



## CADTH Reimbursement Recommendation

# Ciltacabtagene Autoleucel (Carvykti)

**Indication:** For the treatment of adult patients with multiple myeloma, who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, and who are refractory to their last treatment.

**Sponsor:** Janssen Inc.

**Final recommendation:** Reimburse with conditions



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# Summary

## What Is the CADTH Reimbursement Recommendation for Carvykti?

CADTH recommends that Carvykti should be reimbursed by public drug plans for the treatment of adult patients with multiple myeloma (MM) who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, and who are refractory to their last treatment if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Carvykti should only be covered to treat patients who have MM; received at least 3 prior treatments including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody; did not respond to their last treatment, and are in relatively good health (i.e., have a good performance status, as determined by a specialist). Carvykti should not be reimbursed to treat patients whose MM is affecting their brain or spinal cord or patients showing signs that the tissue layers protecting the brain and spinal cord are affected by MM. It also should not be reimbursed in patients who have previously received a treatment that targets B-cell maturation antigen.

### What Are the Conditions for Reimbursement?

Carvykti should only be reimbursed for patients who have not yet been treated with chimeric antigen receptor (CAR) T-cell therapy, if it is prescribed and administered in a hospital setting with adequate resources by specialists with expertise in MM, and if the cost of Carvykti is reduced.

### Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial suggested that treatment with Carvykti resulted in durable responses to treatment within 1 month of administration and may improve overall survival time and the time until disease progression or death. Furthermore, evidence from 5 observational studies consistently suggested that Carvykti may improve response rate, overall survival time, time until disease progression or death, and time until another treatment is required compared with other treatments used in the real world.
- Carvykti may meet some patient needs because it is an additional life-extending treatment option and has manageable side effects.
- The implementation of Carvykti may raise several ethical and equity considerations related to access because of the resource-intensive



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nature of CAR T-cell therapy and the currently limited number of CAR T-cell centres.

- Based on CADTH's assessment of the health economic evidence, Carvykti 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, Carvykti is estimated to cost the public drug plans approximately \$405 million over the next 3 years. However, the actual budget impact is uncertain and may be higher.

## Additional Information

### What Is Multiple Myeloma?

MM is a type of cancer of the plasma cells (the white blood cells that make immunoglobulins) in the bone marrow. Approximately 4,000 Canadians were diagnosed with MM in 2022.

### Unmet Needs in Multiple Myeloma

MM is an incurable disease with a poor prognosis. Many patients do not respond to initial treatments and their disease will relapse, so they will need to try many different treatments. There is a need for additional life-extending treatment options that can delay disease progression, improve quality of life, and reduce side effects.

### How Much Does Carvykti Cost?

Treatment with Carvykti is associated with a one-time infusion cost of \$632,455.

## Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that ciltacabtagene autoleucl be reimbursed for the treatment of adult patients with multiple myeloma (MM) who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, and who are refractory to their last treatment only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

One ongoing phase Ib/II, single-arm, open-label trial (CARTITUDE-1) demonstrated that a single treatment with ciltacabtagene autoleucl resulted in benefits in response rates, overall survival (OS), and progression-free survival (PFS) for adult patients with relapsed or refractory MM (MM) who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody, compared with what is currently observed for these outcomes according to clinical experts. The overall response rate (ORR) was 97.9% (95% confidence interval [CI], 92.7% to 99.7%) in the treated population, which met the prespecified primary end point (i.e., the lower bound of the 95% CI exceeded 30%) and was considered clinically meaningful by clinical experts. Although associated with uncertainty due to the single-arm design of the CARTITUDE-1 trial, the OS and PFS results were also considered clinically meaningful by clinical experts. After a median follow-up of 27.7 months, median OS and PFS were not reached. Among all treated patients, the 24-month OS rate was 76.2% (95% CI, 66.5% to 83.5%) and the 24-month PFS rate was 62.7% (95% CI, 52.2% to 71.5%). Furthermore, despite uncertainty in the results due to methodological limitations (e.g., heterogeneity, risk of bias from residual confounding, small sample sizes, and imprecision), there was consistency in the direction of effects of 5 observational studies, which favoured ciltacabtagene autoleucl over real-world treatment paradigms across all outcomes assessed, including ORR, OS, PFS, and time to next treatment (TTNT). pERC considered that results of the CARTITUDE-1 study showed that treatment with ciltacabtagene autoleucl may have had clinically meaningful benefits in health-related quality of life (HRQoL), but all HRQoL measures were at risk of bias due to missing data and because most patients contributing to the analysis were likely in relatively good health.

Patients identified a need for more effective treatments that improve quality of life, have fewer side effects, and prolong survival without the need for continuous treatment. Given the totality of the evidence, pERC concluded that ciltacabtagene autoleucl may be an effective one-time treatment with manageable side effects that may prolong survival. While recognizing the uncertainty in the evidence, pERC acknowledges that ciltacabtagene autoleucl could potentially have a beneficial effect on HRQoL.

The committee considered analyses conducted by CADTH that evaluated the cost-effectiveness of ciltacabtagene autoleucl relative to current standards of care used to treat MM in patients who had received at least 3 prior lines of therapy. Given the uncertainty associated with the magnitude of effect on PFS and OS relative to current standards of care and the limitations with the modelling approach, CADTH could not estimate a robust single base-case estimate of cost-effectiveness for ciltacabtagene autoleucl. Based on the sponsor's submitted price for ciltacabtagene autoleucl and publicly listed prices for all other drug costs,

the incremental cost-effectiveness ratio (ICER) ranged from \$201,901 to \$286,972 per quality-adjusted life-year (QALY) gained based on possible ranges of the extrapolated OS benefits for ciltacabtagene autoleucl. In all reanalyses, a price reduction would be required for ciltacabtagene autoleucl to achieve an ICER of \$50,000 per QALY gained.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
1. Ciltacabtagene autoleucl should be reimbursed in adult patients aged 18 years or older who meet all the following criteria: <ol style="list-style-type: none"> <li>1.1. documented diagnosis of MM</li> <li>1.2. received at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody</li> <li>1.3. refractory to their last treatment</li> <li>1.4. have good performance status.</li> </ol>	In the CARTITUDE-1 trial, treatment with ciltacabtagene autoleucl demonstrated a clinical benefit in adult patients with a documented diagnosis of MM who had received at least 3 prior lines of therapy or were double refractory to a proteasome inhibitor and an IMiD, and received a proteasome inhibitor, an IMiD, and an anti-CD38 antibody. Almost all patients (n = 96; 99%) enrolled and treated in the CARTITUDE-1 trial were refractory to the last line of prior therapy. The CARTITUDE-1 trial enrolled patients with an ECOG performance status of 0 or 1.	—
2. Ciltacabtagene autoleucl should not be initiated in patients with active CNS involvement or exhibiting signs of meningeal involvement of MM.	The CARTITUDE-1 trial excluded patients with known active or prior history of CNS involvement or exhibiting clinical signs of meningeal involvement of MM. However, based on clinical experts, pERC recognized that patients with a prior history of CNS involvement that has been adequately treated might benefit from ciltacabtagene autoleucl.	—
3. Ciltacabtagene autoleucl should not be reimbursed in patients who have received prior treatment with any therapy that is targeted to BCMA or any CAR T-cell therapy.	Patients with prior exposure to CAR T-cell therapy or any therapy that is targeted to BCMA were not included in the CARTITUDE-1 trial; therefore, the efficacy of ciltacabtagene autoleucl following either of these therapies is unknown.	—
<b>Prescribing</b>		
4. Treatment with ciltacabtagene autoleucl is a one-time therapy.	At this time, CAR T-cell therapy re-treatment has not been established as an efficacious strategy and is not considered standard of care. In the CARTITUDE-1 trial, only 3 patients were re-treated with ciltacabtagene autoleucl; therefore, there is insufficient evidence to support re-treatment.	—

Reimbursement condition	Reason	Implementation guidance
5. Ciltacabtagene autoleucl should only be prescribed by clinicians with expertise in the treatment of MM. Ciltacabtagene autoleucl should be administered in specialized centres with adequate infrastructure, resources, and expertise to facilitate treatment with CAR T-cell therapy.	To ensure that ciltacabtagene autoleucl is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	pERC acknowledges that the availability of specialized centres with adequate infrastructure and resources to administer CAR T-cell therapy in Canada is a barrier that needs to be addressed.
<b>Pricing</b>		
6. A reduction in price.	Based on CADTH reanalyses, a price reduction of 72% to 80% would be required for ciltacabtagene autoleucl to be cost-effective at a WTP threshold of \$50,000 per QALY gained relative to current standards of care. This range reflects uncertainty around the extrapolation of survival in the absence of long-term data. The magnitude of survival benefit is uncertain given the limitations with comparative evidence for ciltacabtagene autoleucl and current standards of care. As outstanding uncertainty remains, it was noted that higher price reductions may be required.	—
<b>Feasibility of adoption</b>		
7. The feasibility of adoption of ciltacabtagene autoleucl must be addressed.	At the submitted price, the incremental budget impact of ciltacabtagene autoleucl is expected to be greater than \$40 million in years 1, 2, and 3. The total budget impact across years 1 to 3 exceeds \$400 million.	—

BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory agent; MM = multiple myeloma; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; WTP = willingness to pay.

## Discussion Points

- Given the uncertainty associated with the design of the CARTITUDE-1 trial, pERC deliberated on ciltacabtagene autoleucl considering the criteria for significant unmet need described in section 9.3.1 of the [Procedures for CADTH Reimbursement Reviews](#). Considering the severity of relapsed or refractory MM in adult patients and the 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 Ib/II trial, based on the totality of the evidence ciltacabtagene autoleucl has the potential to reduce morbidity and mortality associated with the disease.
- pERC considered evidence from 5 observational studies that used individual patient data from the CARTITUDE-1 trial and various real-world cohorts, using propensity scores to adjust for known confounders. Overall, there was consistency in the results of all included observational studies with effect estimates favouring ciltacabtagene autoleucl over real-world treatment paradigms

across all outcomes (ORR, OS, PFS, and TTNT), which pERC accepted despite uncertainty due to the methodological limitations of these studies. Importantly, there was significant heterogeneity between the CARTITUDE-1 trial and the real-world data sources used to generate the external control arms in both design and population characteristics. Propensity scoring methods cannot account for unknown, unmeasured, or unmeasurable confounders, and there is a risk of bias due to residual confounding. Additional limitations included the small sample sizes, which were further reduced by matching and adjustment methods, heterogeneity in population characteristics before and after adjustment, and imprecise estimates.

- Patients and clinicians indicated that HRQoL is an important outcome in the treatment of relapsed or refractory MM. In the CARTITUDE-1 trial, HRQoL was assessed as a secondary outcome. There were clinically meaningful differences in mean change of scores from baseline to study day 100 for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the Quality of Life Questionnaire-Myeloma Module (EORTC QLQ-MY2), 5-Level EQ-5D (EQ-5D-5L) visual analogue scale, the Patient Global Impression of Change (PGIC), and the Patient Global Impression of Severity (PGIS). However, results of these measures were at risk of bias due to missing data, particularly at longer follow-up time points. 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. HRQoL was not assessed in any of the observational studies; therefore, pERC could not draw conclusions about the impact of ciltacabtagene autoleucl on HRQoL relative to other available treatments.
- pERC noted that patients expressed a need for treatments that have fewer side effects. pERC noted that although ciltacabtagene autoleucl is associated with significant short-term toxicity, it is a one-time therapy. However, ongoing support is needed after receiving ciltacabtagene autoleucl. No safety outcomes were included in any of the observational studies; therefore, pERC could not draw definitive conclusions about the safety of ciltacabtagene autoleucl relative to other treatments currently available.
- pERC noted that uncertainties remain regarding the implementation of chimeric antigen receptor (CAR) T-cell therapy and the systems needed to optimize timely access and deliverability of ciltacabtagene autoleucl in the real-world setting. Furthermore, patients identified the need for improved access to CAR T-cell therapies. Ciltacabtagene autoleucl 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 CAR T-cell therapy and it is unlikely that qualified centres will be available in all jurisdictions. The clinical experts noted that the demand for this therapy for the indication reviewed may be greater than the existing capacity in Canada for CAR T-cell therapy. pERC considered that some patients may be unable to travel outside the province or country to receive therapy.
- pERC discussed ethical and equity considerations related to ciltacabtagene autoleucl, including those related to disparities in incidence, diagnosis, treatment, and outcomes of MM, especially for racialized groups, structurally marginalized groups, lower socioeconomic groups, and residents

of rural areas, as well as the physical, mental, psychosocial, and financial burdens of treatment, including burden on caregivers. Ethical and equity issues were also noted in the context of access to ciltacabtagene autoleucl, including geographic barriers to access due to the resource-intensive nature of CAR T-cell therapy and currently limited number of CAR T-cell centres. These barriers, which can disproportionately affect racialized, structurally marginalized, and lower socioeconomic groups, highlight the need for travel and accommodation-related supports as well as clear and simplified referral practices and systems-level support for clinicians practising outside of large metropolitan centres. However, as a single infusion treatment for a disease in which patients currently have had no treatment-free windows, ciltacabtagene autoleucl was discussed as potentially presenting access-related advantages and psychosocial benefits for patients from remote communities. Due to ongoing supply or capacity challenges in delivering ciltacabtagene autoleucl and other CAR T-cell therapies, pERC discussed the ongoing need to develop pan-Canadian guidance outlining fair and equitable priority-setting criteria for patient access.

## Background

MM is a plasma cell cancer caused by the growth of cancer cells in the bone marrow. It was estimated that 4,000 Canadians would be diagnosed with MM in 2022 and that 1,650 Canadians would die from MM. Although new therapies have been introduced that can improve a patient's OS and PFS, MM remains an incurable condition. Some estimates suggest that the median survival for patients with MM is just over 5 years and during this time patients can receive 4 lines of therapy or more. Patients with MM will ultimately relapse and, according to the clinical experts consulted by CADTH for this review, are usually assessed on a monthly basis following therapy to monitor for relapse. Median OS for patients with relapsed or refractory MM is approximately 13 months.

The treatment landscape for MM has changed significantly in the past few years with the emergence of new therapies. The clinical experts consulted by CADTH noted that treatment for patients at relapse depends on patient factors, including age, comorbidities, and previous treatments. Despite an array of therapies, MM remains an incurable disease, and patients eventually relapse and become refractory to available treatments.

The clinical experts and clinician groups consulted by CADTH agreed that there is an unmet need for treatments beyond the third line that prolong survival, delay disease progression, improve quality of life, and minimize side effects. The clinical experts consulted by CADTH also noted that there is a need for treatments to be tolerable for patients with comorbidities and to require a shorter treatment duration and a longer treatment-free interval to reduce the treatment burden on this heavily pretreated patient population with a limited lifespan.

Ciltacabtagene autoleucl underwent review by Health Canada through advance consideration under Notice of Compliance with Conditions (NOC/c) and received NOC/c on February 9, 2023. Ciltacabtagene autoleucl is indicated for the treatment of adult patients with MM, who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, and who are

refractory to their last treatment. It is recommended that ciltacabtagene autoleucl is provided as a single-dose infusion at a dose of  $0.5 \times 10^6$  to  $1.0 \times 10^6$  CAR-positive viable T cells per kg of body weight, with a maximum dose of  $1 \times 10^8$  CAR-positive viable T cells per single infusion.

## Sources of Information Used by the Committee

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

- a review of 1 phase Ib/II, single-arm clinical trial of ciltacabtagene autoleucl in patients with relapsed or refractory MM who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody (CARTITUDE-1); 1 phase I, single-arm study investigating the LCAR-B38M CAR T-cell drug product produced in China expressing an identical CAR protein targeting B-cell maturation antigen (BCMA) (LEGEND-2); 5 observational studies comparing ciltacabtagene autoleucl to real-world clinical practice using individual patient data from the CARTITUDE-1 trial and various external cohorts; and 1 meta-analysis of observational studies
- patients' perspectives gathered by 1 patient group, Myeloma Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with MM
- a panel of 4 clinical specialists with expertise diagnosing and treating patients with MM
- input from 2 clinician groups, including the Canadian Myeloma Research Group (CMRG) and Ontario Health-Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to ciltacabtagene autoleucl from published literature.

## Ethical Considerations

To identify and describe ethical considerations associated with the use of ciltacabtagene autoleucl for the treatment of adult patients with MM who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody, and who are refractory to their last treatment, patient and clinician group, clinical expert, and drug program input gathered in the course of this CADTH review, as well as relevant published literature, were reviewed to identify ethical considerations relevant to the use of ciltacabtagene autoleucl.

- Ethical considerations arising in the context of MM highlighted impacts on patients and caregivers, as well as disparities in incidence, diagnosis, treatment, and outcomes of MM, especially as they affect racialized, structurally marginalized, and lower socioeconomic groups, as well as those residing in rural areas. MM was recognized as a presently incurable condition, for which treatment is burdensome for patients and their caregivers and for which there are no effective fourth-line therapies currently available.

- Ethical considerations arising in the evidence used to evaluate ciltacabtagene autoleucl indicated some limitations in the representativeness of the clinical trial population and the absence of long-term safety and efficacy data, and absence of comparative effectiveness data. Uncertainty about the magnitude of clinical benefit presented challenges for the pharmacoeconomic assessment of ciltacabtagene autoleucl and may expose payers to greater financial risks. How potential value-based agreements for the reimbursement of ciltacabtagene autoleucl are designed has implications for the distribution of the potential benefits and burdens associated with such arrangements (e.g., for patients, the public, payers, and manufacturers). As well, budget forecasting may underestimate the overall budget impact of ciltacabtagene autoleucl if implemented fairly and as needed.
- Ethical considerations arise with respect to balancing the potential benefits and harms related to the use and delivery of ciltacabtagene autoleucl. There are several access considerations regarding ciltacabtagene autoleucl and CAR T-cell therapies in Canada, including those related to geographical access, which may disproportionately affect racialized, structurally marginalized, and lower socioeconomic groups and those lacking caregiver support, as well as inequities that may arise during referral. Considerations related to privacy and culturally sensitive practices also arise in the context of cell and tissue ownership. As well, ethical considerations include supporting a robust and ongoing informed consent process, promoting shared decision-making, and ensuring balanced communication related to CAR T-cell therapies.
- Ethical considerations for health systems include challenges associated with implementing ciltacabtagene autoleucl and scaling of CAR T-cell therapy centres across Canada due to the complex infrastructure and personnel requirements, considerations related to fair priority-setting criteria if demand exceeds manufacturing or delivery capacity, and the opportunity costs associated with reimbursing and implementing a high-cost, resource-intensive therapy.

## Stakeholder Perspectives

### Patient Input

One patient group, Myeloma Canada, provided input for the review of ciltacabtagene autoleucl. Two online surveys were conducted, and a total of 200 patients and 26 caregivers provided complete responses to the patient and caregiver survey, respectively. Patient respondents indicated that their ability to work was most significantly impacted by the symptoms associated with myeloma, followed by the ability to travel and exercise as well as their mental health. Travel cost was identified as the most significant financial implication of treatment, and the majority of patient respondents indicated that they required support from a caregiver for the management of MM or treatment-related symptoms. From the perspective of the caregiver respondents, the ability to travel was most significantly impacted by caring for an individual with MM, followed by the ability to work and to spend time with family and friends. Most patient respondents reported experiencing at least some side effects associated with maintenance therapy after receiving a stem cell transplant as well as some negative impact on their overall well-being and quality of life due to the

side effects associated with maintenance therapy, which was reported by Myeloma Canada to then have a negative impact on caregivers' duties.

The patient respondents identified infections as the most important aspect of myeloma to control. They further indicated that mobility and kidney problems were aspects of myeloma that were important to control. Patient respondents reported that future treatment for MM should improve quality of life, have tolerable side effects, achieve remission, and extend survival without the need for continuous treatment. Patient respondents also highlighted the need for accessibility and portability of treatments and a supportive and communicative care team. Patient respondents further noted the importance of access to alternative newer treatments and minimal trips to the hospital or community treatment centre.

Of the respondents who reported no experience with CAR T-cell therapy, the majority of patients and caregivers indicated that an estimated minimum of 1 to 2 years of extended life without requiring any drugs to control myeloma was extremely desirable; 2 patients indicated this was not desirable. Of note, this desirability was dependent on the severity of side effects and quality of the extended life. With respect to the side effects associated with ciltacabtagene autoleucel, survey respondents who did not have experience with CAR T-cell therapy felt that cytokine release syndrome (CRS) would be the most troublesome side effect, followed by neutropenia, fever, and neuropathy.

## Clinician Input

### **Input From Clinical Experts Consulted by CADTH**

The clinical experts consulted by CADTH highlighted that the most important goals of treatment for patients with relapsed or refractory MM are prolonging survival, delaying disease progression, improving quality of life, and minimizing side effects. The clinical experts also highlighted that there is an unmet need for treatments beyond the third line that are tolerable for patients with comorbidities. The clinical experts noted that it is beneficial for any treatment to require a shorter treatment duration and lead to a longer treatment-free interval to reduce the treatment burden on this heavily pretreated patient population with a limited lifespan. In addition, the clinical experts highlighted that patients' immune systems become weaker after multiple prior lines of therapy, which creates a need for therapies that are tolerated in later lines of therapy. As well, the experts noted that, from the time of diagnosis, patients with high-risk disease have poor responses to treatment, which is worsened in the relapsed or refractory setting. Therefore, there is a great need for therapies that show some improved activity in people with high-risk disease. Patients who relapse quickly after prior lines of therapy (e.g., < 2 years) are also likely to have a very poor prognosis and thus are in great need of a novel intervention.

The clinical experts agreed that the majority of patients with relapsed or refractory MM would eventually be eligible for ciltacabtagene autoleucel, with the exception of those patients who have died before reaching the fourth line or would be ineligible for CAR T-cell therapy due to severe disease progression or poor functional status. Eligible patients would include those who have "adequate" organ function to be able to tolerate CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) (definition of adequate organ function should be broad and left to the discretion of the treating centres) and have a good performance

status (i.e.,  $\leq 2$ ). In the absence of sufficient evidence to guide patient selection for ciltacabtagene autoleucl treatment, the experts suggested that patients who have a short life expectancy ( $< 2$  months), poorly controlled progressive disease, are unable to move to a larger centre for 1 month, or who have poor functional status (Eastern Cooperative Oncology Group [ECOG] performance status  $> 2$ ), may not be suitable for ciltacabtagene autoleucl. The clinical experts noted that the major barrier to uptake would be capacity because the demand may be greater than the existing capacity in Canada for CAR T-cell therapy.

The clinical experts reported that response to treatment is typically assessed by regular monitoring that is part of the management of patients with relapsed or refractory MM. The clinical experts noted that, in some cases, patients may go through pretreatment (i.e., apheresis and conditioning chemotherapy) but not receive ciltacabtagene autoleucl. In these cases, the patients would receive supportive care until the acute crisis is resolved. If patients were to deteriorate substantially between apheresis and time of infusion, they may not proceed with ciltacabtagene autoleucl infusion. The clinical experts reported that ciltacabtagene autoleucl treatment can be provided by oncologists or hematologists in a specialized setting with adequate infrastructure for cell therapy with access to excellent clinical support and multidisciplinary care, including critical and specialist care (e.g., ICU, neurology, nephrology) to manage toxicities and laboratory support to handle and process samples.

### Clinician Group Input

The views of the clinician groups were consistent with the views of the clinical experts consulted by CADTH. Two clinician groups provided input for the review of ciltacabtagene autoleucl: CMRG, represented by 20 clinicians, and OH-CCO Hematology Cancer Drug Advisory Committee, represented by 1 clinician. The clinical groups added that antibody drug conjugates, bispecific antibodies, and cellular therapy that are directed against BCMA on myeloma cells are positioned to fill the triple class-exposed or refractory space but are not currently available in Canada. Both groups indicated that patients with an ECOG performance status of 0 to 2, minimal or no comorbidities, low tumour burden, and adequate organ function and blood counts would be the most likely to have the best outcomes.

### Drug Program Input

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

**Table 2: Responses to Questions From the Drug Programs**

Implementation issues	Response
<b>Considerations for initiation of therapy</b>	
<p>If capacity limitations exist, how would you prioritize which patients should be offered ciltacabtagene autoleucl?</p>	<p>The clinical experts acknowledge that this is a difficult question because all patients are likely to benefit from this therapy. The clinical experts agreed that an important factor is to determine which patients would have the best, most durable response to treatment. In the absence of sufficient evidence to guide patient selection for ciltacabtagene autoleucl treatment, the experts suggested that patients who have a short life expectancy (less than 2 months), poorly</p>

Implementation issues	Response
	<p>controlled progressive disease, are unable to move to a larger centre for 1 month, or who have poor functional status (ECOG &gt; 2), may not be suitable for ciltacabtagene autoleucl. The clinical experts noted that the major barrier to uptake would be capacity because the demand may be greater than the existing capacity in Canada for CAR T-cell therapy. There was some disagreement among the clinical experts on whether or not patients with cytogenetic high-risk groups should be prioritized for ciltacabtagene autoleucl because they have lower efficacy results but are also less likely to benefit from other therapies. pERC could not comment on how to prioritize which patients should be offered ciltacabtagene autoleucl because it was outside of the scope of their review.</p>
<p>According to the inclusion criteria of the CARTITUDE-1 trial, patients had to have an ECOG performance status of 0 or 1. Should ciltacabtagene autoleucl be used in patients with an ECOG performance status &gt; 1?</p>	<p>The clinical experts felt that it would be reasonable to generalize the CARTITUDE-1 results to patients with an ECOG performance status of 2. pERC indicated that patients with good performance status can be considered for CAR T-cell therapy.</p>
<p>Is there a time-limited need to consider patients who were not able to access anti-CD38 (e.g., patients previously treated with the RVD regimen whose disease ended up being refractory to both lenalidomide and bortezomib)?</p>	<p>The clinical experts indicated that it is important to include those patients who have not had the 3 classes of treatment due to lack of funded access to anti-CD38 antibodies. The clinical experts noted they would not expect the outcome of treatment with ciltacabtagene autoleucl to be inferior in these patients compared with patients who met the eligibility criteria of the CARTITUDE-1 trial. pERC noted that patients should have generally received an anti-CD38 antibody to be eligible for ciltacabtagene autoleucl, but agreed with the clinical experts that there is a time-limited need to consider patients who were not able to access an anti-CD38 antibody.</p>
<p>The CARTITUDE-1 trial excluded patients who had received prior treatment with any therapy targeted to BCMA.</p>	<p>pERC did not review evidence supporting the use of ciltacabtagene autoleucl in patients who previously received BCMA-targeted therapy because these patients were excluded from the CARTITUDE-1 trial.</p>
<p>The CARTITUDE-1 trial excluded patients who had received an allogeneic stem cell transplant within 6 months before apheresis or an autologous stem cell transplant ≤ 12 weeks before apheresis.</p>	<p>pERC indicated that patients who have previously received an allogeneic stem cell transplant &gt; 6 months before apheresis or an autologous stem cell transplant &gt; 12 weeks before apheresis could be eligible to receive ciltacabtagene autoleucl.</p>
<b>Considerations for continuation or renewal of therapy</b>	
<p>Similar to other CAR T-cell therapy files wherein CADTH only recommended a one-time dose, is there sufficient evidence to support re-treatment? If there is sufficient evidence, what is the minimum time interval between the first dose and the re-treatment dose?</p>	<p>pERC and the clinical experts noted that only 3 patients were re-treated with ciltacabtagene autoleucl in the CARTITUDE-1 trial, thus there is insufficient information to draw conclusions regarding re-treatment. pERC noted that, at this time, CAR T-cell re-treatment has not been established as an efficacious strategy and is not considered standard of care.</p>
<b>Care provision issues</b>	
<p>Is it safe to administer ciltacabtagene autoleucl in the outpatient setting?</p> <ul style="list-style-type: none"> <li>• Additional resources (nursing, hospital bed, ICU) would be needed to treat adverse events.</li> <li>• Tocilizumab is required to treat cytokine release syndrome.</li> </ul>	<p>The clinical experts indicated that it was safest to administer ciltacabtagene autoleucl in a specialized, in-patient setting. However, the clinical experts noted that eventually (with time and experience) it may be possible to identify patients who are less likely to develop severe complications, such as grade 3 or 4 cytokine release syndrome, and that those patients may be treated in an outpatient setting, such</p>

Implementation issues	Response
<ul style="list-style-type: none"> <li>Resources would also be required outside the cancer system and need to be coordinated with the hospital.</li> </ul>	<p>as complex, malignant hematology programs already in place for acute leukemia patients with resources similar to a transplant program that provides autologous transplants on an outpatient basis.</p> <p>pERC acknowledged that the clinical experts felt that each centre should determine whether it is safe and appropriate to administer ciltacabtagene autoleucl on an outpatient basis. The clinical experts highlighted the need for competent caregivers for patients to potentially receive ciltacabtagene autoleucl as an outpatient, which raises considerations about equitable access to caregiver support as well as potential burdens on caregivers.</p>

BiTE = bispecific T-cell engagers; CAR = chimeric antigen receptor; CD = cluster of differentiation; ECOG = Eastern Cooperative Oncology Group; ICU = intensive care unit; RVd = lenalidomide-bortezomib-dexamethasone.

## Clinical Evidence

### Pivotal Studies and Protocol-Selected Studies

#### Description of Studies

CARTITUDE-1 is a phase Ib/II, single-arm clinical trial of ciltacabtagene autoleucl in patients with relapsed or refractory MM who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody. The main cohort described throughout this review included 113 enrolled patients, and the study was conducted in 16 sites in the US. Of the 113 patients who underwent apheresis, 97 patients received ciltacabtagene autoleucl infusion: 29 (30%) in phase Ib and 68 in phase II (70%). As of the final data cut-off date of January 11, 2022, there were 66 patients (58%) ongoing follow-up. An additional cohort comprised of 9 patients was conducted in 4 sites in Japan; it is hereafter referred to as the Japanese cohort.

The primary objective for the phase Ib study was to characterize the safety of ciltacabtagene autoleucl and confirm the recommended phase II dose. The primary objective for the phase II study was to evaluate the efficacy of ciltacabtagene autoleucl through ORR (at least a partial response [PR] or better) as assessed by an independent review committee (IRC). The ORR and its 2-sided 95% Clopper-Pearson exact CI were assessed, and the P value from a 1-sided exact binomial test for the null hypothesis of ORR of 30% or less was provided. Secondary end points included very good partial response (VGPR) or better rate, duration of response (DOR), minimum residual disease (MRD) negativity rate, time to response, PFS, OS, and HRQoL. An exploratory objective was to characterize the impact of the treatment process on health care resource utilization. The study was funded by Janssen Research & Development.

There were 3 clinical study reports provided in the sponsor's submission: the primary analysis report with a clinical data cut-off date of September 1, 2020; the safety and efficacy update reports with a clinical data cut-off date February 11, 2021; and the final analysis report with a clinical data cut-off date of January 11, 2022. These were used throughout this report unless otherwise specified. Results from phases Ib and II were pooled together because the study procedures and criteria were consistent between both phases.

After enrolment, patients underwent apheresis, received conditioning treatment, and then received the ciltacabtagene autoleucel infusion. Of all patients who were enrolled and received apheresis, 97 (86%) received ciltacabtagene autoleucel. Bridging therapy to maintain disease stability was administered to 73 (75.3%) patients between apheresis and initiation of the conditioning regimen. No patients who received bridging therapy achieved complete response (CR) while on bridging therapy, were all eligible to receive ciltacabtagene autoleucel. The median number of CAR-positive viable T cells infused was [REDACTED] cells (range of [REDACTED] cells) with a median of  $0.709 \times 10^6$  cells/kg administered (range,  $0.51 \times 10^6$  to  $0.95 \times 10^6$  cells/kg). Patients were followed up on days 3, 7, 10, 14, 21, 28, 42, 56, 78, and 100. After day 101, they were followed up every 28 days until study completion, defined as 2 years after the last patient received their initial dose. Three patients were re-treated with ciltacabtagene autoleucel.

The mean age of patients was [REDACTED] years (SD = [REDACTED] years), and the majority of patients were younger than [REDACTED] years ([REDACTED]) and white (n = 69; 71%), with an ECOG performance status of 1 (n = 54; 56%), and International Staging System (ISS) Stage I at baseline (n = 61; 63%). Regarding cytogenetic risk, 23 patients (24%) were high risk at baseline. All patients received at least 3 prior lines of MM therapy, with a median of 6 prior lines (range, 3 to 18 lines). The most common prior antineoplastic drugs used were daratumumab in 94 patients (97%) and bortezomib in 92 patients (95%), and the most common immunomodulatory drugs were lenalidomide in 96 patients (99%) and pomalidomide in 89 patients (92%). Almost all patients (n = 96; 99%) were refractory to the last line of prior therapy, and 85 patients (88%) were triple refractory, meaning refractory to the 3 major classes of therapeutic drugs (proteasome inhibitor, immunomodulatory agent, and anti-CD38 monoclonal antibody).

### Efficacy Results

As of the data cut-off of January 11, 2022, after a median follow-up of 27.7 months (range, 1.5 to 40.4 months) the median OS was not reached. Among all treated patients (i.e., patients who received ciltacabtagene autoleucel at the targeted recommended phase II dose; N = 97), there were 30 deaths (31%), and the 24-month OS rate was [REDACTED]. Among all enrolled patients (N = 113), the 24-month OS rate was [REDACTED]. Median PFS was also not reached. Among all treated patients, [REDACTED] experienced PFS events, and the estimated 24-month PFS rate was [REDACTED]. Among all enrolled patients (N = 113), the 24-month PFS rate was [REDACTED]. ORR in the all-treated analysis set was 97.9% (95% CI, 92.7% to 99.7%), stringent CR was reached by 80 patients (82.5%, 95% CI, 73.4% to 89.4%), VGPR by 12 patients (12.4%, 95% CI, 6.6% to 20.6%), and PR by 3 patients (3.1%, 95% CI, 0.6% to 8.8%). In the all-enrolled analysis set (n = 113), the ORR was 84.1% (95% CI, 76.0% to 90.3%). ORR results from patient subgroups of interest were consistent with the primary analysis; however, the analysis was limited by small sample sizes. Median DOR was not reached. Among all treated patients, the estimated probability that patients remained in response at 12 months was [REDACTED], at 24 months it was [REDACTED], and at 30 months it was [REDACTED]. Of the 61 patients with evaluable samples, 56 (91.8%) patients (95% CI, 81.9% to 97.3%) achieved MRD negativity in bone marrow at  $10^{-5}$  sensitivity following treatment with ciltacabtagene autoleucel. Median time to first response (for patients with PR or better) was 0.95 months (range, 0.9 to 10.7 months) and mean time to first response was 1.4 months (SD = 1.54 months). Median time to best response

was 2.6 months (range, 0.9 to 17.8 months) and median time to CR or better was 2.9 months (range, 0.9 to 17.8 months).

The EORTC QLQ-C30 completion rate at baseline was 92.6% (63 patients) and declined to 83.1% (54 patients) and 65.0% (39 patients) at day 100 and day 156, respectively. The EORTC QLQ-C30 suggested improvements over time compared with baseline, with decreases observed only initially on day 7 for Global Health Status, Physical Functional Scale, and Fatigue Symptom Scale. This initial worsening is consistent with the potential onset of ciltacabtagene autoleucl adverse events (AEs) related to CRS. There appeared to be consistent improvement in the Pain Symptom Scale from baseline. The EORTC QLQ-MY20 completion rate at baseline was ██████% (████ patients) and declined to █████% (████ patients) at day 100, respectively. The EORTC QLQ-MY20 suggested improvements over time compared with baseline. The EQ-5D-5L completion rate at baseline was 92.6% (63 patients) and declined to █████% (████ patients) and ██████% (████ patients) at day 100 and day 156, respectively. The EQ-5D-5L suggested an initial decrease in both utility score and visual analogue score at day 7 followed by continuous improvement through day 100. PGIS completion rate at baseline was █████% (████ patients) and declined to █████% (████ patients) and █████% (████ patients) at day 100 and day 156, respectively. Severity of pain assessed by PGIS was consistently reported as lower than baseline through day 352. PGIC was only completed postinfusion from day 28 where 67% of patients reported improvement, and the proportion increased to 87% by day 100, when the completion rate was 79% (54 patients).

In the Japanese cohort from the CARTITUDE-1 study (n = 9), the median follow-up was 8.5 months and the ORR was 100% (95% CI, 66.4% to 100%). In the all-treated analysis set (n = 9), all DOR, PFS, and OS data were censored at the clinical cut-off; therefore, median DOR, PFS, and OS were not reached. The 9-month PFS rate was 100%, and the estimated 12 month OS rate was 100%.

## Harms Results

All patients in the all-treated analysis set (N = 97) experienced at least 1 AE, with ██████ patients experiencing at least 1 grade 4 AE. The most common any-grade AEs were neutropenia (96%), CRS (95%), anemia (81%), and thrombocytopenia (80%). A total of 53 patients (55%) experienced at least 1 serious AE (SAE), with 30 patients (31%) experiencing a grade 3 or 4 SAE and 6 patients (6%) experiencing a grade 5 SAE. The most common SAEs were CRS (21%), pneumonia (6%), sepsis (5%), and ICANS (5%).

Between apheresis and the start of the conditioning treatment, 8 patients of 113 (7%) died. Overall, 101 patients received the conditioning regimen, and 97 patients went on to receive ciltacabtagene autoleucl. Of the 4 patients who received a conditioning regimen but did not receive ciltacabtagene autoleucl, 1 patient died. Of all treated patients, 30 patients (30.9%) died: 16 due to AEs and 14 due to disease progression. No patients died within 30 days of the initial ciltacabtagene autoleucl infusion, and 2 patients (2.1%) died within 100 days. Only 6 patients (6.2%) had a treatment-emergent AE leading to death that was considered to be related to ciltacabtagene autoleucl; the remaining 10 deaths were not considered to be related to ciltacabtagene autoleucl by the study investigators.

Notable harms identified in the CADTH protocol included CRS, neurologic toxicities, cytopenia, and secondary hypogammaglobulinemia. A total of 92 (95%) patients experienced CRS, with 4 patients (4%)

experiencing a grade 3 or 4 CRS and 1 patient (1%) experiencing grade 5 CRS complicated by secondary hemophagocytic lymphohistiocytosis. A total of 21 patients (22%) experienced CAR T-cell neurotoxicity, including █ patients (10%) at grade 3 or 4. A total of 16 patients (17%) experienced ICANS, including 2 patients (2%) at grade 3 or 4. Other neurotoxicity was reported in 13 patients (13%), including 9 patients (9%) at grade 3 or 4. A total of 96 (99%) patients experienced at least 1 grade 3 or 4 cytopenic AE; the majority were transient, with recovery to grade 2 or better within the first 60 days following ciltacabtagene autoleucl infusion. A total of 12 (12.4%) patients experienced hypogammaglobulinemia, including 2 (2.1%) patients with grade 3 or 4 events.

In the Japanese cohort, all 9 patients experienced at least 1 AE and 8 (88.9%) experienced at least 1 grade 3 or 4 AE. Grade 3 or 4 cytopenias were reported in 8 patients (88.9%). Grade 1 or 2 CRS was reported in 8 (88.9%) patients, and serious AEs were reported in 1 patient (neutropenia, thrombocytopenia, fatigue, and CRS). No patient experienced CAR T-cell neurotoxicity (including ICANS or other neurotoxicity). No death was reported during the study.

## Critical Appraisal

### *Internal Validity*

CARTITUDE-1 was an open-label, single-arm phase Ib/II study in the US (16 centres) and Japan (4 centres). The primary limitation of the CARTITUDE-1 trial was the absence of a comparator group against which the benefits and harms of ciltacabtagene autoleucl could be compared. Single-arm trials are generally not considered confirmatory for efficacy and are subject to several limitations that complicate their interpretation. ORR was tested against a predetermined hypothesis; however, there was no adjustment for multiplicity across the various analyses of the outcome (i.e., the various data cut-offs) so there is an increased risk of type I error. Results for the other outcomes (e.g., DOR, OS, PFS) were descriptive only. This trial does not provide any information about the effects of ciltacabtagene autoleucl relative to available comparator treatments used in Canada. According to the FDA assessment of the CARTITUDE-1 trial, end points such as OS and PFS are uninterpretable due to the lack of a comparator arm, so they were neither reviewed nor included in the FDA label. There were a limited number of patients included in the all-treated analysis set (n = 97) and the all-randomized analysis set (n = 113) of the CARTITUDE-1 trial. The magnitude of the treatment effect estimates observed in a small study sample may not be replicable in a larger study sample or generalizable to the target population in real-world clinical practice.

It cannot be firmly concluded to what extent the improvements in ORR observed in patients would translate into OS benefits. ORR is accepted by the FDA as directly attributable to drug effect in “single-arm trials conducted in patients with refractory tumours where no available therapy exists.”

The interpretation of efficacy in the all-treated analyses are at risk of bias in favour of ciltacabtagene autoleucl. The population excludes patients (n = 16; 14%) who were enrolled and underwent apheresis but were subsequently unable to receive ciltacabtagene autoleucl because they died or their disease progressed or because of AEs or other reasons (e.g., patient choice). This population is not reflective of expected clinical practice and over-represents the healthiest patients. Analyses based on the all-enrolled population are considered most appropriate for estimating the effect of assignment to treatment. As

expected, when both were presented, the results of analyses of the all-treated population were more favourable compared with those of the all-enrolled population. Of the 113 patients who underwent apheresis, 12 patients did not receive the conditioning treatment, including 8 patients who died. The clinical experts noted that, although this is common in relapsed or refractory MM, the proportion of deaths is unusual given how relatively healthy the trial population was. Only 3 patients were re-treated with ciltacabtagene autoleucl, thus there is not enough information to draw conclusions regarding re-treatment.

Subgroup analysis was not specified in the study protocol a priori, and although results for ORR were consistent with the primary analysis results across patient subgroups of interest, the analysis was limited by the small sample size of some groups, such as patients who received a prior allogenic stem cell transplant.

The trial was open label, which can result in a risk of bias in the measurement of the outcomes, particularly for subjective outcomes such as ORR, PFS, HRQoL, and subjective harms. To reduce the risk of directional bias in reported outcomes, response outcomes were assessed by the investigators, an IRC, and a validated computer algorithm. The use of an IRC may have mitigated this risk by following recommendations for end points based on tumour measurements. In addition, although the EORTC QLQ-C30 and EQ-5D-5L are comprehensive and widely used instruments designed to measure HRQoL, neither are currently validated for patients with relapsed or refractory MM. Results for all HRQoL measures were also at risk of bias due to missing data, particularly for longer follow-ups (e.g., data were missing for █% of all treated patients for the EORTC QLQ-C30 at day 100 and for █% of patients by day 156). 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. Given that the trial was nonrandomized, the impact of ciltacabtagene autoleucl on patient-reported outcomes in relation to other therapies is unknown.

Findings from the Japanese cohort of the CARTITUDE-1 trial were consistent with results from the main cohort; however, it only included 9 patients which limits interpretation of cohort findings.

### ***External Validity***

According to the clinical experts consulted by CADTH for this review, the demographic and disease characteristics of the CARTITUDE-1 study population were generally reflective of the Canadian population with relapsed or refractory MM. The mean age of patients in the trial was 62 years, which is younger than the mean age at the time of diagnosis of 70 years in Canada. If there was no access to less-toxic bispecific therapies, clinical experts would have expected a slightly larger proportion of patients to be older than 75 years (15% versus 8% in the trial). However, clinicians can currently access these bispecific therapies through special access programs and would prioritize the older patient population for these therapies, making the trial's age proportions reflective of the current population demographics. All patients met the inclusion criteria of an ECOG performance status of 0 or 1 during screening, but 4 patients (4%) deteriorated to an ECOG performance status of 2 on or before infusion with ciltacabtagene autoleucl. The clinical experts considered it common for patients to deteriorate after apheresis. The clinical experts also mentioned they would have expected potentially more patients with extramedullary plasmacytomas present past the third line of therapy because this would denote worse disease, but that the 13% proportion in the trial is

acceptable. They would have also expected a slightly higher proportion of patients to be of high cytogenetic risk (30% versus 24% in the trial).

The clinical experts consulted by CADTH mentioned that the creatinine clearance required for inclusion in the trial ( $\geq 40$  mL/min/1.73 m<sup>2</sup>) is higher than the level used to indicate poor kidney function in clinical practice ( $\geq 30$  mL/min/1.73 m<sup>2</sup>). They also mentioned that including patients with an ECOG performance status of 2 or less (rather than the trial's criteria of  $< 2$ ) would better align with clinical practice needs. One of the exclusion criteria in the trial was any prior therapy targeted to BCMA, which the clinical experts found concerning because some clinicians would likely give their patients belantamab mafodotin, available through compassionate access, in their management of MM. The clinical experts noted that these patients may still respond well to CAR T-cell therapy and should not be excluded from ciltacabtagene autoleucl eligibility.

Regarding prior therapy used by patients in the trial, the clinical experts noted that potentially all patients would be refractory to daratumumab within the first 3 lines of therapy (compared with 97% of patients in the trial). They also noted that selinexor is currently used as a bridging therapy in the US, but no patients had used selinexor in the trial because selinexor (combined with dexamethasone and bortezomib) was not approved during the time of the trial. Finally, they noted that it was surprising that 19% of patients had used anakinra for treating CRS because it is rarely used in Canadian practice; however, they also noted this may have been due to a global shortage of tocilizumab.

The clinical experts consulted by CADTH for this review did not have any major concerns with the end points used in the CARTITUDE-1 trial. They considered OS, HRQoL, and PFS the most important outcomes, which were secondary end points in the trial. It was noted that MRD negativity rate is not routinely used in clinical practice. All outcomes in the protocol were important to patients, clinicians, and drug plans; although they were evaluated, this trial provides no information about the efficacy and harms of ciltacabtagene autoleucl relative to treatments that would otherwise be used in this patient population in clinical practice.

This study was a multicentre trial in the US. The clinical experts indicated that there are few concerns with generalizing the findings from the pivotal study within the Canadian clinical setting.

## Other Relevant Evidence

### LEGEND-2 Trial

The sponsor also provided long-term (2 year and 4 year) data from LEGEND-2, a phase I, single-arm, open-label study (N = 74) conducted in 4 registered sites in China in patients with relapsed or refractory MM who had received at least 3 prior lines of treatment. The ciltacabtagene autoleucl CAR T-cell drug product studied in CARTITUDE-1 (produced in the US) and the LCAR-B38M CAR T-cell drug product studied in the LEGEND-2 study (produced in China) express an identical CAR protein-targeting BCMA but were produced using different manufacturing and scale-up processes. Unlike ciltacabtagene autoleucl, the LCAR-B38M CAR T-cell dose was split into 3 infusions administered over 7 days, with the number of CAR T cells administered increasing with each infusion. Patients were not required to have received an anti-CD38 antibody in prior therapy, and only 2 patients (2.7%) had received prior anti-CD38 antibody therapy. Patients with a history of allogeneic stem cell transplant were excluded from the trial.

The median age of patients in the LEGEND-2 trial was 54.5 years (range, 27 to 74 years). There was a higher proportion of men (61%) enrolled, and the median time since initial MM diagnosis was 4 years (range, 1 to 9 years). The LEGEND-2 trial provided longer-term safety and efficacy follow-ups than the CARTITUDE-1 trial, with an additional 20.1 month median follow-up. In the LEGEND-2 trial 4-year analysis, median follow-up time from dosing to cut-off was 47.8 months (range, 0.4 to 60.7 months). Median OS was not yet reached but the OS rate at 24 months was ██████% (95% CI, ██████) and the median PFS was 18 months (95% CI, 10.6 to 25.6 months). ORR by sponsor assessment was 87.8% (95% CI, 78.2% to 94.3%), with 54 patients (73%) achieved CR, 6 patients (8%) achieved PR, and 5 patients (7%) achieved VGPR. Median DOR was 23.26 months (95% CI, 13.04 to 32.69 months). The median time for initial response was 1.0 months (range, 0.4 to 3.5 months) and the median time for best response was 3.3 months (range, 0.4 to 28.5 months). All patients experienced at least 1 treatment-emergent AE within 100 days after infusion, with AEs of grade 3 or higher in 45 patients (61%). The most common AEs were pyrexia in 68 patients (92%) and CRS in 68 patients (92%); only 7 patients (10%) experienced CRS of grade 3 or higher. Of the 74 patients in the analysis, 34 deaths (46%) were reported.

### ***Critical Appraisal of LEGEND-2***

The LEGEND-2 trial was an open-label, single-arm phase I study conducted only in China (4 centres). The ciltacabtagene autoleucel CAR T-cell drug product studied in the CARTITUDE-1 trial (produced in the US) and the LCAR-B38M CAR T-cell drug product studied in the LEGEND-2 study (produced in China) express an identical CAR protein targeting BCMA, but they were produced using different manufacturing and scale-up processes. The primary limitation was the absence of a comparator group against which the treatment benefits and harms of the LCAR-B38M CAR T-cell drug product could be compared. As such, there is no evidence of the effect of LCAR-B38M relative to available comparator therapies from this trial. The study protocol mentioned the use of a computerized algorithm and IRC for disease status evaluation; however, findings are reported based on sponsor assessment (based on uniform medical reviews of source hospital medical records) leading to increased risk of bias in the measurement of the outcome, likely favouring LCAR-B38M. HRQoL was not assessed as an end point in this phase I study. The clinical experts consulted by CADTH for this review noted that the baseline characteristics of the LEGEND-2 study population would be closer to patients who are in the second line of therapy (younger and with limited use of daratumumab) rather than the fourth line of therapy and beyond. Moreover, because exposure to an anti-CD38 antibody was not required (only 2 patients had received prior anti-CD38 antibody therapy), this study population does not fully align with the reimbursement criteria for this review. The experts also mentioned that the low proportion of patients with neurotoxicity as an AE (only 1 patient) was not aligned with the results of CARTITUDE-1.

### **Comparative Observational Evidence: Ciltacabtagene Autoleucel Versus Real-World Clinical Practice**

The sponsor submitted evidence consisting of 2 reports of 3 observational studies to compare ciltacabtagene autoleucel to relevant treatment comparators in real-world clinical practice (RWCP): the CARTITUDE-1 trial versus the LocoMMotion study as well as the CARTITUDE-1 trial versus real-world cohorts.

### ***CARTITUDE-1 Versus LocoMMotion***

The first sponsor-submitted report was an observational study comparing the effectiveness of ciltacabtagene autoleucl (from the CARTITUDE-1 trial) versus RWCP as observed in the LocoMMotion prospective cohort study using individual patient data (IPD), with propensity score weighting and regression modelling in an attempt to adjust for known confounders. The following outcomes were planned to be assessed: clinical response (ORR, VGPR, CR or better, MRD), PFS, TTNT, OS, patient-reported outcomes, safety, and resource utilization.

The CARTITUDE-1 study consisted of 113 patients who underwent apheresis and who made up the intention to treat (ITT) population, and 97 patients who were treated with ciltacabtagene autoleucl (modified intention to treat [mITT] population). The selected LocoMMotion cohort consisted of 248 patients in the ITT population and 170 patients in the mITT population. After weighting, the effective ITT and mITT population sizes of the LocoMMotion cohort were 118 and 108 patients, respectively.

Following adjustment, the conditional hazard ratio (HR) for OS was 0.32 (95% CI, 0.17 to 0.58) in the ITT population (median OS = not estimable [NE]; 95% CI, 31.47 months to NE for ciltacabtagene autoleucl versus 11.76 months; 95% CI, 7.16 months to NE for RWCP), and 0.20 (95% CI, 0.09 to 0.41) in the mITT population (median OS = NE; 95% CI, NE to NE versus 11.33 months; 95% CI, 5.45 months to NE), both favouring ciltacabtagene autoleucl.

For PFS, the conditional HR between treatment groups was 0.19 (95% CI, 0.11 to 0.32) in the ITT population (median PFS = 28.03 months; 95% CI, 20.11 months to NE for ciltacabtagene autoleucl versus 4.07 months; 95% CI, 2.86 to 5.09 months for RWCP), and conditional HR = 0.15 (95% CI, 0.08 to 0.29) in the mITT population (median PFS = NE; 95% CI, 24.54 months to NE for ciltacabtagene autoleucl versus 2.73 months; 95% CI, 2.37 to 3.68 months for RWCP), both favouring ciltacabtagene autoleucl.

For ORR, observed proportions from the LocoMMotion study for the ITT and mITT populations were 84.1% and 97.9% for ciltacabtagene autoleucl and 29.8% and 42.9% for RWCP, respectively. The IPW-estimated OR was 22.00 (95% CI, 11.14 to 43.35) in the ITT population and 103.87 (95% CI, 24.17 to 446.37) in the mITT population, both in favour of ciltacabtagene autoleucl.

Overall, there was variation in study design (phase Ib/II, open-label trial versus an observational and noninterventional study), heterogeneity between cohorts before and after adjustment, as well as uncertainty of the results due to the assumptions made and residual confounding. This limits the ability to draw strong conclusions about the comparative efficacy of ciltacabtagene autoleucl with other treatments in this clinical setting where no effective standard of care is available. Given the adjustment of the LocoMMotion population to the CARTITUDE-1 population, the generalizability of the results is similar to that of the CARTITUDE-1 trial. In addition, there were a total of 92 unique regimens received as RWCP in the LocoMMotion study, which may not be reflective of Canadian clinical practice, and there were no Canadian investigative sites included in either the CARTITUDE-1 or LocoMMotion studies, which may impact the generalizability of the results to Canadian patients.

### ***CARTITUDE-1 Versus Real-World Cohorts***

The other sponsor-submitted report included 2 observational studies to compare treatment with ciltacabtagene autoleucel to real-world treatments for triple class–exposed relapsed or refractory MM. In both studies, propensity score weighting was used in an attempt to adjust for known confounders. One analysis compared the IPD from the CARTITUDE-1 trial to the IPD from a cohort of patients in the long-term follow-up of 3 global relapsed or refractory MM clinical trials of daratumumab (POLLUX, CASTOR, and EQUULEUS; hereinafter referred to as the daratumumab trial cohort). The other analysis compared the IPD from the CARTITUDE-1 trial to IPD from a CARTITUDE-1–like cohort of real-world patients receiving current treatment paradigms using data from the Flatiron Health database (hereinafter referred to as the Flatiron cohort). Outcomes included in the analyses consisted of ORR, CR or better rate, PFS, and OS. The outcomes of CR and VGPR were not evaluated in the Flatiron database; therefore, an assessment of ORR and CR or better rate was not possible.

The CARTITUDE-1 trial included 113 patients in the ITT population and 97 patients in the mITT population. A total of 351 and 288 patients were included in the daratumumab trial cohort in the ITT and mITT populations, respectively. After propensity score weighting, the base-case effective sample size (ESS) of the daratumumab trial cohort ITT and mITT populations was 212 and 116, respectively. In the Flatiron cohort, 229 and 196 patients made up the ITT and mITT populations. After adjustment, the ESS for the Flatiron cohort was 192 in the ITT population and 80 in the mITT population.

The HR for OS comparing ciltacabtagene autoleucel versus RWCP in the daratumumab trial cohort was 0.25 (95% CI, 0.17 to 0.38) and HR = 0.20 (95% CI, 0.13 to 0.31) for the ITT population (median OS = not reached [NR]; 95% CI, 31.47 to NE versus 8.05 months 95% CI, 6.34 to 11.30 months), and mITT populations (median OS = NR; 95% CI, NE to NE versus median OS = 10.90 months; 95% CI, 8.18 to 16.20 months), in favour of ciltacabtagene autoleucel. The HRs for OS comparing ciltacabtagene autoleucel with RWCP in the Flatiron cohort were 0.32 (95% CI, 0.19 to 0.52) and HR = 0.25 (95% CI, 0.14 to 0.43) for the ITT population (median OS = NR; 95% CI, 31.47 months to NE] versus median OS = 12.30 months; 95% CI, 9.72 to 15.50 months) and mITT populations (median OS = NR; 95% CI, NE to NE versus median OS = 13.20 months; 95% CI, 9.17 to 21.30 months), in favour of ciltacabtagene autoleucel.

The HR for PFS for ciltacabtagene autoleucel versus RWCP in the daratumumab trial cohort was 0.26 (95% CI, 0.18 to 0.37) in the ITT population (median PFS, ██████████) and HR = 0.24 (95% CI, 0.16 to 0.35) in the mITT population (median PFS = NR; 95% CI, 24.54 months to NR versus median PFS = 5.32 months; 95% CI, 2.76 to 8.31 months), in favour of ciltacabtagene autoleucel. Results for adjusted PFS (aPFS), and real-world PFS (rwPFS) were consistent with the overall PFS analysis for the daratumumab trial cohort. The aPFS HR for ciltacabtagene autoleucel versus RWCP in the Flatiron cohort was 0.22 (95% CI, 0.15 to 0.33) in the ITT population (median aPFS = ██████████) and median aPFS = 0.18; 95% CI, 0.12 to 0.26) in the mITT population (median aPFS = NR; 95% CI, 24.54 months to NR versus 4.53 months; 95% CI, 2.86 to 6.77 months), also in favour of ciltacabtagene autoleucel. In the Flatiron cohort, the rwPFS HR was 0.22 (95% CI, 0.15 to 0.33) in the ITT population ██████████

██████████ and 0.18 (95% CI, 0.10 to 0.23) in the mITT population (median rwPFS = NR; 95% CI, 24.54 months to NR versus 5.88 months; 95% CI, 4.01 to 8.48 months). After IPTW, the odds ratio (OR) for ORR comparing ciltacabtagene autoleucl to RWCP was 22.55 (95% CI, 10.72 to 52.03) in the ITT population and OR = 127.35 (95% CI, 34.24 to 850.09) in the mITT population. Results for ORR were not available in the comparison with the Flatiron cohort.

Results of the base-case analyses and sensitivity analyses were consistent across end points, analysis populations, and across data sources, favouring ciltacabtagene autoleucl over RWCP from both the daratumumab trial cohort and the Flatiron cohort for all outcomes. For all outcomes, the magnitude of effect for ciltacabtagene autoleucl was notably larger than RWCP; however, results were associated with wide 95% CIs, highlighting losses to precision and reducing the ability to draw strong conclusions about the magnitude of the effect. There were important differences in the design of the included studies that limit the ability to draw strong conclusions about the efficacy of ciltacabtagene autoleucl compared with RWCP, including the differences in study design (phase Ib/II, single-arm trial versus published literature from 3 clinical trials [2 phase III RCTs and 1 phase Ib open-label RCT]), and a real-world cohort from electronic health records), which could not be adjusted for using propensity scoring methods, as well as the notable heterogeneity in populations before adjustment, the potential for residual confounding following adjustment, as well as the small sample sizes and wide 95% CIs, highlighting losses to precision.

### **Other Observational Studies Identified in the Literature Search**

In total, 3 published articles met the CADTH-predefined inclusion criteria for this review: the CARTITUDE-1 trial versus the Monoclonal Antibodies in Multiple Myeloma: Outcomes after Therapy Failure (MAMMOTH) trial, the CARTITUDE-1 trial versus the Therapie Monitor database, and a meta-analysis of observational studies.

#### ***CARTITUDE-1 Versus MAMMOTH***

An observational study using IPD from the CARTITUDE-1 trial and the MAMMOTH cohort to evaluate the efficacy of ciltacabtagene autoleucl versus real-world therapies for the outcomes of ORR, PFS, and OS. Propensity score matching was used to attempt to adjust for confounding.

The populations from the CARTITUDE-1 trial consisted of 113 patients in the ITT population and 97 patients in the mITT population. Corresponding populations identified from the MAMMOTH study included 190 and 122 patients in the ITT and mITT populations, respectively. The matched populations included 95 patients in the ITT populations in each cohort and 69 patients in the mITT cohort. In the propensity score-matched analysis, results for PFS and OS favoured patients in the CARTITUDE-1 trial (HR = 0.11; 95% CI, 0.05 to 0.22) compared with the matched MAMMOTH population HR = 0.20; 95% CI, 0.10 to 0.39). For ORR, 80 (84%) patients achieved ORR in the CARTITUDE-1 trial versus 27 (28%) patients in MAMMOTH study (OR = 13.4; 95% CI, 6.6 to 27.3) for the ITT analysis. Results for the mITT population were also consistent with the ITT population.

In general, the results of the analyses from the MAMMOTH study demonstrated a clinical benefit of ciltacabtagene autoleucl over RWCP; however, the reduced sample sizes from propensity score matching,

unexplored heterogeneity, and wide 95% CIs resulted in uncertainty in the results and the magnitude of the observed effects. Given the methodological differences across studies and the risk of bias due to residual confounding, the comparison with external, historical, real-world data are nonconfirmatory and should only be viewed as exploratory.

### ***CARTITUDE-1 Versus Therapie Monitor***

An observational study was submitted evaluating OS and TTNT for patients in the CARTITUDE-1 trial versus patients receiving real-world treatments registered in the Therapie Monitor database in Germany maintained by Oncology Information Service. IPD from both cohorts was used for comparison for the outcomes of OS and TTNT (as proxy for PFS), and propensity score weighting was used to attempt to adjust known confounders.

The ITT and mITT populations for the CARTITUDE-1 study consisted of 113 and 97 patients, and the ITT and mITT populations of Therapie Monitor database consisted of 222 and 174 patients, respectively. After weighting, the ESS for the ITT population was not reported and the ESS for the mITT population was 42 patients. In the ITT population, ciltacabtagene autoleucel was favoured over RWCP for OS (HR = 0.14; 95% CI, 0.07 to 0.25). For TTNT, ciltacabtagene autoleucel was also favoured over RWCP from the Therapie Monitor database (HR = 0.13; 95% CI, 0.07 to 0.24). Results for OS and TTNT in the mITT population were consistent with the ITT population; however, the 95% CIs were wider (OS: HR = 0.26; 95% CI, 0.08 to 0.84; TTNT: HR = 0.24; 95% CI, 0.09 to 0.67).

All analysis methods were appropriate and suggested similar results favouring ciltacabtagene autoleucel over RWCP; however, the results of the present analysis were associated with uncertainty given the reduced sample sizes, the lack of adjustment for potential confounding factors, the notable heterogeneity in patient populations that remained for 6 of 9 key variables after adjustment, and the wide 95% CIs, particularly for the mITT population, resulting in greater uncertainty of the results.

### **Meta-Analysis of Observational Studies**

A frequentist, random-effects meta-analysis of observational studies evaluating ciltacabtagene autoleucel versus physicians' choice of treatment was identified in the published literature. The studies included in the meta-analysis consisted of all studies summarized here and included publications for the comparison of the CARTITUDE-1 study with the LocoMMotion study, the Flatiron cohort, the daratumumab trial cohort, the MAMMOTH cohort, and the Oncology Information Service database. Outcomes included OS, PFS, and ORR. No analyses of ORR were conducted in the all-index dates analyses.

In the ITT population, including all eligible index dates, the overall HR for ciltacabtagene autoleucel compared with RWCP was 0.26 (95% CI, 0.15 to 0.47) for OS and HR = 0.22 (95% CI, 0.1 to 0.49) for PFS. Results for the mITT population were consistent with the ITT population. The OR for ORR in the ITT population was 13.94 (95% CI, 4.88 to 39.84), whereas the OR for ORR in the mITT population was 86.22 (95% CI, 17.96 to 413.88), in favour of ciltacabtagene autoleucel.

Although the comparisons of ciltacabtagene autoleucel to external cohorts from multiple studies provided a large evidence base for comparison, there were important limitations in this evidence, including

methodological differences across the data sources that could not be adjusted for using propensity scores and a risk of confounding (due to the inability to adjust for important prognostic factors and/or differences remaining in the distribution of prognostic factors across cohorts after adjustment). Pooling via meta-analysis could not overcome the limitations of the individual studies; rather, meta-analysis could compound the bias. Results of the included observational comparisons were consistently in favour of ciltacabtagene autoleucl over RWCP for all outcomes assessed. Similarly, results of the meta-analysis were in favour of ciltacabtagene autoleucl for OS, PFS, and TTNT for both the all-index dates and first index dates analyses for both the ITT and mITT populations and in all sensitivity analyses, although the 95% CIs were often wide, which suggests some imprecision, unexplained heterogeneity, and uncertainty in the magnitude of the effects.

## Economic Evidence

**Table 3: Cost and Cost-Effectiveness**

Component	Description
<b>Type of economic evaluation</b>	Cost-utility analysis Decision tree followed by PSM
<b>Target population</b>	Adult patients with relapsed or refractory MM who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody
<b>Treatment</b>	Ciltacabtagene autoleucl
<b>Dose regimen</b>	Single infusion of ciltacabtagene autoleucl at a target dose of $0.5 \times 10^6$ to $1.0 \times 10^6$ CAR-positive viable T cells per kg, with a maximum dose of $1 \times 10^8$ CAR-positive viable T cells
<b>Submitted price</b>	Ciltacabtagene autoleucl (Carvykti): \$632,455 per administration
<b>Treatment cost</b>	One-time cost of \$632,455
<b>Comparators</b>	Weighted basket comparator (SOC) consisting of: <ul style="list-style-type: none"> <li>• carfilzomib-dexamethasone (33.3%)</li> <li>• carfilzomib-dexamethasone-cyclophosphamide (6.9%)</li> <li>• pomalidomide-dexamethasone (27.5%)</li> <li>• pomalidomide-dexamethasone-cyclophosphamide (32.4%)</li> </ul>
<b>Perspective</b>	Canadian publicly funded health care payer
<b>Outcomes</b>	QALYs, LYs
<b>Time horizon</b>	Lifetime (20 years)
<b>Key data source</b>	<ul style="list-style-type: none"> <li>• Efficacy of ciltacabtagene autoleucl was obtained from the single-arm, phase Ib/II CARTITUDE-1 study in adult patients with third-line or later relapsed or refractory MM.</li> <li>• Comparator efficacy was derived from a prospective, observational study and compared using an ITC</li> </ul>
<b>Submitted results</b>	<ul style="list-style-type: none"> <li>• ICER = \$187,779 per QALY (incremental costs: \$469,538; incremental QALYs: 2.50)</li> </ul>



Component	Description
<p><b>Key limitations</b></p>	<ul style="list-style-type: none"> <li>• The clinical efficacy of ciltacabtagene autoleucl was based on a single-arm, open-label phase Ib/II study, leading to highly uncertain PFS and OS results in comparison to SOC.</li> <li>• The sponsor excluded substantial costs from the base-case analysis related to CAR T-cell infusion, such as those associated with determination of patient eligibility, apheresis, bridging therapy, and lymphodepleting conditioning therapy. Therefore, the cost of CAR T-cell infusion was underestimated.</li> <li>• The sponsor excluded some follow-up costs, such as immunoglobulins, that may be incurred after CAR T-cell infusion for the remainder of the patient's life. Therefore, lifetime costs associated with CAR T-cell infusion were underestimated.</li> <li>• OOS products were assumed not to be reimbursed by the public health care payer. There remains uncertainty about whether, under such situations, costs would not be borne by public plans.</li> <li>• The frequency of subsequent therapy use was underestimated in patients who progressed after receiving CAR T cells. Subsequent therapy costs were therefore underestimated for those receiving CAR T-cell therapy.</li> <li>• There is uncertainty pertaining to the utility values in the postprogression health care state given a different source was used. It is unclear if the populations from the studies informing the utility estimates are homogeneous.</li> </ul>
<p><b>CADTH reanalysis results</b></p>	<ul style="list-style-type: none"> <li>• Without long-term evidence, clinical experts consulted by CADTH noted long-term OS is highly uncertain because the durability of impact of ciltacabtagene autoleucl on OS is unknown. CADTH conducted separate analyses involving different assumptions for OS, along with applying changes to CAR T-cell therapy-related costs, immunoglobulin costs, OOS product reimbursement, frequency of subsequent therapy, and utility values.</li> <li>• In CADTH reanalysis A, mortality risk was assumed to remain fairly constant over time using a gamma distribution to extrapolate long-term OS. This therefore assumes the impact of ciltacabtagene autoleucl as evidenced from the trial is permanent and enduring. The ICER for ciltacabtagene autoleucl was \$201,901 per QALY compared with SOC (incremental costs: \$517,233; incremental QALYs: 2.56). Under this reanalysis, a price reduction of 72% would be required for ciltacabtagene autoleucl to be cost-effective at a WTP threshold of \$50,000 per QALY.</li> <li>• In CADTH reanalysis B, the same changes were made as in reanalysis A with an additional change for overall survival. In this reanalysis, an increasing mortality risk over time was assumed instead (e.g., waning impact of ciltacabtagene autoleucl). In this reanalysis, the ICER for ciltacabtagene autoleucl was \$286,972 per QALY compared with SOC (incremental costs: \$521,954; incremental QALYs: 1.82). A price reduction of 80% would be required to achieve cost-effectiveness at a WTP threshold of \$50,000 per QALY.</li> </ul>

CAR = chimeric antigen receptor; ITC = indirect treatment comparison; LY = life-year; MM = multiple myeloma; OOS = out of specification; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; SOC = standard of care; WTP = willingness to pay.

### Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the population was based on incidence only and was thus underestimated, the market share of ciltacabtagene autoleucl was underestimated, and the time horizon was too far into the future. CADTH reanalysis included changes to address these limitations. Based on the CADTH base case, the estimated budget impact of the reimbursement of ciltacabtagene autoleucl for the treatment of third-line or later relapsed or refractory MM is expected to be \$90,059,041 in year 1, \$131,673,837 in year 2, and \$183,710,617 in year 3, for a 3-year total of \$405,443,496. This only assumes individuals initiating fourth-line therapy will receive ciltacabtagene autoleucl. If individuals who initiate fifth-line or higher therapy will also receive ciltacabtagene autoleucl, then the budget impact will increase. A scenario analysis conducted based on patients' eligibility for



ciltacabtagene autoleucl by ECOG performance status resulted in a 3-year budget impact of \$632,434,749, indicating the budget impact is highly sensitive to assumptions around the eligibility criteria.

## pERC Information

### Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, 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:** March 8, 2023

**Regrets:** None

**Conflicts of interest:** None