

## CADTH Reimbursement Recommendation

# Luspatercept (Reblozyl)

**Indication:** For the treatment of adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions

**Sponsor:** Celgene Inc., a Bristol Myers Squibb company

**Final recommendation:** Reimburse with conditions

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## What Is the CADTH Reimbursement Recommendation for Reblozyl?

CADTH recommends that Reblozyl should be reimbursed by public drug plans for the treatment of adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions, if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Reblozyl should only be covered to treat patients who have failed or are not suitable for erythropoietin-based therapy.

### What Are the Conditions for Reimbursement?

Reblozyl should only be reimbursed if prescribed by a specialist in MDS and if the cost of Reblozyl is reduced. Reimbursement should only be renewed if Reblozyl shows benefit to the patient such that the patient no longer requires RBC transfusions.

### Why Did CADTH Make This Recommendation?

- Evidence from 1 study showed that more patients who received Reblozyl did not need a blood transfusion than patients who received placebo.
- Patients expressed the need to reduce blood transfusions, and evidence from the reviewed study suggests that Reblozyl may meet some of the needs expressed by patients.
- Based on public list prices, Reblozyl is not cost-effective compared with best supportive care (RBC transfusions and iron chelators).
- The cost of Reblozyl needs to be reduced by 85% for it to be considered cost-effective at a \$50,000 per quality-adjusted life-year threshold.
- Based on public list prices, Reblozyl will cost the public drug plans \$101,479,111 in the first 3 years.

## Additional Information

### What Are Myelodysplastic Syndromes?

Myelodysplastic syndromes are a group of diseases that prevent the body from making healthy blood cells. Patients may need frequent blood transfusions and may develop blood cancer. Approximately 4 people per 100,000 persons in Canada are diagnosed with a myelodysplastic syndrome each year.

### Unmet Needs in Myelodysplastic Syndromes

There is a need for a treatment that reduces the frequency of blood transfusions in patients who fail erythropoietin-based therapy and improves patients' quality of life.

### How Much Does Reblozyl Cost?

Treatment with Reblozyl is expected to cost between \$152,188 to \$228,281 per patient annually.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that luspatercept should be reimbursed for the treatment of adult patients with red blood cell (RBC) transfusion-dependent anemia associated with very low- to intermediate-risk MDS who have ring sideroblasts only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

One phase III, randomized, double-blind, placebo-controlled trial (MEDALIST, N = 229) evaluated the efficacy and safety of luspatercept in adults with RBC transfusion-dependent anemia associated with very low- to intermediate-risk MDS who have ring sideroblasts and who had failed or were not suitable for erythropoietin-based therapy. This trial demonstrated that treatment with luspatercept in addition to best supportive care (BSC) was associated with a statistically significant reduction in transfusion burden compared with placebo. Red blood cell transfusion independence (RBC-TI) of 8 weeks was observed in 37.91% of patients in the luspatercept group, compared with 13.16% of those in the placebo group, with an odds ratio favouring luspatercept of 5.06 (95% CI, 2.28 to 11.26; P < 0.0001). For the key secondary efficacy outcomes of RBC-TI of 12 weeks at week 48 and week 24, a greater proportion of patients in the luspatercept treatment group achieved RBC-TI than the placebo group. For the key secondary outcome at week 48, 33.3% of the patients in the luspatercept treatment group and 11.84% of the patients in the placebo group achieved RBC-TI for at least 12 weeks, with an odds ratio favouring luspatercept of 4.04 (95% CI, 1.83 to 8.96; P = 0.0003). For the key secondary outcome at week 24, 28.1% of patients in the luspatercept treatment group and 7.89% of the patients in the placebo group achieved RBC-TI for at least 12 weeks, with an odds ratio favouring luspatercept of 5.07 (95% CI, 2.00 to 12.84; P = 0.0002). Patients expressed the need for a treatment that reduces transfusion burden and symptoms and improves health-related quality of life (HRQoL). Based on the evidence reviewed, luspatercept may increase RBC transfusion independence. However, CDEC could not conclude whether luspatercept improves HRQoL.

The sponsor's submitted price for luspatercept is \$2,189 per 25 mg and \$6,567 per 75 mg. The recommended dose of luspatercept depends on treatment response; therefore, the average daily treatment cost ranges from \$416.95 to \$625.43, while the average annual cost of treatment is between \$152,188 and \$228,281 per patient. CADTH estimated the incremental cost-effectiveness ratio (ICER) of luspatercept compared with BSC to be \$623,219 per quality-adjusted life-year (QALY), with a 0% probability of being cost-effective at a \$50,000 per QALY willingness-to-pay (WTP) threshold at the price submitted by the sponsor. A price reduction of 85% would be required for luspatercept to be cost-effective at this threshold. Scenario analyses were conducted around an alternate overall survival (OS) assumption and data cut, and differing baseline disease status assumptions. Based on CADTH scenario analyses, CDEC noted that the ICER for luspatercept compared with BSC could be as high \$1,170,786 per QALY.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason
<b>Initiation</b>	
1. Reimbursement of luspatercept should be restricted to patients who have failed or are not suitable for erythropoietin-based therapy.	In the MEDALIST study, treatment with luspatercept demonstrated a significant benefit in adult patients with RBC transfusion–dependent anemia associated with very low- to intermediate-risk MDS who have ring sideroblasts and who have failed or are not suitable for erythropoietin-based therapy. This is also consistent with Health Canada’s indication.
<b>Renewal</b>	
2. Patients should be RBC transfusion independent over a minimum of 16 consecutive weeks within the first 24 weeks of treatment initiation. Patients should remain transfusion independent and be assessed every 6 months.	Transfusion independence over a minimum of 16 weeks within 24 weeks of treatment initiation was considered a clinically meaningful response according to the Proposed IWG 2018 Hematological Response Criteria and the clinical experts.
<b>Prescribing</b>	
3. Treatment should be initiated by a specialist with expertise in managing and treating patients with MDS.	Accurate diagnosis of patients with myelodysplastic syndromes is important to ensure that luspatercept is prescribed to appropriate patients.
<b>Pricing</b>	
4. A reduction in price.	The ICER for luspatercept compared with BSC is \$623,219 per QALY. A price reduction of 85% would be required for luspatercept to be able to achieve an ICER of \$50,000 per QALY compared to BSC.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; IWG = International Working Group; MDS = myelodysplastic syndromes; QALY = quality-adjusted life-year; RBC = red blood cell.

## Implementation Guidance

Issues that may impact the drug plan’s ability to implement a recommendation as identified by CDEC and the drug plans are summarized in Table 2.

**Table 2: Implementation Guidance From CDEC**

Condition #	Implementation considerations and guidance
1	Patients not suitable for erythropoietin-based therapy may be defined as patients unlikely to respond to erythropoietin (an endogenous erythropoietin level of > 200 U/L in those not previously treated with erythropoiesis-stimulating agents) or who discontinued a prior erythropoiesis-stimulating agent due to adverse event or intolerance.
2	Transfusion independence can be considered maintained if unexpected RBC transfusions are required because of intercurrent illness.

Condition #	Implementation considerations and guidance
3	Regular access to a hematologist for luspatercept administration may be limited for some patients. There is potential for luspatercept to be administered by a health care professional in other settings, such as a community pharmacy.

## Discussion Points

- CDEC discussed the duration of hematologic response of the primary end point (i.e., at least 8 weeks) was not clinically meaningful as per the proposed International Working Group (IWG) 2018 Hematological Response Criteria and supported by the clinical experts, and the appropriate measure would be for patients to be transfusion independent for at least 16 weeks. One of the key secondary end points in the MEDALIST trial was transfusion independence over 12 weeks, which was significantly improved with luspatercept compared with placebo. Given the unmet need of this population, these outcomes were considered of importance to patients.
- In the MEDALIST study, 28.1% of patients who received luspatercept met the 12-week transfusion independence end point within 24 weeks. This translated into a common risk difference of 20.0 (95% CI, 10.92 to 29.08) compared with placebo.
- CDEC discussed that although some patients might benefit from luspatercept, currently there are no biomarkers available that could predict responders and who would benefit from luspatercept.
- Other end points the MEDALIST study evaluated were HRQoL, decreased transfusion burden, OS, progression to acute myeloid leukemia (AML), iron accumulation, iron chelation therapy use, and health care resource utilization. However, none of these outcomes were controlled for multiplicity, and due to limitations associated with statistical methodology, the effect of luspatercept on these outcomes is currently unknown.
- CDEC discussed that thromboembolic events, hypertension, hepatic and renal adverse events, and neoplasms were identified as safety concerns associated with luspatercept. The clinical expert noted that patients at an increased risk of thrombosis should be closely monitored while receiving treatment with luspatercept.

## Background

Luspatercept has a Health Canada indication for treatment of adult patients for the treatment of RBC transfusion-dependent anemia associated with very low- to intermediate-risk MDS who have ring sideroblasts and who have failed or are not suitable for erythropoietin-based therapy. Luspatercept is a recombinant fusion protein consisting of 2 identical chains, each consisting of a modified form of the extracellular domain of human activin receptor type IIB linked to the human immunoglobulin G1 Fc domain. Luspatercept is available as lyophilized powder for solution for subcutaneous injection in 2 strengths: 25 mg/vial and 75 mg/vial. The Health Canada recommended starting dose of luspatercept is 1 mg/kg up to a maximum of 1.75 mg/kg administered by a subcutaneous injection every 3 weeks.

## Sources of Information Used by the Committee

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

- a review of 1 phase III, randomized, double-blind, placebo-controlled trial (MEDALIST, N = 229) in patients with RBC transfusion–dependent anemia associated with very low- to intermediate-risk MDS who have ring sideroblasts and who have failed or are not suitable for erythropoietin-based therapy
- patients’ perspectives gathered by patient groups: the Leukemia & Lymphoma Society of Canada (LLSC) and Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two clinical specialists with expertise diagnosing and treating patients with RBC transfusion–dependent anemia associated with very low- to intermediate-risk MDS who have ring sideroblasts and who have failed or are not suitable for erythropoietin-based therapy
- input from 2 clinician groups: the Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee (OH-Hematology DAC) and the Alberta Tumour Board Myeloid Physicians Group (ATB-MPG)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Input

One joint submission from 2 patient groups, LLSC and AAMAC, was received in response to CADTH’s call for patient input.

LLSC created an online survey to gather input from patients on the treatments for MDS and luspatercept, if applicable. The online survey was available in French and English via Survey Monkey and was open to respondents from December 7, 2020, to January 4, 2021. It was promoted by LLSC and the Canadian MPN Network through social media channels and directly by email. A total of 20 respondents completed the survey, including 18 who identified as patients, 1 who identified as a caregiver, and 1 who identified as a friend or family member answering on behalf of a patient with MDS.

According to the patient input received for this review, 17 respondents identified symptoms of MDS impacting quality of life, with fatigue and infections being mentioned repeatedly, as well as the transfusion schedule. The impact of transfusion schedule was mentioned as an impact on quality of life, with 1 patient stating, “I have weekly transfusions and my life revolves around that.”

Respondents to the survey identified several frontline treatments they received for MDS after their diagnosis. These included blood transfusions, chemotherapy, drug therapy, stem cell or bone marrow transplant, blood cell growth factor therapy, watch-and-wait approach, anti-thymocyte globulin therapy, and immunoglobulin therapy. Respondents reported both positive and negative experiences with these therapies, with adverse effects to the various therapies

and transfusion schedules contributing to the negative experiences. The survey asked participants what factors are most important to consider when making decisions about a new cancer treatment. The most common response was the possible impact on disease. Other factors to consider cited by participants included physician recommendation, quality of life, outpatient treatment, and closeness of home.

None of the patient respondents indicated any experience using luspatercept.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

The clinical experts stated there are no funded or approved treatments available to address key outcomes for patients with transfusion-dependent anemia associated with MDS. Moreover, not all patients respond or tolerate these treatments even if they are obtained (privately or through a compassionate access program). The only therapeutic intervention for the treatment of lower-risk MDS which has demonstrated improvement in OS is iron chelation therapy. Of the disease-modifying therapies used for low-risk MDS, lenalidomide has been shown to improve HRQoL in patients both with and without the del(5q) cytogenetic abnormality. However, lenalidomide has been associated with causing significant neutropenia or thrombocytopenia.

The clinical experts anticipated that luspatercept would be used second line in erythropoiesis-stimulating agent (ESA) failures or first line in patients not expected to respond to ESAs. The clinical expert noted that therapies that increase hemoglobin and decrease RBC transfusion dependence cannot be assumed to improve patient symptoms or HRQoL, particularly when those therapies themselves can have adverse effects.

The clinical experts noted that luspatercept has only been studied in low-risk MDS patients with ringed sideroblasts and who have failed ESA therapy, and there is no evidence that it is in fact superior to ESA therapy in this setting. Luspatercept would either need to establish superiority through a direct comparison with ESAs (i.e., via a randomized controlled trial), or establish a stronger evidence base (i.e., through direct comparison with a control) that it can directly improve a patient-related outcome such as HRQoL, to be a preferred treatment of symptomatic anemia. The clinical experts consulted by CADTH suggested that patients with low-risk IPSS with ringed sideroblasts are the most likely to respond to therapy with luspatercept. The patients who require regular RBC transfusions are the ones most in need of this intervention since transfusion dependency is associated with shorter OS, more cardiac events, and inferior HRQoL. The clinical experts further noted that to identify patients who are most likely to exhibit a response to treatment with luspatercept would be on the basis of their IPSS score, endogenous erythropoietin level, and monthly transfusion needs. A variety of scoring systems are available for this purpose. The clinical experts noted that a clinically meaningful response to treatment would be an improvement in HRQoL using a validated scoring system (e.g., FACT or EQ-5D score). They also noted that a reduction in or elimination of transfusions would be clinically meaningful.

There were 2 opinions among the clinical experts. One expert expressed that since luspatercept is administered as a subcutaneous injection every 3 weeks; reviewing quality of life and/or complete blood count at each visit would be an appropriate interval. Transfusion independence may be evaluated every 8 weeks (with review conducted at the 9-week visit). The second expert expressed that assessment to treatment response should be every month for 6 months then every 3 months.

The clinical experts concurred that no meaningful response, disease progression, intolerable adverse events which do not respond to dose reduction, and failure to achieve a response criterion after 9 weeks, despite dose escalation to 1.75 mg/kg, could be reasonably interpreted as a lack of meaningful response and treatment would be discontinued.

The clinical experts noted that while many patients will likely receive their first subcutaneous injection in a medical setting and would be administered by a health care professional (either inpatient or outpatient), as per the product monograph, the majority of patients should be able to self-administer in the community setting. The diagnosis of low-grade MDS requires a specialist consultation, and the prescription of luspatercept should be limited to individuals with special training in managing the diagnosis (typically a hematologist or oncologist), although once initiated it would be reasonable for non-specialists to continue prescribing and monitoring.

## Clinician Group Input

Clinician input on the review of luspatercept for the treatment of adult patients with very low- to intermediate-risk MDS-associated anemia who have ring sideroblasts and require RBC transfusions was received from 2 groups: the OH-Hematology DAC and the ATB-MPG.

Both groups agreed that the current treatment for patients involves transfusion support with red cell transfusions and ESAs. The clinicians from Alberta noted that ESAs are most effective in patients with low transfusion requirements and erythropoietin levels and are variably funded across the country. They added that there is currently no funding for ESAs in Alberta, although commonly used and considered standard of care, and erythropoietin is recommended in the Alberta clinical practice guidelines for patients with lower-risk MDS. Both groups agreed that patients with del[5q] MDS (approximately 10% of patients) may be treated with lenalidomide. With respect to needs that are not being met with the currently available treatments, both clinician groups agreed that currently there are no other treatment options other than transfusion, ESAs for some patients, and – for a small subset of patients – hypomethylating agents such as azacitidine or decitabine-cedazuridine.

Both clinician groups agreed that luspatercept would be an additional line of therapy for symptomatic anemia for patients who have progressed on ESAs, have not responded to ESAs, or have a high erythropoietin level precluding response to ESA therapy to reduce transfusion and their consequences (i.e., iron overload). Both clinician groups agreed that patients best suited for treatment with luspatercept are lower-risk MDS patients with symptomatic anemia who have failed ESAs or are inappropriate for ESA therapy. The clinicians from Alberta added that patients in this group have no other effective treatment options other than long-term transfusions and iron chelation to help manage the related iron overload with associated side effects of chelation.

Both clinician groups agreed that transfusion frequency (reduction in transfusion requirements) and improvement in hemoglobin are outcomes used to determine whether a patient is responding to treatment in clinical practice. Both groups also agreed that a clinically meaningful response to treatment would be a reduction in transfusions.

With respect to factors that should be considered when deciding to discontinue treatment, the clinicians from Ontario noted that worsening of MDS, progression to a higher risk category, or transformation to AML should be considered. The clinicians from Alberta note that a decrease in hemoglobin without an alternative cause, an increase in transfusion requirements, or the

need to introduce regular transfusions in patients who have been transfusion independent would be factors to consider.

According to both clinician groups, the most appropriate settings for treatment are community settings such as pharmacies, outpatient clinics, and specialty clinics. The clinicians from Alberta added that a hematology or medical oncology specialist would be required to diagnose, treat, and monitor patients who might receive the drug under review. The clinicians from Alberta noted that the benefit to patients who can become transfusion independent (or remain so after developing symptomatic anemia) is very significant and can reduce a significant burden on both patients and the health care institutions who provide regular transfusion support over long time periods to these patients.

## Drug Program Input

The drug plans asked the clinical experts if previous ESA treatment should be considered before funding; their response was yes, it should be considered. They also noted that the trial was limited to patients who had failed a prior course of ESA therapy. However, it would be reasonable to initiate treatment directly with luspatercept in patients predicted to have less than a 25% chance of responding to ESA therapy (i.e., based on NORDIC or similar prognostic scoring system). The drug plans had questions regarding the appropriate place in therapy for luspatercept, and whether previous treatment with ESAs should be required. The plans also requested information about when treatment with luspatercept should be discontinued. The plans also sought the clinical expert's opinion regarding administration of luspatercept, specifically around monitoring hemoglobin levels and ensuring equal access.

## Clinical Evidence

### Pivotal Studies and Protocol-Selected Studies

One pivotal trial (MEDALIST, N = 229) was included in the CADTH systematic review. MEDALIST is an ongoing phase III, randomized, double-blind, placebo-controlled study that aims to evaluate the efficacy and safety of luspatercept in adult patients for the treatment of RBC transfusion-dependent anemia associated with very low- to intermediate-risk MDS who have ring sideroblasts and who have failed or are not suitable for erythropoietin-based therapy. The MEDALIST trial was conducted at 65 sites globally; 4 sites in Canada enrolled 14 patients.

Eligible patients were randomized (2:1) to receive either luspatercept or placebo with BSC. The randomized and double-blind phase of the study was divided into a 24-week primary treatment phase, a 25-week assessment phase, and a 24-week extension phase. Patients received a starting dose of the study drug of 1 mg/kg administered by a subcutaneous injection every 3 weeks. During the treatment period, the dose levels were titrated (increased) stepwise up to a maximum of 1.75 mg/kg or reduced based on a clinical response. The maximum total dose per administration was not to exceed 168 mg. Randomization was stratified based on RBC transfusion burden at baseline ( $\geq 6$  units/8 weeks versus  $< 6$  units/8 weeks) and International Prognostic Scoring System-Revised (IPSS-R) score at baseline (very low or low versus intermediate).

For patients to continue the double-blind treatment beyond the first 24 calendar weeks, the following criteria had to be confirmed by the investigator at the week 25 visit: evidence of clinical benefit (e.g., decrease in RBC transfusion requirement compared with baseline requirement or hemoglobin increase compared with baseline) and absence of disease progression as per IWG MDS criteria for altering the natural history of MDS. Based on the outcome of the MDS disease assessment visit at week 25, patients were either discontinued from treatment and entered into the posttreatment follow-up period or continued with double-blind treatment with the same study drug in the extension phase of the treatment period. As of the data cut on May 8, 2018, 128 patients (83.7%) in the luspatercept treatment group and 68 patients (89.5%) in the placebo treatment group had completed 24 weeks of treatment; 78 patients (51%) in the luspatercept treatment group and 12 patients (15.8%) in the placebo group had completed 48 weeks of treatment.

The primary outcome of the study was the proportion of patients who achieved RBC-TI for at least 8 weeks or longer (any consecutive 56-day period) from week 1 to week 24. The measures upon which the 2 key secondary outcomes were based were the proportion of patients who achieved RBC-TI for at least 12 weeks or greater (any consecutive 84-day period) from week 1 to week 48 and the proportion of patients who achieve RBC-TI for at least 12 weeks or greater (any consecutive 84-day period) from week 1 to week 24.

The baseline characteristics of the patients enrolled in the MEDALIST study were overall well balanced. Approximately two-thirds of the patients in the MEDALIST study were male and White. Mean body weight was 76.2 kg and 77.4 kg in the luspatercept and placebo treatment groups, respectively. The mean age of the patients was 70.5 (SD = 8.68) and 70.7 (SD = 10.88) in the luspatercept and placebo treatment groups, respectively. In the luspatercept and placebo treatment groups, 94.8% and 97.4% of the patients, respectively, were classified as having refractory cytopenia with multilineage dysplasia, according to the WHO classification; 71.2% and 75.0% patients were classified in the low-risk category as per the IPSS-R classification in the luspatercept and placebo treatment groups, respectively. 59.5% of the patients in the luspatercept treatment group and 42.1% of the patients in the placebo treatment group had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1; 5.2% patients in the luspatercept treatment group and 14.5% of the patients in the placebo treatment group had an ECOG performance status of 2.

## Efficacy Results

In the MEDALIST study, the efficacy outcomes identified in the protocol were hematologic response, HRQoL, OS, iron accumulation, iron chelation therapy use, progression to AML, and health care resource utilization. The primary and 2 key secondary efficacy outcomes were analyzed using an intention-to-treat population.

At week 24, a greater proportion of patients in the luspatercept treatment group achieved the primary outcome of RBC transfusion independence for at least 8 weeks or longer (any consecutive 56-day period) than the placebo group. In the luspatercept treatment group, 37.9% of the patients responded to the treatment; 13.16% of the patients in the placebo group achieved the primary end point, with a common risk difference on response rate being 24.56 (95% CI, 14.48 to 34.64). The odds ratio of 5.06 (95% CI, 2.28 to 11.26;  $P < 0.0001$ ) favoured the luspatercept treatment over placebo. The clinical experts consulted by CADTH were of the opinion that the results were not clinically meaningful because 8 weeks is a short duration to assess response.

At week 48 and week 24, a greater proportion of patients in the luspatercept treatment group achieved the 2 key secondary outcomes of RBC transfusion independence for at least 12 weeks or greater (any consecutive 84-day period) than the placebo group. During week 1 to week 48, 33.3% of the patients in the luspatercept treatment group responded to the treatment and 11.84% of the patients in the placebo group responded to the treatment, with a common risk difference on response rate being 21.37 (95% CI, 11.23 to 31.51). The odds ratio of 4.04 (95% CI, 1.83 to 8.96; P = 0.0003) favoured the luspatercept treatment over placebo. During week 1 to week 24, 28.1% of the patients in the luspatercept treatment group responded to the treatment and 7.89% of the patients in the placebo group responded to the treatment, with a common risk difference on response rate being 20.00 (95% CI, 10.92 to 29.08). The odds ratio of 5.07 (95% CI, 2.00 to 12.84; P = 0.0002) favoured the luspatercept treatment over placebo.

Other efficacy outcomes identified in the CADTH review protocol were reported descriptively, including the number of RBC units transfused, duration of RBC transfusion independence, time to RBC transfusion independence, mean change in hemoglobin, modified hematologic improvement), OS, iron accumulation (through serum ferritin levels), iron chelation therapy use, progression to AML, and health care resource utilization. In the absence of any formal statistical testing, whether luspatercept has an effect on any of these outcomes remains unknown. HRQoL was a secondary and exploratory outcome in the MEDALIST study and was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-30) and QoL-E instruments; however, none of these outcomes were controlled for multiplicity. For HRQoL outcomes, no difference in the treatment groups was observed and no minimally important difference for patients with transfusion-dependent anemia associated with MDS was identified from the literature.

Subgroup analyses identified in the CADTH review protocol for which results were available in the MEDALIST study included IPSS-R score (very low risk or low risk versus intermediate risk), and baseline hematological status. The results of the subgroup analysis were aligned with the results of the full study population.

## Harms Results

In the MEDALIST study, 98.0% and 92.1% of the patients in the luspatercept and placebo groups, respectively, reported at least 1 adverse event. The most commonly occurring adverse events were fatigue (26.8% and 13.2% of the patients in the luspatercept and placebo groups, respectively), diarrhea (22.2% and 9.2% of the patients in the luspatercept and placebo groups, respectively), nausea (20.3% and 7.9% of the patients in the luspatercept and placebo groups, respectively), and dizziness (19.6% and 5.3% of the patients in the luspatercept and placebo groups, respectively).

In the MEDALIST study, serious adverse events were reported by 31.4% of the patients in the luspatercept treatment group and 30.3% of the patients in the placebo group. The most commonly reported serious adverse event was pneumonia, which was reported by 2.0% patients in the luspatercept group and 2.6% patients in the placebo group. The proportion of patients who stopped treatment due to an adverse event was 8.5% and 7.9% in the luspatercept and placebo treatment groups, respectively. [REDACTED]

During the treatment period, 3.3% (n = 5) of patients in the luspatercept treatment group and 5.3% (n = 4) of patients in the placebo treatment group had died. In the luspatercept

treatment group, 1 patient died due to multiple organ dysfunction syndrome, 2 patients died of sepsis, 1 patient died due to renal failure, and 1 patient died of a hemorrhagic shock. In the placebo treatment arm, 1 patient died due to general physical health deterioration, 1 patient died due to urosepsis, 1 patient died of sepsis, and 1 patient died of respiratory failure. During the posttreatment period, an additional [REDACTED] and [REDACTED] patients died in the luspatercept treatment group and the placebo treatment group, respectively.

The notable harms identified in the CADTH review protocol included the following: thromboembolic events, hypertension, hepatic and renal events, hypersensitivity reactions, and malignancies. In the luspatercept treatment group, 2.6% (n = 4) of patients experienced a thromboembolic and thrombophlebitis event; in the placebo treatment group, 3.9% (n = 3) of patients experienced a thromboembolic and thrombophlebitis event. Under the system organ class (SOC) of hepatobiliary disorders, [REDACTED] of patients in the luspatercept treatment group and [REDACTED] of patients in the placebo group reported at least 1 associated adverse event. Under the SOC of renal and urinary disorders, [REDACTED] of patients in the luspatercept treatment group and [REDACTED] of patients in the placebo group reported at least 1 associated adverse event. Hypertension was reported as an adverse event in 8.5% of the patients in the luspatercept treatment group and 7.9% patients in the placebo group.

## Critical Appraisal

MEDALIST was a randomized, placebo-controlled, double-blind study. Overall randomization (using an interactive response technology system) and treatment allocation (stratified by RBC transfusion burden at baseline [ $\geq 6$  units/8 weeks versus  $< 6$  units/8 weeks] and IPSS-R score at baseline [very low or low versus intermediate]) were appropriately conducted; however, as noted by the US FDA, blinding in the study may have been inadequate due to the production of the placebo control syringe onsite and the lack of specific instructions to mask the product. This increases the risk of accidental unblinding unacceptably, which may have introduced bias in the results.

The baseline patient, disease, and MDS treatment history characteristics were generally well balanced. A higher number of patients in the luspatercept treatment group progressed to AML, developed nervous system disorders, or fatigue, which led to study drug discontinuation.

The clinical experts consulted by CADTH were of the opinion that the duration of hematologic response of the primary end point — at least 8 weeks (i.e., any consecutive 56 days) — was not clinically meaningful. The appropriate measure for clinical meaningfulness would be transfusion independence for at least 16 weeks, which is in accordance with the proposed IWG 2018 Hematological Response Criteria. A hematologic response of transfusion independence for 12 weeks (i.e., any consecutive 84 days) is more clinically meaningful than 8 weeks. The effect size of the primary end point of transfusion independence for 8 weeks in the study was small; transfusion independence of 8 weeks was obtained in only approximately 38% of patients with a differential response compared with placebo of about 25%; hence, only approximately one-quarter of the patients exposed to luspatercept had any apparent benefit, assuming that fulfillment of the primary objective represents a benefit to the patient.

Only a subset of patients who initially responded in the first 24 weeks were eligible for the extension phase. The interpretation of this end point is therefore problematic because few patients were eligible for the extension phase and therefore could not achieve the end point of 12 weeks response due to the study design.

The clinical experts noted that, based on baseline demographic and disease characteristics, the study population was representative of Canadian patients with transfusion-dependent anemia associated with MDS. In Canada, the average age of an MDS patient is 74 years, which is similar to the mean age of the study population, which was 70.5 years.

## Economic Evidence

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

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with very low- to intermediate-risk MDS-associated anemia who have ring sideroblasts requiring RBC transfusions and have received or are not eligible for erythropoietin-stimulating agents
Treatment	Luspatercept + BSC
Submitted drug price	Luspatercept, powder for reconstitution for subcutaneous injection: \$2,189 per 25 mg vial and \$6,567 per 75 mg vial
Annual cost	The recommended dose is between 1.0 and 1.75 mg/kg every 3 weeks, leading to an average daily cost of \$416.95 to \$625.43 per patient (or \$152,188 to \$228,281 annually), based on a patient weight of 76 kg (MEDALIST trial)
Comparator	BSC alone, comprised of regular RBC transfusions and iron chelation therapy
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (10 years)
Key data sources	<ul style="list-style-type: none"> <li>Phase III MEDALIST trial of luspatercept + BSC vs. placebo + BSC to inform the categorization of patients into baseline health states based on transfusion burden: low transfusion burden, intermediate transfusion burden, and high transfusion burden, as well as a transfusion-independent state for luspatercept responders</li> <li>Other published literature was used to inform other parameters such as incidence of AML and transition to high-risk MDS</li> </ul>
Submitted results <sup>a</sup>	ICER = \$206,439 per QALY for luspatercept + BSC vs. BSC (incremental QALYs: 0.79; incremental costs: \$162,196)

Component	Description
<b>Key limitations</b>	<ul style="list-style-type: none"> <li>• In the sponsor’s base case, OS was estimated by fitting a Gompertz distribution to the OS data observed in MEDALIST and using this to estimate overall survival rates after year 1. This extrapolation of OS data beyond the trial period likely overestimated the OS benefits of luspatercept, given that most patients had discontinued luspatercept after 1.5 years. Clinical experts consulted by CADTH did not expect there to be any residual OS benefit after patients had discontinued treatment with luspatercept.</li> <li>• The sponsor based the clinical inputs from MEDALIST on a data cut from July 2019; however, this full dataset was not part of the original statistical plan for the trial. The CADTH clinical report is based on the May 2018 data cut; as such, the parameter inputs used by the sponsor from MEDALIST could not be fully validated.</li> <li>• Based on feedback from clinical experts, the utility value for the AML state was felt to be overestimated.</li> </ul>
<b>CADTH reanalysis results</b>	<ul style="list-style-type: none"> <li>• The sponsor provided alternative methods to incorporate OS data into the model. CADTH chose the option that modelled OS based on a TI reference curve, to which hazard ratios for patients in the TD and HR MDS states were applied. CADTH also used the May 2018 data cut and a lower utility value in the AML health state.</li> <li>• In the CADTH base case, the ICER for luspatercept + BSC is \$623,219 per QALY compared with BSC.</li> <li>• Based on CADTH reanalyses, the probability of luspatercept being cost-effective at a WTP threshold of \$50,000 per QALY was 0%. A price reduction of 85% would be required for luspatercept to be cost-effective at this threshold.</li> <li>• Scenario analyses were performed to explore other areas of uncertainty, including OS assumptions, different data cuts, and baseline transfusion status. The scenarios that had the largest influence on the ICER were the ones involving baseline transfusion status. When all patients were assumed to start in the HTB state, the ICER was \$1,170,786 per QALY.</li> </ul>

AML = acute myeloid leukemia; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; MDS = myelodysplastic syndrome; OS = overall survival; QALY = quality-adjusted life-year; RBC = red blood cell; WTP = willingness to pay; vs. = versus.

\*Corrected to reflect the May 2018 data cut of the MEDALIST study.

## Budget Impact

The sponsor estimated the budget impact of funding luspatercept for the treatment of adult patients with very low- to intermediate-risk MDS-associated anemia who have ring sideroblasts to be \$25,947,853 in year 1, \$28,395,584 in year 2, and \$21,982,237 in year 3, for a 3-year total of \$76,325,673. CADTH reanalysis excluded patients who were not refractory to ESAs to align with the Health Canada indication and increased the market uptake of luspatercept in years 1 and 2 to align with clinical expert feedback. Based on the CADTH reanalysis, the budget impact of the reimbursement of luspatercept is expected to be \$49,237,991 in year 1, \$39,292,172 in year 2, and \$12,948,948 in year 3, with a 3-year budget impact of \$101,479,111.

## CADTH Canadian Drug Expert Committee Information

### Members of the Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

**Initial meeting date:** July 21, 2021

**Regrets:** None

**Conflicts of interest:** None

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

**Reconsideration meeting date:** November 25, 2021

**Regrets:** One expert committee member did not attend.

**Conflicts of interest:** None