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## CADTH Reimbursement Recommendation

# Treosulfan (Trecondyv)

**Indication:** Treosulfan in combination with fludarabine as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation in adult patients with acute myeloid leukemia or myelodysplastic syndromes at increased risk for standard conditioning therapies

**Sponsor:** Medexus Pharmaceuticals Inc.

**Final recommendation:** Reimburse with conditions

# Summary

## What Is the CADTH Reimbursement Recommendation for Trecondyv?

CADTH recommends that Trecondyv in combination with fludarabine should be reimbursed by public drug plans as part of conditioning treatment before allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) at increased risk for standard conditioning therapies if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Trecondyv in combination with fludarabine should only be covered to treat adult patients with AML or MDS who are eligible for alloHSCT, are at least 50 years old at transplant, and/or have a Hematopoietic Cell Transplantation-Comorbidity Index score greater than 2. Patients should have good performance status.

### What Are the Conditions for Reimbursement?

Trecondyv should only be reimbursed in combination with fludarabine if prescribed by clinicians with appropriate training and experience in transplant centres with alloHSCT programs and if the cost of Trecondyv is not more than the least costly alternative conditioning treatment.

### Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that treatment with Trecondyv in combination with fludarabine resulted in similar chances of cancer returning within 2 years after alloHSCT as compared with busulfan in combination with fludarabine.
- Based on CADTH's assessment of the health economic evidence, Trecondyv does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Trecondyv compared with other conditioning treatments for adult patients with AML or MDS who are considered ineligible for standard conditioning therapies.
- Trecondyv in combination with fludarabine may meet patients' needs to reduce transplant-related complications and prolong survival.
- Based on public list prices, Trecondyv is estimated to cost the public drug plans approximately $650,000 over the next 3 years. However, the actual budget impact is uncertain and will depend on the market uptake of Trecondyv.

# Summary

## Additional Information

### What Is AML and MDS?

AML is a blood and bone marrow cancer that leads to fewer mature blood cells. AML causes weakness, infection, bleeding, and other symptoms and complications. There were 1,090 new cases of AML in Canada in 2016 and 1,184 deaths from AML in 2017. MDS is a group of blood cancers in which the bone marrow makes faulty blood cells that can lead to infections, anemia, or bleeding. Approximately one-quarter to one-third of patients with MDS will progress to AML. The estimated incidence rate of MDS is approximately 4.3 cases per 100,000 people per year.

### Unmet Needs in AML and MDS

Improved conditioning regimens are needed that reduce the risk of transplant-related mortality without increasing the chances that cancer returns after the transplant and have fewer side effects compared with current treatment options.

### How Much Does Trecondyv Cost?

Treatment with Trecondyv is expected to cost $8,316 per patient per course of treatment.

## Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that treosulfan in combination with fludarabine be reimbursed as part of conditioning treatment before allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) who are at increased risk for standard conditioning therapies only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

One phase III, open-label, randomized, active-controlled trial (MC-FludT.14/L; N = 570) demonstrated that treosulfan in combination with fludarabine was noninferior to busulfan in combination with fludarabine in terms of event-free survival (EFS) within 2 years after alloHSCT in adult patients with AML or MDS who are considered ineligible for standard conditioning therapies. The 2-year EFS in the treosulfan group was statistically noninferior (noninferiority margin hazard ratio [HR] of 1.3 was met) compared with the busulfan group (confirmatory analysis; HR = 0.65; 99.9702% confidence interval [CI], 0.36 to 1.19; P = 0.0000164; median follow-up time: 15.4 months and 17.4 months for the treosulfan and busulfan groups, respectively). pERC acknowledged that the 2-year EFS rates at the final analysis were 65.7% (95% CI, 59.5% to 71.2%) and 51.2% (95% CI, 45.0% to 57.0%) for the treosulfan and busulfan groups, respectively, suggesting a trend toward superiority in the treosulfan group (median follow-up time: 29.7 months and 29.4 months for treosulfan and busulfan groups, respectively). Secondary efficacy end points suggested a similar trend in favour of the treosulfan group (2-year overall survival [OS], transplant-related mortality [TRM], nonrelapse mortality [NRM], and graft-versus-host disease [GvHD]– or chronic GvHD–free and relapse- or progression-free survival) or showed little to no difference (incidence of relapse or progression within 2 years after alloHSCT). However, the committee noted that uncertainty remained given the test for superiority was statistically not significant for EFS, the exploratory nature of secondary outcomes, and the need for longer follow-up to confirm an OS benefit.

Patients identified a need for effective treatments that prolong survival, have fewer side effects and posttransplant complications, and improve quality of life, including mental health. pERC concluded that treosulfan in combination with fludarabine may meet patients' needs to prolong survival and to reduce transplant-related complications. The committee discussed that adverse events (AEs) that occurred during the MC-FludT.14/L trial suggested a similar safety profile across the study groups, with little to no difference in the cumulative incidence of GvHD. Health-related quality of life (HRQoL) was not assessed in the MC-FludT.14/L trial.

Using the sponsor's submitted price for treosulfan and publicly listed prices for all other drug costs, the drug acquisition cost of treosulfan in combination with fludarabine was more costly than busulfan in combination with fludarabine. Although the economic evaluation suggested treosulfan was associated with total cost savings compared with busulfan, the finding of cost savings relied on fewer patients experiencing relapse or disease progression, and associated cost savings from avoiding subsequent therapies, hospitalizations,

infusions, and routine care. Due to the uncertainty associated with the comparative clinical efficacy assumptions, the total drug cost of treosulfan should not exceed the total drug cost of busulfan.

## Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Initiation** | | |
| 1. Treatment with treosulfan in combination with fludarabine should be reimbursed in adult patients with AML or MDS who are eligible for alloHSCT and are at increased risk for standard conditioning therapies defined as:<br>1.1. ≥ 50 years old at transplant and/or an HCT-CI score > 2. | Evidence from the MC-FludT.14/L trial demonstrated that treatment with treosulfan in combination with fludarabine as a part of conditioning treatment before alloHSCT resulted in similar clinical benefit for adult patients with AML or MDS who were not eligible for standard conditioning therapies compared with busulfan in combination with fludarabine. | pERC agreed with the clinical experts that extending the age cut-off for ineligibility for standard conditioning therapies to age 55 to 60 years at transplant may be at the discretion of the treating clinician. |
| 2. Patients should have good performance status. | Patients with a Karnofsky Index of ≥ 60% were included in the MC-FludT.14/L trial. | Treating patients with a Karnofsky Index of less than 60% may be at the discretion of the treating clinician. |
| 3. Patients must not have any of the following:<br>3.1. active malignant involvement of the CNS<br>3.2. previous allogeneic HSCT. | The MC-FludT.14/L trial excluded patients with these characteristics and no further evidence was provided for these patients. | — |
| **Prescribing** | | |
| 4. Treosulfan in combination with fludarabine should be prescribed by clinicians with appropriate training and experience in transplant centres with alloHSCT programs. | This helps to ensure that treosulfan in combination with fludarabine is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner. | — |
| 5. Treosulfan should only be reimbursed in combination with fludarabine. | In the MC-FludT.14/L trial, treosulfan was administered in combination with fludarabine; no evidence was reviewed to assess treosulfan monotherapy as this was beyond the scope of the review. | — |
| **Pricing** | | |
| 6. Treosulfan should be negotiated so that it does not exceed the drug program cost of treatment with the least costly comparator reimbursed as conditioning treatment before alloHSCT in adult patients with AML or MDS at increased risk from standard conditioning therapies. | Trial evidence demonstrated that treosulfan in combination with fludarabine as a part of conditioning treatment before alloHSCT resulted in similar clinical benefit as busulfan with fludarabine for adult patients with AML or MDS who were not eligible for standard conditioning therapies. As such, there is insufficient evidence to justify a cost premium for treosulfan over the least expensive conditioning treatment before alloHSCT reimbursed for patients with | — |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| | AML or MDS at increased risk for standard conditioning therapies. | |
| **Feasibility of adoption** | | |
| 7. The feasibility of the adoption of treosulfan in combination with fludarabine must be addressed. | At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption given the difference between the sponsor's estimate and CADTH's estimate. | — |

alloHSCT = allogeneic hematopoietic stem cell transplantation; AML = acute myeloid leukemia; CNS = central nervous system; HCT-CI = Hematopoietic Cell Transplant-Comorbidity Index; MDS = myelodysplastic syndrome; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

## Discussion Points

- pERC recognized that AML and MDS are life-threatening diseases and alloHSCT is considered a curative-intent treatment option for these malignancies. pERC heard from the clinical experts that patients who are ineligible for intensive conditioning therapy, but are otherwise eligible to undergo alloHSCT, have a need for improved conditioning regimens that reduce the risk of TRM due to treatment toxicity and complications (e.g., GvHD) without increasing the incidence of relapse.
- In the MC-FludT.14 trial, the incidence of any treatment-emergent AEs, grade 3 or higher treatment-emergent AEs, serious AEs, and the cumulative incidence of acute GvHD grade III or IV at 100 days and chronic GvHD at 24 months was similar in the 2 study groups. pERC acknowledged input from the clinical experts, noting that the treosulfan's AE profile appears consistent with its cytotoxic and myelosuppressive characteristics and can be adequately managed and mitigated by clinicians experienced in conditioning treatment followed by alloHSCT.
- pERC discussed that Health Canada has approved treosulfan in combination with fludarabine as part of conditioning treatment prior to alloHSCT in pediatric patients older than 1 year with AML or MDS. However, the sponsor did not file a submission for the pediatric population at this time and, therefore, this patient population was beyond the scope of the CADTH review.

## Background

AML is a cancer of the blood and bone marrow characterized by an abnormal and occasionally poor proliferation of immature hematopoietic cells that infiltrate bone marrow, blood, and other tissues. Genetic alterations in myeloid progenitor stem cells alter normal growth and differentiation of myeloblasts. The most recent statistics from the Canadian Cancer Society are that 1,090 Canadians were newly diagnosed with AML in 2016 and 1,184 Canadians died of AML in 2017. According to the clinical experts consulted by CADTH, it is estimated that the percentage of patients in Canada who are not eligible for myeloablative conditioning (MAC) ranges from 30% to 40% for patients with AML; it is higher for patients with MDS because this patient group tends to be older. MDS is a group of blood cancers in which there is a lack of

healthy blood cells and increased abnormal cells in the blood and/or bone marrow. As a result, infections, anemia, or bleeding may occur. MDS will progress to AML in one-quarter to one-third of cases. The estimated overall age-adjusted incidence rate of MDS is 4.3 cases per 100,000 persons per year in the US. At the time of this review, treatment with alloHSCT is the only known curative-intent treatment for patients with AML and for patients with MDS who are high risk.

Conditioning therapy plays a central role in alloHSCT by preparing or "conditioning" the patient's body for the transplant. There are 3 common types of conditioning regimens: MAC, reduced-intensity conditioning (RIC), and nonmyeloablative regimens. Patients who are not eligible for MAC regimens (e.g., older patients and patients with comorbidities) usually receive an RIC regimen, such as busulfan in combination with fludarabine, to minimize treatment-related toxicity, NRM, and TRM; however, lower dose intensity is associated with a higher risk of relapse.

Treosulfan in combination with fludarabine has been approved by Health Canada as part of conditioning treatment prior to alloHSCT in adult patients with AML or MDS at increased risk for standard conditioning therapies and in pediatric patients older than 1 year with AML or MDS. As per the sponsor request, this CADTH review focuses on the indication in adults. The sponsor did not file a submission for the pediatric population at this time and, therefore, this patient population was beyond the scope of the CADTH review.

Treosulfan is given in combination with fludarabine and is available for IV use as a 2-hour infusion. The product monograph recommends a dosage of 10 g/m$^2$ body surface area per day as a 2-hour IV infusion on 3 consecutive days (days −4, −3, and −2) before stem cell infusion (day 0). The total treosulfan dose is 30 g/m$^2$.

## Sources of Information Used by the Committee

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

- a review of 1 phase III, multicentre, open-label, active-treatment, randomized controlled trial in adult patients with AML or MDS indicated for alloHSCT who were considered ineligible for standard conditioning therapies
- patient perspectives gathered by 1 patient group, Leukemia and Lymphoma Society of Canada (LLSC)
- 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 AML or MDS
- input from 2 clinician groups, including Cell Therapy Transplant Canada (CTTC) and Ontario Health (Cancer Care Ontario) Complex Malignant Hematology Advisory Committee (OH-CCO Complex Malignant Hematology Advisory Committee)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

# Stakeholder Perspectives

## Patient Input

CADTH received 1 patient group submission from LLSC, which is a national charitable status organization dedicated to finding a cure for blood cancers and to improve the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support. LLSC conducted an online survey with 108 respondents in July 2023. LLSC noted the decision-making process for stem cell transplant has a significant impact on the mental health of patients and their families. According to the survey, 79% of respondents reported moderate to extreme levels of anxiety, and 83% reported moderate to extreme levels of stress. Some of the highly considered factors by respondents for making a decision about the transplant are OS, disease progression, quality of life, thoughts of "losing time," and posttransplant complications, such as graft rejection, graft failure, infection, GvHD, and toxicity. LLSC highlighted that patients expected that knowing they would have access to conditioning therapy with the potential for increased survivorship and fewer side effects would have a significant positive impact on patients' mental health. When the respondents were asked if there was a conditioning treatment that could reduce toxicity and minimize long-term effects, 62% replied that it would have an extremely positive impact on anxiety, fear, and stress level. There is an even more significant positive impact when there is a potential for a survival benefit; 82% of respondents indicated that a conditioning treatment that could give them improved chances of survivorship would have an extremely positive impact on their outlook.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH stated that the limitation of alloHSCT is increased risk of NRM, which can be from opportunistic infection, GvHD, or other complications. There is still approximately 15% to 20% chance of leukemia or MDS recurrence even after alloHSCT. There remains an unmet need for improved conditioning regimens that can reduce the risk of TRM without increasing the incidence of relapse compared with conventional therapies, which would ultimately improve patients' survival rates and quality of life as per feedback from the clinical experts consulted by CADTH. The clinical experts thought it would not be appropriate to recommend that patients try other treatment options of a conditioning regimen before considering treosulfan because reserving alternative treatment that is potentially beneficial to a later line of therapy is not reasonable to optimize transplant outcomes. The clinical experts expected that treosulfan would cause a shift in the current treatment paradigm. The clinical experts consulted by CADTH indicated that the treosulfan-based conditioning regimen is considered to be an RIC. Patients who are indicated for RIC due to increased risk of NRM because of age (older than 55 or 60 years or high comorbidities such as Hematopoietic Cell Transplantation-Specific Comorbidity Index [HCT-CI] score > 3) would be best suited for conditioning treatment with treosulfan.

According to the clinical experts consulted by CADTH, OS, relapse-free survival, cumulative incidence of NRM, and cumulative incidence of relapse are mainly used for alloHSCT outcome assessment. The clinical experts stated that additional end points include engraftment kinetics, GvHD incidence (acute and

chronic), and infection rate, such as cytomegalovirus viremia incidence. The clinical experts indicated that symptom-based assessments are rarely used to evaluate efficacy and tolerability of transplant regimens. The clinical experts stated that there are 2 occasions when treosulfan can be discontinued or changed to alternative options: if the patient has active leukemia (blasts above 5%) or uncontrolled MDS (blasts above 10%), and will not be cleared to proceed with the transplant process itself or if treosulfan can be switched over to another alternative treatment based on the medical circumstances of the patient. The clinical experts consulted by CADTH indicated that treosulfan in combination with fludarabine for alloHSCT would be used only in experienced allogeneic transplant centres.

### Clinician Group Input

Two clinician groups provided input to the submission: CTTC and OH-CCO Complex Malignant Hematology Advisory Committee. Both clinician groups agreed that allogeneic transplant is a potentially curative therapy for patients with AML or MDS, and the conditioning regimen of MAC or RIC depends on the patient's age and comorbidity score. There are still limitations, such as NRM and GvHD, that impair the outcome of the transplant. It was agreed that treosulfan in combination with fludarabine for alloHSCT would be used only in experienced allogeneic transplant centres.

Because treosulfan is used as part of the conditioning regimen, there is typically no response assessment and usually no need to consider discontinuation during administration, except in case of hypersensitivity. The clinician groups noted, however, that outcomes of transplants with treosulfan-based conditioning will be assessed using standard alloHSCT outcome assessments.

## 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 |
|---|---|
| **Relevant comparators** | |
| The comparator to treosulfan is busulfan. Treosulfan and busulfan are both given in combination with fludarabine as part of a reduced-intensity conditioning regimen before alloHSCT.<br>Busulfan is funded in all provinces. | Comment from the drug programs to inform pERC deliberations. |
| **Considerations for initiation of therapy** | |
| Eligibility for the trial included:<br>• Karnofsky score ≥ 60%<br>• AML in first or consecutive complete response (blast counts < 5% in bone marrow according to WHO Classification of Tumors of the Hematopoietic and Lymphoid Tissues [2008])<br>• MDS (blast counts < 20% in the bone marrow | The clinical experts indicated that the eligibility criteria for the MC-FludT-14/L trial are generally appropriate for allogeneic transplantation in patients with AML or MDS.<br>• The clinical experts stated that it is reasonable to offer transplant in patients with Karnofsky performance status of ≥ 60%.<br>• In the clinical experts' practice, a 10% cut-off for pretransplant blast percentage in bone marrow is used in cases of MDS in some centres. |

| Implementation issues | Response |
|---|---|
| according to WHO Classification of Tumors of the Hematopoietic and Lymphoid Tissues [2008])<br>• indicated for alloHSCT but considered at increased risk for MAC based on age ≥ 50, HSCT-specific comorbidity index > 2, or both.<br>Are these criteria appropriate or applicable for selection in Canadian practice? What criteria should be used to define AML and MDS to identify eligible patients? | The clinical experts confirmed that the results of the MC-FludT-14/L trial can be generalized to patients with 10% cut-off for pretransplant blast percentage for MDS. The experts noted that blast percentage is only 1 factor in assessing MDS risk; other important factors include karyotype and molecular studies.<br>• For MAC criteria, the clinical experts indicated that some centres use an age cut-off of 50 years, while some use 55 to 60 years. The clinical experts commented that biological age by itself is an imperfect predictor of transplant outcome and, thus, it is inappropriate to determine MAC vs. RIC based on age alone. The clinical experts indicated that clinicians consider comorbidities, frailty, and performance status as well.<br>pERC agreed with the clinical experts. |
| Other criteria for eligibility in the trial were age 18 to 70 years, no significant organ dysfunction, and no active or noncontrolled infectious diseases. Should these criteria also apply? | The clinical experts indicated that criteria for eligibility in the MC-FludT-14/L trial regarding age, organ dysfunction, and infectious diseases are common and appropriate criteria for transplantation.<br>Overall pERC agreed with the clinical experts; however, pERC felt that treatment with treosulfan-based conditioning may be appropriate to consider in patients older than 70 years who are otherwise deemed eligible for transplant at the discretion of the treating clinician. |
| The trial did not specify therapies before conditioning. Would standard of care per transplant centre be appropriate for prior therapies? | pERC agreed with the clinical experts that it would be reasonable to let each transplant centre select the standard of care before transplantation. The clinical experts noted that patients will be eligible for transplantation using the treosulfan in combination with fludarabine regimen if they meet the criteria of blasts < 5% for AML and blasts < 20% (or 10%) for MDS before transplantation. |
| Patients with previous alloHSCT were excluded.<br>• Should patients be eligible for a second transplant, and does the type of condition therapy used for the second transplant depend on the type of conditioning therapy that was used for the first transplant? | The clinical experts felt that results from the MC-FludT-14/L trial can be generalized to patients who received a previous alloHSCT. The clinical experts stated that this group of patients is at higher risk of nonrelapse mortality and morbidity. Therefore, they could benefit from treosulfan-based conditioning given treosulfan's good antileukemic efficacy with low toxicity, which is important for patients with a second transplant. The clinical experts agreed that patients would be eligible for a second transplant with either treosulfan-based or busulfan-based conditioning post relapse or graft failure with any types of previous conditioning therapy (i.e., the same or different conditioning regimen could be used for the second transplant).<br>pERC noted that second transplants are unlikely and that there is insufficient evidence to inform a recommendation on the patient eligibility for a second transplant. |
| **Considerations for prescribing of therapy** | |
| Fludarabine dosing is the same as per busulfan protocols.<br>Treosulfan is given 10 mg/m$^2$ IV on days −4, −3, and −2 before stem cell infusion (day 0). Busulfan is given for 2 doses before stem cell infusion. | Comment from the drug programs to inform pERC deliberations. |

| Implementation issues | Response |
|---|---|
| If treosulfan is administered in the inpatient setting, the adoption may be dependent on the extent of drug coverage given the inpatient drug cost falls outside of the provincial drug plan budgets in some jurisdictions. | Comment from the drug programs to inform pERC deliberations. |
| **Generalizability** | |
| Busulfan is used in myeloablative conditioning regimens. Could treosulfan be considered as an alternate in these regimens? | pERC agreed with the clinical experts that there was insufficient evidence to inform a recommendation on generalizing the results from the MC-FludT-14/L trial to the use of treosulfan as standard myeloablative conditioning therapy in these patients. |
| **Funding algorithm (oncology only)** | |
| Treosulfan may replace busulfan in reduced-intensity conditioning regimens. | Comment from the drug programs to inform pERC deliberations. |
| **Care provision issues** | |
| The trial used a standard GvHD prophylaxis protocol of cyclosporine, methotrexate, and (if MUD) antithymocyte globulin. Would it be reasonable for centres to choose to follow this approach and/or use institutional protocol for GvHD prophylaxis? | The clinical experts stated there is heterogeneity from centre to centre in terms of GvHD prophylaxis strategies. For example, some centres may not use antithymocyte globulin. pERC agreed with the clinical experts who suggested that it would be best for patients to receive those GvHD prophylaxis strategies at an institution that has experience with it. |
| **System and economic issues** | |
| The sponsor assumes fairly low uptake for a drug that is becoming the new standard of care for reduced-intensity conditioning regimens. | Comment from the drug programs to inform pERC deliberations. |
| Busulfan is generic. | Comment from the drug programs to inform pERC deliberations. |

alloHSCT = allogeneic hematopoietic stem cell transplantation; AML = acute myeloid leukemia; GvHD = graft-versus-host disease; MAC = myeloablative conditioning; MDS = myelodysplastic syndrome; MUD = matched unrelated donor; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

# Clinical Evidence

## Description of Studies

A sponsor-submitted systematic review identified 1 study: MC-FludT.14/L, a phase III, randomized, parallel-group, open-label, multicentre, international, group-sequential study to evaluate efficacy, noninferiority, and safety of the treosulfan-based conditioning compared with a busulfan-based RIC regimen. The MC-FludT.14/L trial enrolled adult patients with AML or MDS indicated for alloHSCT who were considered ineligible for standard conditioning therapies (i.e., patients aged ≥ 50 years and/or with an HCT-CI score > 2). The study had 2 groups: a treosulfan treatment group and a busulfan treatment group. Eligible adult patients with AML or MDS (N = 570) were randomly assigned at a 1:1 ratio to receive either treosulfan (n = 280) administered IV 10 g/m$^2$ body surface area once a day on day −4, −3, and −2 or busulfan (n = 290) administered IV 0.8 mg/kg every 6 hours on day −4 and −3 followed by alloHSCT on day 0. Patients were recruited in 33 sites in 6 countries; however, there were no sites in Canada. The primary objective in the MC-FludT.14/L trial was to compare EFS of patients within 2 years of receiving alloHSCT between

treosulfan-fludarabine conditioning and busulfan-fludarabine conditioning. The secondary objectives were comparisons of OS, cumulative incidence of engraftment, incidence of complete donor-type chimerism, cumulative incidence of relapse or progression, as well as NRM and TRM. The cumulative incidence of acute and chronic GvHD and other safety end points were also assessed.

Most patients in the MC-FludT.14/L trial final analysis (database lock date: March 16, 2018) were male (60.8%), aged 50 years or older (94.9%), and had AML (63.9%); 39.2% of the patients were female, 5.1% of the patients were younger than 50 years, and 36.1% of the patients had MDS. More patients in the treosulfan group compared with the busulfan group were diagnosed with AML; there were 184 of 268 (68.6%) patients in the treosulfan group who had AML and 168 of 283 (59.4%) in the busulfan group. For the 199 patients with MDS, more patients in the treosulfan group compared with the busulfan group had untreated MDS (50.0% versus 40.9%), and the mean blast count in bone marrow was lower in the treosulfan group compared with the busulfan group (5.83% versus 6.31%).

## Efficacy Results

Three confirmatory interim evaluations and 1 final analysis were planned. Patient recruitment into the trial was stopped after the second interim analysis (also referred as the confirmatory interim analysis) because the noninferiority of treosulfan-based conditioning was established. The data cut-off date was August 19, 2016, for the confirmatory interim analysis, and the database lock date was March 16, 2018, for the final analysis. In the final analysis, a total of 570 patients were randomized (290 in the busulfan group and 280 in the treosulfan group). These patients were recruited in 33 sites in 6 countries, including Finland, France, Germany, Hungary, Italy, and Poland. This study had no sites in Canada.

### Event-Free Survival

EFS was the primary end point in the MC-FludT.14/L trial. Generally, patients in the treosulfan group had fewer EFS events compared to the busulfan group; 68 (30.9%) patients in the treosulfan treatment group and 100 (41.7%) patients in the busulfan group experienced an event in the confirmatory interim analysis, and this proportion increased to 97 (36.2%) patients in the treosulfan treatment group and 137 (48.4%) patients in the busulfan group in the final analysis. The Kaplan-Meier estimate of EFS probability at 24 months after HSCT was 64.0% (95% CI, 56.0% to 70.9%) for the treosulfan group and 50.4% (95% CI, 42.8% to 57.5%) for the busulfan group in the confirmatory interim analysis; in the final analysis, it was 65.7% (95% CI, 59.5% to 71.2%) for the treosulfan group and 51.2% (95% CI, 45.0% to 57.0%) for the busulfan group. The Kaplan-Meier estimate of EFS probability at 36 months after HSCT was 59.5% (95% CI, 52.2% to 66.1%) for the treosulfan group and 49.7% (95% CI, 43.3% to 55.7%) for the busulfan group in the final analysis. The confirmatory interim analysis showed noninferiority in EFS for patients in the treosulfan group compared with patients in the busulfan group (HR = 0.65; 99.9702% CI, 0.36 to1.19; noninferiority P = 0.0000164; superiority P = 0.0051268; both noninferiority and superiority P values were compared against the prespecified 1-sided significance level of 0.000149). Findings of the per-protocol set population were consistent with results for the full analysis set (FAS) population. Generally, subgroup analyses of EFS were consistent with the primary confirmatory interim analysis across all prespecified subgroups, except for patients with matched related donor in risk group II (in confirmatory interim and final analyses) and MDS risk group I (only in the

confirmatory analysis). The clinical experts consulted by CADTH confirmed that the overall subgroup results appeared as anticipated. The clinical experts did not anticipate treosulfan to have differential treatment effects across patients with AML and MDS because the 2 diseases have a similar disease biology.

### Overall Survival

OS was a secondary end point. In the final analysis including the postsurveillance evaluation, patients were followed for a median of 29.7 months (range, 0.4 to 52.1 months) in the treosulfan group and 29.4 months (range, 0.4 to 54.3 months) in the busulfan group. At the time of the postsurveillance evaluation, 81 (30.2%) patients in the treosulfan group and 112 (39.6%) patients in the busulfan group had died (HR = 0.64; 95% CI, 0.48 to 0.87; nominal P = 0.0037). Median OS was not reached in either group. In the final analysis, the Kaplan-Meier estimate of OS survival probabilities decreased from 72.7% (95% CI, 66.8% to 77.8%) to 66.8% (95% CI, 59.9% to 72.9%) in the treosulfan group and 60.2% (95% CI, 54.0% to 65.8%) to 56.3% (95% CI, 49.6% to 62.6%) in the busulfan group from 24 to 36 months. Similar results were observed in the confirmatory interim analysis (database lock date: August 19, 2016).

### Graft Failure

Graft failure was a secondary end point. In the final analysis including the postsurveillance evaluation, patients in the treosulfan group had a lower percentage of graft failure (including primary and secondary) compared with patients in the busulfan group (0.4% versus 3.2%). No event of graft failure was reported during postsurveillance. Similar results were observed in the confirmatory interim analysis.

### Engraftment

Engraftment at 28 days after HSCT was assessed as a secondary end point. In the final analysis, the conditional cumulative incidence of reconstitution of granulopoiesis at 28 days after HSCT was 96.2% (95% CI, 93.4% to 99.1%) for the treosulfan group and 96.8% (95% CI, 94.6% to 99.1%) for the busulfan group (HR = 1.06; 95% CI, 0.91 to 1.24; nominal P = 0.4235). The conditional cumulative incidence of reconstitution of thrombopoiesis at 28 days after HSCT was 94.7% (95% CI, 92.0% to 97.4%) in the treosulfan group and 97.8% (95% CI, 96.3% to 99.4%) in the busulfan group. The HR was 0.80 (95% CI, 0.68 to 0.93; nominal P = 0.0038) in favour of busulfan. Similar results were observed in the confirmatory interim analysis.

### Chimerism

The incidence of complete donor-type chimerism at 28 days after HSCT was assessed as a secondary end point. In the final analysis, the incidence of complete donor-type chimerism was 93.2% (95% CI, 89.4% to 95.9%) in the treosulfan group and 83.3% (95% CI, 78.5% to 87.5%) in the busulfan group at 28 days. The odds ratio was 2.81 (95% CI, 1.58 to 5.01; nominal P = 0.0159) in favour of treosulfan. Similar results were observed in the confirmatory interim analysis.

### Cumulative Incidence of Relapse or Progression

The cumulative incidence of relapse or progression was assessed as a secondary end point. In the final analysis, a slightly lower proportion of patients in the treosulfan group compared to the busulfan group reported relapse or progression; 61 (22.8%) patients in the treosulfan group and 72 (25.4%) patients in the busulfan group experienced relapse or progression. The cumulative incidence of relapse or progression at

24 months after HSCT was 22.0% (95% CI, 16.9% to 27.1%) in the treosulfan group and 25.2% (95% CI, 20.0% to 30.3%) in the busulfan group. The HR was 0.82 (95% CI, 0.59 to 1.16; nominal P = 0.2631) in favour of treosulfan. Similar results were observed in the confirmatory interim analysis.

### GvHD-Free and Relapse- or Progression-Free Survival

The incidence of GvHD-free and relapse- or progression-free survival (GRFS) within 2 years of HSCT was assessed as a secondary end point. In the final analysis, a lower proportion of patients in the treosulfan group compared to the busulfan group experienced GvHD or relapse or progression (48.5% versus 59.7%). The Kaplan-Meier estimate of GRFS probability at 24 months was 50.3% (95% CI, 43.9% to 56.3%) for the treosulfan group and 37.1% (95% CI, 31.1% to 43.1%) for the busulfan group. The HR was 0.73 (95% CI, 0.57 to 0.92; nominal P = 0.0087) in favour of treosulfan. Similar results were observed in the confirmatory interim analysis.

### Chronic GvHD–Free and Relapse- or Progression-Free Survival

The incidence of chronic GvHD–free and relapse- or progression-free survival (CRFS) within 2 years of HSCT was assessed as a secondary end point. In the final analysis, a lower proportion of patients in the treosulfan group (47.8%) compared to the busulfan group (59.4%) experienced extensive chronic GvHD or relapse or progression. The Kaplan-Meier estimate of CRFS probability at 24 months was 51.4% (95% CI, 45.0% to 57.4%) for the treosulfan group and 37.2% (95% CI, 31.3% to 43.2%) for the busulfan group. The HR was 0.70 (95% CI, 0.55 to 0.88; nominal P = 0.0030) in favour of treosulfan. Similar results were observed in the confirmatory interim analysis.

### Nonrelapse Mortality

The cumulative incidence of NRM at 24 months after HSCT was assessed as a secondary end point. In the final analysis, 35 (13.1%) patients in the treosulfan group and 56 (19.8%) patients in the busulfan group died without relapse or progression. The cumulative incidence of NRM at 24 months after HSCT was 12.0% (95% CI, 8.0% to 15.9%) in the treosulfan group and 20.4% (95% CI, 15.5% to 25.2%) in the busulfan group. The HR was 0.63 (95% CI, 0.41 to 0.97; nominal P = 0.0343) in favour of treosulfan. Similar results were observed in the confirmatory interim analysis.

### Transplant-Related Mortality

The cumulative incidence of TRM at 24 months after HSCT was assessed as a secondary end point. In the final analysis, 33 (12.3%) patients in the treosulfan group and 58 (20.5%) patients in the busulfan group died from a transplant-related cause. The cumulative incidence of TRM at 24 months after HSCT was 12.8% (95% CI, 9.2% to 17.7%) in the treosulfan group and 24.1% (95% CI, 19.1% to 30.2%) in the busulfan group. The HR was 0.52 (95% CI, 0.34 to 0.82; nominal P = 0.0043) in favour of treosulfan. Similar results were observed in the confirmatory interim analysis.

### Health-Related Quality of Life

HRQoL was identified as important by patient groups and the clinical experts consulted by CADTH. HRQoL was not assessed in the MC-FludT.14/L trial.

## Harms Results

At least 1 AE was reported for a similar proportion of patients in the treosulfan group compared with the busulfan group (92.6% versus 96.1%). The most common treatment-emergent AEs occurring in at least 20% of patients in the treosulfan and busulfan groups, respectively, included edema in the limbs (22.6% and 13.4%) and vomiting (21.9% and 19.4%), which were reported more frequently in the treosulfan group compared with the busulfan group; oral mucositis (37.8% and 47.7%), fever (34.4% and 35.7%), nausea (33.0% and 41.0%), and hypertension (14.1% and 21.2%) were reported less frequently in the treosulfan group compared with the busulfan group. A similar proportion of patients in the treosulfan and busulfan groups reported grade 3 or higher AEs (54.8% and 53.4%, respectively).

A similar proportion of patients in the treosulfan and busulfan groups reported at least 1 serious AE (8.5% and 7.1%, respectively). The most common serious AEs occurring in at least 1% of patients in the treosulfan and busulfan treatment groups, respectively, included sepsis (3.0% and 1.8%), lung infection (2.2% and 1.1%), and acute kidney injury sepsis (1.1% and 0.4%). None of the patients in the MC-FludT.14/L trial required a dose reduction or discontinuation due to drug-related toxicity. Fewer patients died in the treosulfan group compared with the busulfan group (26.7% versus 37.8%) until 24 months and including the postsurveillance period (30.0% versus 39.6%). Relapse or progression was the most frequent cause of death in the treosulfan group (treosulfan versus busulfan: 12.6% versus 16.6%), whereas transplant-related causes was the most frequent cause of death in the busulfan group (treosulfan versus busulfan: 12.2% versus 20.5%).

In the final analysis, the cumulative incidence of acute GvHD grade III or IV at 100 days was 6.4% (95% CI, 3.4% to 9.3%) in the treosulfan group and 8.1% (95% CI, 4.9% to 11.3%) in the busulfan group. The cumulative incidence of chronic GvHD at 24 months was similar in the 2 treatment groups: 61.7% (95% CI, 55.1% to 68.3%) in the treosulfan group and 60.3% (95% CI, 53.8% to 66.7%) in the busulfan group.

## Critical Appraisal

The MC-FludT.14/L trial was a phase III, randomized, parallel-group, open-label, multicentre, international, group-sequential study to evaluate the noninferiority, efficacy, and safety of treosulfan-based conditioning compared with a busulfan-based RIC regimen. An open-label trial can introduce detection and performance biases in the assessment of subjective outcomes reported by patients, such as AEs. Analyses of disease response outcomes (i.e., EFS, relapse or progression) were based on an independent data monitoring committee to help mitigate the potential for detection and performance biases. The primary analysis of the study results was conducted in the per-protocol set and FAS in the MC-FludT.14/L trial. The FAS included all randomized patients of the safety analysis set with at least 1 documented efficacy parameter. Patients who were randomized but not eligible for the FAS may have had different characteristics and outcomes than those who were eligible. The extent and direction of a potential selection bias cannot be determined because it is not clear whether patients who were excluded from the FAS were systematically different from those who were included.

Because the noninferiority of treosulfan compared to busulfan was demonstrated in the confirmatory interim analysis (database lock date: August 19, 2016), the MC-FludT.14/L trial was stopped early for efficacy based

on the data monitoring committee's recommendation. The CADTH review team notes that the early stop of the trial may have led to an overestimation of the treatment effect because the early stopping rule favours larger effect estimates. The study reported a 99.9702% CI for the HR of EFS in the confirmatory interim analysis, and this interval is considered representative of the range of estimates that are reasonable to maintain trial integrity for the confirmatory interim analysis given the premature stop of the trial.

Of note, only the primary analysis of EFS in the confirmatory analysis was adjusted for multiplicity. The remaining end points (i.e., OS, graft failure, engraftment, chimerism, relapse or progression, and GvHD) in the confirmatory analysis and all end points in the final analysis were considered exploratory and thus not controlled for multiple comparisons. Although the subgroup analyses were prespecified, the study was not powered to detect subgroup differences. HRQoL is considered a relevant outcome by patients with AML or MDS and the clinical experts consulted by CADTH; however, there was no assessment for HRQoL in the MC-FludT.14/L trial. The impact of treosulfan-based conditioning on HRQoL in patients with AML or MDS is not known.

The method used in the analysis of graft failure at 24 months (i.e., observed percentage) included death as a censoring event and did not measure the probability of graft failure by 24 months, but instead the proportion of patients who had graft failure before a censoring event by 24 months. The reported estimates of complete chimerism at 28 days were based on empirical observation of the presence of chimerism at 28 days among patients alive at that time. The interpretation of this outcome should be considered carefully because it does not measure the incidence of chimerism at 28 days among a meaningful population. The defined at-risk population does not consider censoring nor death as a competing risk. The estimates could be interpreted as an approximation of the cumulative incidence at 28 days, but it is at risk of bias. However, the magnitude and direction of this bias is unclear.

The clinical experts consulted by CADTH confirmed that the eligibility criteria of the MC-FludT.14/L trial are in line with previous trials appropriate for the indication. However, patients with previous alloHSCT were excluded, and those patients may be considered eligible for treosulfan conditioning therapy in clinical practice. The MC-FludT-14/L trial defined a threshold of blast counts less than 20% in the bone marrow for MDS and an age cut-off for MAC of 50 years or older. According to the clinical experts consulted by CADTH, a 10% cut-off for pretransplant blast percentage and a MAC age cut-off starting from 55 to 60 years is used in some centres. Busulfan is a relevant comparator to treosulfan as per feedback from the clinical experts consulted by CADTH. *TP53* and *FLT3*-ITD mutations are important prognostic factors in patients with AML or MDS but were not investigated as subgroups. The clinical experts stated that patients with *TP53* and *FLT3*-ITD mutations are at increased risk of relapse even after HSCT. The CADTH review team noted that there may be uncertainty in the interpretation of the study results because it is unknown if the uncontrolled prognostic factors (i.e., *TP53* and *FLT3*-ITD mutation status) were balanced between the treatment groups.

## GRADE Summary of Findings and Certainty of the Evidence

For the pivotal MC-FludT.14/L trial identified in the sponsor's systematic review, Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations,

and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from randomized controlled trials started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for 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. The following list of outcomes was finalized in consultation with expert committee members: EFS, OS, GRFS, CRFS, graft failure, engraftment, complete chimerism, relapse or progression, NRM, TRM, and GvHD. No data were available for HRQoL.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect based on thresholds informed by the clinical experts consulted by CADTH for this review for EFS, OS, GRFS, CRFS, graft failure, engraftment, complete chimerism, relapse or progression, NRM, TRM, and GvHD.

## Table 3: Summary of Findings for Treosulfan Versus Busulfan for Patients With AML or MDS

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Busulfan | Treosulfan | Difference | | |
| **Event-free survival (full analysis set)** | | | | | | | |
| Probability of being alive and event-free at 24 months<br>Follow-up (median):<br>Treosulfan: 15.4 months<br>Busulfan: 17.4 months | 460 (1 RCT) | NR | 50.4 per 100 | 64.0 per 100 (56.0 to 70.9 per 100) | 13.6 more per 100 (3.1 to 24.0 more per 100) | Low[a,b,c] | Treosulfan may result in a clinically important higher probability of patients being alive and event-free at 24 months compared with busulfan. |
| Probability of being alive and event-free at 24 months<br>Follow-up (median):<br>Treosulfan: 29.7 months<br>Busulfan: 29.4 months | 551 (1 RCT) | NR | 51.2 per 100 | 65.7 per 100 (59.5 to 71.2 per 100) | 14.5 more per 100 (6.1 to 22.9 more per 100) | Moderate[a,d,e] | Treosulfan likely results in a clinically important higher probability of patients being alive and event-free at 24 months compared with busulfan. |
| Probability of being alive and event-free at 36 months<br>Follow-up (median):<br>Treosulfan: 29.7 months<br>Busulfan: 29.4 months | 551 (1 RCT) | NR | 49.7 per 100 | 59.5 per 100 (52.2 to 66.1 per 100) | 9.8 more per 100 (0.5 to 19.2 more per 100) | Low[a,b,e] | Treosulfan may result in a clinically important higher probability of patients being alive and event-free at 36 months compared with busulfan. |
| **Overall survival (full analysis set)** | | | | | | | |
| Probability of being alive at 24 months<br>Follow-up (median):<br>Treosulfan: 29.7 months<br>Busulfan: 29.4 months | 551 (1 RCT) | NR | 60.2 per 100 | 72.7 per 100 (66.8 to 77.8 per 100) | 12.5 more per 100 (4.4 to 20.7 more per 100) | Moderate[a,e,f] | Treosulfan likely results in a clinically important higher probability of patients being alive at 24 months compared with busulfan. |
| Probability of being alive at 36 months<br>Follow-up (median): | 551 (1 RCT) | NR | 56.3 per 100 | 66.8 (59.9 to 72.9 per 100) | 10.5 more per 100 (1.3 to 19.7 per 100) | Low[a,e,f] | Treosulfan may result in a clinically important larger proportion of patients being alive at 36 months compared with busulfan. |

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Busulfan | Treosulfan | Difference | | |
| Treosulfan: 29.7 months<br>Busulfan: 29.4 months | | | | | | | |
| **Graft failure** | | | | | | | |
| Observed percentage of patients with graft failure at 24 months<br>Follow-up (median):<br>Treosulfan: NA<br>Busulfan: NA | 551 (1 RCT) | NR | 3.2 per 100 | 0.4 per 100 (0.0 to 2.1 per 100) | 2.8 fewer per 100 (0.6 fewer to 5.0 fewer) | Very low[e,g,h] | The evidence is very uncertain about the effect of treosulfan on the percentage of patients with graft failure at 24 months compared with busulfan. |
| **Engraftment** | | | | | | | |
| Conditional cumulative incidence of reconstitution of granulopoiesis at 28 days after HSCT<br>Follow-up (median):<br>Treosulfan: NA<br>Busulfan: 40.0 days | 551 (1 RCT) | NR | 96.8 per 100 | 96.2 per 100 (93.4 to 99.1 per 100) | 1.3 fewer per 100 (4.7 fewer to 2.0 more per 100) | Low[a,e,i,j] | Treosulfan may result in little to no clinically important difference in the conditional cumulative incidence of reconstitution of granulopoiesis at 28 days after HSCT compared with busulfan. |
| Conditional cumulative incidence of reconstitution of thrombopoiesis (platelet count > 20 × $10^9$/L) at 28 days after HSCT<br>Follow-up (median):<br>Treosulfan: 94.0 days<br>Busulfan: 33.0 days | 551 (1 RCT) | NR | 97.8 per 100 | 94.7 per 100 (92.0 per 100 to 97.4 per 100) | 2.8 fewer per 100 (6.4 fewer to 0.8 more per 100) | Low[a,e,i,j] | Treosulfan may result in little to no clinically important difference in conditional cumulative incidence of reconstitution of thrombopoiesis (platelet count > 20 × $10^9$/L) at 28 days after HSCT compared with busulfan. |
| **Chimerism** | | | | | | | |
| Incidence of complete chimerism at 28 days<br>Follow-up (median):<br>Treosulfan: NA<br>Busulfan: NA | 551 (1 RCT) | NR | 83.3 per 100 | 93.2 per 100 (89.4 per 100 to 95.9 per 100) | 9.8 more per 100 (4.5 to 15.1 more per 100) | Very low[b,e,h] | The evidence is very uncertain about the effect of treosulfan on the incidence of complete chimerism at 28 days compared with busulfan. |

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Busulfan | Treosulfan | Difference | | |
| **Relapse or progression** | | | | | | | |
| Cumulative incidence of relapse or progression at 24 months<br>Follow-up (median):<br>Treosulfan: 26.3 months<br>Busulfan: 22.5 months | 551 (1 RCT) | NR | 25.2 per 100 | 22.0 per 100 (16.9 to 27.1 per 100) | 3.2 fewer per 100 (10.4 fewer to 4.1 more per 100) | Low[a,b,e] | Treosulfan may result in little to no clinically important difference in cumulative incidence of relapse or progression at 24 months compared with busulfan. |
| **GvHD-free and relapse- or progression-free survival** | | | | | | | |
| Proportion of patients being GvHD-free and relapse or progression-free at 24 months<br>Follow-up (median):<br>Treosulfan: 23.7 months<br>Busulfan: 23.7 months | 551 (1 RCT) | NR | 37.1 per 100 | 50.3 per 100 (43.9 to 56.3 per 100) | 13.2 more per 100 (4.6 to 21.8 more per 100) | Low[a,b,e] | Treosulfan may result in a clinically important larger proportion of patients being GvHD-free and relapse- or progression-free at 24 months compared with busulfan. |
| **Chronic GvHD–free and relapse- or progression-free survival** | | | | | | | |
| Proportion of patients being event-free and chronic GvHD–free at 24 months<br>Follow-up (median):<br>Treosulfan:23.7 months<br>Busulfan: 23.7 months | 551 (1 RCT) | NR | 37.2 per 100 | 51.4 per 100 (45.0 to 57.4 per 100) | 14.1 more per 100 (5.5 to 22.8 more per 100) | Moderate[a,e,d] | Treosulfan likely result in a clinically important larger proportion of patients being chronic GvHD–free and relapse- or progression-free at 24 months compared with busulfan. |
| **Nonrelapse mortality** | | | | | | | |
| Cumulative incidence of nonrelapse mortality at 24 months<br>Follow-up (median):<br>Treosulfan: 24.3 months<br>Busulfan: 24.3 months | 551 (1 RCT) | NR | 20.4 per 100 | 12.0 per 100 (8.0 per 100 to 15.9 per 100) | 8.4 fewer per 100 (2.2 to 14.7 fewer per 100) | Low[a,b,c] | Treosulfan may result in a clinically important benefit on nonrelapse mortality at 24 months compared with busulfan. |

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Busulfan | Treosulfan | Difference | | |
| **Transplant-related mortality** | | | | | | | |
| Probability of being dead due to transplant-related causes at 24 months<br>Follow-up (median):<br>Treosulfan: 23.6 months<br>Busulfan: 23.2 months | 551 (1 RCT) | NR | 24.1 per 100 | 12.8 per 100 (9.2 per 100 to 17.7 per 100) | 11.3 fewer per 100 (4.4 to 18.2 fewer per 100) | Low[a,b,c] | Treosulfan may result in a clinically important lower probability of being dead due to transplant-related mortality at 24 months compared with busulfan. |
| **HRQoL** | | | | | | | |
| HRQoL due to treatment | 551 (1 RCT) | NR | NR | NR | NR | NR | There is no evidence available for the effect of treosulfan on HRQoL compared with busulfan. |
| **Harms** | | | | | | | |
| Cumulative incidence of acute GvHD grade III and IV at 100 days<br>Follow-up (median):<br>Treosulfan: 100 days<br>Busulfan: 100 days | 551 (1 RCT) | NR | 8.1 per 100 | 6.4 per 100 (3.4 to 9.3 per 100) | 1.8 fewer per 100 (6.1 fewer to 2.6 more per 100) | Moderate[a,c,k] | Treosulfan likely results in little to no clinically important difference in cumulative incidence of acute GvHD grade III and IV at 100 days compared with busulfan. |
| Cumulative incidence of chronic GvHD at 24 months<br>Follow-up (median):<br>Treosulfan: 23.6 months<br>Busulfan: 20.5 months | 551 (1 RCT) | NR | 60.3 per 100 | 61.7 per 100 (55.1 to 68.3 per 100) | 1.4 more per 100 (7.8 fewer to 10.7 more per 100) | Low[a,c,l] | Treosulfan may result in little to no clinically important difference in cumulative incidence of chronic GvHD at 24 months compared to busulfan. |

CI = confidence interval; EFS = event-free survival; HSCT = hematopoietic stem cell transplantation; HRQoL = health-related quality of life; NA = not available; OS = overall survival; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Rated down 1 level for serious risk of bias. The analysis used the full analysis set (FAS) rather than the intention-to-treat set. Patients who were randomized but not eligible for FAS may have different characteristics and outcomes than those who were eligible, thus may introduce bias.

[b]Rated down 1 level for serious imprecision. There is no established minimal important difference (MID), but the clinical experts consulted by CADTH considered a 5% difference between groups could be a threshold of clinical importance. The point estimate and 1 side of the 95% CI for the between-group difference suggests a clinically important difference for treosulfan vs. busulfan while the other side of the 95% CI suggests no clinically important difference between the 2 groups.

[c]In the confirmatory interim analysis (database lock date: August 19, 2016), the null hypothesis was rejected for noninferiority, whereas the null hypothesis was not rejected for superiority in the primary analysis of EFS.

[d]Imprecision was not rated down. There is no established MID, but the clinical experts consulted by CADTH considered that a 5% difference between groups could be a threshold of clinical importance. The point estimate and the upper and lower bounds of the 95% CI for the between-group difference suggests a clinically important difference between the 2 groups.

[e]The statistical testing for all end points in the final analysis (database lock date: March 16, 2018) with 551 patients in the FAS was not adjusted for multiplicity in the MC-FludT.14/L trial and should be considered as supportive evidence.

[f]Rated down 1 level for serious imprecision for OS at 36 months. There is no established MID, but the clinical experts consulted by CADTH considered 3% the threshold of important difference in the probability of patients who were alive at 24 and 36 months. The point estimate and the upper bound of the 95% CI for the between-group difference suggests a clinically important difference for treosulfan vs. busulfan while the lower bound of the 95% CI for the between-group difference suggests no clinically important difference between the 2 groups. Imprecision was not rated down for OS at 24 months; the point estimate and the upper and lower bounds of the 95% CI for the between-group difference suggest a clinically important difference between the 2 groups.

[g]Rated down 1 level for serious imprecision. There is no established MID, but the clinical experts consulted by CADTH considered a 2% difference between groups in the cumulative incidence of graft failure at 24 months could be a threshold of clinical importance. The point estimate and the upper bound of the 95% CI for the between-group difference suggests a clinically important difference for treosulfan vs. busulfan, while the lower bound of the 95% CI suggests no clinically important difference between the 2 groups.

[h]Rated down 2 levels for very serious risk of bias. The analysis used the FAS rather than the intention-to-treat set. Patients who were randomized but not eligible for FAS may have different characteristics and outcomes than those who were eligible and thus introduce bias. In addition, the method used did not consider the competing risk (i.e., death) and thus introduce bias.

[i]Rated down 1 level for serious indirectness. The interpretation of the effect estimate is limited due to the lack of clarity in the interpretation of the outcome.

[j]Imprecision was not rated down. There is no established MID, but the clinical experts consulted by CADTH considered a 10% difference between groups could be a threshold of clinical importance. The point estimate and the upper and lower bounds of the 95% CI for the between-group difference suggests no clinically important difference between the 2 groups.

[k]Imprecision was not rated down. There is no established MID, but the clinical experts consulted by CADTH considered 10% the threshold of important difference in the cumulative incidence of acute graft-versus-host disease (GvHD) grade III and IV at 100 days. The point estimate and the upper and lower bounds of the 95% CI for the between-group difference suggests no clinically important difference between the 2 groups.

[l]Rated down 2 levels for very serious imprecision. There is no established MID, but the clinical experts consulted by CADTH considered 10% the threshold of important difference in the cumulative incidence of chronic GvHD at 24 months. The point estimate and lower bound of the 95% CI for the between-group difference suggests no clinically important difference between the groups; the upper bound of the 95% CI for difference between groups suggests a clinically important harm in the treosulfan group.

### Long-Term Extension Studies

No long-term extension studies were identified for this review.

### Indirect Comparisons

No indirect evidence was submitted for this review.

### Studies Addressing Gaps in the Systematic Review Evidence

There were no results available for the retrospective study of patients with MDS ineligible to receive MAC conditioning therapy before alloHSCT, which was submitted by the sponsor for addressing the gap that the pivotal study did not include Canadian sites.

## Economic Evidence

### Cost and Cost-Effectiveness

### Table 4: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>PSM |
| **Target population** | Adult patients with AML or MDS at increased risk for standard conditioning therapies before alloHSCT |
| **Treatment** | Treosulfan in combination with fludarabine |
| **Dose regimen** | 10 g/m$^2$ given on 3 consecutive days (days −4 to −2) before stem cell infusion |
| **Submitted price** | Treosulfan: $693.00 per 5 g vial |
| **Treatment cost** | Treosulfan: $8,316.00 per course<br>Treosulfan in combination with fludarabine: $10,621.00 |
| **Comparator** | Busulfan in combination with fludarabine |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, LYs |
| **Time horizon** | Lifetime (40 years) |
| **Key data source** | MC-FludT.14/L trial |
| **Key limitations** | • The sponsor's base case predicted a survival gain with treosulfan of 1.14 LYs. Although the CADTH clinical review reported that the available evidence shows that treosulfan in combination with fludarabine may result in a clinically important benefit in EFS and OS compared with busulfan in combination with fludarabine, these findings were noted to be associated with low to moderate certainty according to GRADE due primarily to limitations with the trial that lead to a serious risk of bias and imprecision. These survival gains are the primary driver of QALY gains and cost savings with treosulfan and are therefore associated with uncertainty (74% of LYs were accrued beyond the trial period).<br>• The model structure was not suitable for the decision problem because it captures the cost of |

| Component | Description |
|---|---|
| | subsequent therapies but does not consider their potential improvements in survival and quality of life for patients with AML or MDS.<br>• The cost of busulfan used in the sponsor's base case may have been underestimated. |
| **CADTH reanalysis results** | • The results of the economic evaluation are based on EFS and OS from the MC-FludT.14/L trial that compared treosulfan- and busulfan-based conditioning treatments over a maximum follow-up of 52 months. Based on this clinical study, the sponsor predicts a gain in survival of 1.14 years, of which 74% of the benefits are predicted beyond the trial. The sponsor's base case considered the survival extrapolations of EFS and OS, which predicted conservative survival benefits for treosulfan compared with busulfan. There is uncertainty with these estimates; however, CADTH could not derive more reliable estimates of the cost-effectiveness of treosulfan in combination with fludarabine.<br>• The sponsor's predicted dominance of treosulfan vs. busulfan (i.e., more QALYs, fewer costs) is highly dependent on fewer patients experiencing relapse or disease progression with treosulfan. The cost savings for treosulfan were largely accrued by patients avoiding costs associated with the relapse or progression health state from subsequent therapies, hospitalization, infusions, and routine care. |

alloHSCT = allogenic hematopoietic stem cell transplantation; AML = acute myeloid leukemia; EFS = event-free survival; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; LY = life-year; MDS = myelodysplastic syndromes; PSM = partitioned survival model; OS = overall survival; QALY = quality-adjusted life-year.

### Budget Impact

CADTH identified the following key limitation with the sponsor's analysis: the market share of treosulfan is underestimated. The CADTH reanalysis included adjusting treosulfan market uptake. Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing treosulfan in combination with fludarabine as conditioning therapy before alloHSCT in adult patients with AML or MDS at increased risk for standard conditioning therapies is expected to be $657,845 (year 1: $143,839; year 2: $218,657; year 3: $295,349).

## 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:** January 10, 2024

**Regrets:** 1 expert committee member did not attend

**Conflicts of interest:** None

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