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CADTH Reimbursement Recommendation

Teclistamab (Tecvayli)

Indication: For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Sponsor: Janssen Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Tecvayli?

CADTH recommends that Tecvayli (teclistamab) be reimbursed by public drug plans for the treatment of adults with relapsed or refractory (r/r) multiple myeloma (MM) 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 the last therapy if certain conditions are met.

Which Patients Are Eligible for Coverage?

Tecvayli should only be covered to treat adults with MM who have received at least 3 prior treatments, have disease that has not responded to their last treatment, and are in relatively good health. Tecvayli should not be reimbursed to treat those whose MM is affecting their brain or spinal cord or those showing signs that the tissue layers protecting the brain and spinal cord are affected by MM. It also should not be reimbursed in those with amyloidosis (a buildup of a protein, amyloid, in organs) that is not secondary to MM, and those with plasma cell leukemia.

What Are the Conditions for Reimbursement?

Tecvayli should only be reimbursed if it is prescribed and administered by health professionals at treatment centres with adequate medical resources and personnel.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Tecvayli may result in response to treatment, delay the time to disease progression, and allow patients to live longer.
- Tecvayli may meet some patient needs because it may be an effective treatment option with manageable side effects.
- Based on CADTH's assessment of the health economic evidence, Tecvayli does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Tecvayli is estimated to cost the public drug plans approximately $180 million over the next 3 years.

Summary

Additional Information

What Is MM?

MM is a cancer of plasma cells (i.e., white blood cells) in the bone marrow (i.e., the soft matter inside bones where blood cells are made). Approximately 4,000 people in Canada were diagnosed with MM in 2022.

Unmet Needs in MM

MM is an incurable disease with a poor prognosis. MM often does not respond to initial treatments and will relapse, so the patient will need to try many different treatments. There is a need for additional treatment options that prolong survival, delay disease progression, improve quality of life, and reduce side effects.

How Much Does Tecvayli Cost?

Treatment with Tecvayli is expected to cost approximately $29,608 per patient for the first 28 days on treatment and $26,964 per patient for all 28-day cycles thereafter.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that teclistamab be reimbursed for the treatment of adult patients with r/r MM who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase I/II, single-arm, open-label trial (MajesTEC-1) demonstrated that treatment with teclistamab may result in benefits in clinical response rates, overall survival (OS), and progression-free survival (PFS) for adults with r/r MM 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 63.0% (95% confidence interval [CI], 55.2% to 70.4%) in this heavily pretreated population, which met the prespecified primary end point [redacted]), and complete response or better was 45.5% (95% CI, 37.7% to 53.4%), which were considered clinically meaningful by clinical experts. Although associated with uncertainty due to the single-arm design of the MajesTEC-1 trial, the OS and PFS results were considered promising by pERC. After a median duration of follow-up of 22.8 months, the median OS was 21.9 months (95% CI, 15.1 to not evaluable [NE] months) and the [redacted]. The median PFS was 11.3 months (95% CI, 8.8 to 16.4 months) and the [redacted]. Furthermore, despite uncertainty in the results of the indirect treatment comparisons (ITCs) because of methodological limitations, there was consistency in the direction of effects that favoured teclistamab over real-world physician's choice (RWPC) therapy across the outcomes assessed, including clinical responses, OS, and PFS. Teclistamab treatment was associated with a manageable toxicity profile.

Patients identified a need for accessible and effective treatment options, beyond the third-line setting, that delay disease progression, prolong survival, improve quality of life, and have manageable side effects with ease of administration. Given the totality of the evidence, pERC concluded that teclistamab may be an effective and more accessible treatment option with manageable side effects that may delay disease progression and prolong survival. While recognizing the uncertainty in the evidence, pERC acknowledges that teclistamab could be more accessible than the relevant comparator, chimeric antigen receptor (CAR) T-cell therapy.

Using the sponsor-submitted price for teclistamab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for teclistamab was $506,518 per quality-adjusted life-year gained compared with treatment of physician's choice in the submitted population. At this incremental cost-effectiveness ratio, teclistamab is not cost-effective at a $50,000 per quality-adjusted life-year willingness-to-pay threshold. A price reduction is required for teclistamab to be considered cost-effective at this threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Teclistamab should be reimbursed in adults aged 18 years or older who meet all the following criteria: 1.1. documented diagnosis of MM 1.2. documented evidence of progressive disease within the previous 6 months 1.3. received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody 1.4. refractory to their last treatment 1.5. must have good performance status.	In the MajesTEC-1 trial, treatment with teclistamab demonstrated a clinical benefit in adults with a documented diagnosis of MM who had received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody; had documented progressive disease; and had an ECOG PS of 0 or 1.	pERC acknowledged that clinicians may consider using teclistamab for patients with an ECOG PS ≥ 2 at their discretion.
2. Teclistamab should not be initiated in patients with active CNS involvement or those who are exhibiting signs of meningeal involvement of MM, primary amyloidosis, or plasma cell leukemia.	The MajesTEC-1 trial excluded patients with active CNS involvement or who were exhibiting signs of meningeal involvement of MM, primary amyloidosis, or plasma cell leukemia.	—
Discontinuation		
3. Treatment with teclistamab should be discontinued upon any of the following, whichever occurs first: 3.1. disease progression 3.2. unacceptable toxicity.	Treatment with teclistamab in the MajesTEC-1 study was given until disease recurrence or unacceptable toxicity, whichever occurred first.	—
Prescribing		
4. Teclistamab should be administered by health professionals at treatment centres with adequate medical resources and personnel to manage severe reactions, including cytokine release syndrome and neurologic toxicities.	To ensure that teclistamab is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	pERC recognized that access to tocilizumab for the treatment of cytokine release syndrome is necessary.
Pricing		
5. A reduction in price	The ICER for teclistamab is $506,518 per QALY gained when compared to TPC. A price reduction of at least 89% would be required for teclistamab to achieve an ICER of $50,000 per QALY compared to TPC. Uncertainty remains because of the limitations of the indirect comparative evidence, and it was noted that higher price reductions may be required.	—

Reimbursement condition	Reason	Implementation guidance
Feasibility of adoption		
6. Feasibility of adoption of teclistamab must be addressed.	At the submitted price, the incremental budget impact of teclistamab is expected to be greater than $40 million in years 2 ($57,027,919) and 3 ($92,228,347).	—

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; MM = multiple myeloma; pERC = pCODR Expert Review Committee; QALY = quality-adjusted life-year; TPC = treatment of physician's choice.

Discussion Points

- Considering the severity of r/r MM in adults and the significant unmet need for effective treatments in the fourth-line and later setting, pERC concluded that although the available efficacy and safety evidence was from a single-arm, noncomparative phase I/II trial, based on the totality of the evidence, teclistamab has the potential to reduce morbidity and mortality associated with the disease.
- pERC discussed additional supporting data for patients previously treated with a B-cell maturation antigen (BCMA)-targeted therapy. The findings from this analysis were consistent with the results from the pivotal cohort in the MajesTEC-1 trial; however, only 40 patients were included, which limits interpretation of the cohort findings. While pERC agreed with the clinical experts that patients previously treated with a BCMA-targeted therapy (e.g., CAR T-cell therapy) may be eligible for treatment with teclistamab, pERC noted that there is limited evidence for using teclistamab in patients previously treated with BCMA-targeted therapy (e.g., CAR T-cell therapy or an antibody-drug conjugate, such as belantamab).
- pERC discussed that the dosage of teclistamab can be switched from weekly to every 2 weeks or monthly dosing after response criteria are met, or due to adverse events (AEs). In the MajesTEC-1 study, patients could change from weekly dosing of teclistamab to every 2 weeks or monthly dosing due to AEs, or if the patient achieved partial response (PR) or better and received a minimum of 4 cycles of therapy (phase 1) or complete response (CR) or better for a minimum of 6 months (phase 2). pERC concluded that there is limited evidence that switching teclistamab to every 2 weeks or monthly dosing is as effective as teclistamab taken weekly.
- pERC discussed the ITCs submitted by the sponsor, including 4 ITCs that used inverse probability of treatment weighting (IPTW) and 2 unanchored matching-adjusted indirect comparisons (MAICs) of teclistamab relative to RWPC therapy, ciltacabtagene autoleucel, belantamab mafodotin, and selinexor plus dexamethasone. pERC noted that although teclistamab was favoured over RWPC therapy for clinical responses, OS, PFS, and time to next treatment (TTNT), the comparative efficacy estimates remain uncertain because of the methodological limitations, heterogeneity in the populations and studies, and potential for residual confounding. pERC noted that indirect evidence comparing the results from the MajesTEC-1 trial to ciltacabtagene autoleucel suggested that treatment with teclistamab was inferior to ciltacabtagene autoleucel for OS, PFS, and TTNT; however,

these findings must be interpreted in the context of the methodological limitations of these studies, which likely limit these findings.

- pERC considered that the results of the MajesTEC-1 study showed that treatment with teclistamab may have had clinically meaningful improvements from baseline in health-related quality of life (HRQoL). Patients and clinicians highlighted improvement in HRQoL as an important outcome and treatment goal for patients with r/r MM. In the MajesTEC-1 trial, HRQoL was assessed as a secondary outcome; however, analyses of HRQoL outcomes were undertaken post hoc, which introduces a risk of bias in the selection of the reported results. In addition, the results of these measures were at risk of bias due to missing data, particularly at longer follow-up time points, as the analyses were performed in patients for whom HRQoL could be evaluated and the size of this population in the MajesTEC-1 study gradually decreased over time. In addition to a diminishing sample size, the patients reporting HRQoL outcomes later in the study are expected to be the healthiest among the population.
- pERC noted that uncertainties remain regarding the implementation of teclistamab and the systems needed to optimize timely access and deliverability of teclistamab in the real-world setting. Teclistamab must be administered at specialized treatment centres with the infrastructure and resources required to administer the treatment and manage AEs. However, a limited number of centres in Canada have the expertise and resources to deliver teclistamab and other cytokine release syndrome (CRS) and cell-associated neurotoxicity syndrome (ICANS) management as needed, and it is unlikely that qualified centres will be available in all jurisdictions. pERC considered that some patients may be unable to travel outside their province or country to receive therapy. pERC acknowledged the input from clinical experts that patients starting treatment with teclistamab will receive the first 2 doses in the hospital, and after that can safely receive ongoing therapy in an outpatient setting on a case-by-case basis.
- pERC noted that patients expressed a need for treatments that have fewer side effects. pERC noted that the AEs in the MajsesTEC-1 study were manageable; however, access to supportive treatments for AEs is needed (e.g., tocilizumab to treat CRS of any grade). No safety outcomes were included in any of the ITCs; therefore, pERC could not draw definitive conclusions about the safety of teclistamab relative to other treatments currently available.
- pERC noted that the Health Canada indication for teclistamab is for the treatment of r/r MM after receiving at least 3 prior lines of therapy. Patients are generally exposed to a PI, an IMiD, and an anti-CD38 mAb in earlier lines of therapy. The clinical experts expressed that patients who are resistant or intolerant to a PI, an IMiD, and an anti-CD38 mAb should be eligible to receive teclistamab at the point that these therapies are no longer effective or appropriate regardless of what line of therapy it is in.
- pERC discussed the cost-effectiveness of teclistamab versus ciltacabtagene autoleucel. It was noted that relative to teclistamab, ciltacabtagene autoleucel was associated with higher costs, but may also provide higher benefit. However, comparative effectiveness is highly uncertain based on the available evidence. Given that ciltacabtagene autoleucel is currently under negotiation at the pan-Canadian

Pharmaceutical Alliance (pCPA) and may not be displaced by teclistamab if funded, pERC noted that the cost-effectiveness of teclistamab relative to RWPC was the more relevant comparison.

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 2022, it was estimated that 4,000 people in Canada were diagnosed with MM and 1,650 people in Canada died from MM. The 5-year survival probability 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 those with MM will relapse and many will have disease that becomes refractory to commonly used therapies. The most common symptoms of MM are fatigue and bone pain, with others including kidney problems, recurrent infections, fever, and nervous system problems. Patients with r/r MM often undergo multiple rounds of treatment, with the duration of remission, depth of response, PFS, and OS decreasing with each subsequent line of therapy. There is no preferred standard of care for treatment of r/r MM in the fourth-line and beyond setting, and at this stage of the disease patients may be exposed to a PI, an IMiD, and an anti-CD38 mAb, and in some cases receiving more than 1 PI or IMiD, which further limits treatment options in later lines of therapy. The clinical experts noted that treatment options at relapse include PI (e.g., bortezomib, carfilzomib)-containing combinations such as cyclophosphamide plus bortezomib and dexamethasone (CYBOR-D), carfilzomib plus dexamethasone with or without cyclophosphamide, or selinexor plus bortezomib and dexamethasone. The clinical experts and clinician groups agreed that there is an unmet need for treatments beyond the third line that prolong survival, delay disease progression, prevent disease complications, improve quality of life, and minimize side effects.

Teclistamab injection is indicated for the treatment of adults with r/r MM 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 the last therapy. Teclistamab is a bispecific antibody that targets the CD3 receptor expressed on the surface of T cells and BCMA expressed on the surface of malignant MM and healthy B-lineage cells and plasma cells. Teclistamab redirects CD3-positive T cells to BCMA-expressing myeloma cells to induce tumour cell destruction. The recommended dosage for teclistamab is 1.5 mg/kg of body weight after receiving step-up doses of 0.06 mg/kg and 0.3 mg/kg of body weight. One to 3 hours before each teclistamab step-up dose and the first full-strength treatment dose, all patients must receive a corticosteroid (16 mg oral or IV dexamethasone), an antihistamine (50 mg oral or IV diphenhydramine or equivalent), and an antipyretic (650 mg to 1,000 mg oral or IV acetaminophen or equivalent).

Sources of Information Used by the Committee

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

- a review of 1 phase I/II, open-label, multicentre clinical study in patients with r/r MM

- patient perspectives gathered by 1 patient group: Myeloma Canada
- input from the public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with r/r MM
- input from 2 clinician groups, the Canadian Myeloma Research Group (CMRG) and the 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
- a review of the indirect evidence from 6 ITCs submitted by the sponsor.

Stakeholder Perspectives

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

Patient Input

CADTH received 1 patient group submission from Myeloma Canada, which has existed for more than 15 years to support the growing number of people in Canada diagnosed with myeloma, and those living longer than ever with the disease access new and innovative therapies. Myeloma Canada gathered information for this review through a patient and caregiver survey (33 patients and 3 caregivers) that was conducted from August 28 to September 6, 2023.

Patient respondents indicated that their ability to travel was the most significantly impacted by symptoms associated with myeloma, followed by their ability to work and to exercise. Patient and caregiver respondents identified the following factors as the most important to myeloma treatment: improved quality of life; manageable side effects; effectiveness of the treatment, especially in achieving remission and having a long and durable response; and treatment accessibility or portability (including fewer or minimal visits to the hospital or cancer centre). In terms of treatment outcomes, of the 22 respondents, 13 rated improved quality of life as extremely important, 6 as very important, and 3 as somewhat important. A total of 17 of the 22 patients rated the estimated minimum of 1 year to 21 months of life extension as extremely desirable, and 5 as very desirable. All caregiver respondents felt that caring for someone with myeloma had the most impact on "anxiety/worry," followed by "interruption of life goals/accomplishments (career, retirement, etc.)."

From August 28 to September 30, 2022, Myeloma Canada also conducted a different survey about a CAR T-cell therapy that received more than 200 responses, 2 of the respondents had experience with CAR T-cell therapy; whereas, in the teclistamab survey that received far fewer (33) total responses, there were 11 patients with teclistamab experience. Myeloma Canada emphasized that this is indicative of the comparative ease with which teclistamab can and has been made accessible to people in Canada who have triple-class exposed r/r MM.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH for this review highlighted that the most important goals of treatment for patients with MM are to prolong survival, delay disease progression, prevent disease complications, improve quality of life, and minimize side effects. The clinical experts noted that clinicians try not to reuse the same drugs in subsequent lines of therapy, and after receiving 3 lines of therapy, the majority of patients will have disease that is triple refractory and will need new families of drugs. The clinical experts also mentioned that beyond the third line of therapy, the treatment options get more restricted, and some patients' disease does not respond to the current standard therapies. Thus, there is a need for treatments for the fourth-line and beyond setting that are tolerable for patients. The clinical experts consulted by CADTH indicated that, given that the prognosis of MM worsens as patients move on to subsequent lines of therapy, any patient with r/r MM will require this intervention. The clinical experts noted that teclistamab in not the first approved treatment that targets BCMA expression on the myeloma cell; however, this drug has a novel mechanism of action that is very different from any currently available therapies. The clinical experts agreed that there is no evidence that some patients are more likely to respond to treatment, and there are no disease-specific characteristics that would make a patient ineligible for treatment with teclistamab. The clinical experts noted that teclistamab represents a new class of drugs that can help sustain quality of life and extend the duration of life in patients with r/r MM.

The clinical experts identified OS, PFS, and clinical response outcomes as the most important outcomes for assessing the response to treatment. They agreed that the best possible response to treatment would be a CR that is minimal residual disease (MRD)-negative, and less important responses include CR, very good partial response (VGPR), PR, and stable disease. The clinical experts further noted that CR and VGPR are the most desirable outcomes in most situations, even achieving stable disease is acceptable. The clinical experts consulted by CADTH indicated that the main reason for discontinuing treatment with teclistamab would be relapse of MM. The clinical experts further noted that, as with any treatment, it can be expected that some patients will be forced to discontinue treatment due to intolerable side effects. The clinical experts consulted mentioned that, currently, all patients receiving teclistamab are treated at tertiary care centres and are admitted to the hospital for the first few doses. The clinical experts also noted that depending on the situation, patients starting treatment with teclistamab will require treatment at a larger hospital capable of providing management and monitoring; however, after patients receive the first few doses of this treatment, they can receive ongoing therapy at community centres and smaller cancer centres.

Clinician Group Input

The clinician group input was obtained from 2 clinician groups, CMRG and OH-CCO's Drug Advisory Committees. CMRG gathered information through teleconferences with physicians, and OH-CCO's Drug Advisory Committees gathered information through videoconferencing and email communications.

Both CMRG and OH-CCO's Drug Advisory Committees mentioned that myeloma remains incurable, and patients' disease eventually becomes refractory to all available funded drugs. One major unmet need mentioned by clinician groups is that patients with advanced disease who have received multiple lines of

treatment and have already received the 3 major drugs (i.e., those who are triple-class exposed or have refractory disease), including an IMiD, a PI, and an anti-CD38 mAb, have no other substantial treatment options other than CAR T-cell therapy. CMRG also emphasized that the clinical features associated with advanced disease and short duration of responses lead to a poor quality of life, significant caregiver burden, and a shortened patient lifespan. Thus, this situation also represents 1 of the most pressing unmet needs in Canada for patients with MM. 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).

Both clinician groups agreed that teclistamab is another option for patients who are triple-class exposed. They believe that, currently, it would be used in sequence after other lines of therapy for myeloma (i.e., after failure of multiple drugs); it is not expected to impact the sequencing of drugs earlier in the disease course or lead to a major change in treatment algorithms before patients become triple-class exposed or have refractory disease.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process.

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs. Refer to Table 2 for details.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	pERC response
Relevant comparators	
How does teclistamab compare to currently funded options in this therapeutic space (i.e., pomalidomide plus dexamethasone with or without cyclophosphamide and carfilzomib plus dexamethasone with or without cyclophosphamide)? Selinexor plus bortezomib and dexamethasone is funded in some jurisdictions as fourth-line therapy (and beyond) for patients who are sensitive to bortezomib but not anti-CD38s and lenalidomide.	pERC agreed with the clinical experts that teclistamab in the MajesTEC-1 study has better progression-free survival when indirectly compared with that of pomalidomide in combination dexamethasone with or without cyclophosphamide, or carfilzomib in combination with dexamethasone with or without cyclophosphamide. However, teclistamab would be used when patients with r/r MM have received pomalidomide or carfilzomib, or both.
Cilta-cel is also used in this setting; however, it is under consideration for negotiation. The CADTH reimbursement conditions for cilta-cel specified that it should not be reimbursed in patients who have received prior treatment with therapy targeting BCMA.	No response required; for pERC consideration.
Considerations for initiation of therapy	
Should patients previously treated with BCMA-targeted therapy (e.g., cilta-cel) be eligible for teclistamab? Is there evidence to support this sequence? Should patients treated with teclistamab be eligible for CAR T-cell therapy (e.g., cilta-cel)? Is there evidence to support this sequence?	While pERC agreed with the clinical experts that it would be reasonable to consider patients previously treated with a BCMA-targeted therapy (e.g., CAR T-cell therapy) eligible for teclistamab, pERC noted that there is limited evidence to support this. PERC additionally noted that there was no evidence included in this CADTH review to support the appropriateness of CAR T-cell therapy in patients previously treated with teclistamab.

Drug program implementation questions	pERC response
The Health Canada approval is for patients who have had at least 3 prior lines of therapy, including a proteosome inhibitor, an IMiD, and an anti-CD38. Patients who could not tolerate a PI, an IMiD, or an anti-CD38 mAb were allowed, per the MajesTEC-1 trial. Are 3 prior lines of therapy required if a patient is resistant to a PI, an IMiD, and an anti-CD38 mAb (e.g., received all 3 classes of these drugs, but across 2 lines of therapy)?	There is no evidence reviewed to inform the use of teclistamab in early lines of therapy. Aligned with the Health Canada–approved indication, the reimbursement request for teclistamab is for the treatment of adults with r/r MM 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 the last therapy. pERC acknowledged the clinical experts' opinion that patients who are resistant to PIs, an IMiD, and an anti-CD38 mAb (i.e., all 3), or are intolerant to any of them and resistant to the others should be eligible to receive teclistamab, regardless of what line of therapy it is in.
Considerations for discontinuation of therapy	
Patients with prolonged treatment interruptions may require readministration of step-up dosing.	No response required; for pERC consideration.
Considerations for prescribing of therapy	
Teclistamab must be administered according to a step-up dosing schedule: • 0.06mg/kg SC on day 1 (step-up dose 1) • 0.3mg/kg SC on day 3 (step-up dose 2; may be given 2 to 7 days after step-up dose 1) • 1.5mg/kg SC on day 5 (first treatment dose; may be given 2 to 7 days after step-up dose 2) • followed by 1.5 mg/kg SC weekly beginning 1 week after first treatment dose. The 10 mg/mL vial is used for step-up dose 1 and step-up dose 2, while 90 mg/mL is used for the remaining doses. The trial protocol allowed patients to be switched to an every 2 weeks dosing schedule (1.5 mg/kg SC every 2 weeks) if they showed a complete response or greater for a minimum of 6 months. Can pERC clarify the dosing schedule for teclistamab, including when every 2 weeks dosing would be appropriate?	pERC acknowledged that clinical experts noted that switching from weekly to every 2 weeks dosing should occur primarily due to side effects, toxicity, or patient choice. The clinical experts also noted that in clinical practice, physicians typically switch to less frequent dosing once the patient has responded to treatment. However, pERC concluded that there is limited evidence that teclistamab, when switched to every 2 weeks dosing, is as effective as weekly dosing.
CRS and ICANS can occur with teclistamab, although the severity and incidence appeared to be low in the trial. Tocilizumab may be needed to treat CRS. Can teclistamab be safely administered in the outpatient setting?	pERC acknowledged that the clinical experts noted that patients starting treatment with teclistamab will first receive 2 to 3 doses in the hospital, and after that they can safely receive ongoing therapy in an outpatient setting on a case-by-case basis. pERC highlighted that hospitalization may likely be needed for patients who have CRS requiring tocilizumab.
The product monograph recommends that patients remain within proximity of a health care facility and monitor daily for 48 hours for signs and symptoms of CRS after administration of all doses within the teclistamab step-up dosing schedule, or alternatively that hospitalization is considered. Patients who experience more than grade 1 CRS should be monitored daily for 48 hours following the next dose of teclistamab and remain within proximity of a health care facility.	No response required; for pERC consideration.

Drug program implementation questions	pERC response
Jurisdictions may encounter capacity issues due to supportive care requirements.	
Generalizability	
Should teclistamab be used in the following patients? Those with: • an ECOG PS greater than 1 • CNS disease that is under treatment or controlled • plasma cell leukemia or amyloidosis.	pERC acknowledged that the clinical experts expressed that teclistamab can be used in patients with MM with an ECOG PS greater than 1, and in patients with CNS disease that is under treatment or controlled, although this is rare. Patients with plasma cell leukemia and those with primary amyloidosis were excluded from the MajesTEC-1 study; however, pERC agreed with the clinical experts who expressed that teclistamab can be used in patients with secondary amyloidosis as a complication of MM. The clinical experts also noted that teclistamab can be used in patients with plasma cell leukemia at usual doses; however, these patients in general are excluded from the trials because their disease is more aggressive.
At the time of funding, should patients receiving alternative therapies (i.e., Pd or Kd with or without cyclophosphamide) be eligible to switch to teclistamab?	pERC agreed with clinical experts that physicians usually would not switch effective treatments until they no longer work; however, it can be switched to another drug if it stops working.
Funding algorithm	
This is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	No response required; for pERC consideration.
There may be interest in sequencing teclistamab with other BCMA-targeted drugs.	No response required; for pERC consideration.
Care provision issues	
Teclistamab is supplied as 153mg/1.7mL (90mg/mL) and 30mg/3mL (10mg/mL); however, drug wastage would be incurred due to the step-up and mg/kg dosing. There is a risk of medication error with 2 different concentrations. The drug may need to be initiated in the inpatient setting, in which case, the drug cost would be outside of the drug program budget in some provinces.	No response required; for pERC consideration.
System and economic issues	
There is concern about feasibility of adoption (budget impact) in light of the cost of prior therapies and potential for subsequent therapies.	No response required; for pERC consideration.
Generic pomalidomide is available, and confidential pricing exists for carfilzomib.	No response required; for pERC consideration.

BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; cilta-cel = ciltacabtagene autoleucel; CNS = central nervous system; CRS = cytokine release syndrome; ECOG = Eastern Cooperative Oncology Group Performance Status; ICANS = immune effector cell-associated neurotoxicity syndrome; IMiD = immunomodulatory drug; Kd = carfilzomib plus dexamethasone; mAb = monoclonal antibody; MM = multiple myeloma; Pd = pomalidomide plus dexamethasone; pERC = pCODR Expert Review Committee; PI = proteosome inhibitor; r/r = relapsed or refractory; SC = subcutaneous.

Clinical Evidence

Systematic Review

Description of Studies

MajesTEC-1 (n = 165) is a phase I/II, open-label, multicentre study assessing the efficacy and safety of teclistamab administered to adults with r/r MM. The study is ongoing and being conducted in 39 sites across 10 countries, including patients in Canada who were enrolled at 4 sites in Canada. The MajesTEC-1 study was conducted in 3 parts, including part 1 or dose escalation (phase 1), part 2 or dose expansion (phase 1) at a proposed recommended phase 2 dose (1.5 mg/kg subcutaneously weekly), and part 3 or dose expansion (phase 2) in cohorts of patients with r/r MM with unmet medical needs (phase 2). The primary objectives reported in phase 1 of the MajesTEC-1 trial were to identify the proposed recommended phase 2 dose and dose schedule assessed to be safe in part 1, and then characterize the safety and tolerability of teclistamab at the proposed recommended phase 2 dose in part 2. The primary objective of phase 2 of the MajesTEC-1 trial was to evaluate the efficacy and safety of teclistamab at the proposed recommended phase 2 dose. In phase 2 of the MajesTEC-1 study, cohort A enrolled patients with r/r MM who had received at least 3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 mAb, while cohort C enrolled patients who had received at least 3 prior lines of therapy that included a PI, an IMiD, an anti-CD38 mAb, and an anti-BCMA treatment (CAR T-cell therapy or an antibody-drug conjugate). The primary efficacy outcome for the MajesTEC-1 trial was ORR and the secondary efficacy outcomes included VGPR or better, CR or better, stringent complete response (sCR), time to response (TTR), duration of response, OS, PFS, MRD-negative rate, and patient-reported outcomes. TTNT was an exploratory outcome in phase 2 of the MajesTEC-1 study. Disease responses were evaluated by an independent research committee (IRC) using International Myeloma Working Group (IMWG) 2016 criteria in both phase 1 and phase 2 cohort A.

In the MajesTEC-1 study, the median age of the patients was 64.0 years (range, 62.5 to 64.0 years), with [redacted]. Ninety-six patients (58.2%) were male and 69 patients (41.8%) were female. Most patients were white (81.2%) and 12.7% identified as Black. Most patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 1 (66.1%), and 33.3% of patients had an ECOG PS of 0. The most common immunoglobulin isotypes were immunoglobulin G (55.2%) and immunoglobulin A (17.6%). The median time from diagnosis of MM to enrolment in the study was 6.0 years (range, 0.8 to 22.7 years). Twenty-eight patients (17.0%) had 1 or more extramedullary plasmacytomas at baseline. Of the 147 patients with baseline cytogenetic data reported, 38 patients (25.9%) had at least 1 high-risk cytogenetic abnormality, including del(17p) abnormality (15.6%) and t(4;14) abnormality (10.9%). Of the 162 patients with baseline International Staging System (ISS) data reported, 85 patients (52.5%) were ISS stage I and 20 patients (12.3%) were ISS stage III.

Efficacy Results

The primary analysis at the clinical cut-off date of September 2021 and the final analysis at the clinical cut-off date of August 2023 were prespecified analyses, and the Clinical Study Reports submitted by the sponsor with clinical cut-offs of March 2022 and January 2023 were interim analyses. As the final report for

the pivotal study is not yet available, information for the following sections was extracted from the Clinical Study Report with a clinical cut-off date of January 4, 2023, which was submitted by the sponsor for this review. However, data from the clinical cut-off date of September 7, 2021, were also used to supplement the included data when necessary.

Overall Survival

At the time of analysis, using the January 4, 2023, data cut-off, the median duration of follow-up was 22.8 months (range, 0.3 to 33.6 months). The estimated median OS was 21.9 months (95% CI, 15.1 to NE months). In the full analysis set (FAS), deaths were reported in [redacted] in phase 1 and [redacted] in phase 2 cohort A of the MajesTEC-1 trial. The 9 months OS probability was [redacted], the 12 months OS probability was [redacted], and the 24 months OS probability was [redacted].

Progression-Free Survival

At the time of analysis, using the January 4, 2023, data cut-off, the estimated median PFS was 11.3 months (95% CI, 8.8 to 16.4 months) in the MajesTEC-1 trial. In the FAS, the 9-month PFS probability was [redacted], the 12-month PFS probability was [redacted], and the 24-month PFS probability was [redacted].

CR or Better

At the time of analysis, using the January 4, 2023, data cut-off, [redacted] in phase 1 and [redacted] achieved CR or better (i.e., CR or sCR).

Stringent Complete Response

[redacted]

MRD-Negativity Status

Updated data regarding the MRD-negativity rate based on the January 4, 2023, clinical cut-off date are not available.

At the time of the data cut-off date of September 7, 2021, 37 patients (24.7%; 95% CI, 18.0% to 32.4%) achieved MRD negativity at 10^{-5} bone marrow cells. Among 43 patients who achieved CR or better, 18 patients (41.9%; 95% CI, 27.0% to 57.9%) achieved MRD negativity at 10^{-5} bone marrow cells.

VGPR or Better

At the time of analysis, using the January 4, 2023, data cut-off, [redacted] in phase 1 and [redacted] achieved VGPR or better (i.e., VGPR, CR, or sCR).

ORR

At the time of analysis, using the January 4, 2023, data cut-off, 104 patients (63.0%) (95% CI, 55.2% to 70.4%) achieved an overall response (PR or better), and ORR was similar across patients treated in phase 1 and phase 2 cohort A [redacted]. Of the 104 responders who achieved PR or better, 51 patients (49.0%) maintained their response until the clinical cut-off date ([redacted]

[redacted]), including 46 patients (44.2%) who were still on treatment. Of the 104 responders, [redacted] had disease progression after initial response, of which [redacted] died after disease progression, [redacted] discontinued the study treatment, and [redacted] remain on study treatment. A total of 19 patients (18.3%) died after achieving response and without experiencing disease progression, and [redacted] had subsequent therapy after response and without progressive disease. Of the 63 respondents who changed their dosing schedule from weekly to every 2 weeks or monthly dosing, 42 patients (66.7%) maintained their response until the clinical cut-off date of January 4, 2023, including 41 patients (65.1%) who remain on treatment.

Subgroup Analysis

Only the results of the ORR subgroup analyses that were deemed clinically meaningful by the clinical experts consulted by CADTH for this review are reported. At the time of analysis, using the January 4, 2023, data cut-off, 32 of 43 patients (74.4%) who received 3 or fewer prior lines of therapy achieved an overall response. Of the 122 patients who received more than 3 prior lines of therapy, 72 patients (59.0%) achieved overall response and 32 of 60 patients (53.3%) with high cytogenetic risk and/or extramedullary disease achieved overall response.

Time to Response

At the time of analysis, using the January 4, 2023, data cut-off, in 104 responders, the median time to first response was 0.9 months (range, 0.2 to 2.3 months), while the median time to best response was 3.6 months (range, 1.7 to 18.7 months). Most patients demonstrated their first response by the start of cycle 2 of the MajesTEC-1 study.

Duration of Response

At the time of analysis, using the January 4, 2023, data cut-off, the median duration of response was 21.6 months (95% CI, 16.2 to NE months) in the MajesTEC-1 trial. Among 104 responders, [redacted] in phase 1 and [redacted] in phase 2 cohort A had disease progression or died due to any cause. The probability of patients remaining in response at 9 months was [redacted]. The probability of patients remaining in response at 18 months was [redacted]. The probability of patients remaining in response at 24 months was [redacted].

Patient-Reported Outcomes

Patient-reported outcomes were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) assessment, the EQ-5D-5L questionnaire, and the Patient Global Impression of Severity (PGIS) scale. The HRQoL results were reported only for phase 2 cohort A of the MajesTEC-1 study. Analyses were conducted in the population of those who had evaluable assessment at baseline and follow-up time points for each domain of the EORTC QLQ-C30 (i.e., cycle 2 day 1, cycle 3 day 1).

EORTC QLQ-C30

At the time of analysis, using the January 4, 2023, data cut-off, the results of a post hoc analysis of the EORTC QLQ-C30 showed [redacted].

At the time of analysis, using the September 7, 2021, data cut-off, meaningful improvement from baseline (i.e., 10 points using the literature-based meaningful change threshold[14]) to cycles 2, 4, and 6 was reported by up to 35.8% of patients for Global Health Status, up to 23.9% of patients for Physical Functioning, up to 68.7% of patients for Fatigue System, and up to 78.8% of patients for Pain.

EQ-5D-5L

At the time of analysis, using the January 4, 2023, data cut-off, the results of a post hoc analysis of the EQ-5D-5L showed [redacted].

At the time of analysis, using the September 7, 2021, data cut-off, meaningful improvement from baseline (i.e., 7 points using the literature-based meaningful change threshold[15,16]) in visual analogue scale scores at cycles 2, 4, and 6 was reported by 23.8%, 28.6%, and 30.2% of patients, respectively. By cycle 8, 50% of patients reported meaningful improvement in the visual analogue scale score.

Time to Next Treatment

TTNT was an exploratory end point in phase 2 cohort A of the MajesTEC-1 study and it was not reported in the Clinical Study Report at the clinical data cut-off date of January 4, 2023.

At the time of analysis, using the September 7, 2021, data cut-off, subsequent antimyeloma therapy and/or death due to progressive disease was reported for [redacted], with a median TTNT of [redacted].

Harms Results

At the time of analysis, using the January 4, 2023, data cut-off, patients in the MajesTEC-1 study experienced at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs occurring in at least 25% of patients in either phase of the study were CRS (72.1%), neutropenia (71.5%), anemia (54.5%), thrombocytopenia (42.4%), lymphopenia (36.4%), diarrhea (33.9%), and pyrexia (31.5%). In the MajesTEC-1 trial, [redacted] experienced Grade 3 TEAEs of Common Terminology Criteria for Adverse Events (CTCAE), [redacted] experienced Grade 4 TEAEs, and [redacted] experienced Grade 5 TEAEs. The most common Grade 3 or 4 TEAEs were neutropenia (65.5%), anemia (37.6%), lymphopenia (34.5%), and thrombocytopenia (22.4%). The most common Grade 5 TEAEs were COVID-19 (10.8%) and general physical health deterioration (2.4%). At the time of the analysis, using the January 4, 2023, data cut-off, 113 patients (68.5%) experienced at least 1 serious TEAE in the MajesTEC-1 trial. The most common serious TEAEs occurring in at least 5% of patients in either phase of the study were COVID-19 (68.5%), pneumonia (20.6%), CRS (10.9%), pyrexia (8.5%), acute kidney injury (5.5%), and general physical health deterioration (5.5%). At the time of analysis, using the January 4, 2023, data cut-off, [redacted] stopped the study treatment due to TEAEs in the MajesTEC-1 trial. The most common reasons for stopping study treatment included [redacted]. A total of [redacted] died during the study, [redacted] who died due to TEAEs.

In the MajesTEC-1 study, several AEs of clinical interest were identified, including CRS, neurologic AEs and neurotoxicity, immune effector ICANS, systemic administration–related reactions, injection-site reactions, hypogammaglobinemia, cytopenia, and infections. At the time of analysis, using the January 4, 2023, data cut-off, 119 patients (72.1%) experienced CRS events, of which 83 patients (50.3%) experienced grade 1 events and 35 patients (21.2%) experienced grade 2 events. One patient (0.6%) experienced a grade 3 CRS

events, and no patients experienced a grade 4 or grade 5 CRS event. [redacted]. In the MajesTEC-1 trial, a total of 132 patients (80.0%) had infections of any grade. The most common infections and infestations included [redacted]. In the MajesTEC-1 study, 71 patients (43.0%) experienced at least 1 grade 3 or 4 infection or infestation, while 21 patients (12.7%) experienced at least 1 grade 5 infection or infestation. At the time of the analysis, using the January 4, 2023, data cut-off, [redacted] experienced at least 1 hypogammaglobulinemia TEAE, including [redacted] with a case of hypogammaglobulinemia, and [redacted] with a case of hypoglobulinemia. A total of 152 patients (92.1%) experienced at least 1 treatment-emergent cytopenic event, including neutropenia (71.5%), anemia (55.8%), thrombocytopenia (42.4%), and lymphopenia (36.4%). A total of 108 patients (65.5%) experienced grade 3 or greater treatment-emergent neutropenia, 62 patients (37.6%) experienced grade 3 or greater anemia, 37 patients (22.4%) experienced grade 3 or greater thrombocytopenia, and 57 patients (34.5%) experienced grade 3 or greater lymphopenia. A total of 61 patients (37.0%) experienced at least 1 injection-site reaction event, including 32.1% grade 1 cases and 4.8% grade 2 cases.

Critical Appraisal

MajesTEC-1 was a multicentre, single-arm, open-label, phase I/II study. Due to the lack of a comparator arm, the benefit of teclistamab compared to placebo or reference treatment was not documented. A single-arm study design is usually used when the purpose of the study is to provide preliminary evidence of the efficacy of a treatment and to collect additional safety data; single-arm studies are not intended to be confirmatory for efficacy. Thus, a single-arm study design has several limitations that complicate the interpretation of the study results. The open-label design of the MajesTEC-1 study may increase uncertainty in subjective outcomes, including clinical response outcomes, PFS, HRQoL, and safety outcomes, and introduce bias because of inherent subjectivity of the outcome in an unblinded assessor. This bias would be less likely in more objective outcomes, such as OS, if assessed against a predetermined hypothesis. According to the FDA, the ORR can be evaluated in a single-arm study as a direct measure of drug antitumour activity if it is defined as the sum of PRs plus CRs. In the MajesTEC-1 trial, the estimated ORR was tested against a predetermined hypothesis of an ORR greater than 45% (with a lower bound of the ORR 2-sided 95% CI above 30%). ORR achieved the predetermined threshold for a positive outcome in the MajesTEC-1 trial. However, for ORR, there was no adjustment for multiplicity across the various analyses of the outcome (i.e., the various data cut-offs), which may have increased the risk of false-positive conclusions. Additionally, as this report presents interim analysis results because a prespecified final analysis was not available, there is the potential that the benefit of teclistamab is overestimated; however, the presence and extent of any overestimation is uncertain.

Disease responses were evaluated by the IRC using IMWG 2016 criteria in both phase 1 and phase 2 cohort A. The time-to-event end points, including OS and PFS, were identified as important outcomes by the clinical experts and the patient and clinician groups consulted by CADTH for this review. However, OS and PFS were not considered primary or key secondary outcomes in the MajesTEC-1 trial, and the lack of a comparator

group limits the estimation of relative effects of teclistamab treatment. In addition, the longer-term efficacy of teclistamab for OS and PFS is unknown as the MajesTEC-1 study is ongoing. The clinical experts and patient and clinician groups consulted by CADTH for this review highlighted improvement in HRQoL as an important outcome and treatment goal for patients with r/r MM. The analyses of HRQoL outcomes were undertaken post hoc, which introduces a risk of bias in the selection of the reported results. In addition, analyses for HRQoL were performed in patients considered evaluable for HRQoL and only for phase 2 cohort A rather than in the intention-to-treat (ITT) population of the MajesTEC-1 trial, which may have biased the results; however, the extent of the bias with respect to the direction and magnitude of the effect is uncertain. The size of the HRQoL-evaluable population in the MajesTEC-1 trial gradually decreased over time, and the rate of missing data was high among those who remained in the study at longer follow-up visits. Therefore, data from later time points should be interpreted with caution due to the possibility that HRQoL scores could be overestimated if patients with better HRQoL were more likely to complete the questionnaires.

According to the clinical experts, the patient population in the MajesTEC-1 study generally reflects patients in clinical practice in this setting. To be enrolled in the MajesTEC-1 study, patients with r/r MM were required to have an ECOG PS of 0 or 1 and have measurable disease. The clinical experts consulted noted that this would not be reflective of clinical practice and that clinicians would prescribe teclistamab to patients with an ECOG PS of 2 or 3 and to patients without biochemically measurable disease. Patients who had previously received antitumour therapy, such as a mAb or cytotoxic therapy within 21 days before the first dose of teclistamab were excluded from the study, which the clinical experts found concerning as a washout period of 21 days is less relevant in this population. One of the exclusion criteria of the pivotal MajesTEC-1 study was any prior BCMA-targeted therapy. Additional supporting data were presented for phase 2 cohort C at the time of the clinical cut-off date of March 16, 2022, to address the use of teclistamab in patients previously treated with BCMA-targeted therapy in accordance with the Health Canada indication for teclistamab. Findings from the phase 2 cohort C of the MajesTEC-1 study were consistent with the results from the pivotal cohort (phase 1 and phase 2 cohort A); however, only 40 patients were included, which limits interpretation of the cohort findings. According to the clinical experts consulted by CADTH, the demographic and disease characteristics of the MajesTEC-1 study population were reflective of patients living in Canada with r/r MM. The mean age of patients in the MajesTEC-1 trial was 64 years, with clinical experts noting that in the real-world setting, the mean age of patients with relapsed disease receiving fourth-line therapy and beyond would be around 70 years. About 26% of patients in the MajesTEC-1 study had at least 1 high-risk cytogenetic abnormality, including del(17p) and t(4;14), although the clinical experts noted that the proportion of patients with cytogenetic risk is slightly higher in clinical practice. In the MajesTEC-1 study, 63 patients (38.2%) switched from weekly to every 2 weeks dosing of teclistamab, including 54 patients who met the response criteria, and 9 patients had switched from every 2 weeks to monthly dosing. The clinical experts consulted by CADTH indicated that there would be more patients in clinical practice switching to less frequent dosing of teclistamab. According to the clinical experts consulted by CADTH, patient and clinician groups input, OS, PFS, clinical response outcomes, and HRQoL are the most important outcomes for assessing response to treatment. However, due to its study design, the MajesTEC-1 trial provides no information about the efficacy and harms of teclistamab relative to treatments that would otherwise be used in this patient population in clinical practice. In the MajesTEC-1 trial, the study population was drawn from

a number of sites around the globe, including Canada. The clinical experts indicated that there are no major concerns with generalizing the findings from the pivotal study to the clinical setting in Canada.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. Table 3 presents the GRADE summary of findings for teclistamab in patients with r/r MM in the MajesTEC-1 study.

Table 3: Summary of Findings for Teclistamab for Patients With r/r MM

Outcome and follow-up	Patients (study), N	Effect	Certainty	What happens
OS				
OS Median follow-up: 22.8 months	165 (1 single-arm trial: phase 1 and phase 2 cohort A)	Median (range) duration of OS of 21.9 months (15.1 months to NE)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on OS when compared with any comparator.
PFS				
PFS Median follow-up: 22.8 months	165 (1 single-arm trial: phase 1 and phase 2 cohort A)	Median (range) duration of PFS of 11.3 months (8.8 months to 16.4 months)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on PFS when compared with any comparator.
CR or better (CR or sCR)				
Proportion of patients who achieved CR or better Median follow-up: 22.8 months	165 (1 single-arm trial: phase 1 and phase 2 cohort A)	455 per 1,000 (95% CI, 377 to 534 per 1,000)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on CR or better when compared with any comparator.
VGPR or better (VPGR, CR, or sCR)				
Proportion of patients who achieved VGPR or better Median follow-up: 22.8 months	165 (1 single-arm trial: phase 1 and phase 2 cohort A)	594 per 1,000 (95% CI, 515 to 670 per 1,000)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on VGPR or better when compared with any comparator.
ORR (PR, VPGR, CR, or sCR)				
Proportion of patients who achieved overall response Median follow-up: 22.8 months	165 (1 single-arm trial: phase 1 and phase 2 cohort A)	630 per 1,000 (95% CI, 552 to 704 per 1,000)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on ORR when compared with any comparator.
Duration of response				
Duration of response (PR or better) Median follow-up: 22.8 months	165 (1 single-arm trial: phase 1 and phase 2 cohort A)	Median (range) duration of response of 21.6 months (16.2 months to NE)	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on duration of response when compared with any comparator.

Outcome and follow-up	Patients (study), N	Effect	Certainty	What happens
Harms				
Proportion of patients with hypogammaglobulinemia Median follow-up: 22.8 months	165 (1 single-arm trial: phase 1 and phase 2 cohort A)	212 per 1,000	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on hypogammaglobulinemia when compared with any comparator.
Proportion of patients with infections Median follow-up: 22.8 months	165 (1 single-arm trial: phase 1 and phase 2 cohort A)	800 per 1,000	Very low[a,b]	The evidence is very uncertain about the effect of teclistamab on infections when compared with any comparator.

CI = confidence interval; CR = complete response; MM = multiple myeloma; NE = not evaluable; ORR = objective response rate; r/r = relapsed or refractory; OS = overall survival; PFS = progression-free survival; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

[a]In the absence of a comparator arm, conclusions about efficacy relative to any comparator cannot be drawn and the certainty of evidence started at very low.

[b]Rated down 1 level for serious study limitations. The results are reported from an interim analysis and the effect may be overestimated. There is a risk of selection bias as it is not clear whether patients were enrolled consecutively.

Additional Supporting Data

In MajesTEC-1, efficacy and safety results for phase 2 cohort C were presented to support the results of the pivotal study in accordance with the Health Canada indication for teclistamab, and to address the question from the Provincial Advisory Group regarding the use of teclistamab in patients previously treated with BCMA-targeted therapy. Phase 2 cohort C enrolled patients with r/r MM who had received 3 or more prior lines of therapy, including a PI, an IMiD, an anti-38 mAb, and a BCMA-targeted treatment (e.g., CAR T-cell therapy or antibody-drug conjugate). At the time of the analysis, using the March 16, 2022, data cut-off, 40 patients received at least 1 dose of teclistamab in phase 2 cohort C and were included in the FAS.

At the time of analysis, using the September 7, 2021, data cut-off, 38 patients were enrolled in phase 2 cohort C, including 22 patients (57.9%) who were still on treatment. The baseline characteristics for these 38 patients are summarized in the follow, because those of the 40 patients enrolled by March 16, 2022, were not reported in the Clinical Study Report. The median age of the patients was 63.5 years (range, 32 to 82 years). A total of 24 patients (63.2%) were male and 14 patients (41.8%) were female. Most patients (89.5%) were white, and 7.9% identified as Black. All patients were triple-class exposed and a majority were penta-exposed (78.9%). The most common immunoglobulin isotypes were immunoglobin G, presenting in 18 patients (47.4%). The median time from diagnosis of MM to enrolment in the phase 2 cohort C was 6.5 years (range, 1.1 to 24.1 years). Eleven patients (28.9%) had at least 1 extramedullary plasmacytoma at baseline. Of the 34 patients with baseline cytogenetic data reported, 11 patients (32.4%) had at least 1 high-risk cytogenetic abnormality, most commonly del(17p). A total of 20 patients (52.6%) were ISS stage I and 9 patients (23.7%) were ISS stage III. Prior anti-BCMA therapy included an antibody-drug conjugate in 71.1% of patients and CAR T-cell therapy in 39.5% of patients.

Efficacy

At the time of the analysis, using the March 16, 2022, data cut-off, the estimated median OS was 13.2 months (95% CI, 8.3 to NE months). The median duration of follow-up was 12.5 months (range, 0.7 to 14.4 months). In phase 2 cohort C, deaths were reported in 17 patients (42.5%) in the FAS, and the proportion of

patients who were censored (i.e., alive at the time of data cut-off) was 23 (57.5%). The estimated 6 months OS probability among patients was [redacted], the 9 months OS probability was [redacted], and the 24 months OS probability was [redacted].

In phase 2 cohort C, the estimated median PFS was [redacted]. By the data cut-off date, a total of 24 patients (60.0%) had a PFS event, and [redacted] were censored. The estimated 6-month PFS probability among patients in phase 2 cohort C was [redacted]. The 9-month PFS probability was [redacted] and the 24-month PFS probability was [redacted].

At the time of the analysis, using the March 16, 2022, data cut-off, 11 patients (27.5%; 95% CI, 14.6% to 43.9%) in phase 2 cohort C achieved CR or better (i.e., CR or sCR), 11 patients (27.5; 95% CI, 14.6% to 43.9%) achieved sCR, 19 patients (47.5%; 95% CI, 31.5% to 63.9%) achieved VGPR or better (i.e., VGPR, CR, or sCR), and 21 patients (52.5%; 95% CI, 36.1% to 68.5%) achieved an overall response (i.e., PR or better). At the time of analysis, using the March 16, 2022, data cut-off, of the 21 patients who achieved PR or better, the median time to first response was 1.2 months (range, 0.2 to 4.9 months), while the median time to best response was 2.9 months (range, 11.1 to 9.5 months). At the time of the analysis, using the March 16, 2022, data cut-off, the estimated median duration of response was not reached in phase 2 cohort C. Among 21 responders (with a PR or better response), 15 patients (23.8%) had disease progression or died due to any cause. The estimated probability of patients remaining in response at 9 months was [redacted], while the probability of patients remaining in response at 12 months was [redacted].

Harms

At the time of the analysis, using the March 16, 2022, data cut-off, all patients in phase 2 cohort C of the MajesTEC-1 study experienced at least 1 TEAE. The most common TEAEs of any grade occurring in at least 20% of patients in phase 2 cohort C were CRS (67.5%), neutropenia (65.0%), anemia (50.0%), thrombocytopenia (45.0%), lymphopenia (45.0%), constipation (35.0), diarrhea (35.0%), pyrexia (32.5%), injection-site erythema (32.5%), and arthralgia (25.0%). In phase 2 cohort C, 9 patients (22.5%) experienced Grade 3 TEAEs, 20 patients (50.0%) experienced Grade 4 TEAEs, and 8 patients (20.0%) experienced Grade 5 TEAEs, per CTCAE. The most common Grade 3 or 4 TEAEs were neutropenia (62.5%), lymphopenia (42.5%), anemia (35.0%), and thrombocytopenia (30.0%). At the time of the analysis, using the March 16, 2022, data cut-off, 24 patients (60.0%) experienced at least 1 serious TEAE. The most common TEAEs were COVID-19 (10.0%), CRS and febrile neutropenia (7.5%), and anemia (5.0%). At the time of the analysis, using the March 16, 2022, data cut-off, no patients experienced a TEAE leading to treatment discontinuation. A total of 17 patients (42.5%) had died, of which 8 patients (20.0%) died within 30 days of the last dose of teclistamab. In phase 2 cohort C of the MajesTEC-1 study, several AEs of clinical interest were identified, including CRS, neurologic AEs and neurotoxicity, ICANS, injection-site reactions, hypogammaglobinemia, cytopenia, infections, and tumour lysis syndrome. At the time of the analysis, using the March 16, 2022, data cut-off, 26 patients (65.0%) in phase 2 cohort C experienced 44 CRS events of any grade. A total of 21 patients (52.5%) in phase 2 cohort C experienced at least 1 neurologic TEAE. The most common neurologic TEAEs included headache (22.5%), ICANS and insomnia (10.0%), encephalopathy (5.0%), peripheral sensory neuropathy (7.5%), dizziness (5.0%), and motor disfunction (5.0%). At the time of the analysis, using the March 16, 2022,

data cut-off, a total of 10 patients (25.0%) experienced at least 1 neurotoxicity event, including headache (12.5%) and ICANS (10.0%). A total of 26 patients (65.0%) in phase 2 cohort C had at least 1 treatment-emergent infection of any grade. The most common infections and infestations included COVID-19 (12.5%), pneumonia (7.5%), bronchitis (10.0%), pneumonia (7.5%), cytomegalovirus infection reactivation (5.0%), implant-site infection (5.0%), and laryngitis (5.0%). A total of 10 patients (25.0%) experienced grade 3 or 4 infections, and 10 patients (25.0%) experienced serious infections. At the time of the analysis, using the March 16, 2022, data cut-off, the proportions of patients with hypogammaglobinemia were not reported. A total of 4 patients (10%) experienced ICANS. All cases of ICANS were concurrent with CRS events, and no patients discontinued treatment due to ICANS. A total of 35 patients (87.5%) in phase 2 cohort C experienced at least 1 treatment-emergent cytopenic event, including neutropenia (67.5%), anemia (50.0%), thrombocytopenia (45.0%), and lymphopenia (45.0%). Hemorrhagic events were reported for 5 patients (12.5%), 1 of which was of grade 2.

Findings from the phase 2 cohort C of the MajesTEC-1 study were consistent with the results from the pivotal cohort (phase 1 and phase 2 cohort A); however, only 40 patients were included, which limits the interpretation of the cohort findings. Given that the patients who took part in phase 2 cohort C were from the MajesTEC-1 study, it is reasonable to expect that the same limitations of the pivotal MajesTEC-1 study (phase 1 and phase 2 cohort A) with respect to internal and external validity are relevant to phase 2 cohort C of the MajesTEC-1 trial.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

The efficacy and safety of teclistamab among adults with r/r MM who received at least 3 prior lines of therapy have been previously assessed in the MajesTEC-1 study. However, no head-to-head evidence of teclistamab compared against other treatments for r/r MM was available for this review. Due to this gap in evidence, the sponsor submitted 6 ITCs, of which 3 were used to inform the pharmacoeconomic model, including 2 comparing the relative efficacy of teclistamab with RWPC therapy (from the LocoMMotion and Daratumumab trials), and another comparing the relative efficacy of teclistamab with ciltacabtagene autoleucel (from the CARTITUDE-1 study). Of the 3 ITCs submitted by the sponsor that were not included in the pharmacoeconomic model, 1 published ITC compared the relative efficacy of teclistamab with RWPC therapy (from Flatiron Health database), 2 conference abstracts compared the relative efficacy of teclistamab with belantamab mafodotin (from the DREAMM-2 trial) and selinexor in combination with dexamethasone (from part 2 of the STORM trial). No systematic review was reported by the sponsor.

Sponsor-Submitted ITCs Used to Inform the Pharmacoeconomic Model

Three ITCs that were used to inform the pharmacoeconomic model were selected because they met the selection criteria. The sponsor stated that they included the most relevant comparators for the submission, and included treatments that are reimbursed in Canada or have received a recommendation for reimbursement from CADTH for the indication under review. Given the absence of a comparator group in the

MajesTEC-1 study, an external control group was used to establish the comparative efficacy of teclistamab versus treatments used in current clinical practice. To estimate the comparative efficacy, an IPTW estimator of the average treatment effect in the treated (ATT) was chosen for the main ITC analyses. This propensity score-based method allowed the RWPC cohorts from the LocoMMotion and Daratumumab trials cohort, as well as the population in the CARTITUDE-1 trial, to be reweighted to match the MajesTEC-1 population. There was sufficient overlap between patient characteristics in the MajesTEC-1 trial and the LocoMMotion, CARTITUDE-1, and 4 Daratumumab trials (APOLLO, POLLUX, CASTOR, and EQUULEUS) to justify weighting techniques that do not depend on matching or excluding incompatible subpopulations. Propensity scores were estimated under an assumed logistic regression model using each cohort (i.e., MajesTEC-1, LocoMMotion, CARTITUDE-1, and the 4 Daratumumab trials cohort) as the dependent variable and selected baseline covariates as independent variables. The estimated propensity scores were then used to derive weights for each participant using the appropriate weighting formulas for the desired target population.

To ensure that the most important clinical factors were balanced between populations, an evidence-informed process (through a literature review of studies conducted to identify clinical outcomes in patients with r/r MM who were triple-class exposed, and input from clinical experts) was used to select the prognostic factors for adjustment. In 2 ITCs comparing the relative efficacy of teclistamab with RWPC therapy from the LocoMMotion trial and ciltacabtagene autoleucel from the CARTITUDE-1 trial, treatment weights were rescaled to sum up to the original number of participants in the comparator studies. For the binary outcomes (e.g., ORR, CR response or better, VGPR response or better), a weighted logistic regression was used to derive an estimate of a conditional odds ratio (OR) and the corresponding 95% CI, transformed to response-rate ratio. For the time-to-event outcomes (e.g., PFS, duration of response, TTNT, and OS), a weighted Cox proportional hazards model was used to derive an estimate of the hazard ratio (HR) and the corresponding 95% CI. Appropriateness of the proportional hazards assumption used in the estimation of the HR of the survival outcomes was assessed based on visual inspection of the log-cumulative hazard plot, visual inspection of the Schoenfeld residuals plot, and performance of the Grambsch-Therneau test (with a P value of less than 0.05 considered to indicate a violation of the assumption).

Teclistamab (the MajesTEC-1 Trial) Versus RWPC (the LocoMMotion Trial)

MajesTEC-1 (n = 165) is an ongoing, phase I/II, multicentre, open-label, single-arm study. Eligible patients must have received a diagnosis of MM under IMWG diagnostic criteria, and have prior exposure to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb, In terms of efficacy outcomes, the primary outcome in the MajesTEC-1 trial was ORR, and secondary outcomes included PR or better response, VGPR or better response, CR or better response, OS, PFS, MRD-negative rate, duration of response, TTR, and the exploratory outcome was TTNT. LocoMMotion (n = 248) is a prospective, noninterventional study of real-life standard of care in patients with a documented diagnosis of MM according to IMWG diagnostic criteria who have received at least 3 prior lines of therapy, including at least PIs, IMiDs, and anti-CD38 mAbs. The primary outcome in the LocoMMotion trial was ORR, and secondary outcomes included VGPR rate, CR rate, sCR rate, MRD-negativity rate, clinical benefit rate, duration of response, TTR, TTNT, PFS, and OS. Approximately 90 unique treatment regimens were used in the LocoMMotion study, including corticosteroids, PIs, IMiDs, alkylating drugs, and anti-CD38 mAbs, and various combinations, reflecting the existing variety of real-life antimyeloma treatments

in this population. A total of 17 prognostic factors that were identified a priori as important for population alignment were available from both populations. Before weighting, moderate (standardized mean difference of greater than 0.1 and less than or equal to 0.2) to substantial (standardized mean difference of greater than 0.2) differences were observed for many of the variables included in the main IPTW analysis. After reweighting, observable differences remained in the ITT populations with regards to refractory status and time to progression on last regimen. Cytogenetic risk was considered an important risk factor; however, was not included in the main analyses due to a high level of missingness in the LocoMMotion cohort (37.1%). As the LocoMMotion population only included a low number of patients who did not identify as white, adding the race variable to the adjustment led to high weights for these patients and decreased balance for all of the other variables.

Following adjustment, the estimated HR of OS and PFS for teclistamab versus RWPC therapy were [redacted]. For duration of disease and TTNT, following adjustment, the estimated HR for teclistamab versus RWPC therapy was [redacted]. For ORR, following adjustment, the OR for teclistamab versus RWPC therapy was [redacted]. For CR or better, following adjustment, the OR for teclistamab versus RWPC therapy was [redacted]. For VGPR or better, following adjustment, the OR for teclistamab versus RWPC therapy was [redacted]. The results of the sensitivity analyses, including the analysis adjusted for all variables, were consistent with the main analysis results. No results for HRQoL and safety outcomes were reported in the ITC comparing the MajesTEC-1 and LocoMMotion trials.

Critical Appraisal

The sponsor-submitted ITC comparing the relative efficacy of teclistamab with RWPC therapy from LocoMMotion had a number of limitations that challenge the internal and external validity of the findings. No systematic search was conducted to identify relevant studies; therefore, there is a risk of selection bias. There was variation in the design of the MajesTEC-1 and LocoMMotion studies, as MajesTEC-1 was a phase I/II trial, while LocoMMotion was an observational, noninterventional study. Both studies were open label, so there is a risk of bias in the measurement of subjective outcomes, particularly PFS, and clinical response outcomes. Objective outcomes, including OS, should be unaffected by the open-label designs. The definitions of end points were similar across the studies; however, the median duration of follow-up was 14.1 months in the MajesTEC-1 trial and 16.1 months in the LocoMMotion study.[29] PFS and the clinical response outcomes were assessed based on IMWG criteria by an IRC in the MajesTEC-1 study and by an independent response review committee in the LocoMMotion study to reduce bias. In the MajesTEC-1 trial, there was a high degree of concordance between ORR assessments by the IRC and by the computerized algorithm utilized. The sensitivity analysis of ORR based on investigator assessment was consistent with the primarily analysis using IRC assessment based on IMWG response criteria, and similar comparisons were done with PFS in the MajesTEC-1 trial. The LocoMMotion study used a total of 90 different treatment regimens and, given that not all treatment regimens are relevant to clinical practice in Canada in the fourth-line and beyond settings (e.g., daratumumab, ixazomib, melphalan), the study results may not be generalizable to clinical practice in Canada. There was notable heterogeneity in the populations of the MajesTEC-1 and LocoMMotion studies.

Of the 17 prognostic factors that were identified a priori, 15 variables were considered in the IPTW analyses for adjustment. Cytogenetic risk was considered an important risk factor by clinical experts; however, was not included in the main analyses due to a high level of missingness in the LocoMMotion cohort (37.1%). The clinical experts consulted by CADTH noted that cytogenetic risk is an important prognostic factor, and omitting this factor could result in potential bias. After reweighting, populations from the MajesTEC-1 and LocoMMotion studies were more balanced, except for observed differences persisting in refractory status and time to progression on the final regimen. While the weighted populations were balanced with respect to known, measured prognostic factors, it remains unclear whether other unmeasured clinically relevant variables were unaccounted for. The variables not included in the planned adjustment set (i.e., unknown or unmeasured prognostic factors) can result in residual confounding and bias the estimates. Assessment of residual bias was not performed or reported, so the results of the IPTW analysis may be considered to have a high risk of residual bias; however, the magnitude and direction of any bias is unknown. In addition, the interpretation of the outcomes is challenging because of systematic differences in study designs. The sponsor stated that due to a small sample size in the MajesTEC-1 and LocoMMotion trials, a scaled ATT weighting approach was used so that treatment weightings were scaled to be summed to the original number of participants in the comparator studies. No information was reported in this IPTW analysis regarding the distribution of weights generated by the weighting process and the number of patients with extremely high and extremely low weights (including patients assigned no weight). Therefore, it remains unclear if patients with no weights (when there is no overlap with the target study) were excluded from the adjusted sample of the LocoMMotion study in accordance with the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document; the effective sample size in the LocoMMotion trial after reweighting to estimate the number of patients who were not weighted. Thus, due to the lack of clarity, the evidence obtained from this IPTW analysis remains uncertain, limiting the interpretation and generalizability of the results. Several sensitivity analyses were conducted, and the results of the sensitivity analyses were consistent with the main analyses. For OS, PFS, TTNT, and clinical response outcomes, the results of the adjusted treatment comparisons were consistent across end points, favouring teclistamab over RWPC therapy, and this is consistent with the opinion of the clinical experts consulted for this review; however, these findings must be interpreted in the context of the methodological limitations of these studies. Safety outcomes were not analyzed in the ITC report, and no justification was provided, which precludes a balanced judgment of comparative benefit relative to comparative harms. Outcomes that are important to patients, such as HRQoL, were also not analyzed in this ITC.

Teclistamab (the MajesTEC-1 Trial) Versus Ciltacabtagene Autoleucel (the CARTITUDE-1 Trial)

MajesTEC-1 (n = 165) is an ongoing, phase I/II, multicentre, open-label, single-arm study. Patients in the MajesTEC-1 study received teclistamab at a recommended dose of 1.5 mg/kg subcutaneously once a week, followed by step-up doses of 0.06 mg/kg and 0.3 mg/kg. The index date in the MajesTEC-1 trial was defined as date of first dose. CARTITUDE-1 (n = 113) is an open-label, single-arm, phase Ib/II clinical trial evaluating the safety and efficacy of ciltacabtagene autoleucel in adults with r/r MM. Eligible patients were diagnosed with MM according to IMWG diagnostic criteria and must have received at least 3 prior lines of therapy or had disease that was double-refractory to an IMiD and a PI. In the CARTITUDE-1 trial, following

apheresis and premedication, ciltacabtagene autoleucel was administered as a single infusion dose of 0.75×10^6 CAR-positive viable T cells per kg. The primary outcome in the CARTITUDE-1 trial was ORR, and secondary outcomes included VGPR rate, CR rate, sCR rate, MRD-negative rate, clinical benefit rate, duration of response, TTR, TTNT, PFS, and OS. The ITT population in the CARTITUDE-1 study included all patients who underwent apheresis with the index date defined as the date of apheresis.

Before weighting, moderate to substantial differences were observed for many of the main analysis variables. After weighting, populations in the MajesTEC-1 and CARTITUDE-1 trials were more balanced. After adjustment, differences remained in the ITT populations with regards to refractory status, age, hemoglobin level, and creatinine clearance. Following adjustment, the estimated HRs of OS and PFS for teclistamab versus ciltacabtagene autoleucel were [redacted]. Following adjustment, the estimated HR of duration of response for teclistamab versus ciltacabtagene autoleucel was [redacted]. Following adjustment, the estimated HR of TTNT for teclistamab versus ciltacabtagene autoleucel was [redacted]. No sensitivity analysis was performed in this ITC. No results for clinical response outcomes, including ORR, CR or better, and VGPR or better, were included in the ITC comparing the MajesTEC-1 and CARTITUDE-1 trials. Nor were results for HRQoL and safety outcomes.

Critical Appraisal

No systematic search was conducted to relevant studies; therefore, there is a risk of selection bias. Both the MajesTEC-1 and CARTITUDE-1 studies included in the ITC were presented with an unclear risk of bias for statistical analysis and a high risk for the measurement of subjective outcomes, such as PFS or clinical response outcomes, because of the open-label study design. Objective outcomes, including OS, should be unaffected by the open-label designs. The MajesTEC-1 cohort represented a broad population from Canada, Europe, and the US, whereas the results from the CARTITUDE-1 trial are drawn from patients from the US only. Therefore, it is unclear whether differences in clinical practice or treatment availability exist across regions, and the direction and magnitude of potential biases remain unclear. After weighting, the populations in the MajesTEC-1 and CARTITUDE-1 trials were more balanced, although observable differences remained between trials in regards to refractory status, age, hemoglobin level, and creatinine clearance. While the weighted populations were balanced with respect to known, measured prognostic factors, it remains unclear whether other unmeasured clinically relevant variables were unaccounted for. The variables not included in the planned adjustment set (i.e., unknown or unmeasured prognostic factors) can result in residual confounding and bias the estimates. Assessment of residual bias was not performed or reported, so the results of the IPTW analysis may be considered to have a high risk of residual bias; however, the magnitude and direction of any bias is unknown. In addition, the interpretation of the outcomes is challenging due to systematic differences in study design and duration of follow-up. The sponsor stated that because of a small sample size in the MajesTEC-1 and CARTITUDE-1 trials, a scaled ATT weighting approach was used to scale treatment weightings so that they were summed to the original number of participants in the comparator studies. No information was reported in this IPTW analysis regarding the distribution of weights generated by the weighting process and the number of patients with extremely high and extremely low weights (including patients assigned no weight). Therefore, it remains unclear if patients with no weights were

excluded from the adjusted sample of the CARTITUDE-1 study in accordance with the NICE DSU Technical Support Document, and what was the effective sample size in the CARTITUDE-1 study after reweighting to estimate the number of patients who were not weighted. Thus, due to the lack of clarity, the evidence obtained from this IPTW analysis remains uncertain, limiting the interpretation and generalizability of the results. No methods for handling missing data were performed or reported in the ITC comparing teclistamab with ciltacabtagene autoleucel. For OS, PFS, and TTNT, the results of the adjusted treatment comparisons were consistent across end points, favouring ciltacabtagene autoleucel over teclistamab; however, these findings must be interpreted in the context of the methodological limitations of these studies. According to the clinical experts consulted by CADTH for this review, the population of the CARTITUDE-1 study was relatively healthy compared to the MajesTEC-1 population. Although all clinical response outcomes (i.e., ORR, CR or better, VGPR or better) were available in both studies, they were not assessed in this analysis. Safety outcomes were not analyzed in the ITC report, and no justification was provided, which precludes a balanced judgment of comparative benefit relative to comparative harms. Outcomes that are important to patients, such as HRQoL, were also not analyzed in this ITC.

Teclistamab (the MajesTEC-1 Trial) Versus Physician's Choice of Therapy (the APOLLO, POLLUX, CASTOR, and EQUULEUS Trials)

MajesTEC-1 (n = 165) is an ongoing, phase I/II, multicentre, open-label, single-arm study. Patients in the daratumumab trials were triple-class exposed and were treated with physician's choice of therapy after discontinuing the trial treatments. The daratumumab trials cohort comprised patients from the long-term follow-up data from the POLLUX, CASTOR, EQUULEUS, and APOLLO trials. Because this ITC analysis retrospectively included patients participating in long-term follow-up clinical trials of daratumumab, it was possible to include patients in the earliest line of therapy initiated after all key selection criteria were met. However, this differed from the MajesTEC-1 study, in which patients may have received additional lines of therapy between the time at which they first met all eligibility criteria and the time at which they were enrolled into the clinical trial. To account for this difference, patients in the daratumumab trials became eligible for this analysis after having at least 3 prior lines of therapy, and patients who received multiple subsequent therapies after meeting eligibility criteria contributed multiple observations. Overall, 1,577 patients were initially included in the daratumumab trials cohort, of which 642 patients were triple-class exposed and had received at least 1 treatment regimen. Of the 642 patients, 427 patients with 806 eligible lines of therapy met the MajesTEC-1 trial's key inclusion criteria.[28] A total of 248 unique regimens were used in the RWPC from the daratumumab trials cohort. The primary outcome in the POLLUX trial was PFS, and secondary outcomes included time to progression, VGPR response or better, MRD-negative rate, ORR, OS, TTR, and duration of response. The primary outcome in the CASTOR trials was PFS, and secondary outcomes included time to progression, VGPR response or better, MRD-negative rate, ORR, OS, and TTR. The primary outcome in the EQUULEUS trial was proportion of AEs and dose-limiting toxicities, and secondary outcomes included ORR, OS, CR or better, and duration of response, and exploratory outcomes included PFS, MRD-negative rate, and pharmacokinetics. The primary outcome in the APOLLO trial was PFS, and secondary outcomes included VGPR or better, MRD-negative rate, ORR, OS, duration of response, TTNT, and TTR. In the daratumumab trials cohort, the index date was defined as the start of each eligible line of therapy.

Before weighting, moderate to substantial differences were observed for many variables. After weighting, substantial differences were observed with regards to prior stem cell transplant, ECOG PS, race, and type of MM. After adjustment, the resulting effective sample size in the daratumumab trial cohort was 264 compared to the original 806. Following adjustment, the estimated HRs for OS and PFS for teclistamab versus PC therapy were [redacted]. Following adjustment, the estimated HR of TTNT for teclistamab versus PC therapy was [redacted]. For ORR, following adjustment, the OR for teclistamab versus PC therapy was [redacted]. For CR or better, the OR for teclistamab versus PC therapy was [redacted]. For VGPR or better, following adjustment, the OR for teclistamab versus PC therapy was [redacted]. The results from the fully adjusted scenario analysis were consistent with the main analysis results. No results for HRQoL and safety outcomes were included in the study comparing the MajesTEC-1 trial and the daratumumab trial cohorts.

Critical Appraisal

There was variation in the design of the MajesTEC-1 trial and 4 daratumumab trials included in the IPTW analysis. MajesTEC-1 was a phase I/II trial, while POLLUX, CASTOR, and APOLLO were open-label, phase III randomized controlled trials, and EQUULEUS was an open-label, nonrandomized, phase Ib study. Both the MajesTEC-1 study and daratumumab trials were open label, so there is a risk of bias in the measurement of subjective outcomes, particularly PFS, and clinical response outcomes. Objective outcomes, including OS, should be unaffected by the open-label designs. In addition, although 3 of the daratumumab trials (POLLUX, CASTOR, and APOLLO) included in the ITC were randomized controlled trials, and EQUULEUS was an open-label, nonrandomized phase Ib study, patients selected from the daratumumab trials cohort were included in the analysis retrospectively. A total of 248 unique treatment regimens were used in the daratumumab trials cohort, of which, many were not relevant to clinical practice in Canada; thus, the study results may not be generalizable to the Canadian setting. There was notable heterogeneity in the populations of the MajesTEC-1 study and daratumumab trials cohort. Nine of the 17 prognostic factors identified a priori were used for ATT weighting in the main analysis. After weighting, populations from the studies were balanced with respect to known, measured prognostic factors. While the weighted populations were balanced with respect to known, measured prognostic factors, it remains unclear whether other unmeasured clinically relevant variables were unaccounted for. The variables not included in the planned adjustment set (unknown or unmeasured prognostic factors) can result in residual confounding and bias the estimates. Assessment of residual bias was not performed or reported. Therefore, the results of the IPTW analysis may be considered to have a high risk of residual bias; however, the magnitude and direction of any bias is unknown. In addition, IPTW cannot adjust for differences related to other sources of heterogeneity, such as differences in study design or median duration of follow-up. After adjustment, the effective sample size was reduced to approximately 32.8% (264 out of 804) of the original sample size in the daratumumab trials cohort. A small effective sample size implies that the estimates are being influenced by a subset of the patients from the daratumumab trials and be caused by a violation of the transportability of the effects across cohorts. The proportional hazards assumption was tested for the time-to-event outcomes, and the Grambsch-Therneau test was significant for PFS and TTNT analyses, indicating potential violation of this assumption. The Cox proportional hazards model assumes that the HR across treatment groups does not change over time; therefore, violation of

the proportional hazards assumption may lead to misleading and erroneous scientific conclusions. For OS, PFS, TTNT, and clinical response outcomes, the results of the adjusted treatment comparisons were consistent across end points, favouring teclistamab over PC therapy, and this is consistent with the opinion of the clinical experts consulted for this review; however, these findings must be interpreted in the context of the methodological limitations of these studies. Safety outcomes were not analyzed in the ITC report, and no justification was provided, which precludes a balanced judgment of comparative benefit relative to comparative harms. Outcomes that are important to patients, such as HRQoL, were also not analyzed in this ITC.

Other ITCs Not Included in the Pharmacoeconomic Models

The ITCs submitted by the sponsor had a number of limitations that challenge the internal and external validity of the findings. No systematic search was conducted to identify the comparator studies included in the 3 ITCs that were not used to inform pharmacoeconomic models; therefore, there is a risk of selection bias. The selection criteria used to identify the comparator were consistent with the objective, and studies were included if they assessed treatment for r/r MM, included patients with triple-class exposed r/r MM who had received at least 3 prior lines of therapy, and reported sufficient efficacy outcomes data. However, no details were provided regarding the timing of the literature review or the databases used. It is not possible to know whether the results may have differed if data from different r/r MM studies or databases had been used. The list of excluded studies is not available and the risk of bias of the included studies was not assessed. Given the absence of a comparator group in the MajesTEC-1 study, an external control group was used to establish relative efficacy of teclistamab versus treatments used in current clinical practice.

Teclistamab (the MajesTEC-1 Trial) Versus RWPC Therapy (Flatiron Health Database)

An ITC using the IPTW approach was conducted to assess the relative efficacy of teclistamab compared with RWPC therapy, using individual patient-level data from the MajesTEC-1 trial (for teclistamab) and the nationwide deidentified electronic health record–derived Flatiron Health database (for the RWPC cohort). Key eligibility criteria of the MajesTEC-1 study were applied to the RWPC cohort, including a diagnosis of MM using IMWG criteria and prior exposure to 3 or more lines of therapy. Patients in the Flatiron cohort who received multiple subsequent therapies after meeting the eligibility criteria contributed multiple observations to the ITC analysis. The MajesTEC-1 cohort included data from 165 patients, while the unadjusted population of the RWPC Flatiron Health cohort included 420 unique patients, corresponding to 766 eligible lines of therapy. The propensity score-based method of IPTW with an ATT weighting was used to reweight the RWPC Flatiron cohort to align with the MajesTEC-1 population and adjust for imbalances between patient populations. For the MajesTEC-1 trial, a clinical cut-off of March 16, 2022, was used, with a median duration of follow-up of 14.1 months. For the RWPC Flatiron cohort, patients who had 2 or more documented clinical visits on or after January 2011 were included, with a median duration of follow-up of 18.2 months. After weighting, the effective sample size of the RWPC Flatiron cohort reduced to 42.6% of the original population.

Following adjustment, the estimated HR of OS for teclistamab versus RWPC therapy from the Flatiron cohort was 0.82 (95% CI, 0.59 to 1.14). For PFS, following adjustment, the estimated HR for teclistamab versus RWPC from the Flatiron cohort was 0.43 (95% CI, 0.33 to 0.56). For TTNT, following adjustment, the

estimated HR for teclistamab versus RWPC from the Flatiron cohort was 0.36 (95% CI, 0.27 to 0.49). No results for safety and HRQoL were included in the ITC that compared the MajesTEC-1 and Flatiron cohorts.

As the Flatiron Health database was not selected using a systematic approach, there is a risk of selection bias. It is not possible to know whether the results may have differed if data from different r/r MM studies or databases had been used. Numerous therapies were used in the RWPC groups from the Flatiron cohort, of which, many were not relevant to clinical practice in Canada; thus, may not be generalized to the Canadian setting. Additionally, patients included in the present analysis initiated eligible lines of therapy between 2016 and 2021; however, clinical practice has changed since the enrolment of patients from these sources and may not be reflective of current treatment standards in Canada. Patients selected from the Flatiron cohort were included in the analysis retrospectively. Data analyzed retrospectively from databases are prone to unique biases (e.g., selection bias, confounding) compared with those collected from prospective interventional studies, which cannot be controlled using IPTW methods. Outcomes in the MajesTEC-1 study were assessed by the IRC, while in the Flatiron cohort they were assessed by the investigators; thus, the risk of bias in the outcome measurements is increased relative to the same outcomes in the MajesTEC-1 study. The duration of follow-up in the MajesTEC-1 trial was 14.1 months versus 18.2 months in the Flatiron cohort. There were important differences in the design of the studies included in this ITC, as the MajesTEC-1 study was a phase I/II study and the Flatiron cohort was a real-world cohort from electronic health records in the US, which limits the ability to draw strong conclusions about the efficacy of teclistamab relative to RWPC therapy due to differences in the clinician and patient behaviours, heterogeneity of treatments for intercurrent events, and differences in data collection and intake. Such methodological differences could not be adjusted for in the IPTW analysis, and the magnitude and direction of any resulting bias is uncertain. There was evidence of heterogeneity between the population of the MajesTEC-1 trial and the Flatiron cohort. It remains unclear how balanced populations were for other variables that may be clinically relevant but could not be adjusted due to lack of data, or those variables that were not part of the planned adjustment (i.e., unknown or unmeasured prognostic factors), which leaves the potential for residual confounding. After weighting, the effective sample size (ESS) of the Flatiron cohort was reduced by 57.4% from the included population. The reduction in the ESS reflects the heterogeneity between the trials among the variables included in the weighting process. A small ESS implies that the weighted estimates are being influenced by a subset of the patients from the Flatiron cohort that may not be representative of the entire study population, which may limit the generalizability of the results. For OS and PFS, the results of the adjusted treatment comparisons were consistent across end points, favouring teclistamab over RWPC therapy from the Flatiron cohort; however, these findings must be interpreted in the context of the methodological limitations of these studies.

Teclistamab (the MajesTEC-1 Trial) Versus Belantamab Mafodotin (the DREAMM-2 Trial)

An unanchored MAIC was conducted to compare the efficacy of teclistamab with belantamab mafodotin using individual patient data from the MajesTEC-1 trial (n = 150) and summary-level data from the DREAMM-2 trial (n = 97). MajesTEC-1 was an open-label, single-arm, phase I/II study, while DREAMM-2 was an open-label, 2-arm, phase II study. The DREAMM-2 eligibility criteria were applied to patients from the ITT population of the MajesTEC-1 trial. Compared to patients in the DREAMM-2 population, the MajesTEC-1 population had a higher proportion of patients who had ISS stage I disease. All patients had

triple-class exposed r/r MM and had received at least 3 prior lines of therapy. Individual patient data from the MajesTEC-1 trial were weighted to match the aggregated DREAMM-2 baseline patient characteristics. The following factors were used to adjust for imbalances between patient populations: refractory status, cytogenetic profile, ISS staging, presence of extramedullary disease, and number of prior lines of therapy. The ESS of the MajesTEC-1 study after propensity score matching was 33 patients. The comparative efficacy of teclistamab relative to belantamab mafodotin was estimated for ORR, CR or better, OS, PFS, and duration of response. For binary outcomes, the relative effects were quantified using an OR and 95% CI derived from a weighted logistic regression analysis, while time-to-event outcomes were estimated using a weighted Cox proportional hazards model.

Following adjustment, the estimated HR for OS for teclistamab versus belantamab mafodotin was 0.95 (95% CI, 0.47 to 1.92). For PFS, following adjustment, the estimated HR for teclistamab versus belantamab mafodotin was 0.63 (95% CI, 0.34 to 1.15), and the estimated HR of duration of response was 0.19 (95% CI, 0.05 to 0.73). Following adjustment, the OR of ORR for teclistamab versus belantamab mafodotin was 2.05 (95% CI, 0.92 to 4.57), while the OR of CR or better was 2.13 (95% CI, 0.80 to 5.65). No results for safety and HRQoL were included in the ITC comparing the MajesTEC-1 and DREAMM-2 trials.

Critical Appraisal

The open-label design of the studies can result in a risk of bias in the study conduct, including the measurement of the outcomes, and increase uncertainty in subjective outcomes such as PFS and ORR. The bias will likely favour the experimental intervention, although the extent of bias is uncertain. The ESS was reduced after adjustment in the MAIC analysis to approximately 22.0% (33 out of 150) of the original population in the MajesTEC-1 study. The reduction in the ESS reflects the heterogeneity between the trials among the variables included in the weighting process. A small ESS implies that the weighted estimates are being influenced by a subset of the patients from the MajesTEC-1 study that may not be representative of the entire study population, which may limit the generalizability of the results. Populations from the studies were balanced with respect to known, measured prognostic factors. It remains unclear how balanced populations were for other variables that may be clinically relevant but could not be adjusted due to lack of data, or those variables that were not part of the planned adjustment (i.e., unknown or unmeasured prognostic factors), which leaves the potential for residual confounding. In the MAIC analysis, results in efficacy estimates were imprecise (i.e., wide CIs) in the end points assessed (including HR = 1), and the upper and lower boundaries of the CIs suggest the potential for different conclusions regarding the efficacy of teclistamab relative to the comparator drugs. Therefore, no superiority conclusions could be drawn from the MAIC submitted by the sponsor due to methodological limitations and imprecision in the effect estimates.

Teclistamab (the MajesTEC-1 Trial) Versus Selinexor Plus Dexamethasone (Part 2 of the STORM Trial)

An unanchored MAIC was conducted to compare the efficacy of teclistamab with selinexor plus dexamethasone using individual patient data from the MajesTEC-1 trial (n = 150) and summary-level data from part 2 of the STORM trial (n = 122). The STORM part 2 eligibility criteria were applied to patients from the ITT population of the MajesTEC-1 study. Compared to patients in part 2 of the STORM trial, the

MajesTEC-1 population had a higher proportion of patients with Revised International Staging System (R-ISS) stage II. The 2 populations were similar in age, ECOG PS, and cytogenetic status. All patients had triple-class exposed r/r MM. After applying the STORM part 2 eligibility criteria, individual patient data from patients in the MajesTEC-1 trial were weighted to match the aggregated baseline patient characteristics from the STORM part 2 trial. For binary outcomes, the relative effects were quantified using an OR and 95% CI derived from a weighted logistic regression analysis, while time-to-event outcomes were estimated using a weighted Cox proportional hazards model. The following factors were used to adjust for imbalances between patient populations: refractory status, cytogenetic profile, ISS staging, presence of extramedullary disease, and number of prior lines of therapy. The ESS of the MajesTEC-1 trial after matching was 37 patients.

Following adjustment, the estimated HR of OS for teclistamab versus selinexor plus dexamethasone was 0.52 (95% CI, 0.28 to 0.95). Following adjustment, the estimated HR of PFS for teclistamab versus selinexor plus dexamethasone was 0.58 (95% CI, 0.30 to 1.11), and the estimated HR of duration of response was 0.04 (95% CI, 0.01 to 0.10). Following adjustment, the OR of ORR for teclistamab versus selinexor plus dexamethasone was 3.14 (95% CI, 1.48 to 6.69), while the OR of CR or better was 16.3 (95% CI, 3.5 to 77.1). No results for safety and HRQoL were included in the ITC comparing the MajesTEC-1 and STORM part 2 trials.

Critical Appraisal

The open-label design of the studies can result in a risk of bias in the study conduct, including the measurement of the outcomes, and increase uncertainty in subjective outcomes such as PFS and ORR. The bias will likely favour the experimental intervention, although the extent of bias is uncertain. The ESS was reduced after adjustment in the MAIC analysis, and the ESS was reduced to approximately 24.7% (37/150) of the original population in the MajesTEC-1 study. The reduction in the ESS reflects the heterogeneity between the trials among the variables included in the weighting process. Small ESS implies that the weighted estimates are being influenced by a subset of the patients from the MajesTEC-1 study that may not be representative of the entire study population, which may limit the generalizability of the results. It remains unclear how balanced populations were for other variables that may be clinically relevant but could not be adjusted due to lack of data, or those variables that were not part of the planned adjustment (i.e., unknown or unmeasured prognostic factors), which leaves the potential for residual confounding. In the MAIC analysis, results in efficacy estimates were imprecise (i.e., wide CIs) in the end points assessed, and the upper and lower boundaries of the CIs suggest the potential for different conclusions regarding the efficacy of teclistamab relative to the comparator drugs. Therefore, no superiority conclusions could be drawn from the MAIC submitted by the sponsor because of methodological limitations and imprecision in the effect estimates.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adults with r/r MM with 3 or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy.
Treatment	Teclistamab
Dose regimen	The recommended starting dose is 0.06 mg/kg on day 1, followed by 0.3 mg/kg on day 3 and 1.5 mg/kg on day 5; 1.5 mg/kg is then given once weekly thereafter.
Submitted price	Teclistamab, 10 mg/mL (30 mg/3 mL) and 90 mg/mL (153 mg/1.7mL), solution for subcutaneous injection: $1,322 and $6,741 for 10 mg/mL and 90 mg/mL, respectively.
Submitted treatment cost	The first 28-day cost of teclistamab is $29,608. Every 28 days after this the cost is $26,964. This assumes a weight of 75 kg.
Comparators	• Mix of currently reimbursed combination therapies (referred to as physician's choice): Kd (33%), KCd (7%), Pd (28%), PCd (32%) • Cilta-cel
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (30 years)
Key data sources	• Teclistamab: single-arm, phase I/II MajesTEC-1 trial (data cut-off: January 4, 2023) • Physician's choice: LocoMMotion prospective noninterventional study (data cut-off: October 2022) • Cilta-cel: single-arm, phase Ib/II CARTITUDE-1 trial (data cut-off: January 2022)
Submitted results	• ICER vs. physician's choice = $454,345 per QALY gained (incremental costs = $468,254; incremental QALYs = 1.03). • ICER vs. cilta-cel: teclistamab was less costly and less effective (incremental costs = −$84,129; incremental QALYs = −2.46).
Key limitations	• Based on clinical expert feedback, the overall survival associated with teclistamab is uncertain relative to physician's choice. This is due to the lack of randomized evidence and the lack of robust long-term survival data beyond 2 years. • Based on clinical expert feedback, once-weekly dosing of carfilzomib was more common in practice in Canada than the twice weekly dosing assumed by the sponsor. As weekly dosing is associated with lower costs due to less frequent dosing, the cost of the Kd regimen was overestimated. • The cost used for a 4 mg pomalidomide capsule was higher than the cost cited in most jurisdictions in Canada. • The generalizability of the modelled population to clinical practice in Canada is unclear. Relative to the MajesTEC-1 trial, patients with r/r MM may be older, have poorer performance status, have more advanced staging, and have a higher prevalence of comorbidities in clinical practice. It is uncertain how these and other confounders may influence the magnitude of benefit for teclistamab relative to physician's choice. • 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 teclistamab relative to SVd is unknown.

Component	Description
	• The sponsor assumed the longer a patient remains progression-free, the greater the reduction in utility when progression occurs. This assumption was considered uncertain based on feedback from clinical experts.
CADTH reanalysis results	• For the CADTH base case, the cost of pomalidomide was updated and carfilzomib was assumed to be administered weekly rather than twice weekly. Further uncertainties were explored in scenario analyses. • In the CADTH base case, teclistamab was more effective (incremental LYs = 1.37; incremental QALYs = 1.03) and associated with greater total costs (incremental costs = $522,024) than physician's choice. This resulted in an ICER of $506,518 per QALY gained. Relative to cilta-cel, teclistamab was less costly and less effective (incremental costs = −$78,899; incremental QALYs = −2.46). • An 89% price reduction would be required for teclistamab to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained relative to physician's choice.

cilta-cel = ciltacabtagene autoleucel; ICER = incremental cost-effectiveness ratio; IMiD = immunomodulatory drug; KCd = carfilzomib plus cyclophosphamide plus dexamethasone; Kd = carfilzomib plus dexamethasone; LY = life-years; mAb = monoclonal antibody; MM = multiple myeloma; PCd = pomalidomide plus cyclophosphamide plus dexamethasone; Pd = pomalidomide plus dexamethasone; PI = proteasome inhibitor; PSM = partitioned survival model; QALY = quality-adjusted life-years; r/r = relapsed and/or refractory; SVd = selinexor plus bortezomib plus 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 newly developed MM receiving therapy in the fourth-line setting is uncertain; the treatment schedule for carfilzomib plus dexamethasone is not reflective of practice in Canada; the cost of pomalidomide is not reflective of most jurisdictions; the dosing schedule for teclistamab is uncertain; and the market share of teclistamab may be underestimated.

CADTH conducted reanalyses of the budget impact analysis by revising the calculation of the costs associated with teclistamab and physician's choice therapies; revising the eligible patient population; adopting a once-weekly dosing schedule for carfilzomib plus dexamethasone; and adjusting the cost of pomalidomide. Based on the CADTH base case, the incremental expenditures associated with the reimbursement of teclistamab for the fourth-line treatment of adults with r/r MM who have demonstrated disease progression on the last therapy, per its reimbursement request, would be $30,276,140 in year 1, $57,027,919 in year 2, and $92,228,347 in year 3, for a 3-year cumulative total of $179,532,406. There is uncertainty in this estimate due to uncertain market uptake of teclistamab, the size of the r/r MM population requiring a fourth-line therapy, and the potential for dose switching.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Meeting date: February 14, 2024

Regrets: Two of the expert committee members did not attend.

Conflicts of interest: None

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