NCPE Assessment

Technical Summary

Talquetamab (Talvey®)

HTA ID 23057

26 May 2025

Applicant: Johnson and Johnson Innovative Medicine

Talquetamab, as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-cluster of differentiation 38 (CD38) antibody and have demonstrated disease progression on the last therapy

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of talquetamab (Talvey®) for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression.

Following assessment of the Applicant's submission, the NCPE recommends that talquetamab (Talvey®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. *

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Johnson and Johnson Innovative Medicine) Health Technology Assessment of talquetamab (Talvey®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health-related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In May 2024, Johnson and Johnson Innovative Medicine submitted a dossier which investigated comparative clinical effectiveness, cost-effectiveness and budget impact of talquetamab (Talvey®) for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM), who have received at least three prior therapies including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-cluster of differentiation 38 (CD38) antibody and have demonstrated disease progression on the last therapy. Johnson and Johnson Innovative Medicine is seeking reimbursement on the Oncology Drug Management Scheme (ODMS).

Talquetamab is a first-in-class bispecific antibody directed against GPRC5D, expressed mainly on plasma cells, and the CD3 receptor on T-cells. Talquetamab is available as 3mg and 40mg vials for subcutaneous injection. Talquetamab should be administered subcutaneously on a once weekly or once every 2 weeks dosing schedule. The licensed dose of talquetamab following the initial step-up phase is 0.4mg/kg once weekly or 0.8mg/kg once every two weeks. The 0.8mg/kg once every two weeks dosing frequency is expected to be the regimen most commonly used in clinical practice.

Clinical Opinion to the Review Group indicated that talquetamab will be mainly used in the fourth-line setting for RRMM, which is when the majority of patients are expected to have received prior treatment with an IMiD, a PI, and an anti-CD38 antibody. There is no universal standard of care (SOC) for patients with RRMM in Ireland who have received a PI, an IMiD and an anti-CD38 antibody and experience disease progression. The Applicant identified six regimens as the most commonly utilised in this treatment setting (herein 'real-world physician's choice (RWPC)'). These regimens were included as a basket comparator which comprised carfilzomib and dexamethasone (car+dex), ixazomib and lenalidomide and dexamethasone (ixa+len+dex), daratumumab and bortezomib and dexamethasone (dar+bor+dex), carfilzomib and lenalidomide and dexamethasone (car+len+dex), pomalidomide and dexamethasone (pom+dex) and pomalidomide and bortezomib and dexamethasone (pom+bor+dex). The basket of treatments was weighted according to estimated clinical utilisation in Ireland, supported by Clinical Opinion to the Applicant and

the Review Group.

The Review Group noted the treatment landscape for RRMM is rapidly evolving. Over the course of this assessment teclistamab (also marketed by Johnson and Johnson Innovative Medicine) was approved for reimbursement and is therefore a relevant comparator. This comparison is not presented here.

1. Comparative effectiveness of talquetamab

The efficacy and safety of talquetamab was investigated in the Phase I-II MonumenTAL-1 trial. MonumenTAL-1 was a single-arm, open-label, multicentre study. MonumenTAL-1 was conducted in three parts: Phase I Part 1 (dose escalation), Phase I Part 2 (dose expansion) and Phase II. Data from Phase I (dose expansion) and Phase II informed the efficacy of talquetamab. In Phase II, participants were included in one of three cohorts (A, B or C). Participants in each of these cohorts previously received at least three prior therapies that included at least one IMiD, one PI, and an anti-CD38 antibody. Participants in Cohort A and Cohort B received a dose of 0.4mg/kg administered once weekly (Q1W). Participants in Cohort C received a dose of 0.8mg/kg once every two weeks (Q2W). Cohort A and C included participants who had no prior exposure to T-cell redirection therapies (i.e., CAR T-cell therapy or bispecific T-cell engagers, such as teclistamab). These cohorts were the focus of the Applicant's submission to the European Medicines Agency (EMA) and NCPE. Cohort B (n=51) included participants who had prior exposure to T-cell redirection therapies. Data from Cohort B were considered exploratory by the EMA. As teclistamab was approved for reimbursement in March 2025, there is potential for patients in Irish clinical practice to receive treatment with a bispecific antibody prior to treatment with talquetamab. As such, the Review Group considered Cohort B of MonumenTAL-1 to be of relevance to the decision problem. Data from Cohort B were provided to the Review Group (not presented here). However, these were not included in the indirect treatment comparison (ITC) or cost-effectiveness model. Thus, the relative effectiveness of talquetamab in this potentially relevant sub-population has not been investigated.

The primary endpoint of Phase II was overall response rate (ORR). Progression-free survival

(PFS) and overall survival (OS) were secondary endpoints. A total of 143 participants received talquetamab at a dose of 0.4mg/kg Q1W (21 participants in Phase I and 122 in Phase II Cohort A; herein '0.4mg/kg Q1W cohort'). A total of 145 participants received talquetamab at a dose of 0.8mg/kg Q2W (36 participants in Phase I and 109 in Phase II Cohort C; herein '0.8mg/kg Q2W cohort'). All participants in Phase II received at least three prior lines of therapy. Results for the 0.4mg/kg Q1W and 0.8mg/kg Q2W cohorts are presented in Table 1.

Table 1 Monumental Clinical Outcomes: 0.4 mg/kg Q1W cohort and 0.8 mg/kg Q2W cohort

Date of interim analysis: January 2023[a]
Expected date of final analysis: 13 April 2026[b]

Outcome	Talquetamab 0.4mg/kg Q1W (n=143)[c]	Talquetamab 0.8mg/kg Q2W (n=145)[d]
Overall response rate (95% CI)	74.1 (66.1, 81.1)	71.7 (63.7, 78.9)
Progression-free survival, median months (95% CI)	7.5 (5.7, 9.4)	14.2 (9.6, NE)
12-month progression-free survival, % (95% CI)	34.9 (27.0, 42.9)	54.4 (45.3, 62.6)
Overall survival, median months (95% CI)	NE (25.6, NE)	NE (20.1, NE)
12-month overall survival, % (95% CI)	76.4 (68.3, 82.7)	77.4 (69.1, 83.7)

CI: confidence interval; **NE:** not estimable; **Q1W:** once every week; **Q2W: once** every two weeks.
[a] Results based on the January 2023 data cut, which represented a median (range) duration of follow up of 18.8 months (range: 0.5, 32.9) for the 0.4mg/kg Q1W cohort and 12.7 months (range: 0.2, 26.1) for the 0.8mg/kg Q2W cohort. Data include Phase I and II.
[b] Expected date of study completion.
[c] Includes 21 participants from Phase I and 122 from Phase II Cohort A.
[d] Includes 36 participants from Phase I and 109 from Phase II Cohort C.

Given the single-arm nature of MonumenTAL-1, causal treatment effects of talquetamab cannot be isolated for time-to-event endpoints such as OS and PFS, nor for health-related quality of life. The Applicant did not provide evidence to support the use of ORR as a surrogate for OS and PFS. Thus, it cannot be concluded that the treatment effect observed with ORR will translate to OS or PFS benefit. This is a major limitation of the clinical evidence.

Indirect Treatment Comparison

Direct comparative trials of talquetamab versus the comparators of relevance to decision making were not conducted by the Applicant. Unanchored ITCs were therefore used to estimate the relative effectiveness of talquetamab versus RWPC and teclistamab. Data from the MonunenTAL-1 study were used to inform efficacy of talquetamab. ITCs were conducted for the 0.4mg/kg Q1W and 0.8mg/kg Q2W cohorts. Given that the 0.8mg/kg Q2W dosing regimen is expected to be most commonly used in Irish clinical practice, data from this

cohort of MonumenTAL-1 were the primary focus of the NCPE assessment. The Review Group agreed with this reasoning, but noted that observed OS and PFS were longer in this cohort compared with the 0.4mg/kg Q1W cohort. The precise reasoning for this is unclear. Therefore, the possibility of a chance overestimation of the treatment effect of talquetamab in this analysis cannot be ruled out. The Applicant conducted an ITC versus RWPC using individual patient-level data (IPD) comprising patients from the prospective, non-interventional LocoMMotion (NCT04035226) and MoMMent (NCT05160584) studies. These studies were pooled. As a scenario, an ITC comparing talquetamab to teclistamab using IPD from the MajesTEC-1 trial (NCT04557098) was conducted. Propensity score methods, using an inverse probability of treatment weighting approach, were used to adjust for differences between patient populations in terms of a number of important prognostic variables. Results of the ITC versus RWPC indicated that talquetamab (0.8mg/kg Q2W cohort) was associated with an improvement in PFS and OS versus RWPC.

A key limitation of the comparative effectiveness analysis was the absence of randomised comparative data and the corresponding use of unanchored ITCs, which are associated with a substantially higher risk of bias and corresponding lower certainty of evidence than randomised controlled trials. The Review Group concluded that while the Applicant's ITC methodology was appropriate and adjusted for a large number of relevant confounders, there was nonetheless a risk of bias from residual confounding (i.e., residual imbalances in prognostic factors between treatment groups after adjustment) and other factors.

2. Safety of talquetamab

The safety data were presented for the 0.4mg/kg Q1W and 0.8mg/kg Q2W cohorts from MonumenTAL-1. A similar safety profile was observed in patients receiving both dosing schedules of talquetamab in MonumenTAL-1, with all patients reporting at least one treatment-emergent adverse event (TEAE) considered to be related to talquetamab. Of note, no relative safety data were provided, which limited a comprehensive assessment of safety.

The most frequently reported TEAEs included cytokine release syndrome (CRS), dysgeusia, weight decreased, skin exfoliation, dry mouth, dry skin, neutropenia, anaemia, lymphopenia, dysphagia and nail disorder. The SmPC carries special warnings for CRS and neurotoxicity.

The SmPC recommends that treatment should be initiated with talquetamab according to the step-up dosing schedule to reduce risk of CRS, and pre-treatment medicinal products should be administered prior to each step-up dose. Patients should remain within the proximity of a healthcare facility and be monitored daily for 48 hours during step-up dosing for signs of CRS and immune effector cell-associated neurotoxicity syndrome (ICANs).

3. Cost effectiveness of talquetamab

Methods

A three-state partitioned survival model was submitted by the Applicant. This included three mutually-exclusive health states; progression-free, progressed disease and death. The treatment effects captured by the model were the delay of disease progression and death. The proportion of patients in each health state over time were derived directly from the OS and PFS area under the curve using treatment group-specific parametric distributions fitted to time-to-event data from MonumenTAL-1 (0.8mg/kg Q2W cohort) and LocoMMotion/MoMMent. In the Applicant base case, using IPD, patients from LocoMMotion/MoMMent were reweighted to match the characteristics of the MonumenTAL-1 trial. In each cycle, patients accrued quality-adjusted life years (QALYs) and costs based on the utilities and costs specified for the health-state occupied, the relevant treatment arm, and the time on treatment.

Utility data for the progression-free disease and progressed disease health states were derived from EQ-5D-5L data collected in MonumenTAL-1 (mapped to EQ-5D-3L using the algorithm by Van Hout et al.) in the Applicant base case. The Applicant applied a time-dependent utility approach in the model for the progression-free health state in the base case. A health-state specific (time-independent) utility value was employed for the progressed disease health state. The Review Group noted that time-dependent utilities became highly uncertain at the end of the follow-up period. Due to this uncertainty, the NCPE-adjusted base case used time-independent health-state specific utility values for both health states. Adverse event disutilities were applied separately in the model. Utilities were age-adjusted according to the UK general population utilities.

The model included drug acquisition, administration, monitoring, subsequent treatment and adverse event costs. These were generally considered appropriate by the Review Group.

The Review Group noted a number of limitations to the Applicant's base case, which were addressed, via changes, to develop the NCPE-adjusted base case. These included using an alternative inverse probability of treatment weighting approach for the ITC with RWPC, using a mean health-state utility value in the progression-free health state and using the lognormal distribution instead of Weibull for time-to-treatment discontinuation of talquetamab.

Results

The results of the Applicant's and NCPE-adjusted base case deterministic cost-effectiveness analysis are presented in Tables 2 and 3, respectively. Note, these are based on the 0.8mg/kg Q2W cohort of MonumenTAL-1. The probabilities of cost-effectiveness, for talquetamab versus RWPC, in the Applicant and NCPE-adjusted base cases was 0% at thresholds of €20,000 per QALY and €45,000 per QALY.

Table 2 Applicant base case incremental cost-effectiveness results [a, b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Talquetamab[c]	300,989	2.86			
RWPC	86,002	1.14	214,986	1.72	124,945

ICER: incremental cost-effectiveness ratio; **QALY:** quality adjusted life year; **RWPC**: Real World Physicians' Choice
[a] Corresponding probabilistic ICER of talquetamab versus RWPC using 1,000 iterations = €123,888/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Costs and outcomes discounted at 4%.
[b] A commercial in confidence PAS is in place for a number of treatments included in the RWPC basket of regimens; not included in this table.
[c] Informed by the 0.8mg/kg Q2W cohort of the September 2024 data cut of MonumenTAL-1.

Table 3 NCPE base case incremental cost-effectiveness results [a, b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Comparison versus RWPC					
Talquetamab[c]	333,999	2.92			
RWPC	92,817	1.32	241,182	1.60	151,066

ICER: incremental cost-effectiveness ratio; **QALY**: quality adjusted life year; **RWPC**: Real World Physicians' Choice
[a] Corresponding probabilistic ICER using 1,000 iterations was €149,655/QALY for talquetamab versus RWPC. Figures in the table are rounded, and so calculations may not be directly replicable. Costs and outcomes discounted at 4%.
[b] A commercial in confidence PAS is in place for a number of treatments included in the RWPC basket of regimens; not included in this table.
[c] Informed by the 0.8mg/kg Q2W cohort of the September 2024 data cut of MonumenTAL-1.

Sensitivity analysis

Deterministic one-way sensitivity analysis indicated that the most influential parameters in the model for both the Applicant and the NCPE-base case related to progressed disease

utility, mean body weight, and drug wastage.

A Price-ICER analysis, conducted using the NCPE-adjusted base case, indicated that for the comparison versus RWPC, a 78% and 65% reduction in the price-to-wholesaler of talquetamab was required to meet the €20,000 per QALY and €45,000 per QALY thresholds, respectively. Commercial-in-confidence patient access scheme discounts are in place for comparator regimens. When these were accounted for, a higher price reduction on talquetamab was required to reach these thresholds.

4. Budget impact of talquetamab

The price-to-wholesaler, to the HSE, per 3mg vial of talquetamab is €381.00. The price-to-wholesaler per 40mg vial is €5,076.00. Using NCPE preferred assumptions, the estimated total cost, per patient, per treatment course of talquetamab is €252,073.87 (including VAT).

The Review Group considered the estimation of eligible patients with RRMM reaching fourth-line treatment to be highly uncertain. RWPC was the only comparator considered in the Applicant base case budget impact model. The Applicant assumed the market share projections for talquetamab would be highest in the first year (32%) and decrease by 5% in each subsequent year. The Applicant stated this was because new BCMA-targeted therapies may become available over that same time period. However, as the timeline of reimbursement of these therapies is highly uncertain, the Review Group did not consider this appropriate. The Review Group therefore adjusted market share projections to increase by 5% each year after year one. The total number of patients treated with talquetamab based on these assumptions was 241. The cumulative five-year gross-drug budget impact, based on the NCPE preferred assumptions, was estimated to be €60.5 million (including VAT). The cumulative five-year net-drug budget impact, based on the NCPE preferred assumptions, was estimated to be €43.1 million (including VAT). Based on the Applicant preferred assumptions (133 patients treated over five years), the estimated five-year cumulative gross drug-budget impact of talquetamab was €24.8 million including VAT. The estimated five-year cumulative net drug-budget impact was €19.8 million including VAT.

5. Patient Organisation Submission

A patient organisation submission was received from Multiple Myeloma Ireland.

6. Conclusion

The NCPE recommends that talquetamab not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.