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Reimbursement Recommendation

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.

Final recommendation: Do not reimburse

Summary

What Is the Reimbursement Recommendation for Talvey?

Canada's Drug Agency (CDA-AMC) recommends that Talvey not be reimbursed by public drug plans for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody (mAb), and who have demonstrated disease progression on or after the last therapy.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical study showed that Talvey may improve treatment response rates in adults with RRMM who have received at least 3 prior lines of therapy. However, no causal conclusions could be drawn about the effect of Talvey on the outcomes important to patients and clinicians (e.g., progression-free survival [PFS] and overall survival [OS]) based on the weak evidence from 1 noncomparative clinical trial.
- The evidence is insufficient to determine whether Talvey meets patient needs for effective, accessible, and portable treatment options that can extend life, delay worsening or spreading of disease, improve quality of life, and reduce side effects.
- Talvey's adverse effect profile may not align with patient values regarding side effects. Notably, dysgeusia — an unfavourable side effect from the patient perspective — was 1 of the most frequently reported adverse events (AEs) with Talvey in the submitted clinical trial. Other frequently reported side effects may be considered unfavourable by patients, as the patient group input reported infections and nail, skin, and oral issues as the least bearable side effects.

Additional Information

What Is Multiple Myeloma?

Multiple myeloma (MM) is a cancer of plasma cells (i.e., white blood cells that make immunoglobulins) in the bone marrow (i.e., the soft matter inside bones where blood cells are produced). In 2023, an estimated 3,900 individuals were diagnosed with MM and about 1,700 deaths occurred due to MM in Canada.

Unmet Needs in MM

MM is an incurable disease with a low chance of recovery. MM often does not respond to initial treatments and will relapse, so the patient will need

Summary

to try many different treatments. There is a need for additional treatment options that allow patients to live longer, delay the worsening or spread of cancer, improve quality of life, and reduce side effects.

How Much Does Talvey Cost?

Treatment with Talvey on a weekly dosing schedule is estimated to cost approximately $31,154 per patient for the first 28 days, followed by $29,129 every 28 days thereafter. For the biweekly dosing schedule, the estimated cost is approximately $36,878 for the first 28 days and $27,184 every 28 days thereafter, per patient.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that talquetamab not be reimbursed for the treatment of adult patients with RRMM who have received at least 3 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.

Rationale for the Recommendation

One ongoing, phase I/II, single-arm, open-label study (the MonumenTAL-1 study) 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% confidence interval [CI], 66% to 81%) in patients with no prior T-cell redirection therapy who received subcutaneous (SC) talquetamab 0.4 mg/kg weekly (model cohort A, N = 143), and 72% (95% CI, 64% to 79%) in those with no prior T-cell redirection therapy who received SC talquetamab 0.8 mg/kg once every 2 weeks (model cohort C, N = 145). 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% to 77.6%). However, due to the single-arm design, pERC was unable to draw causal conclusions about the effect of talquetamab on PFS and overall survival OS, which are important outcomes to patients and clinicians.

Three sponsor-conducted, nonrandomized 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 therapies. Results for talquetamab versus teclistamab were inconsistent across the outcomes assessed, which led to 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 the 0.8 mg/kg biweekly dose of talquetamab was compared to cilta-cel. All of the nonrandomized comparisons were impacted by important methodological limitations, which limited pERC's certainty in these results.

Patients identified a need for effective, accessible, and portable (i.e., requiring fewer or minimal visits to the hospital or cancer centre) 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 the effects of talquetamab on PFS, OS, and health-related quality of life (HRQoL). pERC noted that dysgeusia, which is an unfavourable side effect from the patient perspective, was 1 of the most frequently reported treatment-emergent adverse events (TEAEs) in the MonumenTAL-1 clinical trial. Other frequently reported side effects may also be unfavourable to patients, and the patient group input reported nail-related issues, skin-related issues, and infections as being the least

bearable, along with oral-related issues. Overall, pERC was unable to conclude that talquetamab would meet patients' need for treatments with fewer side effects, given the single-arm design of MonumenTAL-1 trial and the considerable uncertainties around the interpretation of unadjusted comparisons of AE rates from studies of talquetamab versus those from the studies of comparator therapies. pERC acknowledged that the novel therapeutic target of talquetamab may provide potential benefits for patients with RRMM who have received at least 3 prior lines of therapy. However, the clinical evidence submitted for this review did not provide sufficient certainty for the committee to make a recommendation to reimburse.

Discussion Points

- **Sponsor request for reconsideration:** The sponsor requested a reconsideration of the initial draft recommendation not to reimburse talquetamab for the treatment of adult patients with RRMM who have received at least 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. There were 4 issues outlined by the sponsor in the request for reconsideration. Briefly, the sponsor requested that pERC reconsider:
  - the challenge of overcoming refractoriness and treatment resistance in RRMM, and the importance of treatment options with a novel therapeutic target, specifically the GPRC5D-targeting therapy
  - the significant unmet need in patients with prior exposure to BCMA-targeting therapy due to a lack of available alternative therapies
  - the totality of comparative evidence, trial data, and clinical expert opinion in the context of the need for treatments with novel targets, lack of a standard of care, and poor outcomes in triple-class exposed patients
  - talquetamab's potential to address patient needs given its manageable AEs and improved accessibility.

  pERC carefully deliberated on each of the issues identified by the sponsor in their request for reconsideration. Additionally, pERC reviewed and discussed the feedback from patient and clinician groups on the initial draft recommendation as well as the new information provided by the sponsor as part of the reconsideration request. Upon reconsideration, pERC concluded that the available evidence had inherent limitations, including those related to the single-arm phase I/II design of the MonumenTAL-1 trial and the methodologies used in the submitted indirect comparisons, which do not sufficiently support the level of certainty needed for the committee to make a recommendation to reimburse.
- **Unmet needs in RRMM:** During the initial and reconsideration meetings, pERC acknowledged that there is an unmet need for effective treatments for patients with RRMM in the fourth line and later settings. The available efficacy and safety evidence for talquetamab was from a noncomparative phase I/II trial and nonrandomized comparisons, which are associated with uncertainty. Recognizing

that talquetamab offers a distinct mechanism of action, based on the available 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 settings. 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.

- **Patients with prior T-cell redirection therapy**: During the initial meeting, 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 nonrandomized 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 during the initial meeting that talquetamab confers a clinically meaningful benefit to patients previously treated with T-cell redirection therapy, including BCMA-targeted therapy (e.g., CAR T-cell therapy or a BiTE). During the reconsideration meeting, pERC considered feedback from the sponsor and clinician groups on the initial draft recommendation. The committee also discussed the new data submitted by the sponsor as part of the reconsideration request to compare efficacy outcomes of treatment with talquetamab in patients who had prior BCMA-targeted therapy from the MonumenTAL-1 trial versus RWPC therapies, as well as new long-term follow-up data for patients who had prior BCMA-targeted therapy from the MonumenTAL-1 trial. The new data reports, provided in the form of conference presentations, indicated that patients with exposure to a prior BCMA-targeted therapy, treated with talquetamab in the MonumenTAL-1 trial at either a 0.4 mg/kg or 0.8 mg/kg weekly dose, were more likely than those receiving RWPC therapies to experience a treatment response (ORR = 64.9% versus 11.1%), and also had improved PFS (12.3 months versus 4.1 months) and OS (27.1 months versus 14.0 months). The long-term data indicated that, with additional follow-up (20.5 months), ORR remained consistent (66.7%), and the 24-month OS rate was 57.3%. The review team at Canada's Drug Agency (CDA-AMC) noted that, per the CDA-AMC *Procedures for Reimbursement Reviews*, no new information can be filed after the draft review reports have been sent for sponsor review and comment. Therefore, the new data comparing talquetamab to RWPC in patients with exposure to prior BCMA-targeted therapy were not reviewed in detail or critically appraised by the CDA-AMC review team. pERC's assessment was limited to the information provided in the sponsor's reconsideration request and the submitted conference presentations, which were made available to the committee for the purpose of deliberation. pERC agreed with the review team that there were considerable uncertainties in the interpretation of the indirect comparison of data from the MonumenTAL-1 trial, with the pooled data from observational studies evaluating clinical outcomes of RWPC treatments. pERC also noted that there were insufficient data on the use of BCMA-targeted therapies as a later line of therapy after talquetamab.
- **Side effects:** pERC acknowledged that patients need treatments that have fewer side effects. Harms of talquetamab were not assessed in the submitted nonrandomized comparative studies; therefore,

during the initial meeting, pERC could not draw conclusions regarding the comparative safety of talquetamab versus other treatments. pERC noted that the most frequently reported 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 — such as CRS and neurologic toxicity (including immune effector cell–associated neurotoxicity syndrome [ICANS]) — could affect the frequency of patient visits to the hospital or cancer centre, so it is unclear if talquetamab would meet their need for accessible and portable treatment options. During the reconsideration meeting, pERC considered feedback provided by the sponsor, which suggested that talquetamab has a risk of CRS and ICANS that is consistent with other bispecific monoclonal antibodies including teclistamab and elranatamab, and that the rates of grade 3 and 4 CRS were low for talquetamab in the MonumenTAL-1 trial. pERC noted that there were considerable uncertainties in the interpretation of rates from unadjusted (naive) comparisons across different studies by extracting the rate values of the arm of interest, due to differences in the study design, population, outcome measurement, consistency of reporting, timing of enrolment, and length of follow-up. pERC additionally discussed the clinical expert input, which indicated that, despite the comparable ORRs described for talquetamab versus teclistamab, in most cases where physicians may need to choose between the 2 options, they would not opt for talquetamab over teclistamab due to the toxicity profile of talquetamab. Overall, pERC could not conclude that talquetamab would meet patients' need for treatments with fewer side effects.

- **HRQoL:** During the initial meeting, 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. This issue was also discussed at the reconsideration meeting and pERC upheld their initial conclusion.

Background

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 occurred due to MM 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, PFS, and OS 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 CDA-AMC, 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 later settings, and at this stage of the disease, patients may be treated with PIs, IMiDs, and anti-CD38 mAbs, 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 RRMM who have received at least 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. 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 SC 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 2 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 I/II 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
- input from 1 clinical specialist with expertise diagnosing and treating patients with MM
- input from 2 clinician groups, the Canadian Myeloma Research Group (CMRG) and the Ontario Health (Cancer Care Ontario) (OH-CCO) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor's request for reconsideration (described subsequently)
- feedback from the public drug programs, and patient and clinician groups, on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

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 input from a clinical expert consulted for the purpose of this review.

Patient Input

The review team received 1 patient group submission from Myeloma Canada. The group conducted both patient and caregiver surveys from April 17, 2024, 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 which 38 complete responses (from 32 patients and 6 caregivers, all from Canada except 1 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% of 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 the 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, 68% of the eligible respondents rated improved quality of life as extremely important, 9 as very important, and 1 as somewhat important. In addition, 66% of the 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 that it was very desirable. When asked about tolerance of the most common side effects in patients who receive talquetamab, respondents perceived ICANS, CRS, and infections to be the least tolerable side effects, followed by diarrhea and neutropenia. A total of 6 respondents (5 patients and 1 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-line 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 naive 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-line 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 disease 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 International Myeloma Working Group (IMWG) response criteria,[9] and intolerable AEs (e.g., severe dysgeusia and severe myelosuppression). The clinical expert noted that treatment with talquetamab should be initiated and supervised by a specialist (hematologist 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 2 clinician groups: the CMRG and the OH-CCO Hematology Cancer Drug Advisory Committee. A total of 32 clinicians (25 from CMRG and 7 from the OH-CCO's Drug Advisory Committee) provided input for this submission.

Both CMRG and the OH-CCO Drug Advisory Committee emphasized that the overall treatment goals are to delay progression, improve OS, control the disease and associated symptoms, minimize adverse effects, and improve quality of life. While discussing 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 3 major classes of drugs ("triple-class exposed or refractory") including an IMiD, PI, and anti-CD38 mAb. Another unmet need noted by OH-CCO's Drug Advisory Committee is to achieve ease of administration (i.e., SC 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 patients who are triple-class exposed. CMRG indicated that patients with a good performance status, minimal or no comorbidities, relatively low tumour 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 Committee agreed 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 suggested that patients with prior anti-BCMA therapy or bispecific antibody treatment be allowed access to talquetamab. OH-CCO's Drug Advisory Committee also noted that talquetamab might be helpful in patients previously exposed to anti-BCMA treatment.

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 the review team provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing, phase I/II, single-arm, open-label, multicentre, dose-escalation study, the MonumenTAL-1 trial (total N = 501; N at either recommended phase II dose [RP2D] = 339) met the inclusion criteria for the systematic review conducted by the sponsor. The objectives of the MonumenTAL-1 trial were to characterize the safety of talquetamab and the RP2Ds and schedule, to further characterize the safety of talquetamab at the RP2Ds (phase I), and to evaluate the efficacy of talquetamab at the RP2Ds (phase II) in adults with RRMM. The trial enrolled adults with RRMM who had received at least a PI, an IMiD, and an anti-CD38 mAb, and had demonstrated disease progression on or after the last therapy, who did not have prior T-cell redirection therapy (model cohort A at 0.4 mg/kg weekly RP2D, and model cohort C at 0.8 mg/kg every 2 weeks RP2D) or did have prior T-cell redirection therapy (model cohort B at either RP2D). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 in phase I and less than or equal to 2 in phase II, and adequate bone marrow, hepatic, and renal functions. The 3 noncomparative cohorts were analyzed separately. Patients received 1 of the 2 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 every 2 weeks 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 ORR using an independent review committee (IRC) per IMWG criteria, and secondary outcomes of OS, PFS, duration of response (DoR), complete response (CR) or better response rate, and safety. HRQoL was measured via the European

Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) in phase II 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 patients (55% to 57%) than female patients (43% to 46%). Most enrolled patients were white (86% to 90%), followed by Black or African American (6% to 8%) and Asian (1% to 4%). Most patients had an ECOG score of 1 (56% to 60%), and less than 10% of the patients had an ECOG score of 2, indicating good overall performance status. Most patients also had a revised international staging system (R-ISS) disease stage of II (62% to 70%), standard cytogenetic risk (59% to 71%), and triple-drug (PI, IMiD, and anti-CD38 mAb) refractory disease (69% to 84%). The proportions of patients who had penta-drug (at least 2 PIs, 2 IMiDs, and 1 anti-CD38 mAb) refractory disease were 29% in model cohort A, 23% in model cohort C, and 41% in model cohort B.

As model cohort B was not included in the pharmacoeconomic models, and was more exploratory than the other 2 cohorts, the results summary that follows is focused on model cohorts A and C. Results for 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 order from the most important to the least 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 the all treated analysis set among the patients who received RP2D in the MonumenTAL-1 trial.

Overall Survival

At the 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% CI, 68% to 83%) in model cohort A and 77% (95% CI, 69% to 84%) in model cohort C.

Progression-Free Survival

The median PFS was 7.5 months (95% CI, 5.7 to 9.4) in model cohort A, and 14.2 months (95% CI, 9.6 to not estimable [NE]) in model cohort C. The 12-month PFS rate in model cohort A (35%; 95% CI, 27% to 43%) was lower than it was in model cohort C (54%; 95% CI, 45% to 63%).

Overall Response Rate

At the data cut-off, the ORR was 74% (95% CI, 66% to 81%) in model cohort A and 72% (95% CI, 64% to 79%) in model cohort C, with the 1-sided P value < 0.0001 for both cohorts. Results of prespecified clinically relevant subgroup analyses showed that the ORR was higher among patients with no extramedullary plasmacytomas at baseline (ORR = 81.8%; 95% CI, 73.3% to 88.5% in model cohort A; ORR = 81.5%; 95% CI, 72.9% to 88.3% in model cohort C) than those with 1 or more baseline extramedullary plasmacytomas (ORR = 48.5%; 95% CI, 30.8% to 66.5% in model cohort A; ORR = 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.

Duration of Response

At the 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 to 13.3) in model cohort A responders (n = 106), and NE (95% CI, 13.0 to 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% in model cohort A and 76% in model cohort C, and at 12 months was 44% in model cohort A and 69% in model cohort C.

CR or Better

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

Health-Related Quality of Life

HRQoL assessed with the EORTC QLQ-C30 was only reported for phase II of the MonumenTAL-1 trial. 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 a 10-point improvement from baseline through cycle 7, day 1 (i.e., the first 6 months) in the pain, fatigue, global health status (GHS), and physical functioning subscales were [redacted], respectively. In cohort C (0.8 mg/kg every 2 weeks SC and with no prior T-cell redirection therapy), the proportions of patients who achieved at least a 10-point improvement from baseline through cycle 7, day 1 in the 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 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%), and neutropenia (35% and 28%). Serious TEAEs occurred in 53% of patients in model cohort A and 48% of patients in model cohort C; the most frequently reported serious TEAEs were CRS (17% and 10%), pyrexia (6% and 5%), and ICANS (4% in both cohorts). In general, the proportions of patients with overall or specific TEAEs, and specific serious TEAEs, were similar between the 2 cohorts, with a higher rate in model cohort A than 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 model cohort A and model cohort C, for patients with at least 1 neurologic TEAE (86% in both cohorts), neurotoxicity events (31% and 30%), and ICANS (11% in both groups). The rate of CRS was 79% in model cohort A and 75% in model cohort C. The proportion of patients who experienced an infection of any severity was 59% in model cohort A and 66% in model cohort C.

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 as well as bias in the assessment of PFS, ORR, DoR, CR or better, HRQoL, and some AEs, although

assessment bias was mitigated by using an IRC, which 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. Although there was a lack of multiplicity adjustment for the ORR analyses, P values were small, suggesting that these were not false-positive results. ORR was examined in prespecified clinically relevant subgroups; however, the sample size for the subgroup analyses was 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 of the 2 recommended dosing regimens), further limiting interpretation of results for these patients. At the data cut-off and across the model cohorts, [redacted] of patients were lost to follow-up for OS, and [redacted] of patients withdrew consent to study participation. It appears that the impact of missing data on OS and PFS was minimal. The data for OS in all 3 model cohorts were immature; therefore, the treatment benefit of OS based on the analysis at the latest data cut-off would have been subject to uncertainty. At the data cut-off and across the model cohorts, 39% to 58% of patients received 1 or more subsequent antimyeloma therapies, which may influence the assessment of efficacy of talquetamab on OS and PFS. The clinical expert noted that it is reasonable to use the literature-reported, 10-point improvement from baseline value in EORTC QLQ-C30 score as the clinically meaningful improvement threshold in data analysis. The size of the HRQoL-evaluable population in phase II 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 was a lack of ethnic diversity in the data, as most patients in the MonumenTAL-1 trial were white (86% to 90%), while 6% to 8% were Black or African American and 1% to 4% were Asian, among others. Previous studies in the US found that MM is twice as common in African American individuals compared to white or Asian individuals. The clinical expert pointed out that the patients in the MonumenTAL-1 trial were relatively younger and had less severe disease than the RRMM patients typically seen in clinical practice in Canada. These factors may potentially impact the generalizability of the study results, although the extent of this impact is uncertain.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for Grading of Recommendations Assessment, Development and Evaluation (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 cohort.

Table 1 presents the GRADE summary of findings for talquetamab in adult patients with RRMM who have received at least 3 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.

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[a] 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[b]	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[a] 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[b]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg q.2.w. SC on OS when compared with any comparator.
Progression-free survival				
PFS Median (range) follow-up: 18.8 (0.5[a] 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[b]	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[a] 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[b]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg q.2.w. 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[a] 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[b]	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[a] 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[b]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg q.2.w. SC on ORR when compared with any comparator.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
DoR among responders[c]				
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[b]	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[b]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg q.2.w. 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[a] 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[b]	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[a] 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[b]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg q.2.w. 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 II 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[b,d]	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 II 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[b,d]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg q.2.w. SC on EORTC QLQ-C30 pain, fatigue, GHS, and physical functioning scores when compared with any comparator.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Notable harms				
Notable harms Median follow-up: 18.8 (0.5[a] to 32.9) months	143 (1 single-arm trial: phase I/II model cohort A)	CRS: 790 per 1,000 ICANS: 107 per 1,000 Infection: 587 per 1,000	Very low[b]	The evidence is very uncertain about the effect of talquetamab 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[a] to 26.1) months	145 (1 single-arm trial: phase I/II model cohort C)	CRS: 745 per 1,000 ICANS: 110 per 1,000 Infection: 662 per 1,000	Very low[b]	The evidence is very uncertain about the effect of talquetamab 0.8 mg/kg q.2.w. 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 Organisation 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; q.2.w. = every 2 weeks; RP2D = recommended phase II dose; SC = subcutaneous; sCR = stringent complete response; VGPR = very good partial response.

Note: Study limitations (which refer 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 the clinical cut-off date of January 17, 2023, for the 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 I and phase II of the MonumenTAL-1 trial. Model cohort C included patients with no prior T-cell redirection therapy treated at the RP2D of 0.8 mg/kg q.2.w. SC in phase I and phase II of the MonumenTAL-1 trial.

[a]Following this value, there was a "+" symbol, denoting patients who died, in the sponsor's submission.

[b]In the 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.

[c]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.

[d]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 II cohort A, and data were available for 60 patients compared 88 or 99 patients at baseline for phase III cohort C for EORTC QLQ-C30 scales of pain, fatigue, GHS, and physical functioning).

Source: Clinical Study Report for MonumenTAL-1 trial (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 onward) per patient per 28 days Biweekly dosing schedule: $36,878 (cycle 1) and $27,184 (cycle 2 onward) 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 noninterventional 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 CDA-AMC 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 were 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 modelling approach suggested a longer survival benefit in the postprogression period for talquetamab, a concern raised by clinical experts due to the lack of supporting evidence. Specifically, the

Component	Description
	model predicts that 73% and 50% of the incremental survival benefit of talquetamab in the weekly and biweekly dosing groups, respectively, occurs after the treatment has ceased controlling the disease. • 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 health care 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, the sponsor 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 health care 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.
CDA-AMC reanalysis results	• Given the uncertainty regarding the talquetamab dosing schedule likely to be preferred in clinical practice, CDA-AMC conducted base case reanalyses to assess the cost-effectiveness of talquetamab when used on a weekly dosing schedule and a biweekly dosing schedule. The CDA-AMC base case reanalyses were derived by adopting the exponential distribution to extrapolate OS for talquetamab. • In the CDA-AMC 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 (incremental costs: $435,516; incremental QALYs: 1.38). • In the CDA-AMC 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 (incremental costs: $452,471; incremental 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. • CDA-AMC calculated a weighted ICER based on clinical expert input, which indicated that 90% of patients treated with talquetamab would receive biweekly dosing and the remaining 10% would receive weekly dosing. The weighted CDA-AMC 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. • CDA-AMC 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; ITC = indirect treatment comparison; KCd = carfilzomib plus cyclophosphamide plus dexamethasone; Kd = carfilzomib plus dexamethasone; mAb = monoclonal antibody; OS = overall survival; PCd = pomalidomide plus cyclophosphamide plus dexamethasone; Pd = pomalidomide plus dexamethasone; PFS = progression-free survival; PI = proteasome inhibitor; PSM = partitioned survival model; QALY = quality-adjusted life-year; RRMM = relapsed or refractory multiple myeloma; SVd = selinexor plus bortezomib plus dexamethasone; vs. = versus.

Budget Impact

CDA-AMC identified the following limitations in the sponsor's base case: the calculation of the budget impact analysis (BIA) is uncertain, the proportion of patients with newly diagnosed MM receiving therapy in the 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. CDA-AMC 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 CDA-AMC 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 3-year cumulative total of $64,132,073.

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

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for talquetamab for the treatment of adult patients with RRMM who have received at least 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. In their request, the sponsor identified the following issues:

- The sponsor requested that pERC reconsider the challenge of overcoming refractoriness and treatment resistance for patients with RRMM, and the importance of treatment options with a novel therapeutic target. The potential benefits of talquetamab as a GPRC5D-targeting therapy were highlighted in addressing resistance or refractoriness to funded and recommended therapies, providing a distinct safety profile from BCMA-targeting therapies, and supporting individualized treatment decisions.
- The sponsor requested that pERC reconsider the significant unmet need for clinically effective treatments in patients who have received a prior BCMA-targeting therapy due to the lack of standard of care, and lack of treatment options with a non-BCMA target, poor treatment outcomes in patients with RRMM who are triple-class exposed, and expected increase in the number of patients who are exposed to BCMA-targeted therapies.
- The sponsor requested that pERC reconsider the totality of comparative evidence, trial data, and clinical expert opinion in the context of the need for treatments with novel targets, lack of a standard of care, and poor outcomes in triple-class exposed (TCE) patients, and to re-evaluate the net clinical benefit of talquetamab in this context. The sponsor described and cited data (including some data that became available after the original submission) to support arguments about potential efficacy benefits of talquetamab versus RWPC therapies in patients with and without prior exposure to a T-cell redirection therapy and its comparable efficacy to teclistamab; the consistency of efficacy results

across MonumenTAL-1 study cohorts, subgroups, and data cuts; and appropriateness of a single-arm trial design.
- The sponsor requested that pERC reconsider how talquetamab addresses patient needs for an additional treatment option with manageable AEs, which may provide improved accessibility, portability, and ease of implementation when compared to alternative treatments.

In the meeting to discuss the sponsor's request for reconsideration, pERC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- supplemental information provided by the sponsor, including conference abstracts and data cited in the submitted request for reconsideration form
- feedback from 1 clinical specialist with expertise in the diagnosis and treatment of patients with RRMM
- feedback on the draft recommendation from 2 patient groups, Myeloma Canada and the Leukemia and Lymphoma Society of Canada (LLSC)
- feedback on the draft recommendation from 1 clinician group, the OH-CCO Hematology Cancer Drug Advisory Committee
- feedback on the draft recommendation from the public drug programs that participate in the Reimbursement Review process
- feedback on the draft recommendation from the sponsor.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

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, and Danica Wasney.

Initial meeting date: October 9, 2024

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

Reconsideration meeting date: February 12, 2025

Regrets: None

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.