

## Reimbursement Review

# Mosunetuzumab IV (Lunsumio) and Mosunetuzumab SC (Lunsumio SC)

**Sponsor:** Hoffmann-La Roche Limited

**Therapeutic area:** Relapsed or refractory follicular lymphoma

# Summary

## What Is Follicular Lymphoma?

- Follicular lymphoma (FL) is a systemic malignancy of lymphoid tissue characterized by germinal-centre B-cell differentiation, typically presenting as slow-progressing indolent non-Hodgkin lymphoma associated with common relapse and long survival measured in years.
- In Canada, the number of people diagnosed with FL between 1992 and 2010 was estimated to be more than 22,000, corresponding to an age-standardized incidence rate of 38 cases per million persons per year.

## What Are the Treatment Goals and Current Treatment Options for FL?

- The goals of treatment for FL are to induce remission, delay relapse, prolong survival, and improve quality of life while minimizing toxicity and treatment burden.
- Important outcomes include longer survival, durable disease and symptom control, longer remission, improved quality of life, fewer side effects, and maintenance of daily functioning.
- Current treatment options for relapsed or refractory (r/r) FL include localized palliative radiotherapy for selected cases, stem cell transplant in selected patients, chemoimmunotherapy, targeted therapies, immunomodulatory drugs, and chimeric antigen receptor (CAR) T-cell therapies. Emerging bispecific antibodies such as Lunsumio (mosunetuzumab) are expected to address some gaps in treatment by providing a chemotherapy-free, fixed-duration therapy deliverable in outpatient settings.

## What Is Lunsumio and Why Did Canada's Drug Agency Conduct This Review?

- Lunsumio is a drug that is administered by IV infusion or subcutaneous (SC) injection. At the time this review was initiated, Health Canada was reviewing Lunsumio (IV and SC) monotherapy, for adult patients with r/r FL (grades 1 to 3a) who have received at least 2 prior lines of systemic therapy. Health Canada approved Lunsumio IV monotherapy and Lunsumio SC monotherapy, with conditions for the indication, on February 6, 2026, and April 10, 2026, respectively.
- Canada's Drug Agency (CDA-AMC) reviewed Lunsumio (IV and SC) to inform a recommendation to the participating public drug programs on whether they should be reimbursed for the Health Canada-approved indication.

# Summary

## How Did CDA-AMC Evaluate Lunsumio and Lunsumio SC?

- CDA-AMC reviewed the clinical evidence on the beneficial and harmful effects, as well as the economic evidence, of Lunsumio versus other treatments used in Canada for the treatment of adult patients with r/r FL (grades 1 to 3a) who have received at least 2 prior lines of systemic therapy. Rituximab; rituximab plus bendamustine; a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; a combination of rituximab, cyclophosphamide, vincristine, and prednisone; obinutuzumab plus bendamustine; idelalisib; rituximab plus lenalidomide; axicabtagene ciloleucel (axi-cel); and tisagenlecleucel (tisa-cel) were considered relevant treatments to compare with Lunsumio when reviewing the clinical evidence.
- CDA-AMC identified equity and ethical considerations relevant to treating FL with mosunetuzumab.
- The review was informed by materials submitted by the sponsor, which included clinical and economic evidence.
- The review considered 1 patient group submission and 3 clinician group submissions in response to the CDA-AMC call for input, and input from the participating public drug programs around issues that may affect their ability to implement a recommendation.
- Two clinical specialists with expertise in the diagnosis and management of r/r FL, 1 each from Alberta and Ontario, were consulted as part of the review process.

## What Were the Findings?

### Clinical Evidence

- CDA-AMC reviewed the following clinical evidence:
  - 1 ongoing phase I(Ib) and II, single-arm, open-label study (GO29781) that reported outcomes for the Lunsumio IV monotherapy cohort (N = 90) and the Lunsumio SC monotherapy cohort (N = 94)
  - 1 indirect treatment comparison (ITC) comprising 3 matching-adjusted indirect comparisons for 3 comparators (i.e., axi-cel, tisa-cel, and rituximab plus lenalidomide) and 4 propensity score analyses for 2 comparators (i.e., obinutuzumab plus bendamustine and rituximab plus bendamustine).
- Outcomes assessed in the GO29781 study were complete response and overall response (partial response or complete response) and survival,

# Summary

but the treatment effects of Lunsumio are very uncertain because it was not compared with another treatment.

- **Treatment response outcomes (by independent review facility [IRF] assessment):**
  - In the IV cohort, at a median observation time of 18.3 months, the complete response rate (CRR) was 60% and the overall response rate (ORR) was 80%. The median duration of complete response was not reached, with 12- and 18-month event-free rates of 71% and 64%, respectively. The median duration of overall response was 23 months, with 12- and 18-month event-free rates of 62% and 57%, respectively. The median time to next treatment was not reached, with a 12-month event-free rate of 68%.
  - In the SC cohort, at a median observation time of 20.7 months, the CRR was 59% and the ORR was 75%. The median duration of complete response was 21 months, with a 12-month event-free rate of 72%. The median duration of overall response was 22 months, with a 12-month event-free rate of 70%. The median time to next treatment was not reached, with 12- and 18-month event-free rates of 79% and 74%, respectively.
  - These outcomes were considered clinically meaningful by the clinical experts consulted for this review, and they were viewed as attributable to Lunsumio rather than to natural history. However, in the absence of a comparator, a comparative benefit could not be assessed.
- **Survival outcomes:**
  - Median overall survival (OS) was not estimable in either the IV or SC cohort. The 12-month OS rate was 93% in the IV cohort and 90% in the SC cohort.
  - At a median observation time of 18.3 months, the median progression-free survival (PFS) in the IV cohort was 18 months by IRF assessment, with 12-month and 18-month event-free rates of 58% and 47%, respectively.
  - In the SC cohort, the median PFS by IRF assessment was 19 months at a median observation time of 20.7 months, with a 12-month event-free rate of 62%.
  - The clinical experts considered the PFS outcomes in both cohorts to be clinically meaningful for patients with r/r FL (grades 1 to 3a) who have received at least 2 prior lines of systemic therapy, including anti-CD20 and alkylator treatments; however, causal conclusions cannot be drawn from these nonrandomized data.

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- **Health-related quality of life (HRQoL) outcomes:**
  - At cycle 8, a total of 41% of patients in the IV cohort and 35% of patients in the SC cohort had achieved an improvement of at least 3 points from baseline in the Functional Assessment of Cancer Therapy–Lymphoma subscale score. The effects on HRQoL were uncertain due to missing data and the open-label, noncomparative design.
- **Safety outcomes:**
  - In the IV cohort, all patients reported at least 1 adverse event (AE). The most common AEs were cytokine release syndrome (CRS) (46% according to Lee criteria and 44% according to American Society for Transplantation and Cellular Therapy [ASTCT] criteria), fatigue (37%), and headache (31%). AEs of grades 3 to 5 (excluding grade 5 progressive disease) occurred in 70% of patients, with neutropenia (19%) and hypophosphatemia (17%) being the most common events. Serious adverse events (SAEs) occurred in 47% of patients, with CRS (23% according to Lee or ASTCT criteria) being the most common SAE.
  - In the SC cohort, almost all patients (99%) reported at least 1 AE. The most common AEs were injection site reactions (61%), fatigue (35%), and CRS (31% by Lee criteria and 30% by ASTCT criteria). AEs of grade 3 to 5 (excluding grade 5 progressive disease) occurred in 52% of patients, with neutropenia (11%) and hypophosphatemia (5%) being the most common events. SAEs occurred in 39% of patients, with CRS (15% by Lee or ASTCT criteria) being the most common SAE.
  - Notable harms, including CRS (for patients in both the IV and SC treatment groups) and injection site reactions (for patients in the SC group), were consistent with the known safety profile of Lunsumio. The overall safety profile of Lunsumio in the GO29781 study was consistent with the known risks of the drug class, with no unexpected safety findings.
- No long-term extension studies were submitted by the sponsor for this review.
- For the comparison of Lunsumio IV monotherapy versus comparators relevant to contexts in Canada based on the sponsor-submitted ITCs:
  - The ITC results for OS or ORR were very uncertain in the comparisons of Lunsumio versus all comparators, as estimates were affected by imprecision, suggesting that either treatment could have been favoured.

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- For PFS, axi-cel, tisa-cel, or obinutuzumab plus bendamustine may be favoured over Lunsumio; however, the studies were small, and it is unclear whether all treatment effect modifiers and prognostic variables were adjusted for in analyses. For PFS, the comparison between Lunsumio versus rituximab plus lenalidomide was very uncertain, with the estimate affected by imprecision. For PFS, the comparison versus rituximab plus bendamustine was also very uncertain because of imbalances in patient characteristics after matching and violation of model assumptions.
- For CRR, axi-cel may be favoured over Lunsumio, whereas Lunsumio may be favoured over rituximab plus lenalidomide and over obinutuzumab plus bendamustine, with the same limitations noted previously. For CRR, the comparisons versus tisa-cel or rituximab plus bendamustine were very uncertain, with estimates affected by imprecision.
- For treatment discontinuation due to AEs, Lunsumio may be favoured over obinutuzumab plus bendamustine, with the same limitations noted previously. The comparisons versus rituximab plus lenalidomide or versus rituximab plus bendamustine were very uncertain, and analyses for axi-cel and tisa-cel (CAR T-cell therapies) were not feasible as CAR T-cell therapies are administered as a 1-time infusion and cannot be discontinued.
- Overall, ITC findings for most comparisons were considered very uncertain due to several limitations, including serious imprecision, small sample sizes, decreases in the number of patients at risk during follow-up, and violations of model assumptions for some comparisons.
- No HRQoL outcomes were assessed in the ITC.

## Economic Evidence

- Lunsumio is available as a solution for IV infusion (1 mg/mL) and as a solution for SC injection. At the submitted price of \$411.00 per 1 mg for the IV form, the 28-day cycle cost of Lunsumio IV is expected to be \$34,524 for the first cycle (21-day cycle = \$25,893), \$32,880 for the second cycle (21-day cycle = \$24,660), and \$16,440 for subsequent cycles (21-day cycle = \$12,330) per patient, based on the Health Canada–recommended dosage. At the submitted price of \$1,518.70 per 5 mg for the SC form, the 28-day cycle cost of Lunsumio SC is expected to be \$38,474 for the first cycle (21-day cycle = \$28,855) and \$18,224

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for subsequent cycles (21-day cycle = \$13,668) per patient, based on the Health Canada–recommended dosage.

- Key clinical efficacy data used in the economic analysis (PFS and OS) for Lunsumio were derived from sponsor-submitted ITCs, with the efficacy of Lunsumio informed by the GO29781 trial. Indirect evidence submitted by the sponsor suggests that the comparative efficacy of Lunsumio versus comparators is very uncertain. The ITCs for OS were affected by substantial imprecision and were very uncertain in the comparisons between Lunsumio and all comparators, suggesting that either treatment could be favoured. Results also suggested that axi-cel, tisa-cel, and obinutuzumab plus bendamustine may be favoured over Lunsumio for PFS, and the comparisons between Lunsumio versus rituximab plus lenalidomide and between Lunsumio versus rituximab plus bendamustine for PFS were very uncertain. Overall, findings from the ITCs are very uncertain due to several identified limitations, such as heterogeneity, unmeasured confounding, population differences, and small sample sizes, in addition to residual uncertainty inherent in the indirect comparisons. For all comparisons, it is unclear whether assumptions underlying the ITCs were met and whether treatment effect modifiers and prognostic variables were adjusted for appropriately. These limitations prevent CDA-AMC from drawing definitive conclusions on the relative efficacy or safety of Lunsumio compared with axi-cel, tisa-cel, rituximab plus lenalidomide, obinutuzumab plus bendamustine, or rituximab plus bendamustine.
- No robust evidence reviewed for this submission suggested that Lunsumio provided a greater health benefit compared to axi-cel, tisa-cel, rituximab plus lenalidomide, obinutuzumab plus bendamustine, or rituximab plus bendamustine. If there are no differences in health outcomes between Lunsumio and comparators, then the total cost of Lunsumio to the health system should not exceed that of the least costly comparator for the treatment of adult patients with r/r FL (grade 1 to 3a) who have received at least 2 prior lines of systemic therapy.
- CDA-AMC estimates that the budget impact of reimbursing Lunsumio for the treatment of adult patients with r/r FL (grade 1 to 3a) who have received at least 2 prior lines of systemic therapy will result in savings of approximately \$6 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of \$109 million on Lunsumio over this period. The actual budget impact of reimbursing Lunsumio will depend on which

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treatments are displaced by Lunsumio, the market uptake of Lunsumio, and the confidential negotiated prices of comparators. Additionally, 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 the CDA-AMC estimate.

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## Abbreviations

|                 |                                                                   |
|-----------------|-------------------------------------------------------------------|
| <b>AE</b>       | adverse event                                                     |
| <b>AESI</b>     | adverse event of special interest                                 |
| <b>ASTCT</b>    | American Society for Transplantation and Cellular Therapy         |
| <b>axi-cel</b>  | axicabtagene ciloleucel                                           |
| <b>CAR</b>      | chimeric antigen receptor                                         |
| <b>CCOD</b>     | clinical cut-off date                                             |
| <b>CDA-AMC</b>  | Canada's Drug Agency                                              |
| <b>CI</b>       | confidence interval                                               |
| <b>CR</b>       | complete response                                                 |
| <b>CRR</b>      | complete response rate                                            |
| <b>CRS</b>      | cytokine release syndrome                                         |
| <b>DOCR</b>     | duration of complete response                                     |
| <b>DOR</b>      | duration of response                                              |
| <b>ECOG PS</b>  | Eastern Cooperative Oncology Group Performance Status             |
| <b>FACT-Lym</b> | Functional Assessment of Cancer Therapy for Lymphoma              |
| <b>FL</b>       | follicular lymphoma                                               |
| <b>FLIPI</b>    | Follicular Lymphoma International Prognostic Index                |
| <b>GRADE</b>    | Grading of Recommendations Assessment, Development and Evaluation |
| <b>HRQoL</b>    | health-related quality of life                                    |
| <b>ICER</b>     | incremental cost-effectiveness ratio                              |
| <b>IPD</b>      | individual patient data                                           |
| <b>IRF</b>      | independent review facility                                       |
| <b>ITC</b>      | indirect treatment comparison                                     |
| <b>KM</b>       | Kaplan-Meier                                                      |
| <b>MAIC</b>     | matching-adjusted indirect comparison                             |
| <b>NALT</b>     | new antilymphoma treatment                                        |
| <b>NE</b>       | not estimable                                                     |
| <b>NHL</b>      | non-Hodgkin lymphoma                                              |
| <b>ORR</b>      | overall response rate                                             |
| <b>OS</b>       | overall survival                                                  |
| <b>PFS</b>      | progression-free survival                                         |
| <b>POD24</b>    | progression of disease within 24 months                           |
| <b>PR</b>       | partial response                                                  |

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| <b>PSA</b>      | propensity score analysis                                             |
| <b>QALY</b>     | quality-adjusted life-year                                            |
| <b>QoL</b>      | quality of life                                                       |
| <b>R-CHOP</b>   | rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone |
| <b>RCT</b>      | randomized controlled trial                                           |
| <b>R-CVP</b>    | rituximab, cyclophosphamide, vincristine, and prednisone              |
| <b>RP2D</b>     | recommended phase II dose                                             |
| <b>r/r</b>      | relapsed or refractory                                                |
| <b>SAE</b>      | serious adverse event                                                 |
| <b>SC</b>       | subcutaneous                                                          |
| <b>SD</b>       | standard deviation                                                    |
| <b>tisa-cel</b> | tisagenlecleucel                                                      |
| <b>TTNT</b>     | time to next treatment                                                |

## Background

### Introduction

The objectives of this report are as follows:

- Review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of mosunetuzumab 1 mg/mL IV infusion and mosunetuzumab 10 mg/mL or 45 mg/mL for SC administration for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL). The focus will be placed on comparing mosunetuzumab IV and mosunetuzumab subcutaneous (SC) to relevant comparators in clinical practice in Canada and identifying gaps in the current evidence, and this focus is outlined in [Table 1](#).
- Review and critically appraise the economic information submitted by the sponsor, including a cost-effectiveness analysis and budget impact analysis. The focus of the Economic Review is aligned with the scope of the Clinical Review, unless otherwise stated. For most reviews, Canada's Drug Agency (CDA-AMC) developed a base case, informed by clinical expert input, the available clinical evidence, and the best interpretation of the economic evidence based on the information provided by the sponsor.

The application was submitted by the sponsor before receiving a Notice of Compliance with conditions from Health Canada. This report reflects the anticipated indication and recommended dosing for mosunetuzumab IV and mosunetuzumab SC during the initial CDA-AMC review period.

**Table 1: Information on the Application Submitted for Review and on the CDA-AMC Review**

| Item                                                       | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Information on the application submitted for review</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Drug</b>                                                | <b>Mosunetuzumab IV concentrate for solution for intravenous infusion</b> <ul style="list-style-type: none"> <li>• 1 mg dose in a 2 mL vial containing 1 mL of liquid concentrate (1 mg/mL)</li> <li>• 30 mg dose in a 50 mL vial containing 30 mL of liquid concentrate (1 mg/mL)</li> </ul> <b>Mosunetuzumab SC solution for subcutaneous injection</b> <ul style="list-style-type: none"> <li>• 5 mg dose in a 2 mL vial containing 0.5 mL of solution (10 mg/mL)</li> <li>• 45 mg dose in a 2 mL vial containing 1 mL of solution (45 mg/mL)</li> </ul> |
| <b>Sponsor</b>                                             | Hoffmann-La Roche Limited                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Health Canada indication</b>                            | <ul style="list-style-type: none"> <li>• <b>Mosunetuzumab IV:</b> As monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (grades 1 to 3a) who have received at least 2 prior lines of systemic therapy</li> <li>• <b>Mosunetuzumab SC:</b> Same as mosunetuzumab IV</li> </ul>                                                                                                                                                                                                                                  |
| <b>Health Canada approval status</b>                       | <ul style="list-style-type: none"> <li>• <b>Mosunetuzumab IV:</b> NOC/c</li> <li>• <b>Mosunetuzumab SC:</b> NOC/c</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Health Canada review pathway</b>                        | Advance consideration under NOC/c                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>NOC/c or NOC date</b>                                   | <ul style="list-style-type: none"> <li>• <b>Mosunetuzumab IV:</b> February 6, 2026 (NOC/c)</li> <li>• <b>Mosunetuzumab SC:</b> April 10, 2026 (NOC/c)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                            |

| Item                                     | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mechanism of action</b>               | A bispecific antibody inducing T-cell–mediated B-cell lysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Recommended dose</b>                  | <p><b>Mosunetuzumab IV administration</b></p> <p>1 mg, 2 mg, 30 mg, and 60 mg, according to cycles and the following:</p> <ul style="list-style-type: none"> <li>• Cycle 1, day 1: 1 mg</li> <li>• Cycle 1, day 8: 2 mg</li> <li>• Cycle 1, day 15: 60 mg</li> <li>• Cycle 2, day 1: 60 mg</li> <li>• Cycle 3 to cycle 8 if in CR (or to cycle 17 if stable disease or PR), day 1: 30 mg</li> </ul> <p><b>Mosunetuzumab SC administration</b></p> <p>5 mg and 45 mg, according to cycles and the following:</p> <ul style="list-style-type: none"> <li>• Cycle 1, day 1: 5 mg</li> <li>• Cycle 1, day 8: 45 mg</li> <li>• Cycle 1, day 15: 45 mg</li> <li>• Cycle 2 to cycle 8 if in CR (or to cycle 17 if stable disease or PR), day 1: 45 mg</li> </ul>                                                                                                              |
| <b>Submission type</b>                   | Initial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Sponsor's reimbursement request</b>   | Per indication                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Submitted price</b>                   | <p>\$1,518.70 per 5 mg SC</p> <p>\$411.00 per 1 mg solution for IV infusion</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Information on the CDA-AMC review</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Review type</b>                       | Standard                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Clinical review focus<sup>a</sup></b> | <p>Population: as defined in the Health Canada indication</p> <p>Subgroups: none identified for inclusion in the report</p> <p>Intervention: per recommended dosage</p> <p>Comparators:</p> <ul style="list-style-type: none"> <li>• Chemoimmunotherapy: rituximab plus bendamustine, R-CHOP, R-CVP, obinutuzumab<sup>b</sup> plus bendamustine</li> <li>• Targeted therapies: idelalisib<sup>b</sup></li> <li>• Immunomodulatory: rituximab, rituximab plus lenalidomide</li> <li>• CAR T-cell therapies: axicabtagene ciloleucel,<sup>b</sup> tisagenlecleucel<sup>b</sup></li> </ul> <p>Outcomes: OS, PFS, CRR, ORR, DOR, DOCR, time to next treatment, HRQoL (measured via the EORTC QLQ-C30, FACT-Lym subscale), standard harms outcomes (AEs, SAEs, grade 3 or higher AEs, WDAEs, deaths), and notable harms outcomes (CRS, neutropenia, and neurologic AEs)</p> |

AE = adverse event; CAR = chimeric antigen receptor; CDA-AMC = Canada's Drug Agency; CR = complete response; CRR = complete response rate; CRS = cytokine release syndrome; DOCR = duration of complete response; DOR = duration of response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; HRQoL = health-related quality of life; NOC = Notice of Compliance; NOC/c = Notice of Compliance with conditions; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, and prednisone; SAE = serious adverse event; SC = subcutaneous; WDAE = withdrawal due to adverse event.

<sup>a</sup>The Economic Review aligns with the scope of the Clinical Review, unless otherwise stated.

<sup>b</sup>CDA-AMC has previously issued a reimbursement recommendation for this drug for the same indication or a similar indication.

## Submission History for the Drug Under Review

CDA-AMC has not previously reviewed mosunetuzumab administered via IV or SC routes through the Reimbursement Review process.

## Sources of Information

The contents of the Reimbursement Review report are informed by materials submitted by the sponsor, input received from interested parties (patient groups, clinician groups, and drug programs), and input from clinical experts consulted for this review.

Calls for patient group and clinician group input are issued for each Reimbursement Review. One patient group submission from Lymphoma Canada and 3 clinician group submissions from the Lymphoma and Leukemia Society of Canada Nurses Network, the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee, and Lymphoma Canada were received. Lymphoma Canada collected patient input through an anonymous online survey distributed nationally via email and social media between October 30, 2025, and November 28, 2025. A total of 79 patients with FL responded to the survey. The Nurses Network gathered input through individual interviews and written feedback from oncology nurses working in cancer centres across Canada. The Lymphoma Canada Clinician Group collected input via email feedback from 4 hematology experts across Canada. The Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee gathered clinician input through email consultation with committee members. The full submissions received are available in the Patient and Clinician Group Input document on the [project landing page](#). The drug programs provide input on each drug being reviewed through the reimbursement review process by identifying issues that may affect their ability to implement a recommendation.

Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical and economic evidence. Relevant patient and clinician group input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections of this report.

Each review team includes at least 1 clinical expert with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two clinical specialists with expertise in the diagnosis and management of r/r FL, 1 each from Alberta and Ontario, participated in this review.

## Disease Background

FL is a systemic malignancy of lymphoid tissue characterized by germinal centre B-cell differentiation.<sup>1</sup> It is the most common form of indolent non-Hodgkin lymphoma (NHL) and is characterized by slow-progressing disease, common relapse, and untreated survival measured in years.<sup>2,3</sup> Patients with FL most commonly present with painless peripheral adenopathy, often with widespread but asymptomatic disease at diagnosis; systemic B symptoms such as fever, night sweats, or weight loss occur in a minority (approximately 20%) of patients.<sup>3</sup> FL is most commonly associated with the t(14;18) chromosomal translocation, resulting in *BCL2* overexpression. However, such translocation is not specific to FL.<sup>3,4</sup>

Between 1992 and 2010, approximately 22,625 patients were diagnosed with FL.<sup>2</sup> The age-standardized incidence rate of this malignancy in Canada was estimated to be 38.3 cases per million persons per year.<sup>2</sup> The age-standardized mortality rate for FL during this time period was 1.3 cases per million individuals per year.<sup>2</sup> Geographic analysis showed that Prince Edward Island, New Brunswick, Nova Scotia, and Manitoba had the highest incidence rates ( $\leq 47.6$  cases per million per year), and Nova Scotia and Quebec had the highest mortality rates in Canada ( $\leq 1.78$  deaths per million per year).<sup>2</sup> There is variation in FL incidence across Canada, potentially coinciding with regions with high levels of herbicide use, primary mining activity, and manufacturing activity.<sup>2</sup>

More recent estimates suggest that NHL is the fifth most commonly diagnosed cancer in Canada, accounting for approximately 4% of new cancers in females and 5% in males, with FL representing an estimated 20% to 30% of NHL cases.<sup>2,5</sup>

Input from 79 patients with FL described experiencing fatigue (47%), enlarged lymph nodes (34%), abdominal pain and/or indigestion (32%), night sweats (25%), and bodily aches and pains (22%). Survey respondents also reported a substantial impact on quality of life (QoL) at diagnosis. Psychological and practical effects were also common, including stress (73%) and anxiety (73%) related to diagnosis and disease uncertainty (including watch-and-wait management), fear of progression (62%), difficulty sleeping (51%), frequent health care visits (33%), and reduced ability to carry out daily activities (30%).

## Current Management

### Treatment Goals

Patients identified longer survival, durable disease and symptom control, longer remission, improved QoL, and fewer side effects as the most important treatment outcomes. Patients also emphasized the importance of having treatment choice, predictable benefits, and therapies that balance effectiveness with tolerability to minimize treatment burden and preserve daily functioning.

The clinical experts consulted for this review noted that the primary goals for FL (an incurable, chronic disease) are to induce remission, prevent or delay relapse, prolong survival, mitigate toxicity, and improve QoL. They highlighted the need for effective, well-tolerated, chemotherapy-free options that reduce clinic visits and treatment burden, particularly for patients who are older or have frailty. This aligns with input from clinician groups, who emphasized achieving durable disease control, delaying progression, and preserving QoL while minimizing treatment-related toxicity. Both noted that important outcomes include symptom improvement, maintenance of daily functioning, minimizing repeated exposure to chemotherapy, and access to outpatient therapies with manageable administration and monitoring requirements.

### Current Treatment Options

In Canada, patients with asymptomatic, low-burden r/r FL may be managed with observation. Localized palliative radiotherapy is an option for selected cases. Chemoimmunotherapy remains widely used in the form of regimens such as rituximab plus bendamustine; obinutuzumab plus bendamustine; rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; rituximab, cyclophosphamide, vincristine, and prednisone

(R-CVP); or obinutuzumab, cyclophosphamide, vincristine, and prednisone, although the clinical experts consulted for this review noted that response rates decline and cumulative toxicities, including cytopenias, infections, and secondary malignancies, increase with each relapse.<sup>6,7</sup> The clinician groups agreed that repeated chemotherapy introduces acute and long-term complications and becomes less effective over time. Autologous stem cell transplant may be considered for younger patients who are eligible for transplant, particularly in second-line settings with an increased risk for disease (e.g., progression of disease within 24 months [POD24]), while allogeneic transplant is reserved for highly selected multiple-relapse cases due to mortality risks unrelated to disease relapse.<sup>6,8,9</sup> Targeted and immunomodulatory options include rituximab plus lenalidomide, which is not universally funded in Canada, and zanubrutinib plus obinutuzumab, which has been approved by Health Canada but is not reimbursed nationally; tazemetostat has not been submitted for approval in Canada and idelalisib is rarely used because of toxicity concerns.<sup>10-17</sup> Chimeric antigen receptor (CAR) T-cell therapies such as axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are funded for use as a third-line or later treatment and provide durable responses, but they require specialized centres and pose logistical, toxicity, and equity challenges because of age, comorbidity, and geographic barriers.<sup>18,19</sup> The clinician groups emphasized that these access limitations leave many patients without funded novel options outside clinical trials. Emerging bispecific antibodies, such as mosunetuzumab, are expected to address some gaps by providing a chemotherapy-free, fixed-duration therapy deliverable in outpatient settings.<sup>20,21</sup> Supportive care measures, including transfusions, infection prophylaxis, and psychosocial support, remain integral to managing treatment burden and maintaining QoL.

Key characteristics of mosunetuzumab (IV and SC) are summarized, along with other treatments available for r/r FL in the Supplemental Material document available on the [project landing page](#), in Appendix 1, Table 1.

## Unmet Needs and Existing Challenges

Patients with FL reported ongoing unmet needs due to limited and declining treatment options in later lines of therapy, with decreasing satisfaction as disease progresses. Existing challenges include treatment-related side effects, cumulative treatment burden, travel and access barriers (particularly for patients living far from cancer centres), and lack of availability of certain therapies in Canada.

The clinical experts consulted for this review emphasized that patients with r/r FL typically experience multiple relapses requiring successive treatments. They noted that with each line of chemoimmunotherapy, the lymphoma becomes more resistant to cytotoxic drugs, resulting in lower response rates, shorter remission durations, and higher cumulative toxicities, including cytopenias, infections, and immunosuppression. The clinical experts pointed out that novel, non-cross-resistant treatments, such as treatments that target oncogenic driver pathways or that harness the immune system, are required. The clinical experts indicated that CAR T-cell therapy is available as a third-line option but is associated with serious risks and logistical barriers, and many patients are ineligible due to age, comorbidities, frailty, or geographic constraints. Consequently, there is a critical need for effective, well-tolerated, chemotherapy-free, time-limited therapies that can be administered conveniently in outpatient settings. Additional unmet needs include better second-line options to prolong remission, strategies for patients with early progression

(POD24), and treatments that minimize clinic visits for patients who are older or have frailty. Equity concerns were noted, as structural barriers such as distance from tertiary centres and socioeconomic factors disproportionately affect access for marginalized populations.

Clinician group input aligned with these observations and highlighted persistent gaps in later lines of therapy due to limited durability of response and cumulative toxicities. They stressed the lack of a publicly funded, fixed-duration, systemic therapy for outpatients that offers durable disease control while preserving QoL. Although CAR T-cell therapy exists, only a subset of patients can realistically access it due to age, comorbidity, manufacturing delays, and centre capacity, leaving many patients — particularly those in rural or remote areas — without funded novel options outside clinical trials. The clinicians also described substantial treatment burden with current regimens, including frequent visits to specialized centres, long times in treatment chairs, complex monitoring, and associated financial and psychosocial strain. They identified an urgent need for better-tolerated, chemotherapy-sparing treatments with predictable safety profiles and flexible outpatient delivery, ideally suitable for community oncology settings to make access to care more equitable and to reduce overall burden.

## Considerations for Using the Drug Under Review

The contents in this section have been informed by input from the clinical experts consulted for the purpose of this review and from clinician groups, as well as the reimbursement conditions proposed by the sponsor (refer to the Supplemental Material document available on the [project landing page](#), Appendix 1, Table 2). The implementation questions from the public drug programs and corresponding responses from the clinical experts consulted for this review are summarized in the Supplemental Material document, Appendix 1, Table 3. The following has been summarized by the review team.

### Place in Therapy

The clinical experts consulted for this review noted that mosunetuzumab would primarily be used as a third-line or later treatment for adults with r/r FL (grades 1 to 3a) who have received at least 2 prior lines of systemic therapy. They indicated that it would likely replace chemoimmunotherapy and rituximab plus lenalidomide in this setting due to its favourable efficacy, safety profile, and chemotherapy-free mechanism of action. The clinical experts indicated that mosunetuzumab is considered suitable for most patients, particularly those who are older, have comorbidities, or prefer outpatient therapy with lower toxicity. They highlighted its role as an alternative for patients who are ineligible for CAR T-cell therapy or require a rapidly available option, and as a potential bridge or subsequent therapy for patients whose disease relapses after CAR T-cell treatment.

The clinician groups anticipated similar use, noting that mosunetuzumab is a single-drug, off-the-shelf CD20×CD3 T-cell engager administered with step-up dosing and fixed-duration outpatient treatment. They emphasized its role primarily as a third-line or later treatment, especially for patients who have progressed after anti-CD20–based chemoimmunotherapy or who have limited tolerance for additional chemotherapy. The clinician groups noted that mosunetuzumab may offer an outpatient alternative that does not require leukapheresis or cell manufacturing, making it more accessible for patients who are ineligible for, unable to

access, or decline CAR T-cell therapy. Overall, clinician groups expected mosunetuzumab to expand the number of later-line options and address a significant unmet need in clinical practice in Canada.

### ***Patient Population***

The clinical experts noted that mosunetuzumab is intended for adults with r/r FL (grades 1 to 3a) who have received at least 2 prior lines of systemic therapy, including an anti-CD20 antibody and an alkylating agent. According to the clinical experts, patients most in need are those with early progression (POD24), heavily pretreated disease, short remission durations, or intolerance to chemotherapy. These patients can be identified through clinical history, Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores, and standard diagnostic tools such as imaging and biopsy. The clinical experts noted that no companion diagnostic is required, as most patients express the CD20 antigen, and a biopsy is not always safe or feasible. Diagnosis relies on routine pathology and imaging, which are widely available in Canada, although access may be more challenging in rural areas.

The clinical experts agreed with the sponsor's proposed initiation criteria (e.g., grade 1 to 3a FL,  $\geq 2$  prior regimens including anti-CD20 and alkylator agents, and ECOG PS scores of 0 or 1) as appropriate and feasible, but they noted that treatment may also be reasonable for selected patients with ECOG PS scores of 2 or 3 when decline is disease-related and thought to improve with treatment. The clinical experts pointed out that treatment should generally be initiated in patients who have symptoms or increased tumour burden. They noted that patients least suitable for treatment with mosunetuzumab include those unable to attend monitoring visits, or those who have transformed FL, grade 3b disease, uncontrolled infection, or poor prognosis due to severe comorbidities. Ethical and equity considerations include ensuring access for patients in remote regions and minimizing travel burdens through community-based administration where possible.

### **Assessing the Response to Treatment**

The sponsor did not propose a renewal condition, and the clinical experts consulted for this review agreed that formal renewal criteria are not necessary because mosunetuzumab is administered as a fixed-duration regimen of 8 or 17 cycles. The clinical experts noted that response should be assessed using imaging (CT or PET) after 8 cycles and again at the end of therapy, consistent with trial practice and routine standards in Canada. Interim imaging before the end of cycle 8 is recommended to determine whether treatment should stop at 8 cycles for complete responders or continue to 17 cycles for partial responders. The clinical experts indicated that these assessments align with clinical practice in Canada and are feasible to implement.

The clinical experts noted that a clinically meaningful response is defined as achieving a partial response (PR) or complete response (CR) according to Lugano criteria, typically associated with symptom improvement and reduction in disease burden. Minimum response for continuation is evidence of a clinical benefit without progression. They noted that stable disease may be acceptable as a clinical benefit. According to the clinical experts, timing of assessment in the trial (after cycle 8 and after cycle 17) reflects standard follow-up and would not pose challenges in clinical practice in Canada. Routine imaging after treatment completion is not required; follow-up should be symptom-driven. Frequency of assessment should follow physician discretion, with imaging at interim and end-of-treatment points.

## Discontinuing Treatment

The clinical experts noted that mosunetuzumab should be discontinued upon completion of the planned fixed-duration course of 8 or 17 cycles, or earlier in cases of disease progression or unacceptable toxicity. The sponsor proposed discontinuation criteria of documented disease progression or relapse, initiation of new anticancer therapy, and unacceptable toxicity, consistent with the study protocol. The clinical experts agreed that these conditions are appropriate and straightforward to implement in practice. They emphasized that re-treatment may be considered for patients who previously achieved a disease response and tolerated therapy well, provided there was a meaningful treatment-free interval (ideally at least 6 months in length and preferably closer to 12 months). According to the clinical experts, decisions should remain individualized, considering clinical status and alternative options.

## Prescribing Considerations

The clinical experts also noted that diagnosis, prescribing, and administration of mosunetuzumab should be managed by hematologists or oncologists experienced in bispecific antibodies and their toxicities. They agreed that corticosteroid premedication during early cycles is appropriate and can be easily implemented. The clinical experts noted that no additional restrictions on dosage or frequency were recommended beyond the fixed-duration regimen used in trials, and use in combination with other systemic therapies is not supported outside clinical studies. The clinical experts noted that mosunetuzumab can be administered in outpatient clinics or community cancer centres equipped to manage cytokine release syndrome (CRS) and related adverse events (AEs). They highlighted that potential regional variation in specialist access should be considered, and they emphasized the need for training additional staff and having more centres to improve equity. Ethical considerations should also include ensuring equitable access and minimizing patient burden by enabling treatment closer to home.

# Clinical Review

## Methods

The review team considered studies in the sponsor's systematic review (pivotal studies), sponsor-submitted long-term extension study results, indirect treatment comparisons (ITCs), and studies addressing gaps in the evidence for inclusion. Eligible studies for the systematic review included published and unpublished pivotal studies and phase III and IV randomized controlled trials (RCTs), or other designs as relevant. Relevant patients and interventions were defined by the indication and the recommended dosing in the product monograph. CDA-AMC did not identify any subgroups as potentially important for informing the reimbursement recommendation. Relevant comparators were drugs and nondrug treatments used in clinical practice in Canada to treat patients described in the indication under review. These treatments included rituximab monotherapy; rituximab plus bendamustine; R-CHOP; rituximab plus lenalidomide; R-CVP; obinutuzumab plus bendamustine; idelalisib; axi-cel; and tisa-cel. ITCs submitted by the sponsor were included.

The review team selected outcomes and follow-up times for review considering the sponsor's summary of clinical evidence, clinical expert input, and patient and clinician group input. Included outcomes are those considered relevant to expert committee deliberations, and they were selected in consultation with committee members. Evidence from the systematic review for the most important outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.<sup>22,23</sup> The following outcomes were assessed using GRADE because they address important treatment goals for r/r FL and are considered important to patients according to patient and clinician input:

- overall survival (OS)
- progression-free survival (PFS)
- complete response rate (CRR)
- duration of complete response (DOCR)
- overall response rate (ORR)
- duration of response (DOR)
- time to next treatment (TTNT)
- health-related quality of life (HRQoL) assessed with the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) subscale
- grade 3 or higher AEs (excluding grade 5 progressive disease)
- grade 5 (fatal) AEs.

Methods for data extraction, risk of bias appraisal, and certainty of evidence assessment are provided in the Supplemental Material document in Appendix 2.

## Clinical Evidence

In this report, the following sources of evidence submitted by the sponsor are reviewed and appraised:

- 1 pivotal study included in the systematic review (the GO29781 study)
- 1 ITC submission comprising 3 matching-adjusted indirect comparisons (MAICs) for 3 comparators and 4 propensity score analyses (PSAs, for 2 comparators).

## Systematic Review

### *Description of Studies*

#### Study Characteristics

The characteristics of the included study are summarized in [Table 2](#). Details pertaining to the eligibility criteria, interventions and comparators, and relevant outcome measures are provided in the Supplemental Material document, Appendix 3.

The GO29781 study included separate IV and SC cohorts to address different objectives. The GO29781 study was a phase I(Ib) and II, multicentre, open-label trial with dose-escalation and expansion phases that evaluated mosunetuzumab as monotherapy and in combination with atezolizumab in patients with r/r B-cell NHL and chronic lymphocytic leukemia. Two cohorts from the GO29781 study form the primary focus of

this report: the mosunetuzumab IV monotherapy B11 expansion r/r FL cohort treated at the recommended phase II dose (RP2D) of 1.0 mg, 2.0 mg, and 60.0 mg, with 30.0 mg from cycles 3 and later, and the mosunetuzumab SC monotherapy F2 expansion r/r FL cohort treated at the RP2D (5.0 mg, 45.0 mg, and 45.0 mg). These are hereafter referred to as the IV cohort and the SC cohort, respectively.

The pivotal IV cohort (B11 expansion r/r FL cohort in the GO29781 study) enrolled 90 adults with histologically confirmed FL (grades 1 to 3a), ECOG PS scores of 0 or 1, and a disease refractory to 2 or more prior lines of systemic therapy, including an anti-CD20-directed therapy and an alkylating agent, across 49 sites in 7 countries (Australia, Canada, Germany, South Korea, Spain, UK, and US), including 3 centres in Canada. Patients received mosunetuzumab IV at the RP2D using a step-up regimen: cycle 1 consisted of 1 mg on day 1, followed by 2 mg on day 8, and 60 mg on day 15; the day 1 dose of cycle 2 was 60 mg, followed by 30 mg on day 1 of cycles 3 through 8, for a fixed-duration treatment of 8 cycles.<sup>24</sup>

The pivotal SC cohort (F2 expansion r/r FL cohort in the GO29781 study) enrolled 94 adults with r/r FL (grades 1 to 3a) who had received at least 2 prior lines of systemic therapy (detailed in the Supplemental Material document, Appendix 3). Patients received mosunetuzumab SC at the RP2D using a step-up regimen: cycle 1 consisted of 5 mg on day 1, followed by 45 mg on day 8, and 45 mg on day 15; and by 45 mg on day 1 of cycles 2 through 8, for a fixed-duration treatment of 8 cycles. The primary objective for the SC cohort was to evaluate pharmacokinetic noninferiority compared with the IV regimen, with additional assessments of safety and efficacy.<sup>25</sup>

Mosunetuzumab IV and SC were administered for 8 cycles, unless a patient experienced unacceptable toxicity or disease progression. For patients who achieve a CR, no further treatment beyond 8 cycles was required. Patients who achieved a PR or had stable disease in response to treatment with mosunetuzumab after 8 cycles continued to receive mosunetuzumab every 21 days for up to 17 cycles, unless a patient experienced unacceptable toxicity or disease progression. For both IV and SC cohorts, mosunetuzumab was administered in settings equipped for emergency management. Corticosteroid prophylaxis (dexamethasone or methylprednisolone) was used during early cycles and after any CRS event, with optional use of acetaminophen and antihistamines. The primary end point for mosunetuzumab IV was CRR assessed by an independent review facility (IRF), also referred to as independent review committee. The key secondary end points including investigator-assessed CRR and IRF-assessed and investigator-assessed ORR, DOR, DOCR, PFS, OS, and HRQoL. Safety was also evaluated.

**Table 2: Characteristics of Studies Included in the Systematic Review**

| Study name, design, and sample size                                                                                                                                       | Key inclusion criteria                                                                                                                                                                                                                                                                                                                             | Key exclusion criteria                                                                                                                                | Intervention and comparator                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Relevant end points                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>GO29781 study</p> <p>Phase I and II, multicentre, open-label, dose-escalation and dose-expansion study</p> <p>Total N:</p> <p>IV cohort = 90</p> <p>SC cohort = 94</p> | <ul style="list-style-type: none"> <li>• Aged 18 years or older</li> <li>• Histologically confirmed FL (grade 1 to 3a) <ul style="list-style-type: none"> <li>◦ Relapsed or refractory to 2 or more previous lines of treatment, including an anti-CD20 therapy and an alkylating agent</li> </ul> </li> <li>• ECOG PS scores of 0 to 1</li> </ul> | <p>People who are pregnant or lactating, or intending to become pregnant during the study or within 3 months after the last dose of mosunetuzumab</p> | <p>Mosunetuzumab IV was administered in 21-day cycles with cycle 1 consisting of step-up dosing:</p> <ul style="list-style-type: none"> <li>• Cycle 1: 1 mg on day 1, 2 mg on day 8, 60 mg on day 15</li> <li>• Cycle 2: 60 mg on day 1</li> <li>• Cycle 3 and onward: 30 mg on day 1</li> </ul> <p>Results of the IV cohort were compared to a historical control<sup>a</sup></p> <p>Mosunetuzumab SC was administered in 21-day cycles with cycle 1 consisting of step-up dosing:</p> <ul style="list-style-type: none"> <li>• Cycle 1: 5 mg on day 1, 45 mg on day 8, 45 mg on day 15</li> <li>• Cycle 2 and onward: 45 mg on day 1</li> </ul> <p>Results of the SC cohort were compared to the IV cohort of interest to assess noninferiority.</p> | <p><b>Primary:</b></p> <ul style="list-style-type: none"> <li>• CRR by IRF</li> </ul> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>• ORR by IRF and by investigator</li> <li>• DOR</li> <li>• DOCR</li> <li>• PFS</li> <li>• OS</li> <li>• HRQoL (EORTC QLQ-C30, FACT-Lym subscale, EQ-5D-5L)</li> </ul> <p><b>Exploratory:</b></p> <ul style="list-style-type: none"> <li>• Time to next treatment</li> </ul> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>• AEs</li> <li>• SAEs</li> <li>• AESIs</li> </ul> |

AE = adverse event; AESI = adverse event of special interest; CRR = complete response rate; DOCR = duration of complete response; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; FL = follicular lymphoma; HRQoL = health-related quality of life; IRF = independent review facility; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse event; SC = subcutaneous.

<sup>a</sup>This analysis was conducted for the primary end point alone.

Source: Sponsor's submissions.<sup>25,26</sup> Details included in the table are from the sponsor's summary of clinical evidence.

## Statistical Testing and Analysis Populations

Primary end point testing for the pivotal IV cohort used an exact binomial test at a 2-sided alpha of 5% and only the primary end point was controlled for type I error.<sup>27</sup> Secondary end points, including investigator-assessed CRR, ORR, and time-to-event outcomes, were summarized using Kaplan-Meier (KM) methods with Brookmeyer-Crowley confidence intervals (CIs) for medians and Greenwood's formula for pointwise CIs; these analyses were descriptive and did not employ multiplicity adjustment. For the IV cohort, the study was powered on the IRF-assessed CR rate with a 2-sided significance level of 5%, an assumed historical control CRR of 14% informed by single-arm trials of copanlisib and idelalisib, and an expected treatment effect of a 14% increase to 28%.<sup>27-30</sup> The dose-expansion stage targeted approximately 80 patients and was based on the total number of participants rather than an event-driven design; this sample size yields exact Clopper-Pearson 95% CIs that rule out a true CRR of 14% and provides approximately 83% power to detect the prespecified increase at a 2-sided alpha level of 5%.<sup>27</sup> For the planned analyses, more than 80 patients could be enrolled to ensure at least 60 patients whose disease was refractory to both anti-CD20 therapy and an alkylating agent.<sup>24,27</sup> Under the umbrella protocol, each expansion cohort was considered an independent trial for hypothesis testing and there was no hierarchical testing across cohorts. The efficacy-evaluable population comprised all enrolled patients and was used for efficacy analyses except for the analyses of patient-reported outcomes. The safety analysis population included all patients who received at least 1 dose, and the patient-reported outcome—evaluable population included all enrolled patients with a baseline and at least 1 postbaseline assessment.<sup>27</sup>

For the SC cohort, the primary statistical objective was pharmacokinetic noninferiority to the IV regimen based on 2 coprimary end points, the observed cycle 3 serum trough concentration, and the area under the concentration-time curve over 0 to 84 days. Noninferiority required that the lower bound of the 90% CI for the geometric mean ratio of SC versus IV be greater than or equal to 0.8 for both end points, each tested at a 1-sided type I error rate of 5%. Sample size planning used simulations under a population pharmacokinetic model with projected geometric mean ratios of approximately 1.06 for the area under the concentration-time curve over 0 to 84 days and 1.57 for cycle 3 serum trough and a coefficient of variation of 50%, indicating that about 36 patients would provide 80% power; the enrolled population of approximately 64 patients was expected to provide sufficient power for the pharmacokinetic noninferiority analyses.<sup>24,31</sup> Retrospective efficacy comparisons of SC versus IV were descriptive and exploratory without formal hypothesis testing and used multivariate regression and inverse probability-weighted propensity score methods to adjust for baseline imbalances; analyses adhered to the intention-to-treat principle without weight trimming and included sensitivity analyses by baseline CD20 expression.<sup>31-33</sup> The efficacy-evaluable and safety analysis populations were defined as in the IV cohort.<sup>31</sup>

In the sections that follow — Patient Disposition, Baseline Characteristics, and Treatment Exposure and Concomitant Medications — data for the IV cohort are reported for the clinical cut-off date (CCOD) of August 27, 2021, and data for the SC cohort are reported for the CCOD of February 1, 2024.

## Patient Disposition

Patient disposition for the GO29781 study is summarized in the Supplemental Material document, Appendix 4.

- **IV cohort:** Ninety patients were enrolled in the pivotal IV cohort and received mosunetuzumab IV at the RP2D (1 mg on cycle 1 day 1, 2 mg on day 8, 60 mg on day 15, followed by 60 mg on cycle 2 day 1 and 30 mg on day 1 of cycles 3 to 8 [or up to cycle 17]). At the August 2021 data cut-off, all patients had either completed or discontinued their initial treatment, with 54 patients (60.0%) completing treatment and 36 patients (40.0%) discontinuing. The most common reason for discontinuation was progressive disease (25 patients [27.8%]), followed by AEs (4 patients [4.4%]) and physician decision (4 patients [4.4%]). Re-treatment was permitted for patients who achieved a CR and later relapsed.
- **SC cohort:** In the pivotal SC cohort, 94 patients were enrolled and received mosunetuzumab SC at the RP2D (cycle 1: 5 mg on day 1, 45 mg on days 8 and 15; cycle 2 day 1: 45 mg; cycles 3 to 8 [or up to cycle 17] day 1: 45 mg). At the February 2024 cut-off, 59 patients (62.8%) had completed initial treatment and 34 patients (36.2%) had discontinued, most commonly due to progressive disease (22 patients [23.4%]), followed by AEs and death (each 4.3%). Five patients received re-treatment and were active at that cut-off point.

In both the IV and SC cohorts, no major protocol deviations affecting patient disposition were noted.

## Baseline Characteristics

A summary of key baseline patient characteristics in the GO29781 study is presented in [Table 3](#).

In the IV cohort (N = 90), patients had a median age of 60 years, with a lower proportion of females (39%) than males (61%). In terms of race, there were smaller proportions of patients who were American Indian or Alaska Native (1%), Asian (9%), or Black or African American (4%) than were white (82%), and a small proportion were of unknown race (3%) [wording of original source]. At baseline, 59% of patients had an ECOG PS score of 0 and 41% had an ECOG PS score of 1. Most had advanced disease (77% with Ann Arbor stage III or IV disease and 44% with a Follicular Lymphoma International Prognostic Index [FLIPI] score  $\geq 3$ ). The median number of prior therapies was 3. The most common prior treatments included anti-CD20 agents (100%), alkylating agents (100%), PI3K inhibitors (19%), and immunomodulatory imide drugs (14%). Refractoriness was common, with 69% of patients whose disease was refractory to the last therapy, 79% refractory to anti-CD20 therapy, and 53% double-refractory; 52% reporting POD24.

Baseline characteristics in the SC cohort (N = 94) were generally similar to those in the IV cohort. In the SC cohort, patients had a median age of 65 years, with a higher proportion of males (56%) than females (44%). Most were Asian (11%) or white (85%), with few from other groups. At baseline, 67% of patients had an ECOG PS score of 0 and 33% had an ECOG PS score of 1. Most had advanced disease (87% Ann Arbor stage III or IV; 56% FLIPI score  $\geq 3$ ). The median number of prior therapies was 3. The most common prior treatments included anti-CD20 agents (100%), alkylating agents (100%), immunomodulatory imide drugs (27%), and PI3K inhibitors (12%). Refractoriness was common, with 63% refractory to the last therapy, 67% refractory to anti-CD20 therapy, and 46% double-refractory; 44% had POD24.

**Table 3: Summary of Key Baseline Characteristics From the GO29781 Study**

| Characteristic                                                             | Mosunetuzumab IV<br>(N = 90)<br>CCOD: August 27, 2021 | Mosunetuzumab SC<br>(N = 94)<br>CCOD: February 1, 2024 |
|----------------------------------------------------------------------------|-------------------------------------------------------|--------------------------------------------------------|
| <b>Demographic characteristics</b>                                         |                                                       |                                                        |
| <b>Age, years</b>                                                          |                                                       |                                                        |
| Mean (SD)                                                                  | 60.0 (12.0)                                           | 64.5 (9.8)                                             |
| Median (range)                                                             | 60 (29 to 90)                                         | 65 (35 to 84)                                          |
| <b>Sex, n (%)</b>                                                          |                                                       |                                                        |
| Female                                                                     | 35 (38.9)                                             | 41 (43.6)                                              |
| Male                                                                       | 55 (61.1)                                             | 53 (56.4)                                              |
| <b>Race, n (%)<sup>a</sup></b>                                             |                                                       |                                                        |
| American Indian or Alaska Native                                           | 1 (1.1)                                               | 0                                                      |
| Asian                                                                      | 8 (8.9)                                               | 10 (10.6)                                              |
| Black or African American                                                  | 4 (4.4)                                               | 2 (2.1)                                                |
| Native Hawaiian or other Pacific Islander                                  | 0                                                     | 1 (1.1)                                                |
| White                                                                      | 74 (82.2)                                             | 80 (85.1)                                              |
| Unknown                                                                    | 3 (3.3)                                               | 1 (1.1)                                                |
| <b>Disease characteristics</b>                                             |                                                       |                                                        |
| <b>ECOG PS at baseline, n (%)</b>                                          |                                                       |                                                        |
| 0                                                                          | 53 (58.9)                                             | 63 (67.0)                                              |
| 1                                                                          | 37 (41.1)                                             | 31 (33.0)                                              |
| <b>Time from initial diagnosis to study entry (months), median (range)</b> | 82.2 (11 to 292)                                      | 95.1 (15 to 424)                                       |
| <b>Ann Arbor stage of III or IV, n (%)</b>                                 | 69 (76.7)                                             | 82 (87.2)                                              |
| <b>Bulky disease (&gt; 6 cm), n (%)</b>                                    | 31 (34.4)                                             | 23 (24.5)                                              |
| <b>SPD (mm<sup>2</sup>), median (range)</b>                                | 3,014 (234 to 15,799)                                 | 2,560.3 (176 to 19,676)                                |
| <b>FLIPI score ≥ 3 (high risk), n (%)</b>                                  | 40 (44.4)                                             | 53 (56.4)                                              |
| <b>Number of prior lines of antilymphoma therapies, n (%)</b>              |                                                       |                                                        |
| 1                                                                          | 0                                                     | 0                                                      |
| 2                                                                          | 34 (37.8)                                             | 44 (46.8)                                              |
| 3                                                                          | 28 (31.1)                                             | 18 (19.1)                                              |
| > 3                                                                        | 28 (31.1)                                             | 32 (34.0)                                              |
| Median number (range)                                                      | 3 (2 to 10)                                           | 3 (2 to 9)                                             |
| <b>Prior cancer therapies, n (%)</b>                                       |                                                       |                                                        |
| Anti-CD20                                                                  | 90 (100)                                              | 94 (100)                                               |

| Characteristic                                                                  | Mosunetuzumab IV<br>(N = 90)<br>CCOD: August 27, 2021 | Mosunetuzumab SC<br>(N = 94)<br>CCOD: February 1, 2024 |
|---------------------------------------------------------------------------------|-------------------------------------------------------|--------------------------------------------------------|
| Alkylator                                                                       | 90 (100)                                              | 94 (100)                                               |
| Autologous SCT                                                                  | 19 (21.1)                                             | 19 (20.2)                                              |
| PI3K inhibitor                                                                  | 17 (18.9)                                             | 11 (11.7)                                              |
| IMiD                                                                            | 13 (14.4)                                             | 25 (26.6)                                              |
| BTKi                                                                            | 6 (6.7)                                               | 6 (6.4)                                                |
| CAR T-cell                                                                      | 3 (3.3)                                               | 4 (4.3)                                                |
| <b>Refractory to last prior therapy, n (%)</b>                                  | 62 (68.9)                                             | 59 (62.8)                                              |
| <b>Refractory to any prior anti-CD20, n (%)</b>                                 | 71 (78.9)                                             | 63 (67.0)                                              |
| <b>Relapse to any prior anti-CD20, n (%)</b>                                    | 19 (21.1)                                             | 31 (33.0)                                              |
| <b>Double-refractory to prior anti-CD20 and alkylator therapies, n (%)</b>      | 48 (53.3)                                             | 43 (45.7)                                              |
| <b>POD24 (&lt; 24 months from start of first systemic therapy to PD), n (%)</b> | 47 (52.2)                                             | 41 (43.6)                                              |

BTKi = Bruton tyrosine kinase inhibitor; CAR = chimeric antigen receptor; CCOD = clinical cut-off date; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMiD = immunomodulatory imide drug; PD = progressive disease; POD24 = progression of disease within 24 months; r/r = relapsed or refractory; RP2D = recommended phase II dose; SC = subcutaneous; SCT = stem cell transplant; SD = standard deviation; SPD = sum of (tumour) product diameters.

Note: This table summarizes data from the GO29781 study for patients with r/r FL (grades 1 to 3a) who had received at least 2 prior lines of systemic therapy and were treated with mosunetuzumab monotherapy. The mosunetuzumab IV column reflects the B11 RP2D expansion cohort, and the mosunetuzumab SC column reflects the F2 RP2D expansion cohort.

\*Racial categories used in the table are as reported in the source and may not align with Canada's Drug Agency inclusive language guidelines.

Sources: GO29781 Update Interim Clinical Study Report<sup>26</sup> and GO29781 Primary Pharmacokinetics Non-Inferiority Clinical Study Report.<sup>25</sup> Details included in the table are from the sponsor's summary of clinical evidence.

## Treatment Exposure and Concomitant Medications

Details of patients' treatment exposures and use of concomitant medications in the GO29781 study are provided in the Supplemental Material document, Appendix 4.

In the IV cohort, the median number of cycles was 8 (range, 1 to 17), with 21 patients (23.3%) receiving fewer than 8 cycles, 53 patients (58.9%) receiving 8 cycles, 5 patients (5.6%) receiving 9 to 16 cycles, and 11 patients (12.2%) receiving 17 cycles. The median relative dose intensity was 98.7%, and 73 patients (81.1%) received a dose intensity of more than 90%. The median treatment duration was 4.9 months (range, 0.03 months to 13.2 months). All 90 patients in the IV cohort had at least 1 concomitant medication started after baseline, with the most commonly used (in ≥ 30% of the patients) being dexamethasone (96.7%), paracetamol (95.6%), and diphenhydramine (48.9%).

In the SC cohort, the median number of cycles received was 8 (range 1 to 17), with 21 patients (22.3%) receiving fewer than 8 cycles, 59 patients (62.8%) receiving 8 cycles, 8 patients (8.5%) receiving 9 to 16 cycles, and 6 patients (6.4%) receiving 17 cycles. The median relative dose intensity was 95.6%, and 79 patients (84.0%) received a dose intensity of more than 90%. The median treatment duration was 5 months (range, 0.5 months to 17.7 months). All 94 patients in the SC cohort had at least 1 concomitant medication

started after baseline, with the most commonly used (in  $\geq 30\%$  of the patients) being dexamethasone (98.9%), paracetamol (95.7%), and diphenhydramine (41.5%).

Overall, in the GO29781 study, patients across both dose-expansion r/r FL cohorts (IV and SC) received a median of 8 treatment cycles, corresponding to a median treatment duration of 4.9 months in each cohort, and more than 95% of patients completed all planned study doses. Patients in the SC cohort had a slightly longer median time on study (20.7 months at the CCOD of February 1, 2024) compared with those in the IV cohort (18.3 months at the CCOD of August 27, 2021). In general, the most frequent medications started after baseline in both IV and SC cohorts were standard medications for lymphoma patients who receive anticancer treatment (uric acid-reducing agents and/or hydration/electrolytes) and/or protocol-recommended premedications (corticosteroids, antipyretics, antihistamines), and/or standard treatments for AEs, including CRS, neutropenia, anemia, and infections.

## ***Critical Appraisal***

### **Internal Validity**

The GO29781 study is a single-arm, open-label, phase I(Ib) and II clinical trial, which included separate IV and SC cohorts to address different objectives. The single-arm design and lack of comparator groups are key limitations, precluding a direct assessment of comparative efficacy and safety. Interpretation of the results is limited by the lack of comparative data, as the extent to which the observed effects reflect the effects of mosunetuzumab remains unclear. RCTs are methodologically designed to minimize bias by balancing both known and unknown variables between treatment groups through randomization, allowing for a causal inference between intervention and outcomes. The sponsor is conducting a phase III, open-label, multicentre RCT in adult patients with r/r FL (grades 1 to 3a) who have received at least 1 line of systemic therapy to evaluate the efficacy and safety of mosunetuzumab plus lenalidomide compared with rituximab plus lenalidomide (the CELESTIMO trial<sup>34</sup>). However, study results from the CELESTIMO trial are not yet available because the trial is ongoing. In the current review, without a concurrent control group, observed outcomes cannot be definitively attributed to mosunetuzumab, and comparisons with other therapies rely on indirect or historical evidence. Interpretation should also consider the relatively small sample size and the relatively high proportion of patients who discontinued initial treatment (40% in the IV cohort and 36% in the SC cohort), as these factors may affect the precision and completeness of longer-term outcome assessments within the study follow-up period.

In the IV cohort, the primary efficacy end point was the CR rate assessed by an IRF. Response evaluation was based on established lymphoma response criteria and standardized imaging schedules, which supports consistency in outcome assessment. The use of an IRF reduces the risk of measurement bias, particularly in an open-label study. The reported investigator-assessed response outcomes were generally consistent with IRF-assessed findings, supporting the reliability of response assessments. The clinical experts consulted for this review indicated that investigator-assessed outcomes are common for longer-term follow-ups, particularly when IRF assessments are not available. Because of the open-label design of the trial, subjective response outcomes measures (e.g., HRQoL and patient-reported AEs) are at risk of measurement or reporting bias, although the extent and direction of this bias are unclear.

The primary efficacy analysis for the IV cohort compared the observed CR rate with a prespecified historical control rate (14%). The study was powered to detect a statistically significant improvement relative to this threshold, and the primary end point was met. The use of a historical comparator introduces important limitations arising from differences in patient populations, assessment methods, and trial design between studies, which may affect comparability. According to the sponsor, the GO29781 study was a globally focused trial for which copanlisib was a suitable comparator at the time of recruitment. However, the clinical experts consulted for this review noted that copanlisib has limited relevance and may not be a suitable comparator because it is not approved or publicly funded in Canada for the indication under review. As a result, the magnitude of treatment benefit relative to currently available therapies remains uncertain, and using a historical control rate was considered supportive evidence only. However, the consulted clinical experts confirmed that a CRR of 14% was a clinically relevant threshold, and they noted that the achieved CRRs (60.0% in the IV cohort and 58.5% in the SC cohort) are considered clinically important and likely to be valid.

The SC cohort was designed to evaluate pharmacokinetic noninferiority relative to the IV formulation based on prespecified exposure parameters. The noninferiority criteria were met, suggesting similar systemic exposure between SC and IV administration. However, the clinical experts noted that pharmacokinetic outcomes alone do not establish clinical equivalence. Efficacy (CRR, along with the other outcomes assessed by GRADE) and safety outcomes in the SC cohort were descriptive, and comparisons with the IV cohort were exploratory and based on nonrandomized data. Although statistical adjustments were performed, residual confounding cannot be excluded, and these comparisons should be interpreted cautiously.

Multiplicity was controlled for the primary end point in the IV cohort but not for secondary efficacy outcomes. Secondary and exploratory end points, including ORR, DOR, DOCR, PFS, and OS, were analyzed descriptively, and the results are considered supportive evidence only. Similarly, efficacy outcomes in the SC cohort were descriptive, and no formal hypothesis testing was performed. For both the IV and SC cohorts, the duration of follow-up was likely sufficient for assessing efficacy responses and some safety outcomes. However, the median OS had not been reached for either cohort, and the upper limit of the 95% CI for median PFS had not been reached for the IV cohort alone, suggesting that a longer follow-up duration is required to fully characterize the effects of mosunetuzumab on OS and PFS.

For both IV and SC cohorts, missing data were handled using conservative assumptions for all outcomes. Patients without documented disease response assessments were classified as nonresponders, which reduces the likelihood of overestimating treatment effects. Time-to-event outcomes were analyzed using KM methods, which are appropriate for censored data. However, estimates at later time points may be unreliable because of the small numbers of patients remaining under observation, increasing uncertainty in outcomes over time.

In the GO29781 study, step-up dosing was used during the initial cycles of mosunetuzumab to reduce the risk of CRS, and standardized premedication was administered before each dose to minimize CRS and infusion-related reactions. These measures likely contributed to consistent safety management across study

sites. The clinical experts indicated that these approaches are consistent with clinical practice and did not raise major concerns regarding the internal validity of safety findings.

Patient-reported outcomes were collected in an open-label setting, making them subjective and susceptible to potential reporting bias. By cycle 8, FACT-Lym subscale scores were available for analysis for 66% of patients enrolled in the IV cohort (59 of 90 patients) and 68% of patients in the SC cohort (64 of 94 patients), with data missing for 34% and 32% of patients, respectively. There is a risk of attrition bias, and any conclusions drawn from the subset of the population available at cycle 8 could be biased in favour of mosunetuzumab.

### External Validity

The clinical experts consulted for this review noted that the eligibility criteria for the GO29781 study were generally aligned with the population expected to receive mosunetuzumab in clinical practice. Patients were required to have r/r FL (grades 1 to 3a) after at least 2 prior lines of systemic therapy, including anti-CD20 therapy and an alkylating agent, which reflects the intended later-line use of mosunetuzumab. The clinical experts indicated that these criteria supported the study population, which is broadly representative of patients who would be eligible for treatment in clinical practice in Canada.

In the GO29781 study, patients were required to have an ECOG PS score of 0 or 1. This excludes patients with poorer functional status, who may be encountered in clinical practice. Therefore, generalizability to patients with reduced functional status remains uncertain. However, the clinical experts indicated that treatment may be considered for selected patients with an ECOG PS score of 2, although evidence in this population is limited.

Baseline disease characteristics were consistent with an advanced, heavily pretreated population, as most patients had advanced-stage lymphoma and had received multiple prior lines of therapies. The clinical experts indicated that these characteristics are reflective of patients who would be considered for mosunetuzumab in practice.

The median age of enrolled patients was approximately 60 years, and most patients were male and white. The limited representation of other racial and ethnic groups may reduce the generalizability of findings to more diverse populations. However, the clinical experts indicated that there is no clear biological rationale to expect differences in treatment effects by ethnicity.

In the GO29781 study, mosunetuzumab was administered using step-up dosing with premedication to reduce the risk of CRS, and the protocol-specified, fixed-duration treatment, with discontinuation after achieving a CR or completion of the planned treatment period. Also, re-treatment following disease progression was permitted in certain circumstances. The clinical experts indicated that this dosing approach is consistent with the product monograph and is feasible in clinical practice in Canada. Although monitoring requirements during treatment initiation may require specialized resources, the clinical experts noted that mosunetuzumab can generally be administered in outpatient settings with appropriate monitoring and supportive care, which they considered available in most oncology facilities.

The study evaluated clinically relevant efficacy outcomes, including CRR, DOCR, ORR, DOR, PFS, and OS. The clinical experts commented that these outcomes are commonly used in clinical trials and are considered meaningful in the management of FL. However, they also pointed out that the duration of follow-up remains limited relative to the typically indolent course of the disease. The evidence in this report is primarily based on the sponsor-suggested data cut-off points, which provided median follow-up durations of 15 to 22 months for key efficacy outcomes across the IV and SC cohorts. These correspond to the updated interim analysis for the IV cohort and the primary analysis for the SC cohort, and full clinical study reports were available. This evidence is aligned with the data submitted to Health Canada. In addition, 3-year and 4-year outcomes for the IV cohort were included in the results section of this review when available. The clinical experts consulted by CDA-AMC interpreted the available data as showing durable responses consistent with the IV cohort's updated interim analysis results. For the SC cohort, efficacy and safety outcomes were available only for a follow-up period of less than 2 years. The clinical experts also emphasized that longer-term follow-up is needed to fully characterize the durability of response and long-term safety.

The study was conducted across multiple countries, including Canada, supporting generalizability to clinical settings in Canada. The clinical efficacy outcomes in the SC cohort appeared to be comparable to those of the IV formulation, and the clinical experts noted that SC administration may offer practical advantages, including greater convenience. However, the efficacy comparisons between the IV and SC formulations were exploratory.

## Results

The key efficacy and harms results and findings from the GRADE assessment are presented in this section. For the IV cohort, results are reported for the CCOD of August 27, 2021 (updated interim analysis), and for the SC cohort, results are reported for the CCOD of February 1, 2024. Additional updated results (e.g., 3-year or 4-year outcomes available for some investigator-assessed outcomes for the IV cohort) are also included. Detailed efficacy and harms results can be found in the Supplemental Material document, Appendix 4.

### Efficacy

Key efficacy results include the following.

- **IV cohort:** At the CCOD of August 27, 2021, the median observation time for patients in the IV cohort (i.e., median time on study) was 18.3 months (range, 2.0 months to 27.5 months), which was applicable for outcomes of CRR and ORR. Median follow-up durations for OS, PFS, DOCR, TTNT, and FACT-Lym subscale were not assessed. Median follow-up duration for DOR by IRF assessment was 14.9 months (range, 0 months to 23 months; 95% CI, 13.4 months to 16.6 months).
  - **OS:** Eight of 90 patients (8.9%) had died, with a KM-estimated 12-month OS rate of 93.0% (95% CI, 87.6% to 98.4%). The median OS was not estimable (NE), with a 95% CI of NE to NE. At the 4-year analysis (CCOD: May 13, 2024), median OS remained NE and the estimated 48-month OS rate was 82.7% (95% CI, 74.7% to 90.7%).
  - **PFS:** Forty-two of 90 patients (46.7%) had an IRF-assessed PFS event (disease progression or death), with disease progression as the earliest event in all but 1 case (41 of 42). The median

- PFS was 17.9 months (95% CI, 10.1 to NE), the 12-month event-free rate was 57.7% (95% CI, 46.9% to 68.4%), and the 18-month event-free rate was 47.0% (95% CI, 34.4% to 59.6%). At the 4-year analysis (CCOD: May 13, 2024), the median investigator-assessed PFS was 24.0 months (95% CI, 12.0 to NE) and the 48-month event-free rate was 38.6% (95% CI, 27.1% to 50.2%).
- **CRR:** By IRF assessment, 54 of 90 patients achieved a CR, corresponding to a CRR of 60.0% (95% CI, 49.1% to 70.2%). The investigator-assessed CRR was also 60.0% (95% CI, 49.1% to 70.2%) and remained consistent at the 3-year and 4-year analyses (CCODs: May 2, 2023, and May 13, 2024).
  - **DOCR:** Sixteen of 54 patients (29.6%) who achieved an IRF-assessed CR subsequently experienced disease progression; the median DOCR in months was NE (95% CI, 14.6 to NE), with event-free rates (i.e., proportion of patients maintaining CR) of 71.4% (95% CI, 57.9% to 84.9%) at 12 months and 63.7% (95% CI, 48.0% to 79.4%) at 18 months. At the 4-year analysis (CCOD: May 13, 2024), the median investigator-assessed DOCR was 51.8 months (95% CI, 46.4 to NE) and the 45-month event-free rate was 64.0% (95% CI, 27.1% to 50.2%).
  - **ORR:** By IRF assessment, 72 of 90 patients achieved an overall disease response (PR or CR), corresponding to an ORR of 80.0% (95% CI 70.3% to 87.7%). The 3-year and 4-year analyses (CCODs: May 2, 2023, and May 13, 2024) reported the same (investigator-assessed) ORR of 77.8%.
  - **DOR:** Of 72 responders (PR or CR), 29 (40.3%) had disease progression or died; the KM-estimated median DOR was 22.8 months (95% CI, 9.7 to NE), although this was based on less than 10% of responders remaining at risk of experiencing an event. Event-free rates at 12 and 18 months were 61.8% (95% CI, 50.0% to 73.7%) and 56.9% (95% CI, 44.1% to 69.6%), respectively. At the 4-year analysis (CCOD: May 13, 2024), with a median study duration of 49.4 months, the median investigator-assessed DOR was 46.4 months (95% CI, 18.7 to NE) and the 45-month event-free rate was 50.1% (95% CI, 37.5% to 62.6%).
  - **TTNT:** The median time to a new antilymphoma treatment (NALT) or death was not reached at primary analysis (median time of TTNT = NE; 95% CI, 16.2 months to NE). Thirty-three of 90 patients (36.7%) had initiated NALT or died, with NALT as the earliest event in 30 cases and death in 3 cases. The 12-month event-free rate was 68.1% (95% CI, 58.3% to 77.9%). At the 3-year analysis (CCOD: May 2, 2023), median TTNT was 37.3 months (95% CI, 18.0 to NE), and the estimated 36-month TTNT rate was 51.8% (95% CI, 40.8% to 62.8%).
  - **FACT-Lym subscale score:** The mean FACT-Lym subscale score at baseline was 47.6 points (standard deviation [SD] = 8.5), based on data available for 81 of the 90 patients, indicating some burden of lymphoma-specific symptoms and concerns. The proportions of patients who achieved a clinically meaningful improvement in lymphoma symptoms (defined as a  $\geq 3$ -point increase from baseline) at cycles 2, 4, 6, and 8 were 28.4% (23 out of 81 patients), 44.0% (33 of 75), 40.9% (27 of 66), and 40.6% (26 of 64), respectively. Mean changes from baseline at cycles 2, 4, 6, and 8 were -1.0 points (SD = 7.7), 2.7 points (SD = 6.7), 2.8 points (SD = 7.4), and 1.6 points (SD = 7.5), respectively.

- **SC cohort:** At the CCOD of February 1, 2024, the median observation time for patients in the SC cohort (i.e., median time on study) was 20.7 months (range, 1 month to 34 months), which was applicable for outcomes of CRR and ORR. Median follow-up duration for OS was 21.9 months (range, 1 month to 34 months; 95% CI, 20.0 months to 23.3 months). Median follow-up duration for PFS, DOCR, TTNT, and FACT-Lym subscale were not individually assessed. Median follow-up duration for DOR by IRF assessment was 16.0 months (range, 0 months to 23 months; 95% CI, 14.8 months to 19.4 months).
  - **OS:** At the CCOD of February 1, 2024, the KM-estimated OS rates were 90.2% (95% CI, 84.1% to 96.3%) at 12 months, and 89.6% (95% CI, 82.5% to 96.6%) at 18 months. The median OS was NE (95% CI, NE to NE).
  - **PFS:** The median IRF-assessed PFS was 18.5 months (95% CI, 12.9 to 24.0 months). The 12-month PFS rate was 62.3% (95% CI, 52.1% to 72.5%). At the CCOD of July 24, 2024, the median PFS was 23.7 months (95% CI, 14.6 months to NE).
  - **CRR:** By IRF assessment, 55 of 94 patients achieved a CR, corresponding to a CRR of 58.5% (95% CI, 47.9% to 68.6%).
  - **DOCR:** The median DOCR was 20.8 months (95% CI, 18.8 months to NE) for IRF-assessed CR. The KM-estimated proportion of patients maintaining CR at 12 months was 72.4% (95% CI, 59.9% to 84.8%). At the CCOD of July 24, 2024, the median DOCR was 34.6 months (95% CI, 20.7 to NE).
  - **ORR:** The IRF-assessed ORR (PR or CR) was 74.5% (95% CI, 64.4% to 82.9%). Subgroup analyses showed that the IRF-assessed ORR was numerically lower in the 59 patients who were refractory to any last prior therapy (64%; 95% CI, 51% to 76%) compared with the 35 patients who were not refractory (91%; 95% CI, 54% to 85%). A similar pattern was observed for the characteristic of refractory to any prior anti-CD20 therapy, with an ORR of 65% (95% CI, 52% to 77%) in the 63 patients who were refractory and 94% (95% CI, 79% to 99%) in the 31 patients who were not. At the CCOD of July 24, 2024, the ORR in the SC cohort was 76.6% (72 of 94 patients).
  - **DOR:** The median IRF-assessed DOR was 22.4 months (95% CI, 16.8 to 22.8). At 12 months, 69.9% of patients (95% CI, 58.5% to 81.4%) maintained a CR or PR. At the CCOD of July 24, 2024, the median DOR was 22.8 months (95% CI, 18.8 to NE).
  - **TTNT:** The KM-estimated median time to NALT was NE (95% CI, NE to NE). Twenty-three of 94 patients (24.5%) initiated a NALT, and no deaths were reported. The 12-month event-free rate was 78.6% (95% CI, 69.8% to 87.4%) and the 18-month event-free rate was 74.3% (95% CI, 64.7% to 83.9%).
  - **FACT-Lym subscale score:** The mean FACT-Lym subscale score at baseline was 48.1 points (SD = 9.6), based on data available for 86 of the 94 patients, indicating some burden of lymphoma-specific symptoms and concerns. The proportions of patients who achieved a clinically meaningful improvement in lymphoma symptoms (defined as a  $\geq 3$ -point increase from

baseline) at cycles 2, 4, 6, and 8 were 34.5% (30 of 87 patients), 43.0% (34 of 79), 38.4% (28 of 73), and 35.2% (25 of 71), respectively. Mean changes from baseline at cycles 2, 4, 6, and 8 were 1.6 points (SD = 7.1), 2.5 points (SD = 7.3), 2.9 points (SD = 7.4), and 2.6 points (SD = 7.4), respectively. At the 3-month follow-up, the mean improvement was 3.4 points (SD = 6.7), exceeding the clinically meaningful threshold of at least 3 points.

- Sensitivity analyses were conducted to assess the potential impact of COVID-19–related deaths or treatment discontinuations (3 deaths in the SC cohort were attributed to COVID-19) for OS, PFS, CRR, DOCR, ORR, and DOR. The influence on the reported efficacy outcomes was minimal. No sensitivity analyses were conducted for TTNT or FACT-Lym subscale score.

## Harms

Key harms results include the following.

- **IV cohort (median follow-up, 7.0 months; range, 0.1 month to 16.8 months):**

- **AEs:** All 90 patients experienced an AE. The most frequently reported AEs were CRS (41 patients [45.6%]) by Lee grade,<sup>35</sup> fatigue (33 patients [36.7%]), headache (28 patients [31.1%]), pyrexia (26 patients [28.9%]), and hypophosphatemia (24 patients [26.7%]).
- **Grade 3 to 5 AEs (excluding grade 5 progressive disease):** Sixty-three patients (70.0%) experienced a grade 3 to 5 AE (excluding grade 5 progressive disease). The most common events were neutropenia (17 patients [18.9%]), and hypophosphatemia (15 patients [16.7%]).
- **Serious adverse events (SAEs):** A total of 91 SAEs were reported by 42 patients (46.7%). The most frequently occurring SAEs included CRS in 21 patients (23.3%), acute kidney injury in 3 patients (3.3%), and urinary tract infection in 3 patients (3.3%). At the CCOD of May 2, 2023, a total of 42 patients (46.7%) had experienced an SAE, of which 30 cases (33.3%) were considered related to mosunetuzumab. At the CCOD of May 13, 2024, a total of 43 patients (47.8%) had experienced an SAE.
- **Withdrawal due to AEs:** Four of 90 patients (4.4%) discontinued mosunetuzumab due to AEs. The AEs leading to discontinuation included CRS in 2 patients (2.2%), as well as Epstein-Barr viremia and Hodgkin disease in 1 patient (1.1%) each; both were considered by the investigator to be unrelated to mosunetuzumab. At the CCOD of May 2, 2023, AEs leading to discontinuation occurred in 4 patients (4.4%). No new CRS events were reported, and there were no fatal or serious events or AEs of grade 3 or 4. No evidence of chronic toxicity was observed. Commonly reported AEs of any grade included neutropenia and pyrexia, each in 26 patients (28.9%). No febrile neutropenia events were reported. As of the CCOD of May 13, 2024, the safety profile remained consistent, with no new AEs and no additional cases of discontinuation due to AEs.
- **Deaths:** Two patients (2.2%) experienced grade 5 (fatal) AEs following initial mosunetuzumab treatment. One event was disease progression (preferred term: malignant neoplasm progression), and the other was death not otherwise specified; both were assessed by the investigator as unrelated to mosunetuzumab. At the CCODs of May 2, 2023, and May 13, 2024, no new fatal AEs related to mosunetuzumab were reported.<sup>20-21</sup>

- **Adverse events of special interest (AESIs):** Forty-one of 90 patients (45.6%) experienced 76 CRS events as defined by Lee criteria, and 40 patients (44.4%) experienced 71 CRS events according to American Society for Transplantation and Cellular Therapy (ASTCT) criteria following initial mosunetuzumab treatment. Most CRS events were managed with supportive care (symptomatic management of constitutional symptoms), with or without anti–interleukin-6 or corticosteroid therapy, and all events resolved. At the CCOD of May 2, 2023, CRS according to ASTCT criteria was reported in 40 patients (44.4%). Most events were of low grade (grade 1 to 2: n = 38 [42.2%]; grade 3 to 4: n = 2 [2.2%]) and primarily occurred during cycle 1. The median time to CRS onset was 5 hours (range, 1 hour to 24 hours) on cycle 1 day 1 and 27 hours (range, 0 hours to 391 hours) on cycle 1 day 15. The median CRS duration was 3 days (range, 1 day to 29 days). For management, 4 patients (4.4%) received both corticosteroids and tocilizumab, and 3 patients (3.3%) received only tocilizumab. Details of other AESIs (neurologic AEs, neutropenia, febrile neutropenia, thrombocytopenia, anemia, hemophagocytic lymphohistiocytosis, tumour lysis syndrome, tumour flare, hepatic AEs, infections, pneumonitis or interstitial lung disease) are reported in the Supplemental Material document, Appendix 4.
- **SC cohort (median follow-up, 7.9 months; range, 1 month to 19 months):**
  - **AEs:** At the CCOD of February 1, 2024, almost all patients (98.9%) in the SC cohort experienced at least 1 AE. The most frequently reported AEs of any grade were injection site reactions (60.6%), fatigue (35.1%), CRS (30.9% by Lee criteria and 29.8% by ASTCT criteria), and diarrhea (20.2%).
  - **Grade 3 to 5 AEs (excluding grade 5 progressive disease):** Forty-nine patients (52.1%) experienced a grade 3 to 5 AE (excluding grade 5 progressive disease). The most common events were neutropenia (10 patients [10.6%]), and hypophosphatemia (5 patients [5.3%]).
  - **SAEs:** SAEs were reported in 39.4% of patients. The most frequent SAE was CRS (14.9%), pneumonia associated with COVID-19 (4.3%), malignant neoplasm progression (3.2%), and COVID-19, pyrexia, febrile neutropenia, sepsis, cytomegalovirus infection reactivation, device-related infection, general physical health deterioration, and hyperglycemia (each in 2 patients [2.1%]).
  - **Withdrawal due to AEs:** Seven of 94 patients (7.4%) discontinued mosunetuzumab due to AEs. COVID-19 pneumonia was the only AE leading to discontinuation in more than 1 patient (3.2%; 2 events of grade 5 and 1 of grade 4). Other AEs leading to discontinuation occurred in 1 patient each: COVID-19 (grade 5), general physical health deterioration (grade 5), hemophagocytic lymphohistiocytosis (grade 5), and pneumonitis (grade 3).
  - **Deaths:** Eight of 94 patients (8.5%) experienced grade 5 (fatal) AEs following initial treatment with mosunetuzumab SC. Three events were disease progression (preferred term: malignant neoplasm progression). The remaining 5 nonprogression grade 5 AEs were COVID-19–related pneumonia (2 patients), COVID-19 (1 patient), general physical health deterioration (1 patient), and hemophagocytic lymphohistiocytosis (1 patient).

- **AESIs:** Details of other AESIs, including neurologic AEs, hematologic AEs, hemophagocytic lymphohistiocytosis, tumour flares, hepatic AEs, infections, and pneumonitis or interstitial lung disease, are reported in the Supplemental Material document, Appendix 4.
- **CRS:** CRS was reported in 29 patients (30.9%) based on Lee criteria and in 28 patients (29.8%) based on ASTCT criteria. Most CRS events were grade 1 to 2 in severity as determined by both grading systems; no grade 4 or grade 5 CRS events were observed. CRS events were limited to cycle 1, primarily after day 1 and day 8 doses, with the highest frequency following day 1 dosing. No CRS events occurred in subsequent cycles. CRS events leading to mosunetuzumab dose interruption or modification occurred in 2 patients (2.1%) under both grading systems. No patients discontinued mosunetuzumab due to CRS. All CRS events resolved by the CCOD, with a median duration of 2.0 days (range, 1 day to 15 days).
- **Injection site reactions:** At the CCOD of February 1, 2024, a total of 65 patients (69.1%) experienced 172 injection site reactions. All events were grade 1 or 2 in severity and assessed by the investigator as related to mosunetuzumab. No serious reactions were reported, and no patients discontinued treatment due to injection site reactions. Dose interruption or modification occurred in 2 patients (2.1%). The median time to onset of the first injection site reaction was 16 days (range, 1 day to 309 days), and the median duration was 8 days (range, 1 day to 181 days). By the February 1, 2024, CCOD, 99.4% of events had resolved.

### Summary of Findings and Certainty of the Evidence

Although GRADE guidance is not available for noncomparative studies, the review team assessed pivotal single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at very low certainty with no opportunity for rating up.

**Table 4: Summary of Findings for Mosunetuzumab IV Monotherapy in Adult Patients With r/r FL (Grade 1 to 3a) Who Have Received at Least 2 Prior Lines of Systemic Therapy**

| Outcome and follow-up                    | Patients, N (studies)   | Effect                                                                                                        | Certainty <sup>a</sup> | What happens                                                                                                        |
|------------------------------------------|-------------------------|---------------------------------------------------------------------------------------------------------------|------------------------|---------------------------------------------------------------------------------------------------------------------|
| <b>Survival outcomes</b>                 |                         |                                                                                                               |                        |                                                                                                                     |
| OS<br>Median time on study: 18.3 months  | 90 (1 single-arm trial) | Median OS, months: NE (95% CI, NE to NE)<br>OS probability:<br>• At 12 months: 93.0% (95% CI, 87.6% to 98.4%) | Very low               | The evidence about the effect of mosunetuzumab IV on OS when compared with any comparator is of very low certainty. |
| PFS<br>Median time on study: 18.3 months | 90 (1 single-arm trial) | Median PFS, months: 17.9 (95% CI, 10.1 to NE)<br>PFS probability:                                             | Very low               | The evidence about the effect of mosunetuzumab IV on PFS when compared with                                         |

| Outcome and follow-up                                                                                                       | Patients, N (studies)   | Effect                                                                                                                                                                                                                                                                                                                                             | Certainty <sup>a</sup> | What happens                                                                                                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                             |                         | <ul style="list-style-type: none"> <li>At 12 months: 57.7% (95% CI, 46.9% to 68.4%)</li> <li>At 18 months: 47.0% (95% CI, 34.4% to 60.0%)</li> </ul>                                                                                                                                                                                               |                        | any comparator is of very low certainty.                                                                                                                                       |
| <b>Treatment response outcomes</b>                                                                                          |                         |                                                                                                                                                                                                                                                                                                                                                    |                        |                                                                                                                                                                                |
| Complete response (CRR, DOCR) <sup>b</sup><br>Median time on study: 18.3 months                                             | 90 (1 single-arm trial) | Median time to event (DOCR), months: NE (95% CI, 14.6 to NE)<br><ul style="list-style-type: none"> <li>CRR at data cut-off date: 60.0% (95% CI, 49.1% to 70.2%)</li> </ul> CR probability:<br><ul style="list-style-type: none"> <li>At 12 months: 71.4% (95% CI, 57.9% to 84.9%)</li> <li>At 18 months: 63.7% (95% CI, 48.0% to 79.4%)</li> </ul> | Very low               | The evidence about the effect of mosunetuzumab IV on CRR and DOCR when compared with any comparator is of very low certainty.                                                  |
| Overall response (ORR, DOR) <sup>b</sup><br>Median time on study: 18.3 months<br>Median follow-up time for DOR: 14.9 months | 90 (1 single-arm trial) | Median time to event (DOR), months: 22.8 (95% CI, 9.7 to NE)<br><ul style="list-style-type: none"> <li>ORR at data cut-off date: 80.0% (95% CI, 70.3% to 87.7%)</li> </ul> OR probability:<br><ul style="list-style-type: none"> <li>At 12 months: 61.8% (95% CI, 50.0% to 73.7%)</li> <li>At 18 months: 56.9% (95% CI, 44.1% to 69.6%)</li> </ul> | Very low               | The evidence about the effect of mosunetuzumab IV on ORR and DOR when compared with any comparator is of very low certainty.                                                   |
| Time to next treatment <sup>c</sup><br>Median time on study: 18.3 months                                                    | 90 (1 single-arm trial) | Median time to event, months: NE (95% CI, 16.2, NE)<br>Event-free proportion:<br><ul style="list-style-type: none"> <li>At 12 months: 68.1% (95% CI, 58.3% to 77.9%)</li> </ul>                                                                                                                                                                    | Very low               | The evidence about the effect of mosunetuzumab IV on time to next treatment when compared with any comparator is of very low certainty.                                        |
| <b>HRQoL</b>                                                                                                                |                         |                                                                                                                                                                                                                                                                                                                                                    |                        |                                                                                                                                                                                |
| FACT-Lym subscale, ranging from 0 (worst HRQoL) to 60 (best HRQoL)<br>Median time on study: 18.3 months                     | 81 (1 single-arm trial) | Proportion of patients with a $\geq 3$ -point increase in FACT-Lym subscale from baseline: <sup>d</sup><br><ul style="list-style-type: none"> <li>At cycle 2: 28.4%</li> <li>At cycle 4: 44.0%</li> <li>At cycle 6: 40.9%</li> <li>At cycle 8: 40.6%</li> </ul>                                                                                    | Very low               | The evidence about the effect of mosunetuzumab IV on FACT-Lym subscale when compared with any comparator is of very low certainty.                                             |
| <b>Harms</b>                                                                                                                |                         |                                                                                                                                                                                                                                                                                                                                                    |                        |                                                                                                                                                                                |
| Grade 3 or higher AEs (excluding grade 5 PD)<br>Median follow-up: 7.0 months <sup>e</sup>                                   | 90 (1 single-arm trial) | <ul style="list-style-type: none"> <li><math>\geq 1</math> event: 70.0%</li> <li>Most common:<sup>f</sup> neutropenia (18.9%), hypophosphatemia (16.7%)</li> </ul>                                                                                                                                                                                 | Very low               | The evidence about the effect of mosunetuzumab IV on grade 3 or higher AEs (excluding grade 5 progressive disease) when compared with any comparator is of very low certainty. |
| Grade 5 (fatal) AEs<br>Median follow-up: 7.0 months <sup>e</sup>                                                            | 90 (1 single-arm trial) | <ul style="list-style-type: none"> <li><math>\geq 1</math> event: 2.2%</li> </ul>                                                                                                                                                                                                                                                                  | Very low               | The evidence about the effect of mosunetuzumab IV on grade 5 (fatal) AEs when compared with any                                                                                |

| Outcome and follow-up | Patients, N (studies) | Effect | Certainty <sup>a</sup> | What happens                         |
|-----------------------|-----------------------|--------|------------------------|--------------------------------------|
|                       |                       |        |                        | comparator is of very low certainty. |

AE = adverse event; CCOD = clinical cut-off date; CDA-AMC = Canada's Drug Agency; CI = confidence interval; CR = complete response; CRR = complete response rate; DOCR = duration of complete response; DOR = duration of response; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; FL = follicular lymphoma; HRQoL = health-related quality of life NE = not estimable; OR = overall response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; r/r = relapsed or refractory.

Notes: All serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, and publication bias are documented in the table footnotes.

The CCOD for the data in this table was August 27, 2021 (updated interim analysis).

Follow-up durations for OS, PFS, DOCR, time to next treatment, and FACT-Lym subscale were not individually assessed, and the median observation time for patients in the cohort (i.e., median time on study) was reported.

<sup>a</sup>In the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn, and the certainty of evidence starts at very low and cannot be rated up. The CDA-AMC review team assessed pivotal single-arm trials for study limitations (internal validity or risk of bias), inconsistency across studies, indirectness, and publication bias. Because the lack of a comparator arm prevents determination of the intervention's effect relative to any comparator, the certainty of evidence for single-arm trials was rated as very low. When the certainty of the evidence was very low, the evidence was described as "very uncertain."

<sup>b</sup>The results were based on an IRF assessment.

<sup>c</sup>The results were based on an investigator assessment. According to the study protocol, time to next treatment was based on local site data entry of follow-up antilymphoma therapies and did not require an independent review facility assessment.

<sup>d</sup>Based on the literature, a clinically meaningful improvement on the FACT-Lym subscale is defined as an increase of 3 or more points. The median number of mosunetuzumab IV treatment cycles was 8.

<sup>e</sup>The median follow-up duration for safety outcomes was the same as the median duration of treatment, defined as the time from first dose to the end of the 90-day safety follow-up period or the earliest of CCOD, initiation of new antilymphoma treatment, study discontinuation, or start of re-treatment, whichever was earlier.

<sup>f</sup>Reported in 10% or more of patients.

Sources: GO29781 Update Interim Clinical Study Report<sup>26</sup> and sponsor's submission.<sup>36</sup> Details included in the table are from the sponsor's summary of clinical evidence.

**Table 5: Summary of Findings for Mosunetuzumab SC Monotherapy in Adult Patients With r/r FL (Grade 1 to 3a) Who Have Received at Least 2 Prior Lines of Systemic Therapy**

| Outcome and follow-up                                                           | Patients, N (studies)   | Effect                                                                                                                       | Certainty <sup>a</sup> | What happens                                                                                                                  |
|---------------------------------------------------------------------------------|-------------------------|------------------------------------------------------------------------------------------------------------------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------|
| <b>Survival outcomes</b>                                                        |                         |                                                                                                                              |                        |                                                                                                                               |
| OS<br>Median follow-up: 21.9 months                                             | 94 (1 single-arm trial) | Median OS, months: NE (95% CI, NE to NE)<br>OS probability:<br>• At 12 months: 90.2% (95% CI, 84.1% to 96.3%)                | Very low               | The evidence about the effect of mosunetuzumab SC on OS when compared with any comparator is of very low certainty.           |
| PFS<br>Median time on study: 20.7 months                                        | 94 (1 single-arm trial) | Median PFS, months: 18.5 (95% CI, 12.9 to 24.0)<br>PFS probability:<br>• At 12 months: 62.3% (95% CI, 52.1% to 72.5%)        | Very low               | The evidence about the effect of mosunetuzumab SC on PFS when compared with any comparator is of very low certainty.          |
| <b>Treatment response outcomes</b>                                              |                         |                                                                                                                              |                        |                                                                                                                               |
| Complete response (CRR, DOCR) <sup>b</sup><br>Median time on study: 20.7 months | 94 (1 single-arm trial) | Median time to event (DOCR), months: 20.8 (95% CI, 18.8 to NE)<br>• CRR at data cut-off date: 58.5% (95% CI, 47.9% to 68.6%) | Very low               | The evidence about the effect of mosunetuzumab SC on CRR and DOCR when compared with any comparator is of very low certainty. |

| Outcome and follow-up                                                                                                       | Patients, N (studies)   | Effect                                                                                                                                                                                              | Certainty <sup>a</sup> | What happens                                                                                                                                                  |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                             |                         | CR probability:<br>• At 12 months: 72.4% (95% CI, 59.9% to 84.9%)                                                                                                                                   |                        |                                                                                                                                                               |
| Overall response (ORR, DOR) <sup>b</sup><br>Median time on study: 20.7 months<br>Median follow-up time for DOR: 16.0 months | 94 (1 single-arm trial) | Median time to event (DOR), months: 22.4 (95% CI, 16.8 to 22.8)<br>• ORR at data cut-off date: 74.5% (95% CI, 64.4% to 82.9%)<br>OR probability:<br>• At 12 months: 69.9% (95% CI, 58.5% to 81.4%)  | Very low               | The evidence about the effect of mosunetuzumab SC on ORR and DOR when compared with any comparator is of very low certainty.                                  |
| Time to next treatment <sup>c</sup><br>Median time on study: 20.7 months                                                    | 94 (1 single-arm trial) | Median time to event, months: NE (95% CI, NR)<br>Event-free proportion:<br>• At 12 months: 78.6% (95% CI, 69.8% to 87.4%)<br>• At 18 months: 74.3% (95% CI, 64.7% to 83.9%)                         | Very low               | The evidence about the effect of mosunetuzumab SC on time to next treatment when compared with any comparator is of very low certainty.                       |
| <b>HRQoL</b>                                                                                                                |                         |                                                                                                                                                                                                     |                        |                                                                                                                                                               |
| FACT-Lym subscale, ranging from 0 (worst HRQoL) to 60 (best HRQoL)<br>Median time on study: 20.7 months                     | 87 (1 single-arm trial) | Proportion of patients with a $\geq 3$ -point increase in FACT-Lym subscale from baseline: <sup>d</sup><br>• At cycle 2: 34.5%<br>• At cycle 4: 43.0%<br>• At cycle 6: 38.4%<br>• At cycle 8: 35.2% | Very low               | The evidence about the effect of mosunetuzumab SC on FACT-Lym subscale when compared with any comparator is of very low certainty.                            |
| <b>Harms</b>                                                                                                                |                         |                                                                                                                                                                                                     |                        |                                                                                                                                                               |
| Grade 3 or higher AEs (excluding grade 5 PD)<br>Median follow-up: 7.9 months <sup>e</sup>                                   | 94 (1 single-arm trial) | • $\geq 1$ event: 52.1%<br>• Most common: <sup>f</sup> neutropenia (10.6%), hypophosphatemia (5.3%)                                                                                                 | Very low               | The evidence about the effect of mosunetuzumab SC on grade 3 or higher AEs (excluding grade 5 PD) when compared with any comparator is of very low certainty. |
| Grade 5 (fatal) AEs<br>Median follow-up: 7.9 months <sup>e</sup>                                                            | 94 (1 single-arm trial) | • $\geq 1$ event: 8.5%                                                                                                                                                                              | Very low               | The evidence about the effect of mosunetuzumab SC on grade 5 (fatal) AEs when compared with any comparator is of very low certainty.                          |

AE = adverse event; CCOD = clinical cut-off date; CDA-AMC = Canada's Drug Agency; CI = confidence interval; CR = complete response; CRR = complete response rate; DOOR = duration of complete response; DOR = duration of response; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; FL = follicular lymphoma; HRQoL = health-related quality of life; IRF = independent review facility; NE = not estimable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; r/r = relapsed or refractory; SC = subcutaneous.

Notes: All serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, and publication bias are documented in the table footnotes.

The CCOD for the data in this table was February 1, 2024.

Follow-up durations for PFS, DOOR, time to next treatment, and the FACT-Lym subscale were not individually assessed, and the median observation time for patients in the cohort (i.e., median time on study) was reported.

<sup>a</sup>In the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn, and the certainty of evidence starts at very low and cannot be rated up. The CDA-AMC review team assessed pivotal single-arm trials for study limitations (internal validity or risk of bias), inconsistency across studies, indirectness, and publication bias. Because the lack of a comparator arm prevents determination of the intervention's effect relative to any comparator, the certainty of evidence for single-arm trials was rated as very low. When the certainty of the evidence was very low, the evidence was described as "very uncertain."

<sup>b</sup>The results were based on IRF assessment.

<sup>c</sup>The results were based on investigator assessment. According to the study protocol, time to next treatment was based on local site data entry of follow-up antilymphoma therapies and did not require IRF assessment.

<sup>d</sup>Based on the literature, a clinically meaningful improvement on the FACT-Lym subscale is defined as an increase of 3 points or more. The median number of mosunetuzumab SC treatment cycles was 8.

<sup>e</sup>The median follow-up duration for safety outcomes was the same as the median duration of treatment, defined as the time from first dose to the end of the 90-day safety follow-up period or the earliest of CCOD, initiation of new antilymphoma treatment, study discontinuation, or start of re-treatment, whichever was earlier.

<sup>f</sup>Reported in 5% or more of patients.

Sources: GO29781 Primary Pharmacokinetics Non-Inferiority Clinical Study Report<sup>25</sup> and sponsor's submission.<sup>36</sup> Details included in the table are from the sponsor's summary of clinical evidence.

## Long-Term Extension Studies

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

## Indirect Evidence

In the absence of direct evidence comparing mosunetuzumab to other relevant treatment in the third-line setting or beyond for patients relapsed or refractory FL, the sponsor submitted indirect comparisons.

### *Description of Indirect Treatment Comparison*

The sponsor submitted an ITC analysis set comprising 3 MAICs and 4 PSAs to assess the comparative effectiveness and safety of mosunetuzumab versus therapies relevant in the context of care and practice in Canada (axi-cel, tisa-cel, obinutuzumab plus bendamustine, rituximab plus lenalidomide, and rituximab plus bendamustine) for outcomes of interest.

The clinical evidence for mosunetuzumab was derived from the GO29781 study, a dose-escalation study that did not include a common comparator arm.<sup>37</sup> In the absence of anchored comparisons, unanchored MAICs were conducted when only aggregate data were available for comparator trials, and PSAs were performed when individual patient data (IPD) were available for both treatments.<sup>38,39</sup> Comparator selection was based on clinical relevance (based on input from experts consulted by the sponsor for the ITC) and data availability, and populations were aligned to the inclusion and exclusion criteria of the target trials where feasible.<sup>40</sup>

## Study Selection and Review Methods

In the sponsor-conducted systematic literature review, eligible studies included adult patients with r/r FL receiving third-line or later treatment.<sup>37</sup> The intervention of interest was mosunetuzumab, and comparators were treatments relevant in the context of care and practice in Canada, including axi-cel, tisa-cel, obinutuzumab plus bendamustine, rituximab plus bendamustine, and rituximab plus lenalidomide.<sup>38</sup> For this Reimbursement Review submission to CDA-AMC, the sponsor did not include comparators — including copanlisib, duvelisib, idelalisib, umbralisib, tazemetostat, rituximab monotherapy, R-CVP, R-CHOP, and epcoritamab with or without rituximab plus lenalidomide — in the pharmacoeconomic analysis because these treatments are not approved or funded in Canada for third-line treatment of r/r FL. The ITCs in this Clinical Review report also excluded these comparators to maintain alignment with pharmacoeconomic approaches.<sup>41</sup> The clinical experts consulted for this review considered this approach reasonable and

appropriate, noting that, in clinical practice in Canada, the most relevant comparators for third-line or later treatment of r/r FL are CAR T-cell therapies such as axi-cel and tisa-cel, followed by rituximab plus lenalidomide or chemoimmunotherapy, while zanubrutinib plus obinutuzumab is not funded and therefore was not included as a comparator. Zanubrutinib plus obinutuzumab was included in the sponsor's ITC analyses; however, because it is not reimbursed by public drug plans in Canada and was not considered relevant for the ITCs, the information was included only in the Supplemental Material document, Appendix 6.

Outcomes assessed were OS, PFS, ORR, CRR, and treatment discontinuation due to AEs.<sup>39</sup> Time points for outcome assessments were not specified. Eligible study designs included RCTs (phase I to III), controlled clinical trials, extension phases, observational studies, case-control studies, cross-sectional surveys, case series, and treatment guidelines; both published and unpublished studies were considered.<sup>40</sup> Notable exclusions included pediatric populations, and other mature B-cell lymphoma subtypes.<sup>42</sup>

Searches were conducted in Embase, MEDLINE, Evidence-Based Medicine Reviews, and the University of York Centre for Reviews and Dissemination on April 17, 2021, and updated on December 24, 2021; August 9, 2023; and May 23, 2025.<sup>41</sup> Articles were screened independently by 2 reviewers. Data extraction was performed by 1 analyst and verified for 100% of data elements by a second analyst or project lead, with disputes referred to a third party. Risk of bias was assessed independently by 2 reviewers using the NICE 7-criteria checklist for randomized trials and the Downs and Black checklist for nonrandomized studies, with disagreements resolved through discussion or arbitration.<sup>42</sup>

### ITC Analysis Methods

For additional information on the analysis methods for the ITC analysis set, refer to Appendix 6 in the Supplemental Material document. For end points that were both IRF- and investigator-assessed, IRF end points were used.

In the ITCs, the clinical evidence for mosunetuzumab was derived from the mosunetuzumab dose-expansion IV monotherapy for the RP2D cohort (B11 expansion r/r FL cohort) of the GO29781 study, comprising 90 patients receiving third-line or later treatment for r/r FL based on the January 3, 2022, CCOD, which aligns with the economic model informed by the same IV formulation data and CCOD. Unanchored MAICs were used when only aggregate data were available for comparators, and PSAs were conducted when IPD were available for both treatments.<sup>38</sup> Adjustment factors were identified through systematic review and sponsor-consulted expert input and prioritized according to prognostic and effect-modifying relevance. High-priority factors included the number of prior therapies, refractoriness to last therapy and anti-CD20 therapy, early disease relapse (POD24), prior stem cell transplant, size of the largest lymph node, FLIPI risk group, age, Ann Arbor stage, LDH level, bone marrow involvement, and hemoglobin level. Low-priority factors included duration of prior disease response, B symptoms, and ECOG PS score. Low-priority factors were included when feasible based on data availability and were deprioritized or excluded when their inclusion resulted in substantial loss of effective sample size or instability in weighting. Sensitivity analyses examined the impact of including all prognostic factors. Covariate definitions were harmonized across trials, and missing data were imputed using conservative assumptions. Continuous variables reported as medians were converted to means or dichotomized using median thresholds.<sup>41,42</sup>

For MAICs, IPD from the GO29781 study were weighted to match comparator trial characteristics using a logistic regression model, with parameters estimated by the method of moments. Bootstrap methods (percentile and bias-corrected and accelerated) were used to derive CIs for weighted hazard ratios and odds ratios. Analyses aimed to maximize the bias-variance trade-off while retaining clinically important covariates, and low-priority factors were included when feasible but excluded from base-case adjustments when their inclusion reduced the effective sample size to below prespecified thresholds (< 40% of the original sample size or 36 of 90 patients), with sensitivity analyses exploring alternative covariate sets and imputations. Outlier weights were capped or removed to maintain stability.<sup>42</sup>

PSAs employed propensity score matching and inverse probability of treatment weighting to estimate average treatment effects. Survival outcomes were analyzed using KM and Cox proportional hazards models, and binary outcomes using logistic regression. Bootstrapping was applied for CIs due to small sample sizes and rare events. Residual confounding was assessed through balance diagnostics, effective sample size checks, and sensitivity analyses;<sup>41</sup> however, it cannot be fully excluded, given the unanchored nature of the comparisons.<sup>42</sup>

### Summary of Included Studies

A total of 236 studies from 367 publications were identified through the systemic literature review, which was most recently updated in May 2025.<sup>41</sup> Of those, 58 evaluated treatments of interest to the sponsor were considered for MAIC feasibility assessment. Following detailed review, 29 studies with all comparators (broader comparators than the current review) initially met the eligibility criteria for MAIC analyses, based on the following conditions: studies of patients with third-line or later treatment for FL (n = 11); mixed-line FL studies in which the median number of prior lines was at least 2 ( $\geq 50\%$  third line) or results were reported for third-line or later treatment (n = 6); mixed lymphoma studies where more than 80% of patients had FL or results were reported for FL patients (n = 4); mixed-line and mixed lymphoma studies meeting both criteria (n = 6); and studies requested for inclusion by Roche (the AUGMENT and EORTC 20981 trials) (n = 2).<sup>41</sup> Five of the 29 studies (including the GADOLIN, GO29365, and CONTRALTO trials) were conducted by the sponsor with IPD available, and were therefore included in PSAs.<sup>43</sup>

According to the sponsor, reliable ITCs versus rituximab were not feasible because of several limitations associated with small sample sizes, unavailability of information on some important prognostic factors, and important residual imbalances after adjusting for differences in the available factors.

After excluding studies with interventions deemed not relevant, 6 studies for 5 comparators were included in the ITC evidence, comprising the GO29781 study;<sup>26</sup> for MAIC, axi-cel (ZUMA-5;<sup>44</sup> N = 127), tisa-cel (ELARA;<sup>45</sup> N = 94), rituximab plus lenalidomide (AUGMENT;<sup>11</sup> N = 147); and for PSA, obinutuzumab plus bendamustine (GADOLIN;<sup>46</sup> N = 80), and bendamustine plus rituximab (GO29365<sup>47</sup> and CONTRALTO;<sup>48</sup> N = 46 combined).<sup>41</sup> Median follow-up durations range from 20.2 months to 41.7 months across these studies. Baseline characteristics are outlined in the Supplemental Material document, Appendix 6.

### ***Critical Appraisal of ITCs***

The methods for searching, study selection, and data extraction were deemed adequate by the CDA-AMC review team. Risk of bias was assessed using the National Institute for Health and Care Excellence (NICE) Quality of Effectiveness Estimates from Non-randomised Studies (QuEENS) checklist<sup>49</sup> across all comparisons; however, it appeared the sponsor assessed the risk of bias at the study level, rather than for each end point, and the risk of bias for each study therefore may not apply universally to all end points included in the ITCs.

The sponsor-submitted ITCs using MAIC and PSA methods are subject to several methodological limitations that affect the internal validity, interpretability, and generalizability of the findings. Differences in inclusion and exclusion criteria were observed between the GO29781 study and comparator studies, which could result in systematic differences in patient populations across trials. Although filtering procedures based on common eligibility criteria were applied to improve the population overlap before conducting the ITCs, this approach was not feasible for all comparisons. For example, comparator datasets used to conduct MAICs versus axi-cel and rituximab plus lenalidomide enrolled populations of patients with r/r FL rather than exclusively recruiting patients receiving third-line or later treatment, with the proportion of patients receiving second-line treatment ranging from approximately 2% to 53%. Given the prognostic importance of the number of prior therapies, these differences may have biased results against mosunetuzumab. According to the clinical experts, baseline risk in the mosunetuzumab cohort after weighting was generally comparable to that in the axi-cel and tisa-cel arms. In contrast, patients in the AUGMENT study (rituximab plus lenalidomide arm, with fewer previous therapies, no double refractoriness to both an anti-CD20-containing regimen and an alkylating agent, not refractory to rituximab monotherapy, and a higher proportion of patients with an ECOG PS score of 0 compared with the patients in the GO29781 study), the GADOLIN study (obinutuzumab plus bendamustine arm, with a lower proportion of patients who had at least 3 prior therapies than in the GO29781 study), and the GO29368 and CONTRALTO studies (rituximab plus bendamustine arm, with a lower proportion of patients whose disease was refractory to the last line of treatment, a higher proportion of patients with an ECOG PS score of 0, and longer time since completion of last therapy than in the GO29781 study) were at lower risk, which could contribute to residual imbalance and introduces additional uncertainties in comparisons.

For an unanchored MAIC to produce unbiased treatment effect estimates, all effect modifiers and prognostic variables must be adjusted in the analysis. The clinical experts considered the approach used to identify and prioritize prognostic and effect-modifying factors (high-priority, low-priority, and deprioritized) in the base-case and supplemental models to be reasonable and appropriate. The consulted clinical experts highlighted age, number of prior therapies, refractoriness to the last line of therapy and to anti-CD20 therapy, early disease relapse (POD24), duration of prior disease response, disease stage, FLIPI score, and bulk disease as the most important prognostic factors. Adjustment for all prognostic factors and effect modifiers was constrained by incomplete reporting and limited overlap across studies. Except for comparisons against obinutuzumab plus bendamustine and versus rituximab plus bendamustine, it was not possible to adjust for all known prognostic variables (e.g., bulk disease) without substantially reducing the effective sample size. In several analyses, compromises were required to balance bias and variance, which may have

introduced confounding. The consulted clinical experts further emphasized that the choice and interpretation of comparators should reflect these baseline risk differences, with particular caution when comparing mosunetuzumab to rituximab plus lenalidomide, to obinutuzumab plus bendamustine, or to rituximab plus bendamustine, given that these regimens are typically prescribed in clinical settings for patients with more favourable baseline prognostic characteristics. As with all nonrandomized indirect comparisons, residual bias due to unmeasured or unknown confounders cannot be ruled out. Unadjusted and matched-adjusted baseline covariates were reported in the sponsor's submission materials. However, the complete baseline demographic and disease characteristics for patients were not reported after matching; only the balance of patient characteristics relevant to the covariates used in the matching were reported. It is therefore unclear if other relevant patient characteristics were balanced between groups.

The MAIC versus axi-cel was also affected by data limitations related to the ZUMA-5 study. The ZUMA-5 study did not report the number of PFS or OS events, requiring digitization of published survival curves and generation of pseudo-IPD, which may introduce measurement error and bias. In addition, efficacy data from the ZUMA-5 study for the ITCs were collected only up to 24 months, creating uncertainty as to whether the MAIC reflects outcomes assessed beyond 24 months. The clinical experts noted that, notwithstanding these constraints, the underlying risk profile of mosunetuzumab patients was broadly comparable to those of the CAR T-cell cohorts.

In the PSAs, matching and weighting procedures did not consistently achieve balance across all key prognostic factors, and residual imbalances were observed in some analyses. Although models were subsequently adjusted to partially address these imbalances using a doubly robust approach, this secondary adjustment was feasible only for summary measures such as hazard ratios and odds ratios. It could not be applied to KM survival curves, which were therefore derived from partially adjusted populations and should be interpreted with caution. For example, in the comparison versus obinutuzumab plus bendamustine, full matching failed to achieve good balance for several prognostic factors, including age, FLIPI score, refractory status, Ann Arbor stage, high LDH levels, double refractoriness, and POD24. In the comparison versus rituximab plus bendamustine, both optimal pair matching and inverse probability of treatment weighting failed to achieve good balance for multiple variables, including ECOG PS scores and high LDH levels.

Differences in end point definitions across trials further complicated interpretation of the ITC results. Tumour response outcomes such as ORR and CR were assessed using International Working Group criteria in the GO29781 study, whereas comparator studies for axi-cel, tisa-cel, and rituximab plus bendamustine used Lugano criteria. These methodological inconsistencies may limit the comparability of efficacy outcomes and introduce additional uncertainty into the estimated treatment effects.

In several ITC analyses of OS and PFS, both adjusted and unadjusted analyses resulted in crossed survival curves, suggesting potential violations of the proportional hazards assumption. Under these circumstances, relative hazard ratios should be interpreted with caution, as they may not adequately reflect time-varying differences between treatments.

Additional limitations were identified in specific comparisons. For example, in the ITC comparing mosunetuzumab with rituximab plus bendamustine, fewer comparator-control effective sample sizes

(approximately 32) were available than intervention effective sample sizes in the mosunetuzumab arm (approximately 68). As a result, the reduction in the effective sample size suggests poor population overlap, which may not be representative of the entire sample. The reduction in sample sizes appropriate for analysis may contribute to imprecision, increasing the uncertainty of the results.

Across almost all ITC analyses, effective sample sizes after adjustment were small, with 30% to 78% of patients lost across the ITC studies. Combined with a low number of events for certain end points, this resulted in wide CIs and imprecise estimates. The reduced effective sample sizes also indicate that adjusted analyses reflect highly selected patient subsets, further limiting the generalizability of the findings to the broader population of interest.

Overall, while the use of MAICs and PSAs was appropriate in the absence of head-to-head evidence, the ITC results should be interpreted cautiously. Residual confounding, limited population overlap, end point heterogeneity, small effective sample sizes, and violation of model assumptions in select analyses introduce uncertainty around the estimated comparative treatment effects and limit the robustness of the conclusions. The ITC assessed the end points of CRR, ORR, OS, PFS, and discontinuation due to AEs, but other efficacy end points of interest to patients and clinical experts, such as HRQoL, were not investigated.

### ***Efficacy and Harms Results of ITC***

Key ITC results are presented in [Table 6](#), which summarizes comparisons of mosunetuzumab with relevant comparators. These include 3 MAICs comparing mosunetuzumab with 3 comparators (axi-cel, tisa-cel, and rituximab plus lenalidomide) and 4 PSAs comparing mosunetuzumab with 2 comparators (obinutuzumab plus bendamustine and rituximab plus bendamustine).

For the comparative estimates (hazard ratios or odds ratios), results were considered to be very uncertain when the estimates were affected by serious imprecision. These estimates were characterized by wide 95% CIs spanning the null alongside additional sources of uncertainty, including small effective sample sizes, a decrease in the number of patients at risk over follow-up, and violations of model assumptions for some comparisons. In such cases, the upper bound of the 95% CI could indicate a substantial benefit, while the lower bound could indicate a substantial harm (or vice versa for some outcomes). As a result, the direction, magnitude, and certainty of the estimated comparative effects were unclear for such comparisons.

**Table 6: Summary of ITC Results Comparing Mosunetuzumab IV Monotherapy With Relevant Comparators**

| Comparator<br>(source of data), method of estimation                            | ESS after matching (absolute numbers)                                               | Hazard ratio (95% CI)                                                               |                                                                                     | Odds ratio (95% CI)                                                                  |                                                                                       |                                                                                       |
|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
|                                                                                 |                                                                                     | OS <sup>a</sup>                                                                     | PFS <sup>a</sup>                                                                    | CRR <sup>b</sup>                                                                     | ORR <sup>b</sup>                                                                      | Discontinuation due to AEs <sup>a</sup>                                               |
| Base-case MAIC results for adjusted models (bootstrap median HR/OR with 95% CI) |                                                                                     |                                                                                     |                                                                                     |                                                                                      |                                                                                       |                                                                                       |
| Axicabtagene ciloleucel (ZUMA-5)                                                |  |  |  |  |  |  |

| Comparator<br>(source of<br>data), method<br>of estimation                                     | ESS after<br>matching<br>(absolute<br>numbers) | Hazard ratio (95% CI) |                  | Odds ratio (95% CI) |                  |                                            |
|------------------------------------------------------------------------------------------------|------------------------------------------------|-----------------------|------------------|---------------------|------------------|--------------------------------------------|
|                                                                                                |                                                | OS <sup>a</sup>       | PFS <sup>a</sup> | CRR <sup>b</sup>    | ORR <sup>b</sup> | Discontinuation<br>due to AEs <sup>a</sup> |
| Tisagenlecleucel<br>(ELARA)                                                                    |                                                |                       |                  |                     |                  |                                            |
| Rituximab plus<br>lenalidomide<br>(AUGMENT)                                                    |                                                |                       |                  |                     |                  |                                            |
| <b>Propensity score analyses results for the comparison of mosunetuzumab IV vs. comparator</b> |                                                |                       |                  |                     |                  |                                            |
| <b>Obinutuzumab plus bendamustine (GADOLIN trial)</b>                                          |                                                |                       |                  |                     |                  |                                            |
| Full matching<br>plus covariate<br>adjustment                                                  |                                                |                       |                  |                     |                  |                                            |
| IPTW                                                                                           |                                                |                       |                  |                     |                  |                                            |
| <b>Rituximab plus bendamustine (CONTRALTO and GO29365 trials)</b>                              |                                                |                       |                  |                     |                  |                                            |
| IPTW plus<br>covariate<br>adjustment                                                           |                                                |                       |                  |                     |                  |                                            |
| “Doubly robust”<br>regression<br>adjustment                                                    |                                                |                       |                  |                     |                  |                                            |

AE = adverse event; CI = confidence interval; CRR = complete response rate; ESS = effective sample size; IPTW = inverse probability of treatment weighting; M = mosunetuzumab; MAIC = matching-adjusted indirect comparison; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; vs. = versus.

Note: Results with CIs not crossing 1 are shown in bold.

<sup>a</sup>A hazard ratio of less than 1 provides evidence of improved outcomes for mosunetuzumab compared with the comparator.

<sup>b</sup>An odds ratio of greater than 1 provides evidence of improved outcomes for mosunetuzumab compared with the comparator.

<sup>c</sup>At the time this review was conducted, public access to this treatment regimen was not available in Canada.

Source: Sponsor's submission.<sup>42</sup> Details included in the table are from the sponsor's summary of clinical evidence.

## Studies Addressing Gaps in the Systematic Review Evidence

No other studies are included in this review. The sponsor did not identify a gap in the systematic review evidence.

## Discussion

This report summarizes the evidence for mosunetuzumab for adults with r/r FL (grades 1 to 3a) who had received at least 2 prior lines of systemic therapy based on 1 phase I(Ib) and II study, and 1 ITC analysis set.

## Efficacy

FL is a heterogeneous and typically indolent malignancy characterized by a relapsing disease course, with periods of response to treatment and recurrence. Although OS is often prolonged, patients who experience disease relapse after multiple lines of therapy face progressively shorter remission durations, reduced responsiveness to subsequent treatments, and an increased risk of transformation to aggressive lymphoma. In this context, the IV (N = 90) and SC (N = 94) cohorts of the GO29781 study provided the primary evidence supporting the efficacy of mosunetuzumab in adult patients with r/r FL (grades 1 to 3a) who had received at least 2 prior lines of systemic therapy. Both cohorts were investigated under a single protocol, but each was considered an independent study. Mosunetuzumab demonstrated clinically meaningful antitumour activity in each cohort. In the IV cohort, notable CRR (60%) and ORR (80%) by IRF assessment were observed at the updated interim analysis (CCOD: August 27, 2021; median time on study of 18.3 months), with the DOR and DOCR suggesting durable responses in a substantial proportion of patients. The CRR exceeded the prespecified historical benchmark (14%), and the investigator-assessed responses were generally consistent with IRF assessments, reducing the risk of measurement bias and increasing confidence in the reliability of the findings, particularly at the 3-year and 4-year follow-up when only investigator-assessed treatment response outcomes were available. The durability of response observed with mosunetuzumab IV (median DOR at the updated interim analysis [median follow-up of 14.9 months] = 23 months; OR probability at 18 months = 57%) is clinically relevant given the fixed-duration treatment strategy, because sustained CRs may allow for prolonged disease control without the need for continuous therapy. The observed response rates and durability of response in the SC cohort (median time on study of 21.9 months) appeared generally consistent with those observed in the IV cohort. However, efficacy analyses in the SC cohort were descriptive and not powered for formal hypothesis testing, and comparisons between cohorts were exploratory and based on nonrandomized data. Although statistical adjustments were applied to account for baseline differences, residual confounding cannot be excluded, and conclusions regarding comparative efficacy between administration routes should be interpreted cautiously.

HRQoL was assessed using the FACT-Lym subscale instrument and provides additional context regarding patient experience during treatment. At cycle 8, data were available for approximately two-thirds (66%) of enrolled patients in both cohorts. Among those with available data, the mean change from baseline in FACT-Lym subscale scores was small in both groups, with an increase of 1.6 points (SD = 7.5) in the IV cohort and 2.6 points (SD = 7.4) in the SC cohort. Although a proportion of patients reported improvement of at least 3 points, which may suggest clinically meaningful improvement in lymphoma-related symptoms, this occurred in 41% of patients in the IV cohort and 35% of patients in the SC cohort, while others experienced stable or worsened scores. Interpretation of these findings is limited by the open-label study design, which may introduce reporting bias in patient-reported outcomes, and by the presence of missing data, with approximately one-third of patients lacking evaluable HRQoL data at cycle 8. Patients with missing assessments may differ systematically from those with available data, particularly if missingness is related to disease progression or treatment tolerability, which may bias results. The relatively small mean changes observed, combined with variability in individual responses and incomplete data, increase uncertainty regarding the magnitude and consistency of any HRQoL benefit associated with mosunetuzumab.

The GO29781 study did not include randomization, which limits the ability to control for confounding factors and prevents causal inference about the effects of mosunetuzumab. The absence of a concurrent comparator group in both the IV and SC cohorts limits the ability to determine the magnitude of benefit of mosunetuzumab relative to currently available therapies in Canada. Comparisons with historical controls and cross-study comparisons are inherently uncertain due to differences in patient populations, prior therapies, outcome definitions, and assessment methods. In addition, the historical comparator used to support the primary analysis was derived from studies of therapies that are not approved or publicly funded in Canada, which limits the relevance of this comparison to clinical practice in Canada. According to the sponsor, a single-arm design was used for the GO29781 trial due to the heterogeneous biology and presentation of FL, although a phase III, open-label, multicentre RCT evaluating mosunetuzumab in combination with lenalidomide compared with rituximab plus lenalidomide is under way with patients with r/r FL; however, results from this trial are not yet available. As such, the current evidence base remains primarily derived from single-arm data, and uncertainty remains regarding the comparative efficacy of mosunetuzumab relative to other treatment options. Although KM methods were used appropriately to analyze time-to-event outcomes (DOCR, DOR, PFS, and OS), estimates at later time points are less precise due to smaller numbers of patients remaining under observation. Furthermore, the fixed-duration treatment design, which included discontinuation after achieving a CR or completing the planned treatment course, reflects the intended treatment strategy but may influence estimates of response durability and complicates comparisons with therapies administered until disease progression. The clinical experts also indicated that mosunetuzumab treatment duration should be individualized in clinical practice, taking into account side effects. Once a CR is achieved, treatment can be stopped, as there is no clinical rationale to continue mosunetuzumab thereafter. The TTNT findings suggest a durable treatment effect with mosunetuzumab that clinical experts considered clinically meaningful, although the certainty of this evidence remains limited due to the single-arm design.

In the absence of head-to-head evidence, ITC results provide contextual information on the comparative efficacy of mosunetuzumab versus relevant therapies for r/r FL (grade 1 to 3a) who have received at least 2 prior lines of systemic therapy; however, these findings are subject to important methodological limitations and should be interpreted with caution. According to the clinical experts, the treatment landscape for FL is heterogeneous, and in third-line and later settings, the most relevant comparators for the mosunetuzumab Reimbursement Review are CAR T-cell therapies (axi-cel and tisa-cel), followed by rituximab plus lenalidomide or chemoimmunotherapy. Overall, the ITC results suggest that CAR T-cell therapies demonstrate more favourable efficacy than mosunetuzumab for certain end points, particularly PFS and CRR, with axi-cel and tisa-cel statistically favoured in some analyses. The clinical experts noted that there are multiple logistical limitations with CAR T-cell therapy, including eligibility, accessibility, manufacturing limitations, and delays, such that active off-the-shelf treatments such as mosunetuzumab offer an important advantage. In contrast, mosunetuzumab showed favourable comparative efficacy versus several non-CAR T-cell regimens, including improvements in PFS and CRR compared with rituximab plus lenalidomide or obinutuzumab plus bendamustine in select analyses. Interpretation of these findings remains limited by heterogeneity in study populations and end point definitions, incomplete adjustment for prognostic factors, small effective sample sizes, violation of model assumptions in select analyses, and residual confounding inherent to MAIC and PSA methodologies. As a result, the magnitude and certainty of the estimated

comparative effects remain uncertain, and the generalizability of these findings to clinical practice in Canada is limited.

## Harms

Mosunetuzumab was associated with AEs consistent with its mechanism as a T-cell–engaging therapy, with CRS being the most common AESI in both the IV and SC cohorts of the GO29781 study. In both cohorts, CRS events occurred mainly during early treatment cycles and during the step-up dosing period, typically within cycles 1 to 3, with the median time to CRS AE onset from most the recent dose of 2 days (range, 1 day to 8 days). Most CRS events were low grade, resolved within 1 to 3 days, and were manageable with supportive care, dose interruptions, or pharmacologic interventions such as corticosteroids or tocilizumab. The clinical experts indicated that the step-up schedule and premedication with corticosteroids, antihistamines, and antipyretics effectively reduced CRS risk and severity. No fatal CRS event was reported. In the IV cohort, grade 3 or 4 CRS (by ASTCT criteria) occurred in 2 of 90 patients, and in the SC cohort, grade 3 CRS occurred in 2 of 94 patients, with no grade 4 CRS events observed in the SC group. The predictable timing of CRS onset supports administration predominantly in the outpatient setting, with early doses monitored at appropriately equipped centres and later doses potentially delivered closer to home.

Beyond CRS, other commonly reported AEs included infections, neutropenia, fatigue, headache, gastrointestinal symptoms, hypophosphatemia in both cohorts, and injection site reactions in the SC cohort. These events were generally low grade, reversible, and consistent with the known safety profile of mosunetuzumab and with expectations for heavily pretreated lymphoma populations. The SC formulation demonstrated a safety profile similar to the IV formulation, with no new safety signals identified. The fixed-duration treatment approach may also help limit toxicity compared with indefinite therapies. Overall, the clinical experts consulted for this review found the safety profile to be acceptable and manageable with appropriate monitoring and supportive care. However, comparative safety could not be assessed because of the single-arm design, and rare or long-term toxicities beyond 3 to 4 years may not be fully characterized given the sample size and follow-up duration.

The ITC analyses suggest that, for treatment discontinuation due to AEs, mosunetuzumab was statistically favoured over obinutuzumab plus bendamustine in the PSA, while findings were very uncertain in comparisons with rituximab-based regimens, suggesting either the treatment or the comparator could be favoured. For this outcome, comparisons with CAR T-cell therapies were not feasible as such therapies are administered as a single infusion and could not be discontinued. As with the efficacy analyses, interpretation of these comparative safety findings is constrained by methodological limitations, including heterogeneity across studies, incomplete adjustment for prognostic factors, small effective sample sizes, and residual confounding. In addition, besides treatment discontinuation due to AEs, the ITC evidence did not include other clinically relevant safety outcomes, including CRS, which is a key AE associated with mosunetuzumab. These factors introduce uncertainty regarding the robustness and applicability of the comparative harms results. No definitive conclusions could be drawn regarding the relative harms of mosunetuzumab versus comparators.

## Ethics and Equity Considerations

Based on the input from patient and clinician groups, and the clinical experts consulted for this review, mosunetuzumab may address an important unmet need for adult patients with r/r FL who have limited treatment options following multiple prior therapies. The fixed-duration treatment approach may reduce the treatment burden compared with continuous therapies, potentially improving QoL and reducing cumulative toxicity. The option for outpatient administration may also reduce the need for prolonged hospital visits, which may benefit patients and caregivers.

However, access to mosunetuzumab may be influenced by geographic and health system factors. Administration requires monitoring for CRS, particularly during early cycles, and access to clinicians experienced in managing immunotherapy-related toxicities. Patients in rural or remote areas, or those receiving care in centres with limited experience in managing CRS, may face barriers to accessing treatment safely. Ensuring equitable access may require appropriate infrastructure, training, and supportive care resources.

Patients enrolled in the GO29781 study had limited racial and ethnic diversity, with most identifying as white. According to the clinical experts consulted by CDA-AMC, this distribution is less likely to meaningfully affect the generalizability of the findings for patients in Canada, although the underrepresentation of other groups, including Indigenous Peoples, could be noted. There is limited evidence in patients with poorer performance status, who are commonly seen in clinical practice. The clinical experts noted that selected patients with poorer performance status may still be candidates for treatment, but evidence in these populations is limited. Continued data collection, including real-world evidence, will be important to better understand long-term outcomes, safety, and effectiveness in diverse patient populations.

## Conclusion

One ongoing phase I(Ib) and II, single-arm, open-label study (GO29781) provided evidence regarding the efficacy and safety of mosunetuzumab IV monotherapy and mosunetuzumab SC monotherapy in adults with r/r FL (grades 1 to 3a) who had received at least 2 prior lines of systemic therapy. The evidence for the treatment effect of mosunetuzumab from the GO29781 study is very uncertain due to its single-arm design, which makes confirmatory causal conclusions difficult to draw given the absence of a comparator group. However, according to the clinical experts consulted by the review team, the CRR and ORR findings were clinically meaningful and durable for both the IV and SC cohorts and can be attributed to mosunetuzumab rather than to natural history or other factors, despite the study's noncomparative design. The clinical experts also noted that, given the natural history of the disease and their clinical experience, the PFS results observed in the GO29781 study appear to be clinically meaningful for patients with r/r FL (grades 1 to 3a) who have received at least 2 prior lines of systemic therapy, including anti-CD20 and alkylator treatments. The HRQoL results were inconclusive because of the open-label design and missing of data in both the IV and SC cohorts. Notable harms in the GO29781 study, including CRS and injection site reactions (for the SC cohort), were consistent with the known safety profile of mosunetuzumab.

The sponsor-submitted ITC results for OS or ORR were very uncertain in the comparisons of mosunetuzumab versus all comparators, suggesting that either treatment could be favoured.

For PFS, results suggest that axi-cel, tisa-cel, and obinutuzumab plus bendamustine may be favoured over mosunetuzumab, whereas the comparisons versus rituximab plus lenalidomide or versus rituximab plus bendamustine were very uncertain.

For CRR, axi-cel may be favoured over mosunetuzumab, whereas mosunetuzumab may be favoured over rituximab plus lenalidomide and over obinutuzumab plus bendamustine. Results for the comparisons versus tisa-cel or versus rituximab plus bendamustine were very uncertain for CRR.

For treatment discontinuation due to AEs, mosunetuzumab may be favoured over obinutuzumab plus bendamustine. Comparisons versus rituximab plus lenalidomide or versus rituximab plus bendamustine were very uncertain, and analyses for axi-cel and tisa-cel were not feasible.

For all comparisons, it is unclear whether the assumptions underlying the ITCs were met or whether treatment effect modifiers and prognostic variables were appropriately adjusted for. Overall, the findings are very uncertain due to several identified limitations, such as heterogeneity, unmeasured confounding, population differences, small sample sizes, violation of model assumptions in select analyses, and residual uncertainty inherent to indirect comparisons. These limitations identified in the ITCs prevented CDA-AMC from drawing definitive conclusions on the relative efficacy or safety of mosunetuzumab compared with the comparators.

## Economic Review

### Methods

The review team appraised the pharmacoeconomic evidence submitted by the sponsor on the cost-effectiveness and budget impact of mosunetuzumab compared to other relevant treatments for adult patients with r/r FL (grade 1 to 3a) who have received at least 2 prior lines of systemic therapy.

### Summary of the Submitted Economic Evaluation

The sponsor submitted a cost-utility analysis to estimate the cost-effectiveness of mosunetuzumab from the perspective of a public health care payer in Canada over a lifetime horizon of 40 years. The modelled population comprised patients with r/r FL (grades 1 to 3a) who have received at least 2 prior lines of systemic therapy, which is aligned with the Health Canada indication and is based on the participants in the GO29781 trial (median follow-up period: 18.3 months). The sponsor's base-case analysis included costs related to drug acquisition and administration, postprogression therapies, AE management, and supportive care.

The sponsor's base case consisted of 10 pairwise cost-effectiveness results. In all analyses, 98% of predicted quality-adjusted life-year (QALY) gains were based on extrapolation as opposed to trial data.

- Mosunetuzumab IV compared to axi-cel: Mosunetuzumab is dominant (incremental costs = -\$210,229; incremental QALYs = 2.18); mosunetuzumab IV is predicted to reduce health care costs and increase QALYs.

- Mosunetuzumab IV compared to tisa-cel: The incremental cost-effectiveness ratio (ICER) is \$98,060 per QALY gained (incremental costs = −\$171,713; incremental QALYs = −1.75); mosunetuzumab IV is predicted to reduce health care costs but also reduce QALYs.
- Mosunetuzumab IV compared to rituximab plus lenalidomide: Mosunetuzumab is dominated (incremental costs = \$131,602; incremental QALYs = −1.30); mosunetuzumab IV is predicted to increase health care costs and reduce QALYs.
- Mosunetuzumab IV compared to obinutuzumab plus bendamustine: The ICER is \$76,536 per QALY gained (incremental costs = \$64,714; incremental QALYs = 0.85); mosunetuzumab IV is predicted to increase both costs and QALYs.
- Mosunetuzumab IV compared to rituximab plus bendamustine: The ICER is \$76,282 per QALY gained (incremental costs = \$126,413; incremental QALYs = 1.66); mosunetuzumab IV is predicted to increase both costs and QALYs.
- Mosunetuzumab SC compared to axi-cel: Mosunetuzumab is dominant; (incremental costs = −\$216,183; incremental QALYs = 2.20); mosunetuzumab SC is predicted to reduce health care costs and increase QALYs.
- Mosunetuzumab SC compared to tisa-cel: The ICER is \$100,322 per QALY gained (incremental costs = −\$178,069; incremental QALYs = −1.77); mosunetuzumab SC is predicted to reduce health care costs but also reduce QALYs.
- Mosunetuzumab SC compared to rituximab plus lenalidomide: Mosunetuzumab is dominated (incremental costs = \$125,499; incremental QALYs = −1.08); mosunetuzumab SC is predicted to increase health care costs and reduce QALYs.
- Mosunetuzumab SC compared to obinutuzumab plus bendamustine: The ICER is \$62,783 per QALY gained (incremental costs = \$58,089; incremental QALYs = 0.93); mosunetuzumab SC is predicted to increase health care costs and increase QALYs.
- Mosunetuzumab SC compared to rituximab plus bendamustine: The ICER is \$73,174 per QALY gained (incremental costs = \$120,005; incremental QALYs = 1.64); mosunetuzumab SC is predicted to increase health care costs and increase QALYs.

CDA-AMC identified several key issues with the sponsor's analysis (refer to [Table 7](#); full details are provided in the Supplemental Material document, Appendix 11).

**Table 7: Key Issues With the Sponsor's Economic Submission**

| Issue                                                                                 | What evidence is there to inform this issue?                                                                                                     | How was this issue addressed by CDA-AMC?                                                         | Did CDA-AMC explore uncertainty in a scenario analysis? |
|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| The comparative clinical efficacy of mosunetuzumab vs. comparators is very uncertain. | The CDA-AMC review team concluded that comparative efficacy of mosunetuzumab vs. comparators is very uncertain because of a lack of head-to-head | CDA-AMC could not address this issue in the base case due to a lack of robust clinical evidence. | No scenario analysis was conducted.                     |

| Issue                                                                                                                                                                              | What evidence is there to inform this issue?                                                                                                                                                                                                                                                                                                                                                                                                                                                   | How was this issue addressed by CDA-AMC?                                                                                                                | Did CDA-AMC explore uncertainty in a scenario analysis? |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
|                                                                                                                                                                                    | evidence and several limitations identified with the ITC. Because of the low certainty of evidence to inform PFS and OS, the additional incremental benefit predicted with mosunetuzumab is very uncertain.                                                                                                                                                                                                                                                                                    |                                                                                                                                                         |                                                         |
| The OS benefit predicted for mosunetuzumab relative to axi-cel, obinutuzumab plus bendamustine, or rituximab plus bendamustine is likely overestimated in the sponsor's base case. | The CDA-AMC review team concluded that the indirect comparisons submitted by the sponsor for OS were very uncertain in the comparison between mosunetuzumab and all comparators where estimates were affected by imprecision, suggesting that either treatment could be favoured. Between 98% and 99% of the health differences between mosunetuzumab and comparators accrued during the extrapolated period.                                                                                  | CDA-AMC could not address this issue due to the structure of the submitted model and lack of robust OS data.                                            | No scenario analysis was conducted.                     |
| Mosunetuzumab treatment costs are likely underestimated.                                                                                                                           | Time receiving treatment for mosunetuzumab was informed by the GO29781 trial, whereas time receiving treatment for the comparators was based on PFS. This leads to a shorter time receiving treatment for patients treated with mosunetuzumab relative to the comparators, likely underestimating costs of mosunetuzumab. When using the PFS approach to estimate time receiving treatment for mosunetuzumab, this increased from 8.4 cycles lasting 21 days to 8.8 cycles of the same length. | CDA-AMC did not address this limitation because it was not expected to substantially affect the estimates of cost-effectiveness.                        | No scenario analysis was conducted.                     |
| Health state utility values are uncertain.                                                                                                                                         | Health state utility values were based on immature data from the GO29781 trial, reflected the US-based value set, and may be overestimated.                                                                                                                                                                                                                                                                                                                                                    | CDA-AMC did not address this limitation due to uncertainty associated with the health state utility values from the alternative data sources.           | No scenario analysis was conducted.                     |
| Subsequent therapy costs are uncertain.                                                                                                                                            | The distribution of subsequent treatment regimens, which were informed by clinical expert input obtained by the sponsor, did not meet face validity. Re-treatment with mosunetuzumab may have been overestimated and more                                                                                                                                                                                                                                                                      | CDA-AMC did not address this limitation due to constraints in the PSM structure and uncertainties surrounding the distribution of subsequent therapies. | No scenario analysis was conducted.                     |

| Issue                                    | What evidence is there to inform this issue?                                                                                                                                                                                                                                           | How was this issue addressed by CDA-AMC?                                                                                         | Did CDA-AMC explore uncertainty in a scenario analysis? |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
|                                          | patients who were originally treated with rituximab plus lenalidomide, obinutuzumab plus bendamustine, or rituximab plus bendamustine may receive mosunetuzumab than was assumed by the sponsor. Subsequent therapy costs may be underestimated or overestimated and remain uncertain. |                                                                                                                                  |                                                         |
| The health impacts of CRS are uncertain. | There was a lack of clinical evidence to support the assumption that the proportion of patients with CRS requiring hospitalization and ICU admission would be the same between the mosunetuzumab IV and mosunetuzumab SC.                                                              | CDA-AMC did not address this limitation due to a lack of data informing CRS events among patients treated with SC mosunetuzumab. | No scenario analysis was conducted.                     |

axi-cel = axicabtagene ciloleucel; CDA-AMC = Canada's Drug Agency; CRS = cytokine release syndrome; ICU = intensive care unit; ITC = indirect treatment comparison; OS = overall survival; PFS = progression-free survival; SC = subcutaneous; vs. = versus.

Note: Full details of the issues identified by CDA-AMC are provided in the Supplemental Material document, Appendix 11.

## CDA-AMC Assessment of Cost-Effectiveness

The CDA-AMC clinical review appraised the ongoing phase I(Ib) and II, single-arm, open-label GO29781 study and concluded that the evidence for the treatment effect of mosunetuzumab is very uncertain due to the single-arm design, which makes confirmatory causal conclusions difficult to draw given the absence of a comparator group. There have been no head-to-head trials of mosunetuzumab versus comparators. The indirect comparisons submitted by the sponsor for OS were very uncertain in the comparison between mosunetuzumab and all comparators where estimates were affected by imprecision, suggesting that either treatment could be favoured. Results also suggested that axi-cel, tisa-cel, and obinutuzumab plus bendamustine may be favoured over mosunetuzumab for PFS; also, the comparisons between mosunetuzumab versus rituximab plus lenalidomide and between mosunetuzumab versus rituximab plus bendamustine for PFS were very uncertain. Overall, findings from the ITCs are very uncertain due to several identified limitations such as heterogeneity, unmeasured confounding, population differences, and small sample size, in addition to residual uncertainty inherent in the indirect comparisons. For all comparisons, it is unclear if assumptions underlying the ITCs were met and whether treatment effect modifiers and prognostic variables were adjusted for appropriately. These limitations prevent CDA-AMC from drawing definitive conclusions on the relative efficacy or safety of mosunetuzumab compared with axi-cel, tisa-cel, rituximab plus lenalidomide, obinutuzumab plus bendamustine, and rituximab plus bendamustine for the treatment of adult patients with r/r FL (grades 1 to 3a) who have received at least 2 prior lines of systemic therapy.

The indirect evidence for mosunetuzumab versus comparators is therefore very uncertain and there is insufficient evidence to determine whether mosunetuzumab provides a greater health benefit over

comparators. Additional limitations in the economic analysis were identified, including underestimated mosunetuzumab treatment costs, uncertainty surrounding health state utility values, subsequent therapy costs, and the health impacts of CRS. As such, no reanalyses were performed due to insufficient evidence to support an incremental benefit with mosunetuzumab versus comparators. Mosunetuzumab was associated with higher per-cycle drug acquisition costs compared to rituximab plus lenalidomide, obinutuzumab plus bendamustine, and rituximab plus bendamustine (refer to the Supplemental Material document, Appendix 8, Table 19).

## Summary of the Budget Impact

The sponsor submitted a budget impact analysis to estimate the 3-year (2026–2028) budget impact of reimbursing mosunetuzumab for use in the population whose disease met the Health Canada indication. The sponsor assumed that the payer would be CDA-AMC–participating public drug plans and derived the size of the eligible population using an epidemiologic approach. The price of mosunetuzumab was aligned with the price included in the sponsor’s economic evaluation, while the prices of comparators were based on publicly available list prices. Additional information pertaining to the sponsor’s submission is provided in the Supplemental Material document, Appendix 12.

CDA-AMC identified a number of issues with the sponsor’s estimated budget impact and made changes to model parameters and assumptions in consultation with clinical experts to derive the CDA-AMC base case (refer to the Supplemental Material document, Appendix 12). CDA-AMC estimated that 1,744 patients would be eligible for mosunetuzumab over a 3-year period (year 1 = 578 patients; year 2 = 581; year 3 = 585), of whom 873 would be expected to receive mosunetuzumab (year 1 = 231 patients; year 2 = 291; year 3 = 351). The estimated incremental budgetary savings of reimbursing mosunetuzumab is predicted to be approximately \$6 million over the first 3 years, with an expected expenditure of \$109 million on mosunetuzumab. The actual budget impact of reimbursing mosunetuzumab will depend on which treatments are displaced by mosunetuzumab, the market uptake of mosunetuzumab, and the confidential list prices of comparators.

## Conclusion

Based on the CDA-AMC clinical review of the sponsor-submitted ITCs, the comparative efficacy of mosunetuzumab versus all comparators is very uncertain. The ITCs for OS were very uncertain in the comparison between mosunetuzumab and all comparators where estimates were affected by imprecision, suggesting that either treatment could be favoured. Results also suggested that axi-cel, tisa-cel, and obinutuzumab plus bendamustine may be favoured over mosunetuzumab for PFS; also, the comparisons between mosunetuzumab versus rituximab plus lenalidomide and between mosunetuzumab versus rituximab plus bendamustine for PFS were very uncertain. Overall, findings from the ITCs are very uncertain due to several identified limitations, such as heterogeneity, unmeasured confounding, population differences, and small sample size, in addition to residual uncertainty inherent in the indirect comparisons. For all comparisons, it is unclear whether assumptions underlying the ITCs were met and whether treatment effect modifiers and prognostic variables were adjusted for appropriately. These limitations prevent CDA-AMC from drawing definitive conclusions on the relative efficacy or safety of mosunetuzumab compared with axi-cel,

tisa-cel, rituximab plus lenalidomide, obinutuzumab plus bendamustine, and rituximab plus bendamustine for the treatment of adult patients with r/r FL (grades 1 to 3a) who have received at least 2 prior lines of systemic therapy. Consequently, the predicted incremental QALYs with mosunetuzumab are very uncertain. Given the uncertainty in the comparative clinical evidence, there is insufficient evidence to determine whether mosunetuzumab provides greater health benefits over comparators. If there are no differences in health outcomes between mosunetuzumab and comparators, then the total costs of mosunetuzumab to the health system should not exceed those of the least costly comparator for the indicated population.

The 3-year expenditure on mosunetuzumab (i.e., not accounting for current expenditure on comparators) is estimated to be \$109 million. Using public list prices, the budgetary savings of reimbursing mosunetuzumab to the public drug plans in the first 3 years is estimated to be \$6 million. The actual impact of reimbursing mosunetuzumab will depend on which treatments are displaced by mosunetuzumab, the market uptake of mosunetuzumab, and the confidential list prices of comparators. 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 the CDA-AMC estimate.

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**ISSN:** 2563-6596

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