Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Talquetamab (Talvey)

Indication: For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on or after the last therapy

Sponsor: Janssen Inc.

Recommendation: Do Not Reimburse

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Recommendation

The pCODR Expert Review Committee (pERC) recommends that talquetamab not be reimbursed for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least three prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 monoclonal antibody (mAb), and have demonstrated disease progression on or after the last therapy.

Rationale for the Recommendation

One ongoing, phase 1/2, single-arm, open-label study (MonumenTAL-1) demonstrated that treatment with talquetamab may result in a benefit in response rates for adults with RRMM who have received at least 3 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. The overall response rate (ORR) was 74% (95% CI: 66% to 81%) and 72% (95% CI: 64%, 79%) in patients with no prior T-cell redirection therapy who received subcutaneous talquetamab 0.4 mg/kg weekly (Model Cohort A, N = 143) and 0.8 mg/kg once every 2 weeks (Model Cohort C; N = 145), respectively. In patients treated with either dose of talquetamab who had prior T-cell redirection therapy (Model Cohort B; N = 51), the ORR was 64.7% (95% CI: 50.1%, 77.6%). However, pERC was unable to draw causal conclusions about the effect of talquetamab on progression-free survival (PFS) and overall survival (OS), which are important outcomes to patients and clinicians, due to the single-arm design.

Three non-randomized comparative studies assessed the efficacy of talquetamab in patients with no prior T-cell redirection therapy (Model Cohorts A and C in the MonumenTAL-1 trial) against real-world physician's choice (RWPC) of various treatments, teclistamab, and ciltacabtagene autoleucel (cilta-cel). The comparative evidence suggested a benefit of talquetamab compared to RWPC. Results for talquetamab versus teclistamab were inconsistent across the outcomes assessed, which caused uncertainty about which drug might be favoured overall. Lastly, the evidence suggested that the 0.4 mg/kg weekly dose of talquetamab may be inferior to cilta-cel for some outcomes, and differences were uncertain when 0.8 mg/kg talquetamab given biweekly was compared to cilta-cel. All the non-randomized comparisons were impacted by methodological limitations, which limited pERC's certainty in these results.

Patients identified a need for effective, accessible and portable (i.e., fewer or minimal visits to the hospital or cancer center) treatment options beyond the third-line setting, that delay disease progression, prolong survival, improve quality of life, and have manageable side effects. Given the totality of the evidence, pERC could not conclude that talquetamab would meet these needs. Methodological limitations precluded pERC from drawing definitive conclusions about talquetamab's effects on PFS, OS, and health-related quality of life (HRQoL). In addition, pERC determined that talquetamab's adverse effect profile may not align with patient values regarding side effects. pERC noted that dysgeusia is an unfavorable side effect from the patient perspective and dysgeusia was one of the most frequently reported treatment-emergent adverse events in the MonumenTAL-1 clinical trial. Other frequently report side effects may also be unfavourable to patients, since the patient group input reported nail related issues, skin related issues and infections as least bearable along with oral-related issues.

Discussion Points

- **Unmet needs in RRMM:** pERC acknowledged that there is an unmet need for effective treatments for patients with RRMM in the fourth line and later setting. The available efficacy and safety evidence for talquetamab was from a noncomparative phase 1/2 trial and nonrandomized comparisons that are associated with uncertainty. Based on the totality of the evidence, pERC could not definitively conclude that talquetamab has the potential to reduce morbidity and mortality associated with RRMM in patients in the fourth line and later setting. pERC also carefully considered the unmet needs of patients with RRMM who have previously received BCMA-directed therapy, as these patients may have limited treatment options in subsequent lines of therapy. pERC discussed the data from Cohort B in the MonumenTAL-1 trial, which enrolled patients who had prior T-cell redirection therapy, including BCMA-directed bispecific T-cell engagers (BiTEs) and CAR T-cell therapy. pERC noted that Cohort B had a small sample size (N = 51) and, overall, the outcomes observed in the MonumenTAL-1 trial were not as favourable in Cohort B as those observed in Cohorts A and C. Furthermore, Cohort B was not included in the non-randomized comparisons, therefore there remains an evidence gap comparing talquetamab to other treatments in those who have received prior T-cell redirection therapy. As such, pERC could not conclude that talquetamab confers a clinically meaningful benefit in patients previously treated with T-cell redirection therapy, including BCMA-targeted therapy (e.g., CAR T-cell therapy or a BiTE). Lastly, pERC noted that there was limited data on the use of BCMA-targeted therapies as a later line of therapy after talquetamab, so it is unclear whether talquetamab would be beneficial to those patients.
- **Side effects:** pERC acknowledged that patients need treatments that have fewer side effects. Harms were not assessed in the non-randomized studies, so pERC could not draw conclusions regarding the comparative safety of talquetamab versus other treatments. pERC noted that the most frequently reported treatment-emergent adverse events (TEAEs) in the MonumenTAL-1 trial were cytokine release syndrome (CRS), dysgeusia, anemia, weight decrease, pyrexia, and neutropenia. pERC noted that some of these side effects may not be bearable to patients, such as dysgeusia. Furthermore, some of the serious toxicities associated with talquetamab like CRS and neurologic toxicity (including immune effector cell-associated neurotoxicity syndrome [ICANS]) could affect the frequency of patient visits to the hospital or cancer center, so it is unclear if talquetamab would meet their need for accessible and portable treatment options. Overall, pERC could not conclude that talquetamab would meet patients' need for treatments with fewer side effects.
- **HRQoL:** pERC noted that patients and clinicians highlighted improvement in HRQoL as an important outcome and treatment goal for patients with RRMM. The results for HRQoL from the MonumenTAL-1 trial were inconclusive due to the open-label design and missing outcome data. These limitations also precluded pERC from examining how the TEAEs may have impacted patients' HRQoL. HRQoL also was not assessed in the nonrandomized comparative studies, so there was no evidence on how HRQoL with talquetamab compares to other treatments for RRMM. As a result, pERC could not conclude that talquetamab would meet this important need.

Background

Multiple Myeloma (MM) is a plasma cell cancer characterized by clonal proliferation of malignant plasma cells (B-cells) and overproduction of the abnormal immunoglobulin monoclonal protein (M-protein). In Canada, an estimated 3,900 individuals were diagnosed with MM and approximately 1,700 deaths due to MM occurred in 2023. The 5-year survival for patients with MM is estimated to be approximately 50%, and although survival rates have improved in recent years due to advances in therapeutic options, MM remains incurable. The majority of patients with MM will relapse and many patients will become refractory to commonly used therapies. Patients with RRMM often undergo multiple rounds of treatment, with the duration of remission, depth of response, progression-free survival, and overall survival decreasing with each subsequent line of therapy. The clinical expert and clinician groups consulted for this review pointed out that the key treatment goals for patients with RRMM are to delay progression, control the disease and associated symptoms, and prolong survival. According to the Provisional Funding Algorithm for Multiple Myeloma developed by CADTH, patients with drug resistance cannot be treated again with the same drug, except for dexamethasone, which is found in all regimens. There is no preferred therapy for RRMM in the fourth line and beyond settings, and at this stage of the disease patients may be treated with PIs, IMiD, and anti-CD38 and in some cases receive more than 1 PI or IMiD, further limiting treatment options in later-lines of therapy.

Talquetamab has been approved by Health Canada for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior lines of therapy, including a PI, an IMiD and an anti-CD38 mAB, and have demonstrated disease progression on or after the last therapy. Talquetamab is a bispecific antibody that targets GPRC5D on MM cells and CD3 receptors on T-cells. Talquetamab is administered as a weekly or biweekly subcutaneous injection. The recommended dosage for talquetamab is 0.4 mg/kg of body weight once weekly after receiving step-up doses of 0.01 mg/kg and 0.06 mg/kg of body weight, or 0.8 mg/kg of body weight every two weeks after receiving step-up doses of 0.01 mg/kg, 0.06 mg/kg, and 0.4 mg/kg of body weight.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase 1/2 study in adult patients with RRMM who had received at least 3 prior lines of therapy, and 3 studies addressing gaps in the systematic review evidence
- patients' perspectives gathered by 1 patient group, Myeloma Canada
- input from public drug plans that participate in the CDA-AMC review process
- 1 clinical specialist with expertise diagnosing and treating patients with MM
- input from 2 clinician groups, the Canadian Myeloma Research Group (CMRG) and Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (OH-CCO's Drug Advisory Committees)
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to the review team's call for input and from clinical expert consulted for the purpose of this review.

Patient Input

The review team received one patient group submission from Myeloma Canada. The group conducted both patient and caregiver surveys from April 17 to May 10, 2024, across Canada and internationally via email and social media. A total of 86 responses to the patient survey were received, of whom 38 complete responses (32 patients and 6 caregivers, all from Canada except one patient) were recorded based on their eligibility criteria. Among these 38 respondents, 32 were eligible for the treatment under review and 6 had experience with it. Regarding receiving prior lines of therapy, 19 among those 32 eligible respondents indicated 3 lines of therapy, 9 respondents indicated 4 lines, and 4 respondents indicated 5 lines of therapy or more. In addition, 97% respondents indicated that they had received an autologous stem-cell transplant (ASCT) to treat their myeloma.

Respondents to the survey indicated that infections were the most important aspect related to myeloma to control, followed by fatigue, kidney problems, and pain. Respondents noted that among elements of their daily activities and quality of life, their ability to travel was the most significantly impacted by symptoms associated with myeloma, followed by ability to exercise and to conduct volunteer activities. Respondents felt that interruption of life goals or accomplishments had the greatest impact on their quality of life, followed by loss of sexual desire and anxiety or worry. Patient and caregiver respondents identified the following factors as the most important to myeloma treatment: quality of life, manageable side effects, effectiveness of treatment (especially in achieving remission and having a durable response), and treatment accessibility or portability (including fewer or minimal visits to the hospital or cancer centre).

In terms of treatment outcomes, 21 of the 31 eligible respondents rated improved quality of life as extremely important, 9 as very important, and 1 as somewhat important. In addition, 21 of the 32 eligible respondents indicated that an estimated minimum 1 year of extended life at this stage in their myeloma journey was extremely desirable, and 9 indicated very desirable. When asked about their tolerance of the most common side effects in patients who receive talquetamab, respondents perceived ICANS, cytokine release syndrome (CRS), and infections to be the least tolerable side effects, followed by diarrhea and neutropenia. A total of 6 respondents (5 patients and one caregiver) indicated having experience with talquetamab. Regarding the most frequently experienced talquetamab side effects, 6 respondents rated oral-related and nail related issues as the least bearable side effect, followed by skin-related issues and infections. Most of these patients noted that the overall side effects while receiving talquetamab were manageable.

Clinician Input

Input From Clinical Expert Consulted for This Review

The clinical expert consulted for this review noted that fourth line treatment for MM is challenging because there are limited available therapies. Moreover, tolerability of treatment is important as patients with RRMM are usually frail. The clinical expert noted that talquetamab could be appropriate to be used as a fourth or later line treatment, being a potential treatment in patients who have received prior BCMA-directed therapy (e.g., belantamab, cilta-cel, teclistamab, or elranatamab), or for patients naïve to prior BCMA-targeted therapy. The clinical expert indicated that patients treated with talquetamab would be also eligible for subsequent BCMA-targeted therapy. The clinical expert noted that the patients best suited for talquetamab would be those who need the fourth or later line treatment and have an adequate performance status and reasonable hematologic function. The clinical expert indicated that there is no biomarker to predict treatment response and no companion test is necessary; however, the treatment centre must have an appropriate setup for monitoring and treatment of CRS, and should have access to infectious diseases consultative services. The clinical expert indicated that treatment response is typically measured biochemically every 4 weeks. The clinical expert noted that the treatment discontinuation factors include disease progression according to the IMWG response criteria,[9] and intolerable adverse events (e.g., severe dysgeusia, and severe myelosuppression). The clinical expert noted that treatment with talquetamab should be initiated and supervised by a specialist (hematologists or medical oncologist with appropriate training). The clinical expert indicated that the first few doses of talquetamab treatment should be administered at a site with knowledge and expertise in managing CRS, and the subsequent doses could be administered in a community setting.

Clinician Group Input

Clinician group input on the review of talquetamab was received from two clinician groups - the Canadian Myeloma Research Group (CMRG) and Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (OH-CCO's Drug Advisory Committees). A total of 32 clinicians (25 from CMRG and 7 from OH-CCO's Drug Advisory Committees) provided input for this submission.

Both CMRG and OH-CCO's Drug Advisory Committees emphasized that the overall treatment goals are to delay progression, improve overall survival, control the disease and associated symptoms, minimize adverse effects, and improve quality of life. While discussing about the unmet needs of patients, CMRG highlighted that myeloma remains incurable and patients eventually become refractory to all available funded agents. CMRG emphasized that the highest unmet need consists of patients with advanced disease who have received multiple lines of treatment and have already received the three major classes of drugs ("triple-class exposed or refractory") including an IMID, PI and anti-CD38 monoclonal antibody. Another unmet need noted by OH-CCO's Drug Advisory

Committees is to achieve ease of administration (i.e., subcutaneous injection and no need for apheresis) and a different target than other bispecific antibodies with talquetamab.

Similar to the clinical expert consulted for this review, both clinician groups agreed that talquetamab could be another option for triple-class exposed patients. CMRG indicated that patients with a good performance status, minimal or no comorbidities, relatively low tumor burden, adequate organ function, and satisfactory blood counts are the most likely to have the best outcomes with talquetamab. CMRG noted that overall, patients with poor disease-related prognostic factors, such as extramedullary myeloma and high-risk cytogenetics, should be eligible for talquetamab.

CMRG added that clinically meaningful responses usually correlate with at least a partial remission by IMWG Consensus Criteria. Both CMRG and OH-CCO's Drug Advisory Committees agreed upon that treatment discontinuation should be based on ongoing efficacy or response, disease progression, and long-term tolerability or significant toxicities. Given that prior anti-BCMA exposure does not preclude responsiveness to talquetamab, CMRG would suggest that patients with prior anti-BCMA therapy or bispecific antibody treatment be allowed access to talquetamab. OH-CCO's Drug Advisory Committees also noted that talquetamab might be helpful in previously anti-BCMA treatment exposed patients.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for talquetamab:

- relevant comparators
- consideration for initiation of therapy
- consideration for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability
- funding Algorithm
- care provision issues
- system and economic issues

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing trial, Phase 1/2, single-arm, open-label, multicenter, dose-escalation study, MonumenTAL-1 (Total N =501; N at either recommended Phase 2 doses [RP2Ds] = 339) met the inclusion criteria for the systematic review conducted by the sponsor. The objectives of MonumenTAL-1 were to characterize the safety of talquetamab and the recommended Phase 2 doses (RP2Ds) and schedule, and to further characterize the safety of talquetamab at the RP2Ds (Phase 1), and to evaluate the efficacy of talquetamab at the RP2Ds (Phase 2) in adults with RRMM. The trial enrolled adults who did not (Model Cohort A at 0.4 mg/kg weekly RP2D, and Model Cohort C at 0.8 mg/kg every 2 weeks [Q2W] RP2D) or did (Model Cohort B at either RP2D) have prior T-cell redirection therapy, with RRMM who have received at least a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on or after the last therapy. Patients had an ECOG performance status of 0 and 1 in Phase 1, and less than or equal to 2 in Phase 2, and adequate bone marrow, hepatic and renal functions. The 3 non-comparative cohorts were analyzed separately. Patients received one of the two RP2Ds: 0.4 mg/kg SC weekly on days 1, 8, 15, and 22 of a 28-day cycle (preceded by step-up doses of 0.01 mg/kg and 0.06 mg/kg) or 0.8 mg/kg SC Q2W on days 1 and 15 of a 28-day cycle (preceded by step-up does of 0.01 mg/kg, 0.06 mg/kg, and 0.3 mg/kg). The outcomes relevant to this review included the primary outcome of overall response rate (ORR) by

independent review committee (IRC) per International Myeloma Working Group (IMWG) criteria, and secondary outcomes of overall survival (OS), progression-free survival (PFS), duration of response (DoR), CR or better response rate, and safety. HRQoL via European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC-QLQ-C30) was measured in Phase 2 only as a secondary outcome.

The trial population had a mean age of 61 to 65 years and a mean MM duration of 7.2 to 7.7 years across the Model Cohorts. There were more male (55% to 57%) than female patients (43% to 46%). Most enrolled patients were white (86% to 90%), followed by Black or African American, and Asian. Most patients had an ECOG score of 1 (56% to 60%), and under 10% of the patients had an ECOG score of 2, indicating good overall performance status; R-ISS disease stage of II (62% to 70%), standard cytogenetic risk (59% to 71%), and triple-drug refractory disease refractory (PI, IMiD, and anti-CD38 antibody) (69% to 84%). The proportions of patients who had penta-drug refractory (at least 2 PIs, 2 IMiDs and 1 anti-CD38 mAb) were 29% in Model Cohort A, 23% in Model Cohort C, and 41% in Model Cohort B, respectively.

As Model Cohort B was not included in the pharmacoeconomic m odels, and was more exploratory as compared to the other two cohorts, the results summary below is focused on Model Cohorts A and C. Results of Model Cohort B are presented in the main body of this report.

Efficacy Results

The key efficacy results from the MonumenTAL-1 study are summarized in Table 1, in an order from the most important to the less important outcomes suggested by the clinical expert consulted for this review. Efficacy outcomes for this review were from the most recent analyses (clinical cut-off date of January 17, 2023) for all treated analysis set among the patients who received RP2D in MonumenTAL-1.

OS

At data cut-off, the OS data were immature. Median OS was not reached in any Model Cohorts. The 12-month OS rate was 76% (95% confidence interval [CI]: 68% to 83%) in Model Cohort A, and 77% (95% CI: 69% to 84%) in Model Cohort C.

PFS

The median PFS was 7.5 months (95% CI: 5.7, 9.4) in Model Cohort A, and 14.2 months (95% CI: 9.6, not estimable) in Model Cohort C. The 12-month PFS rate in Model Cohort A (35%; 95% CI: 27% to 43%) appears lower than in Model Cohort C (54%; 95% CI: 45% to 63%).

ORR

At data cut-off, ORR was achieved by 74% (95% CI: 66% to 81%) and 72% (95% CI: 64%, 79%) of patients in Model Cohort A and Model Cohort C, respectively, with the one-sided P value of < 0.0001 for both cohorts. Results of prespecified clinically relevant subgroups analyses showed that the ORR seemed higher among patients with no extramedullary plasmacytomas at baseline (81.8%; 95% CI, 73.3% to 88.5% in Model Cohort A; 81.5%; 95% CI, 72.9% to 88.3% in Model Cohort C) than those with 1 or more baseline extramedullary plasmacytomas (48.5%; 95% CI, 30.8% to 66.5% in Model Cohort A; 43.2%; 95% CI, 27.1% to 60.5% in Model Cohort C). It was not the intent of the study to formally test for subgroup differences.

DoR

At data cut-off, the median DoR was reached among responders in Model Cohorts A and B, but not in Model Cohort C. The median DoR was 9.5 months (95% CI: 6.7, 13.3) in Model Cohort A responders (n = 106), and not estimable (NE) (95% CI: 13.0, NE) in Model Cohort C responders (n = 104). The event-free rate for DoR at 6 months was 67% in Model Cohort A and 82% in Model Cohort C, at 9 months was 52% and 76%, and at 12 months was 44% and 69%.

CR or better

At data cut-off, CR or better response was achieved by 34% (95% CI: 26% to 42%) of patients in Model Cohort A and 39% (95% CI: 31%, 47%) of patients in Model Cohort C.

HRQoL

HRQoL assessed with EORTC-QLQ-C30 was only reported for Phase 2 of MonumenTAL-1. In cohort A (talquetamab 0.4 mg/kg weekly SC and with no prior T-cell redirection therapy), the proportions of patients who achieved at least 10 points improvement from baseline through Cycle 7 Day 1 (i.e., the first 6 months) in pain, fatigue, GHS, and physical functioning subscales were [redacted], respectively. In cohort C (0.8 mg/kg Q2W SC and with no prior T-cell redirection therapy), the proportions of patients who achieved at least 10 points improvement from baseline through Cycle 7 Day 1 in pain, fatigue, GHS, and physical functioning subscales were [redacted] respectively.

Harms Results

All patients in the study reported at least 1 TEAE. The most frequently reported TEAEs were cytokine release syndrome (CRS) (79% in Model Cohort A and 75% in Model Cohort C), dysgeusia (50% and 49%), anemia (45% and 46%), weight decrease (41% in both cohorts), pyrexia (39% and 28%), neutropenia (35% and 28%). Serious TEAEs occurred to 53% and 48% of patients in Model Cohorts A and C, mostly were CRS (17% and 10%), pyrexia (6% and 5%), and ICANS (4% in both cohorts). In general, proportion of patients with overall or the specific TEAEs, and specific serious TEAEs were similar between the two cohorts, with a higher rate in Model Cohort A compared to Cohort C for serious TEAEs, and pyrexia and neutropenia of any severity.

Likewise, the rates of adverse events of special interest (AESIs) were similar between the Model Cohort A and Model Cohort C, for patients with ≥ 1 treatment-emergent neurologic AE (86% in both cohorts), neurotoxicity events (31% and 30%), and ICANS (11% in both groups). The rate of CRS in Model Cohort A was 79% and in Model Cohort C was 75%. The proportion of patients who experienced an infection of any severity in Model Cohort A was 59% and in Model Cohort C was 66%.

Critical Appraisal

The primary limitation of the MonumenTAL-1 study was the absence of a comparator group to assess the efficacy and harms of talquetamab compared to placebo or an active treatment; therefore, the interpretation of the results is limited by its single-arm design. The open-label design introduces a potential performance bias and bias in the assessment of PFS, ORR, DoR, CR or better, HRQoL and some AEs, although assessment bias was mitigated by using IRC who performed tumour assessment per the IMWG criteria[9] for the tumour-response outcomes. ORR and the 95% CI excluded the predetermined thresholds for null hypotheses (30% for Model Cohorts A and C, and 15% for Model Cohort B) for all 3 Model Cohorts (P values < 0.0001), and this effect can be attributed to talquetamab despite the single arm design. Despite that there was the lack of multiplicity adjustment for the ORR analyses, p-values were small, suggesting that these were not false-positive results. ORR was examined in pre-specified clinically relevant subgroups; however, the sample size for the subgroup analyses were small, and the analyses were not adjusted for multiplicity, limiting interpretation of the data. The review team noted the smaller sample size (N = 51) of Model Cohort B (patients with prior T-cell redirection therapy who received either one of the 2 recommended dosing regimens), further limiting interpretation of results for these patients. At data cut-off and across the Model Cohorts, [redacted] of the patients were lost to follow-up for OS, and [redacted] of the patients withdrew consent to study participation. It appears the impact of missing data on OS and PFS is minimal. The data for OS in all the 3 Model Cohorts were immature; therefore, the treatment benefit of OS based on the analysis at the latest data cut-off would have been subjected to certain degree of uncertainty. At data cut-off and across the Model Cohorts, 39% to 58% of the patients received 1 or more subsequent anti-myeloma therapy, which may influence the assessment of efficacy of talquetamab on OS and PFS. The clinical expert commented that it is reasonable for the use of the literature-reported, 10-point improvement from baseline value in the EORTC-QLQ-C30 scores as the clinically meaningful improvement threshold in data analysis. The size of the HRQoL-evaluable population in Phase 2 gradually decreased over time. At Cycle 7 Day 1, only [redacted] all treated patients in Cohort A, [redacted] in Cohort C, and [redacted] in Cohort B provided data for the EORTC-QLQ-C30 assessment, which further increased risk of bias due to incomplete reporting or missing data for this outcome.

There is a lack of ethnic diversity as most patients in MonumenTAL-1 were white (86% to 90%), followed by Black or African American (6% to 8%) and Asian (1% to 4%), among the others. Previous studies in the US found that MM is twice as common in African-American individuals compared to Caucasian or Asian individuals. The clinical expert pointed out that the patients in MonumenTAL-1 were relatively younger and with a less severe disease, compared to the RRMM patients seen in clinical practice in Canada. These factors may potentially impact the generalizability of the study results, although the extent of such influence is uncertain.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with the clinical expert, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: OS, PFS, ORR, DoR, CR or better, EORTC QLQ-C30, and notable harms, for patients in Model Cohort A and Model Cohort C separately. The outcomes in Model Cohort B were not assessed using GRADE, due to the small sample size and the exploratory nature of that population cohort.

Table 1 presents the GRADE summary of findings for talquetamab in adult patients with RRMM who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on or after the last therapy.

Table 1: Summary of Findings for Talquetamab for Adult Patients With Refractory or Relapsed Multiple Myeloma

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Overall survival				
OS Median (range) follow-up: 18.8 (0.5+ to 32.9) months	143 (1 single-arm trial: Model Cohort A)	Median (95% CI) OS, months: NE (25.6 to NE) OS probability (95% CI): • At 12 months: 764 per 1,000 (683 to 827 per 1,000)	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.4 mg/kg weekly SC on OS when compared with any comparator.
OS Median (range) follow-up: 12.7 (0.2+ to 26.1) months	145 (1 single-arm trial: Model Cohort C)	Median (95% CI) OS, months: NE (20.1 to NE) OS probability (95% CI): • At 12 months: 774 per 1,000 (691 to 837 per 1,000)	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg Q2W SC on OS when compared with any comparator.
Progression-free survival				
PFS Median (range) follow-up: 18.8 (0.5+ to 32.9) months	143 (1 single-arm trial: Model Cohort A)	Median (95% CI) PFS, months: 7.5 (5.7 to 9.4) PFS probability (95% CI): • At 12 months: 349 per 1,000 (270 to 429 per 1,000)	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.4 mg/kg weekly SC on PFS when compared with any comparator.
PFS Median (range) follow-up: 12.7 (0.2+ to 26.1) months	145 (1 single-arm trial: Model Cohort C)	Median (95% CI) PFS, months: 14.2 (9.6 to NE) PFS probability (95% CI): • At 12 months: 544 per 1,000 (453 to 626 per 1,000)	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg Q2W SC on PFS when compared with any comparator.
Overall response rate				
ORR (sCR, CR, VGPR, or PR) Median (range) follow-up: 18.8 (0.5+ to 32.9) months	143 (1 single-arm trial: Model Cohort A)	ORR (sCR, CR, VGPR, or PR) events (95% CI) at data cut-off date: 741 per 1,000 (661 to 811 per 1,000)	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.4 mg/kg weekly SC on ORR when compared with any comparator.
ORR (sCR, CR, VGPR, or PR) Median follow-up: 12.7 (0.2+ to 26.1) months	145 (1 single-arm trial: Model Cohort C)	ORR (sCR, CR, VGPR, or PR) events (95% CI) at data cut-off date: 717 per 1,000 (637 to 789 per 1,000)	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg Q2W SC on ORR when compared with any comparator.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Duration of response among responders[b]				
DoR Median (range) follow-up: 18.9 (2.7 to 32.9) months	106 (1 single-arm trial: Model Cohort A)	Median (95% CI) DoR, months: 9.5 (6.7 to 13.3) DoR event-free probability (95% CI): • At 6 months: 672 per 1,000 (572 to 753 per 1,000) • At 9 months: 515 per 1,000 (414 to 606 per 1,000) • At 12 months: 435 per 1,000 (338 to 528 per 1,000)	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.4 mg/kg weekly SC on DoR when compared with any comparator.
DoR Median (range) follow-up: 12.9 (4.1 to 29.0) months	104 (1 single-arm trial: Model Cohort C)	Median (95% CI) DoR, months: NE (13.0 to NE) DoR event-free probability (95% CI): • At 6 months: 822 per 1,000 (732 to 884 per 1,000) • At 9 months: 763 per 1,000 (665 to 837 per 1,000) • At 12 months: 693 per 1,000 (578 to 782 per 1,000)	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg Q2W SC on DoR when compared with any comparator.
CR or better response rate				
CR or better (sCR, or CR) Median (range) follow-up: 18.8 (0.5+ to 32.9) months	143 (1 single-arm trial: Model Cohort A)	CR or better (sCR, or CR) events (95% CI) at data cut-off date: 336 per 1,000 (259 to 419 per 1,000)	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.4 mg/kg weekly SC on CR or better response rate when compared with any comparator.
CR or better (sCR, or CR) Median follow-up: 12.7 (0.2+ to 26.1) months	145 (1 single-arm trial: Model Cohort C)	CR or better (sCR, or CR) events (95% CI) at data cut-off date: 386 per 1,000 (307 to 471 per 1,000)	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg Q2W SC on CR or better response rate when compared with any comparator.
HRQoL (measured with EORTC-QLQ-C30, 0 [best] to 100 [worst] for pain and fatigue, 0 [worst] to 100 [best] for GHS and physical functioning)				
Proportion of patients with a 10-point improvement Time point: Cycle 7 Day 1	54 (1 single-arm trial: Phase 2 Cohort A)	Pain score: [redacted] per 1,000 Fatigue: [redacted] per 1,000 GHS: [redacted] per 1,000 Physical functioning: [redacted] per 1,000	Very low[a,c]	The evidence is very uncertain about the effect of talquetamab 0.4 mg/kg weekly SC on EORTC-QLQ-C30 pain, fatigue, GHS, and physical functioning scores when compared with any comparator.
Proportion of patients with a 10-point improvement Time point: Cycle 7 Day 1	60 (1 single-arm trial: Phase 2 Cohort C)	Pain score: [redacted] per 1,000 Fatigue: [redacted] per 1,000 GHS: [redacted] per 1,000 Physical functioning: [redacted] per 1,000	Very low[a,c]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg Q2W SC on EORTC-QLQ-C30 pain, fatigue, GHS, and physical functioning scores when compared with any comparator.
Notable harms				
Notable harms	143 (1 single-arm	CRS: 790 per 1,000 ICANS: 107 per 1,000	Very low[a]	The evidence is very uncertain about the effect of talquetamab

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Median follow-up: 18.8 (0.5+ to 32.9) months	trial: Phase 1/2 Model Cohort A)	Infection: 587 per 1,000		0.4 mg/kg weekly SC on CRS, ICANS, and infection when compared with any comparator.
Notable harms Median follow-up: 12.7 (0.2+ to 26.1) months	145 (1 single-arm trial: Phase 1/2 Model Cohort C)	CRS: 745 per 1,000 ICANS: 110 per 1,000 Infection: 662 per 1,000	Very low[a]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg Q2W SC on CRS, ICANS, and infection when compared with any comparator.

CI = confidence interval; CR = complete response; CRS = cytokine release syndrome; DoR = duration of response; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item; GHS = global health status; HRQoL = health-related quality of life; ICANS = immune effector cell-associated neurotoxicity syndrome; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; Q2W = once every 2 weeks; RP2D = recommended Phase 2 dose; SC = subcutaneous; sCR = stringent complete response; VGPR = very good partial response.

Note: Study limitations (which refers to internal validity or risk of bias), indirectness, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. Data presented in this table were based on analyses at clinical cut-off date of January 17, 2023 for all treated analysis set and patients that received RP2D. Model Cohort A included patients with no prior T-cell redirection therapy treated at the RP2D of 0.4 mg/kg weekly SC in Phase 1 and Phase 2 of MonumenTAL-1. Model Cohort C included patients with no prior T-cell redirection therapy treated at the RP2D of 0.8 mg/kg Q2W SC in Phase 1 and Phase 2 of MonumenTAL-1. "+" denotes patients who died.

[a]In absence of a comparator arm, conclusions about efficacy relative to any comparator cannot be drawn and certainty of evidence started at very low without the opportunity to rate up.

[b]DoR was calculated as the number of months from first documented response to progression or death due to any cause. Number of events referred to number of responders (PR or better) who developed disease progression or died due to any cause.

[c]Rated down 2 levels for very serious risk of bias due to the open-label nature of the study and the subjective nature (patient-reported) of the outcome. There were substantial missing outcome data at Cycle 7 Day 1 (data were available for 53 or 54 patients compared to 108 patients at baseline for Phase 2 Cohort A, and data were available for 60 patients compared 88 or 99 patients at baseline for Phase 3 Cohort C for EORTC-QLQ-C30 scales of pain, fatigue, GHS, and physical functioning).

Source: Clinical Study Report for MonumenTAL-1 (2023). Details included in the table are from the sponsor's Summary of Clinical Evidence.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adult patients with RRMM, with greater than or equal to 3 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb, and who have demonstrated disease progression on or after the last therapy.
Treatment	Talquetamab
Dose regimen	Weekly dosing schedule: step-up dosing of 0.01 mg/kg on Day 1 and 0.06 mg/kg on Day 4, followed by first treatment dose of 0.4 mg/kg on Day 7. Subsequent treatment doses of 0.4 mg/kg once weekly thereafter. Biweekly dosing schedule: step-up dosing of 0.01 mg/kg on Day 1, 0.06 mg/kg on Day 4, 0.4 mg/kg on Day 7, followed by first treatment dose of 0.8 mg/kg on Day 10. Subsequent treatment doses of 0.8 mg/kg once biweekly thereafter.
Submitted price	2 mg/mL: $545.00 per single-use vial 40 mg/mL: $7,300.00 per single-use vial
Submitted treatment cost	Weekly dosing schedule: $31,154 (cycle 1) and $29,129 (cycle 2 onwards) per patient per 28 days. Biweekly dosing schedule: $36,878 (cycle 1) and $27,184 (cycle 2 onwards) per patient per 28 days.
Comparators	• Basket of currently reimbursed combination therapies (referred to as physician's choice): Kd (24%); KCd (11%); Pd (28%); and PCd (38%). • Teclistamab • Cilta-cel
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (30 years)
Key data sources	Comparisons are presented pairwise due to heterogeneity between comparator trials. • Talquetamab: single-arm, phase I/II MonumenTAL-1 study (data cut-off: January 17, 2023). Cohort A followed a weekly dosing schedule and Cohort C followed a biweekly dosing schedule. • Physician's choice: LocoMMotion (data cut-off: October 2022) and MoMMent (data cut-off: March 2023) prospective non-interventional studies. • Teclistamab: single-arm, phase I/II MajesTEC-1 trial (data cut-off: January, 2023) • Cilta-cel: single-arm, phase Ib/II CARTITUDE-1 trial (data cut-off: January 2022)
Key limitations	• The comparative clinical efficacy of talquetamab relative to relevant alternatives remains uncertain due to the absence of head-to-head clinical trials and robust long-term clinical data. Clinical experts consulted by CADTH emphasized that the impact of talquetamab on OS beyond 5 years is highly uncertain due to the lack of randomized evidence. • The generalizability of the modelled population to Canadian clinical practice is unclear. The clinical data used in the economic model was restricted to patients from the MonumenTAL-1 trial who did not have prior exposure to T-cell redirection therapies, leading to uncertainty about the magnitude of clinical benefit in a more diverse real-world patient population. • The sponsor's modeling approach suggested a longer survival benefit in the post-progression period for talquetamab, a concern raised by clinical experts due to the lack of supporting evidence. Specifically, the model predicts that 73% and 50% of the incremental survival benefit of talquetamab in the weekly and bi-weekly dosing groups, respectively, occurs after the treatment has ceased controlling the disease.

Component	Description
	• The dosing schedule for talquetamab in clinical practice remains uncertain, with options for weekly or biweekly administration as outlined in the product monograph. Clinical experts suggest that the biweekly schedule is likely preferred due to potential benefits in reducing healthcare resource utilization, improving chair time availability, and enhancing patient quality-of-life through less frequent injections. • The sponsor assumed that teclistamab would be administered weekly. Although the product monograph currently describes a weekly dosing schedule for teclistamab, its manufacturer has stated that the adoption of a biweekly dosing schedule is planned for submission to Health Canada. Biweekly dosing has important implications for the total drug acquisition costs of teclistamab, as well as reduced healthcare resource use related to treatment administration. • Based on clinical expert feedback, SVd is a relevant comparator for this indication. As this was not considered by the sponsor, the cost-effectiveness of talquetamab relative to SVd is unknown.
CADTH reanalysis results	• Given the uncertainty regarding the talquetamab dosing schedule likely to be preferred in clinical practice, CADTH conducted base case reanalyses to assess the cost-effectiveness of talquetamab when used on a weekly dosing schedule and a biweekly dosing schedule. The CADTH base case reanalyses were derived by adopting the exponential distribution to extrapolate OS for talquetamab. • In the CADTH reanalysis of talquetamab on a weekly dosing schedule, talquetamab was associated with an ICER of $315,994 per QALY gained compared with physician's choice (incr. costs: $435,516; incr. QALYs: 1.38). • In the CADTH reanalysis of talquetamab on a biweekly dosing schedule, talquetamab was associated with an ICER of $332,182 per QALY gained compared with physician's choice (incr. costs: $452,471; incr. QALYs 1.36). In both reanalyses, talquetamab was less costly and more effective than teclistamab but less costly and less effective than cilta-cel. • To be considered cost-effective at a WTP threshold of $50,000 per QALY gained relative to physician's choice, talquetamab would require a price reduction of 92% for the weekly dosing schedule and 86% for the biweekly dosing schedule. • CADTH calculated a weighted ICER based on clinical expert input, which indicated that 90% of talquetamab-treated patients would receive biweekly dosing and the remaining 10% would receive weekly dosing. The weighted CADTH base case suggests that talquetamab has an ICER of $330,563 per QALY gained relative to physician's choice. In this scenario, an 87% price reduction would be required for talquetamab to be cost-effective compared to physician's choice at a WTP threshold of $50,000 per QALY gained. • CADTH conducted scenario analyses to evaluate the impact of adopting a biweekly dosing schedule for teclistamab on the cost-effectiveness of talquetamab. In these scenarios, talquetamab was no longer less costly and more effective than teclistamab. Instead, talquetamab was associated with incremental costs and QALYs relative to teclistamab, resulting in an ICER of $262,786 per QALY gained for patients on a weekly dosing schedule and $164,551 per QALY gained for patients on a biweekly dosing schedule.

ICER = incremental cost-effectiveness ratio; IMiD = immunomodulatory drug; incr. = incremental; ITC = indirect treatment comparison; KCd = carfilzomib + cyclophosphamide + dexamethasone; Kd = carfilzomib + dexamethasone; mAb = monoclonal antibody; OS = overall survival; PCd = pomalidomide + cyclophosphamide + dexamethasone; Pd = pomalidomide + dexamethasone; PFS = progression-free survival; PI = proteasome inhibitor; PSM = partitioned survival model; QALY= quality-adjusted life-year; RRMM = relapsed/refractory multiple myeloma; SVd = selinexor + bortezomib + dexamethasone; vs. = versus.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the calculation of the budget impact analysis is uncertain; the proportion of patients with NDMM receiving therapy in fourth line is uncertain; the dosing schedule for talquetamab is uncertain; the dosing schedule for teclistamab is uncertain; and the projected market shares of talquetamab are uncertain. CADTH conducted reanalyses of the BIA by revising the calculation of the costs associated with talquetamab, teclistamab, and physician's choice therapies; as well as revising the size of the eligible patient population.

Based on the CADTH base case, the incremental expenditures associated with the reimbursement of talquetamab for the fourth line treatment of adult patients with RRMM who have demonstrated disease progression on the last therapy, as per its reimbursement request, would be $14,412,850 in Year 1, $24,090,852 in Year 2, and $25,628,370 in Year 3, for a three-year cumulative total of $64,132,073.

CADTH conducted scenario analyses to address remaining uncertainty. Assuming talquetamab is administered on a weekly dosing schedule resulted in an increase of talquetamab's estimated three-year budget impact to $80,282,930. Assuming teclistamab is administered on a biweekly dosing schedule resulted in an increased of talquetamab's estimated three-year budget impact to $96,023,409. Assuming the projected market shares for each drug, teclistamab and talquetamab, are 33%, 37% and 37% in Years 1, 2, and 3, respectively, resulted in an increase of talquetamab's estimated three-year budget impact to $72,718,011.

pERC Information

Members of the Committee:

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, Danica Wasney.

Meeting date: October 9, 2024

Regrets:

Three expert committee members did not attend.

Conflicts of interest:

None