-µg dose level:</u>** Response: 64% (95% CI, 48-78) Very good PR (VGPR) or better: 52% CR or better: 23% Median time to response: 1.2 months (range, 0.3-6.8) Median time to a CR or better: 2.3 months (range, 2.1-6.8) Median duration of response: 7.8 months (95% CI, 4.6-NR) Response in patients with triple-class–refractory disease: 70% Response in patients with a penta-drug–refractory disease: 78%	❖ **4 dose-limiting toxic effects** occurred during the <u>dose-escalation phase:</u> • A grade 4 increased lipase level in a patient with a pancreatic plasmacytoma who had received IV talquetamab at a dose of 7.5 µg/kg weekly; this elevated lipase level began to resolve when the patient discontinued treatment. • A grade 3 maculopapular rash in a patient who had received the 2nd subcutaneous dose of Talquetamab (135 µg/kg weekly); the rash began to resolve when the patient discontinued treatment. • A grade 3 maculopapular rash that occurred after a patient had received the first weekly subcutaneous dose at 800 µg/kg; this rash resolved after 28 days, and the patient resumed treatment with subcutaneous talquetamab at a dose of 405 µg/kg weekly (the 405-µg dose level) after skipping two doses. • A grade 3 rash that occurred after a patient had received the first subcutaneous dose of

[8] Such as evidence of serious active viral, bacterial, or uncontrolled systemic fungal infection; active autoimmune disease or a documented history of autoimmune disease; psychiatric conditions, dementia, or altered mental status; any other issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site.

Patients who received the most active subcutaneous doses (135, 405, and 800 µg/ kg weekly and 800 and 1200 µg/kg every other week):

Response: 68% (95% CI, 58-76)

Patients who received the most active intravenous doses (20 to 180 µg/ kg weekly):

Response: 72% (95% CI, 46-90)

Pharmacokinetics, immunogenicity, and pharmacodynamics:

- Concentration–time profiles showed a less fluctuating and more sustained pattern after subcutaneous administration than after IV administration, with a lower peak-to-trough ratio.
- Both doses that were recommended for a phase 2 study had similar pharmacokinetic profiles at steady state, with serum exposure maintained over the 90% maximal effective concentration in an ex vivo cytotoxicity assay, findings that provided support for both dose schedules.
- Talquetamab therapy increased T-cell activation and induced cytokines, with similar activation at both doses recommended for a phase 2 study.
- The baseline frequency and signal intensity of GPRC5Dpositive plasma cells were similar in patients who had a response and those who did not have a response.

GPRC5D Expression:

- GPRC5D RNA expression was highly variable in skin samples and very low in lung samples.
- GPRC5D RNA was detected in 80 of 498 skin samples (16%; >2 transcripts per million), and all 80 samples expressed at least 2 of 3 hair follicle–associated genes.
- These findings confirmed that cutaneous GPRC5D expression was limited to hair follicles.
- Examination of slides stained with hematoxylin and eosin and corresponding to the 5 highest and 5 lowest GPRC5D-expressing samples revealed the presence of hair follicles only in the samples with high expression. Although low levels of GPRC5D transcript in lung samples were detected by means of RNA sequencing, no GPRC5D expression in lung sections (including the airways, lymphoid tissues, alveoli, and pleura) was detected by means of immunohistochemical analysis and in situ hybridisation.
- GPRC5D transcript was detected by means of in situ hybridisation in select motor neurons in the inferior olivary nucleus, but not in the cerebellum. GPRC5D protein was not detected in either tissue.

UPDATE: Efficacy results in patients receiving Talvey ® 0.4 mg/kg weekly (n=143, median follow up 18.8 months)[7]:

- Overall response rate (ORR=sCR+CR+VGPR+PR): 74.1% (95% CI, 66.1-81.1)
- Stringent complete response (sCR): 23.8%
- CR: 9.8%
- VGPR: 25.9%
- PR: 14.7%
- Median DOR: 9.5 months (95% CI, 6.7-13.3)
- Median time to first response: 1.2 months
- MRD negativity ratea
- MRD negativity rate in all treated patients: 30.8% (95% CI, 23.3-39.0)

Talquetamab at a dose of 800 µg/kg every other week (the 800-µg dose level); the rash resolved after 14 days, and the patient resumed treatment at the full dose after skipping one dose.

- After these events, the dose-limiting toxicity criteria were modified to exclude the first occurrence of a glucocorticoid-responsive grade 3 rash that began to resolve within 7 days after treatment.
- The maximum tolerated dose was not reached.
- The 405-µg dose level (with step-up doses of 10 and 60 µg/kg) and the 800-µg dose level (with step-up doses of 10, 60, and 300 µg/kg) were chosen for confirmation in part 2 of this study on the basis of collective safety, efficacy, pharmacokinetic, and pharmacodynamic data.
- **Patients who received subcutaneous talquetamab at the 405-µg dose level:**
  - Serious AEs: 43%
  - Grade 3 or 4 AEs: 87%
  - Recurrent CRS: 30%
  - Infections: 47%
  - Grade 3 or 4 infections: 7%
  - Treatment-related neurotoxic events: 10%
  - Nail-related AEs: 57%
  - Skin-related AEs: 67%
- **Patients who received subcutaneous talquetamab at the 800-µg dose level:**
  - Fatal AEs: n=3[9]
  - Serious AEs: 34%
  - Grade 3 or 4: 86%
  - Recurrent CRS: 27%
  - Infections: 34%
  - Grade 3 or 4 infections: 7%
  - Treatment-related neurotoxic events: 5%
  - Nail-related AEs: 27%
  - Skin-related AEs: 70%
- **Patients who received IV talquetamab:**
  - Serious AEs: 34%
  - Grade 3 or 4: 90.2%

[9] Neuroendocrine carcinoma, sepsis, and basilar artery occlusion (n=1 each); none of the deaths were considered by the investigators to be related to talquetamab.

- MRD negativity rate in patients achieving CR or sCR
- Number of patients with CR or better: 54.2% (95% CI, 39.2-68.6)

UPDATE: Efficacy results in patients receiving Talvey ® 0.8 mg/kg every 2 weeks (n=145, median follow-up 12.7 months)[7]:

- Overall response rate (ORR=sCR+CR+VGPR+PR): 71.7% (95% CI, 63.7-78.9)
- sCR: 29.7%
- CR: 9.0%
- VGPR: 22.1%
- Partial response (PR) 11.0%
- Median DOR: NE (95% CI, 13.0-NE)
- Median time to first response: 1.3 months
- MRD negativity rate in all treated patients: 29.7% (95% CI, 22.4-37.8)
- MRD negativity rate in patients achieving CR or sCR: 42.9% (95% CI, 29.7-56.8)

Patient-reported outcomes

The evaluation of patient-reported outcomes is not provided by the MonumenTAL-1 trial.

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM

The ESMO-MCBS for haematological malignancies was not applicable because the primary endpoint "frequency and type of dose-limiting toxic effects, AEs, and laboratory abnormalities" could not be assessed.

Risk of bias - study level (case series) [13]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial[10]	yes	yes	yes	no[11]
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	no	yes	yes	unclear[12]	yes
Overall risk of bias: moderate								

[10] Heterogenous baseline characteristics.
[11] Open-label study.
[12] The trial is currently ongoing; final analysis data is not yet available.

Ongoing trials [14]		
NCT number/trial name	Description	Estimated study completion date
NCT03399799/ MonumentTAL	Please see above.	03/2025
NCT05455320/ MonumenTAL-3	A phase 3 study comparing talquetamab in combination with daratumumab or in combination with daratumumab and pomalidomide vs. daratumumab in combination with pomalidomide and dexamethasone in participants with MM that returns after treatment or is resistant to treatment.	05/2029

Available assessments

- A Health Technology Briefing „Talquetamab for previously treated relapsed or refractory multiple myeloma“ was published by NIHR in January 2022 [15].
- No further assessments were identified via NICE, CADTH, G-BA and ICER.

Other aspects and conclusions

- In July 2023, the CHMP adopted a **positive opinion**, recommending the granting of a conditional marketing authorisation for Talvey®, indicated as monotherapy for the treatment of adult patients with relapsed and refractory MM, 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. This indication is **currently not approved by the FDA**; however, in December 2022, a **biologics license application has been submitted** to the FDA for talquetamab for the treatment of patients with relapsed or refractory MM.
- **MonumenTAL-1 (NCT03399799)** is an **ongoing, phase 1, open-label**, multicentre study of talquetamab; consisting of a dose-escalation phase (part 1) and a dose-expansion phase (part 2). Eligible patients were ≥18 years of age, had measurable myeloma according to the IMWG criteria, were not able to receive established therapies without unacceptable side effects or had disease that had progressed with established therapies. Patients were excluded if they had prior grade 3 CRS related to any T cell redirection or any prior GPRC5D targeting therapy, prior antitumor therapy, received a cumulative dose of corticosteroids equivalent to ≥140 mg of prednisone within the 14-day period before the first dose of study drug or previously received an ASCT.
- The **primary endpoints** were the frequency and type of dose-limiting toxic effects (study part 1 only), AEs and laboratory abnormalities. At the 2 subcutaneous doses recommended for a phase 2 study (405 µg/kg weekly and 800 µg/kg every other week), common AEs were CRS (in 77% and 80% of the patients, respectively), skin-related events (in 67% and 70%), and dysgeusia (in 63% and 57%). One dose-limiting toxic effect of grade 3 rash was reported in a patient who had received talquetamab at the 800-µg dose level.
- The evaluation of **patient-reported outcomes is not provided** by the MonumenTAL-1 trial.
- The **ESMO-MCBS for haematological malignancies was not applicable** because the primary endpoint “frequency and type of dose-limiting toxic effects, AEs, and laboratory abnormalities” could not be assessed.
- The **risk of bias** of MonumenTAL-1 trial was considered **moderate**; it is increased by the open-label design of the study, heterogenous baseline characteristics and the ongoing status of the trial.
- Beside the phase 1 MonumenTAL-1 trial, **one phase 3** trial, assessing the efficacy and safety of talquetamab in combination with daratumumab or in combination with daratumumab and pomalidomide vs. daratumumab in combination with pomalidomide and dexamethasone in participants with MM that returns after treatment or is resistant to treatment, was identified.
- For the assessed indication, the **availability of safety and efficacy data is poor**. Robust phase 3 data, including the evaluation of patient-reported outcomes, is **urgently required**.

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Abbreviations: AE=adverse event, AJ=adjustment, ASCO=American Society of Clinical Oncology, ASCO=American Society for Clinical Oncology, ASCT=autologous stem cell transplants, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CR=complete response, CRS=cytokine release syndrome, DCEP=Dexamethasone, DOR=duration of response, DT-PACE=dexamethasone, thalidomide cisplatin, doxorubicin, cyclophosphamide, etoposide, cyclophosphamide, etoposide, cisplatin, ECOG=Eastern Cooperative Oncology Group, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GPRC5D=G protein–coupled receptor, family C, group 5, member D, HCV=hepatitis C virus, HR=hazard ratio, I=intervention, ICANS=immune effector cell-associated neurotoxicity syndrome, IMWG=International Myeloma Working Group, Int.=intention, IV=intravenous, MG=median gain, MM=multiple myeloma, MRD=minimal residual disease, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, RNA=ribonucleic acid, SAE=serious adverse event, sCR=stringent complete response, ST=standard treatment, VGPR=very good partial response

References:

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