Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Recommendation

Reimbursement Recommendation

(Draft)

Rozanolixizumab (Rystiggo)

Indication: For the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) or anti-muscle specific tyrosine kinase inhibitor (MuSK) antibody positive.

Sponsor: UCB Canada Inc.

Recommendation: Reimburse with Conditions

Publication Date: April 2025

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Recommendation

The CDA-AMC Canadian Drug Expert Committee recommends that rozanolixizumab be reimbursed as an add-on therapy for the treatment of adult patients with generalized myasthenia gravis (gMG) who are either acetylcholine receptor (AChR) or muscle-specific kinase (MuSK) antibody positive and for whom symptoms persist despite conventional therapy with acetylcholinesterase inhibitors (AChEIs), corticosteroids, and/or non-steroidal immunosuppressive therapies (NSISTs) only if the conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

One Phase 3, double-blind, randomized placebo-controlled trial (MyCarinG, N=200 patients) demonstrated that treatment with rozanolixizumab results in added clinical benefit for adult patients with AChR-positive or MuSK-positive gMG compared with placebo. The primary outcome indicated that after 43 days of treatment, reduction in symptom severity was clinically significantly better with rozanolixizumab than with placebo as measured by changes from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) scores (least square mean difference between groups of -2.586 (95% CI -4.091 to -1.249, p<0.001). The between-group difference in patients achieving at least a 2-point improvement in this outcome (i.e., MG-ADL responders) was 39.8% (95% CI 24.2 to 55.4) in favour of rozanolixizumab. Treatment response was also statistically significantly better with rozanolixizumab than placebo as indicated by a least square mean difference between groups of -3.483 (95% CI -5.614 to -1.584; p<0.001) in Quantitative Myasthenia Gravis (QMG) scores. Assessment of patients' health related quality of life (HQRoL) using the disease-specific Myasthenia Gravis Quality of Life 15-Item (MG-QoL15r) scale showed that rozanolixizumab would likely improve patients' quality of life related to myasthenia gravis better than placebo, with a between-group least square mean difference of -2.245 (95% CI -4.096 to -0.394).

Patients identified a decrease in the number of exacerbations, reduction in medication side effects, the maintenance of independence, reducing the number of serious hospital admissions and health related quality of life as key important outcomes. CDEC concluded that rozanolixizumab may meet some of the patients' needs, including offering another mode of administration with the potential of at-home administration, which may meet a need for improved independence and improving patients' quality of life related to myasthenia gravis with minimal side effects.

At the sponsor submitted price for rozanolixizumab, publicly listed price for rituximab, eculizumab, or efgartigimod alfa, and prices based on published literature for PLEX and IVIg/SCIg, rozanolixizumab plus CT may be more or less costly than other advanced treatments. Given the uncertainty with the comparative clinical evidence, the total drug cost of rozanolixizumab should not exceed the total drug cost with the least costly advanced treatments for gMG.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with rozanolixizumab should be reimbursed for adult patients with gMG who have all of the following: 1.1. Positive serologic test for either AChR or MuSK antibody 1.2. MG-ADL score at baseline of ≥3 (with at least 3 points coming from non-ocular symptoms) 1.3. MGFA class II to IV disease 1.4. Symptoms persisting despite stable doses of conventional therapy with AChEIs, corticosteroids, and/or NSISTs	The results from one phase III, multicentre, double-blind, randomized, placebo-controlled trial (MyCarinG) demonstrated that compared with placebo, treatment with rozanolixizumab results in a statistically significantly reduction of 2 in the primary outcome of MG-ADL in adult patients (aged ≥ 18 years) with gMG who are either AChR or MuSK antibody positive. The enrolled patients in MyCarinG enrolled adult patients had an MG-ADL score ≥ 3, MGFA class of II to IV, and symptoms persist despite a stable dose of conventional therapy with AChEIs, corticosteroids, and/or NSISTs at baseline.	Stable dose may be defined as adequate trial (as determined by the treating physician) of at least 1 of AChEIs, CSs, and/or NSISTs in the previous 12 months. CDEC noted that rituximab may be available in some jurisdictions. However, CDEC heard from the clinical experts that access to rituximab remains a barrier for some patients.
2. Rozanolixizumab should not be initiated: 2.1. during a gMG exacerbation or crisis, or 2.2. thymectomy within 6 months.	Patients were excluded from the MyCarinG trial if they had had thymectomy within 6 months before screening. The efficacy and harms of rozanolixizumab in such patients are unknown.	—
3. MG-ADL score must be measured and provided by physician at baseline	In line with other targeted treatments for gMG, and aligns with the MyCarinG trial in which baseline MG-ADL score was measured and used to determine response to treatment	—
4. The maximum duration of initial authorization is for 6 weeks.	In the MyCarinG trial, rozanolixizumab was administered as a SC infusion once weekly for 6 weeks. In addition, the recommended dosage by Health Canada is administered as a subcutaneous infusion once weekly for 6 weeks.	
Renewal		
5. Reimbursement of treatment with rozanolixizumab should be continued if, after the initial 6 weeks of treatment, there is documented improvement in disease symptoms, indicated by a reduction in MG-ADL score of 2 points or greater. Reassessment should occur every 12 months thereafter	Although no MID has been estimated, an improvement of approximately 2 points in the total MG-ADL score is a recommended response threshold that indicates clinical improvement at the level of individual patients with MG. In the MyCarinG trial, after the 6-week treatment period, patients entered an 8-week observation period. Patients who completed the 6-week treatment period	After the initial 6-week treatment period, patients can be observed up to an 8-week period. After the initial 6 weeks of rozanolixizumab, if a patient has responded, treatment would be given as long as the patient continues to have a clinically meaningful response. In terms of maximum duration of treatment, treatment with rozanolixizumab would probably be given as long as

Reimbursement condition	Reason	Implementation guidance
	and 8-week observation period had the opportunity to roll over into MG0004, an OLE study which assessed the long-term safety and efficacy of rozanolixizumab weekly dosing regimen for 52 weeks.	rozanolixizumab continued to be effective, or disease spontaneously remitted.
6. For subsequent renewal, the physician must provide proof of no worsening of MG-ADL score.	This is to ensure that patients are maintaining their response to treatment with rozanolixizumab	There is the possibility of rozanolixizumab being used for 1 year or more years. If a patient had responded to rozanolixizumab after the initial weekly injections for 6 weeks and was stable for a year but worsens afterward. A patient who continued to receive treatment after the initial weekly injections for 6 weeks but was no longer receiving rozanolixizumab (i.e., was an initial responder but was no longer receiving treatment) can reinitiate therapy, if they meet the initiation criteria. The patient would not be expected to try standard care (AChEIs, corticosteroids, and/or NSISTs) again.
Prescribing		
7. Rozanolixizumab should be prescribed by or in consultation with a neurologist with expertise in managing patients with gMG.	Accurate diagnosis and follow-up of patients with gMG are important to ensure that rozanolixizumab is prescribed to appropriate patients.	—
8. Rozanolixizumab should not be used concomitantly with rituximab, efgartigimod alfa, and/or complement inhibitors such as eculizumab.	The MyCarinG trial did not assess such combinations, and the efficacy and safety of rozanolixizumab in combination with rituximab, efgartigimod alfa, eculizumab, or ravulizumab is unknown	
Pricing		
9. Rozanolixizumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly advanced treatment reimbursed for the treatment of gMG.	Given the uncertainty associated with the comparative clinical evidence, there is insufficient evidence to justify a cost premium for rozanolixizumab over the least expensive advanced treatment reimbursed for gMG.	—
Feasibility of adoption		
10. The economic feasibility of adoption of rozanolixizumab must be addressed	At the submitted price, the incremental budget impact of rozanolixizumab is expected to be greater than $40 million in years 2 and 3.	—

AChEIs = acetylcholinesterase inhibitors; AChR = acetylcholine receptor; CT = conventional therapy; CSs = corticosteroids; gMG = generalized Myasthenia Gravis; IVIg = intravenous immunoglobulin; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis-Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MuSK = muscle-specific tyrosine kinase; NSIST = non-steroidal immunosuppressive therapy; OLE=open-label extension PLEX=plasma exchange; QMG = Quantitative Myasthenia Gravis

Discussion Points

- **Limited evidence in MuSK-positive population:** CDEC noted that while the MyCarinG trial included patients with gMG who were either AChR or MuSK antibody positive and who were being considered by the Investigator for additional treatment such as IVIg or PLEX., less than 10% of those enrolled were MuSK positive. CDEC observed that the clinical expert projected that the proportion of gMG patients with MuSK positive antibodies in his practice was about 5%, which would suggest that the small size of the MuSK positive subgroup in the MyCarinG trial aligns with what happens in clinical practice. However, the small sample limits any conclusions that can be drawn about the efficacy or safety of rozanolixizumab in the MuSK-positive subpopulation.
- **Prior treatments:** CDEC noted that although most patients (96%) included in the MyCarinG trial had received at least one prior therapy, many of the patients had only been treated with 1 class of conventional therapy (AChEIs only:15.5%, steroid only: 27.5%, and NSIST only: 13.5%). CDEC observed that the post-hoc subgroup analysis evaluating response in patients who had 2 or more prior therapies had limitations, including small sample size and lack of information about the adequacy of trial with alternative therapies, limiting the conclusions that could be drawn from it.
- **Lack of direct comparative evidence:** In the absence of trials directly comparing rozanolixizumab to other drugs used for treating gMG, CDEC considered the evidence from the sponsor-submitted indirect treatment comparisons assessing the efficacy and harms of rozanolixizumab versus comparators. The committee noted that the submitted network meta-analysis (NMA) was limited by imprecision and heterogeneity in the included studies, and the results from the matching-adjusted indirect comparison (MAIC) were uncertain due to potential for residual confounding, small sample size, imprecision and generalizability of evaluating treatment response. Therefore, a definitive conclusion could not be drawn from the ITCs regarding the comparative efficacy of rozanolixizumab versus eculizumab or efgartigimod alfa. Comparative data on harms were not reported.
- **Efficacy:** CDEC noted that the effect estimates for the efficacy outcomes (MG-ADL, QMG, and MG-QoL) exceeded the suggested thresholds identified by the clinical expert as clinically meaningful, and assessments using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach moderate certainty in evidence. CDEC noted that overall, treatment with rozanolixizumab resulted in consistently greater decreases from Baseline in MG–ADL score at Day 43 across all subgroups compared with placebo (not rated with GRADE), however, the wide confidence interval associated with outcomes for MuSK-positive patients indicated imprecision that may be due to the small sample size of the subgroup.
- **Long-term outcomes:** CDEC noted that the treatment duration of the pivotal MyCarinG trial was 6 weeks, with responses assessed at day 43, and the long-term extensions phase did not involve any comparators. Therefore, CDEC could not draw any conclusions on the comparative long-term efficacy and harms of rozanolixizumab.
- **Cost-effectiveness of rozanolixizumab:** CDEC discussed that if other recently recommended treatments for refractory gMG are reimbursed by CDA-AMC participating drug plans, there is no robust comparative clinical evidence for rozanolixizumab to be priced more than the lowest cost advanced treatment reimbursed for AChR or MuSK antibody positive refractory gMG.

Background

Myasthenia gravis (MG) is a rare, chronic, autoimmune neuromuscular disease in which antibodies against the neuromuscular junction disrupt neuromuscular transmission, resulting in localized or generalized skeletal muscle weakness. Patients experience a variety of symptoms including fatigue, droopy eyelids, diplopia, neck weakness, difficulty swallowing or chewing, speech disturbances, difficulty breathing, and upper and/or lower limb weakness. Based on serology, 85% of patients with generalized MG (gMG) are acetylcholine receptor (AChR) antibody positive, 8% are muscle-specific kinase (MuSk) antibody positive, 1% are lipoprotein-related protein 4 (LRP4) antibodies positive, and the remaining 6% of cases are seronegative with no detectable antibodies. Globally, the incidence of MG varies from 4 to 30 cases per million person-years and the prevalence ranges from 150 to 200 cases per million. In Canada, the incidence and prevalence of gMG are estimated at 23 per 1 million person-years and 26.3 per 100,000, respectively. The mortality rate of MG has been reported to be between 0.06 to 0.89 per million person-years. The symptoms of gMG occur unpredictably and fluctuate in nature, intensity, and severity on a day-to-day basis throughout a patient's life, requiring intervention or treatment change. The unpredictable exacerbation and myasthenic crisis, in combination with a variety of symptoms result in a chronic disease with significant burden negatively impacting a patients' quality of life.

There are currently no Canadian guidelines for the treatment of gMG. The MGFA international consensus guidelines for the management of MG were updated in 2020 and are now the most recent guidelines for the management of MG. According to these guidelines and Canadian clinical experts, the goal of treatment for patients with gMG is to reduce disease symptoms as well as adverse effects of MG therapy and to allow the patient to function and work normally with good health-related QoL (HRQoL). Other treatment goals include avoiding MG exacerbations and myasthenic crises, minimizing hospitalizations and intensive care unit admissions, and reducing the numbers and doses of therapies (especially corticosteroid use) required for symptom control.

Conventional therapy for all gMG patients generally begins with AChEIs, though AChEI can worsen MuSK MG symptoms, and so may not be used in all MuSK gMG patients. If AChEI therapy alone provides insufficient symptom relief, immunosuppressive therapy with a corticosteroid such as prednisone is administered. In patients who either do not respond to corticosteroids, who have significant comorbidities such that long-term corticosteroid treatment is contraindicated, or in whom doses of corticosteroids cannot be tapered, treatment with NSISTs such as azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, or methotrexate may be initiated either alone or in combination with corticosteroids. It can take several months to years, depending on the NSIST, for the drug to produce a clinically relevant effect and reduce a patient's gMG symptoms. While patients wait for NSIST treatment to take effect, they may experience MG exacerbations and/or myasthenic crises which require acute use of intravenous or subcutaneous immunoglobulin or PLEX. If patients continue to experience gMG symptoms, the dose may be increased or the drug switched to an alternative NSIST.

It is estimated that 15 to 40% of patients will continue to experience symptoms despite conventional therapy with AChEIs, corticosteroids, and/or NSISTs. Patients with AChR-positive gMG whose symptoms persist despite conventional therapy would be eligible for treatment with rituximab, chronic intravenous or subcutaneous immunoglobulin and/or chronic PLEX. Currently, rozanolixizumab is the only targeted therapy approved by Health Canada for the treatment of MuSK-positive gMG. Patients with MuSK-positive gMG are less responsive to AChEIs and are frequently intolerant to pyridostigmine at conventional doses. Patients with MuSK antibodies typically respond well to corticosteroids and NSISTs but tend to remain dependent on corticosteroids despite concomitant therapy with NSISTs. For patients with MuSK-positive gMG whose symptoms persist despite treatment with corticosteroids and NSISTs, options include rituximab and PLEX, while intravenous immunoglobulin is usually less effective. Rituximab is recommended by international consensus guidance for MuSK-positive gMG patients who have an unsatisfactory response to initial immunotherapy. That is in contrast to patients with AChR-positive gMG where rituximab is only considered if patients fail or do not tolerate other immunotherapies.

Rozanolixizumab has a Health Canada approved indication for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) or anti-muscle specific tyrosine kinase inhibitor (MuSK) antibody positive. Rozanolixizumab is a humanized immunoglobulin (Ig) G4 monoclonal antibody that decreases serum IgG concentration by inhibiting the binding of IgG to neonatal fragment crystallizable receptor (FcRn), a receptor that normally protects IgG from intracellular degradation and recycles IgG back to the cell surface. It is available as one 280mg/2mL (i.e., 140mg/mL) single-dose vial. The recommended dosage (based on body weight) is administered as a solution for subcutaneous infusion using an infusion pump at a rate of 20mL/hour once weekly for 6 weeks.

Sources of Information Used by the Committee

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

- a review of 1 phase 3, randomized, double-blind and placebo-controlled study (MyCarinG) in adult patients with gMG; with 2 long-term extension studies (MG0004 and MG0007);
- 4 indirect treatment comparisons
- patients' perspectives gathered by 1 patient group: Muscular Dystrophy Canada
- input from 1 clinician group: Neuromuscular Disease Network for Canada
- input from public drug plans that participate in the reimbursement review process
- 1 clinical specialist with expertise diagnosing and treating patients with gMG
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

- There was one patient group submission, from Muscular Dystrophy Canada, who collected input via survey and semi-structured virtual interview, for a total sample of 194 patients.
- Patients reported issues with productivity, fatigue, low energy levels and quality of life, mental health, respiratory health, mobility and strength, independence, relationships and social participation, eyes/vision, speech and swallowing. Respondents stated that the impact of gMG extended beyond physical symptoms, impacting the quality of life and the well-being of their families.
- Outcomes of importance to patients include a decrease in the number of exacerbations, reduction in medication side effects, maintenance of independence, and reducing the number of serious hospital admissions.
- With respect to their experience with currently available therapies, the main themes that emerged included their negative experiences with steroids, that conventional treatments take a long time to take effect, and the treatment pathway involved a lot of trial and error.

Clinician Input

Input From Clinical Experts Consulted for this Review

- The clinical expert consulted on this review noted numerous needs that are not being met by current therapy, including that 10% of patients are refractory to all currently available treatments, that there is a delayed effect to immunosuppressants, and the harms associated with conventional therapies notably the corticosteroids. The clinical expert noted that it is these refractory patients that are most likely to require hospitalization or costly and more involved rescue therapies such as IVIg and PLEX, on a more chronic basis.
- The clinical expert sees rozanolixizumab as add-on therapy, for use in similar manner to IVIg and efgartigimod, specifically in patients who have tried glucocorticoids and/or a steroid-sparing agent and had an inadequate response, or in whom steroids could not be tapered or side effects were intolerable. The clinical expert also noted the potential for rozanolixizumab to act as bridging therapy while waiting for the typically delayed effects of immunosuppressants several months after initiation.
- The clinical expert believed that the patients most likely to respond to rozanolixizumab would be the type included in the pivotal trial, namely those who are MuSK-positive or AChR-positive, and continue to be symptomatic (based on their Myasthenia Gravis Activities of Daily Living [MG-ADL] score) despite trials of first line therapy.
- According to the clinical expert, response to treatment would be assessed, using patient's subjective response (symptoms), and whether there has been improved functional capacity according to the treating clinician. Treatment would be discontinued for lack of response (although how long a trial is currently unclear), and side effects. The clinical expert estimated that they would

suggest a trial of 3 to 6 months before discontinuing for lack of efficacy. Also, treatment discontinuation may be considered if the patient determines their treatment goals have been achieved based on the response.

Clinician Group Input

- Input was received from 1 clinician group, the Neuromuscular Disease Network for Canada (NMD4C), which included responses from 5 of the clinicians in the group.
- The clinician group was generally in agreement with the views of the clinical expert consulted with respect to unmet needs, patients most likely to respond to treatment, and that key outcomes are the MG-ADL and Quantitative Myasthenia Gravis (QMG) scores.
- The clinician group did not indicate whether they had experience using rozanolixizumab, however they did note that it is likely to replace standard immunoglobulin therapies.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for rozanolixizumab:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues

The clinical expert consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
Clinical Experts: If both efgartigimod alfa and rozanolixizumab were available through public reimbursement, which agent would be preferred and why— for patients with AChR antibody positive gMG?	The clinical expert noted that the choice between efgartigimod alfa and rozanolixizumab would largely come down to patient preference, as they did not see a clear advantage of one over the other. *CDEC agreed with the clinical expert*
Clinical Experts: If both rituximab and rozanolixizumab were available through public reimbursement, which agent would be preferred for patients with MuSK antibody positive gMG?	The clinical expert noted that although efficacy-wise there are no data to necessarily prefer one over the other, rituximab has some significant safety issues associated with it that might make it the less favourable of these two options. Rituximab also does not have approval for the treatment of MuSK gMG. *CDEC noted the clinical expert's comment*

Drug program implementation questions	Clinical expert response
Clinical Experts: If you had access to rituximab through public reimbursement, would it be used as a first line treatment in patients with AChR or MuSK? If so, in what clinical situations?	The clinical expert noted that rituximab would not be first line for AChR-positive patients. The clinical expert noted that for patients who are MuSK-positive, rituximab might be first line in those who are more severely impacted by their disease (MG-ADL of 5 or higher), such as patients with swallowing difficulties, or at least might be used early if there is limited benefit from glucocorticoids or IVIg/PLEX. *CDEC noted the clinical expert's comment*
Clinical Experts: What is the prevalence of patients with MuSK antibody positive gMG in your practice?	The clinical expert estimated that patients who are MuSK positive make up about 5% of gMG patients in their practice. *CDEC noted the clinical expert's comment*
Clinical Experts: Does rozanolixizumab meet an unmet need for adult patients with AChR or MuSK antibody positive gMG symptoms despite conventional treatment?	The clinical expert noted that rozanolixizumab meets an unmet need for patients who are refractory to or intolerant of other therapies. *CDEC noted the clinical expert's comment*
Considerations for initiation of therapy	
Example: The disease scoring system used in the trial is not used in Canadian clinical practice; it would be challenging to include it in eligibility criteria. Patients enrolled in the MycarinG (MG0007) trial, must have met the following criteria: • Documented diagnosis of gMG • Positive record of autoantibodies against AChR or MuSK • MGFA Class II to IVa • MG-ADL score of at least 3 (with ≥3 points from a non-ocular symptom) and a QMG score of at least 11 • Considered for additional treatment such as IVIg or PLEX by the Investigator. The primary end point was change from Baseline to Day 43 in MG-ADL score. **Clinical Experts:** Do the scores in the above criteria align with what you would see in practice of initiating treatment? **CDA-AMC** Should the initiation criteria align with the inclusion criteria?	The clinical expert noted that the inclusion criteria for the MyCarinG trial are consistent with the patients they would encounter in their practice. The clinical expert noted that it would be reasonable for the initiation criteria to align closely with the trial's inclusion criteria, except where a patient for whom IVIg or PLEX may not be appropriate is being considered for additional treatment. Such patients may benefit from rozanolixizumab. *CDEC agreed with the clinical expert*
Clinical Expert: 1. If patients with AChR antibody positive gMG experience treatment failure with Vyvgart or	The clinical expert believed that patients with AChR positive gMG who experience treatment failure with

Drug program implementation questions	Clinical expert response
rituximab, would they be eligible for treatment with rozanolixizumab? 2. If patients with MuSK antibody positive gMG experience treatment failure on rituximab, would they be eligible for treatment with rozanolixizumab?	efgartigimod or rituximab, should be eligible for treatment with rozanolixizumab. The clinical expert believed that patients with MuSK positive gMG who experience treatment failure on rituximab should be eligible for treatment with rozanolixizumab. *CDEC agreed with the clinical expert*
Clinical Experts: Under what conditions can a patient restart treatment with rozanolixizumab?	The clinical expert noted that they would look at the patient response, then treat when needed. The clinical expert added that you do not want to re-treat for minor symptoms, but you also do not want the patient to deteriorate too much before intervening *CDEC agreed with the clinical expert*
Considerations for prescribing of therapy	
Rozanolixizumab is administered via a short (<18 minute) SC injection using an infusion pump and a single-dose vial of rozanolixizumab vial once weekly for 6 weeks. **Clinical Expert:** Efgartigimod alfa is administered as IV over 1 hour once weekly for 4 doses. Does the shorter infusion time and subcutaneous administration influence your choice of therapies?	The clinical expert believed that they would prefer a shorter infusion time and a subcutaneous route of administration because these use less resources and are preferred by patients. *CDEC agreed with the clinical expert*
Drug administration Example: Intrathecal administration requires special training and facilities. • The draft product monograph states that rozanolixizumab should only be prepared and infused by a healthcare professional. • UCB Canada will offer an optional patient support program (PSP) providing patient education and health care professional support for administration of rozanolixizumab at program infusion clinics or in the patient's home. • Following the first treatment cycle, subsequent cycles are administered according to clinical evaluation. • The frequency of treatment cycles may vary by patient. Pooled data from the phase 3 and extension studies suggest a mean annualized rate of 17.8 infusions (2.97 completed cycles) and 3.4 initiated cycles. **Clinical Experts:** Are there any scenarios where administration at a clinic would be preferred over at home treatments?	The clinical expert noted that generally speaking, administration at a clinic would not be preferred over home administration, with the lone exception of the first dose, where you may wish to observe the patient in case they have a reaction. *CDEC agreed with the clinical expert*

Drug program implementation questions	Clinical expert response
Consistency with prescribing criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space **CDA-AMC:** Should the prescribing criteria align with efgartigimod alfa?	The clinical expert believed that yes, it would be reasonable for the criteria to align with Vyvgart, with the addition of an indication for MuSK gMG (which Vyvgart does not have). *CDEC agreed with the clinical expert.*
System and economic issues	
Concerns regarding the anticipated budget impact and sustainability Example: Provision of this drug in the first line setting may translate into substantial budget impact. A prioritization scheme may be required. • The price of each single-dose vial is $12,260.2760. • The sponsor assumed the average annual cost of rozanolixizumab is $436,956 per patient. • Quality-adjusted life years at a similar cost as efgartigimod alfa.	*This is a comment from the drug programs to inform CDEC deliberations.*
Additional costs to be considered (other than related to care provision as detailed above) The sponsor indicated that they would offer an optional patient support program (PSP) providing patient education and health care professional support for administration of rozanolixizumab at program infusion clinics or in the patient's home.	*This is a comment from the drug programs to inform CDEC deliberations.*
Presence of confidential negotiated prices for comparators Example: Comparators A and B have successfully gone through price negotiations for the same indication. • Efgartigimod alfa is currently under negotiation with pCPA.	*This is a comment from the drug programs to inform CDEC deliberations.*

AChR = acetylcholine receptor; gMG = generalized Myasthenia Gravis; IVIg = intravenous immunoglobulin; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis-Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MuSK = muscle-specific tyrosine kinase; NSIST = non-steroidal immunosuppressive therapy; pCPA =pan Canadian Pharmaceutical Alliance; PLEX=plasma exchange; PSP = patient support program; QMG = Quantitative Myasthenia Gravis; SC = subcutaneous

Clinical Evidence

Systematic Review

Description of Studies

MycarinG was a Phase 3, sponsor-funded, double-blind randomized controlled study. Eligible patients were adults over 18 years of age with AChR-positive or MuSK-positive gMG (MGFA disease class II-IVa), a MG-ADL score ≥3 (with at least a score of 3 from non-ocular symptoms), a QMG score ≥11, and who were being considered by the Investigator for additional treatment such as IVIg or PLEX. The study began enrolling patients in June 2019 and concluded in October 2021, with a final data cut-off date of September 17, 2021. A total of 200 patients were enrolled and randomized in a 1:1:1 ratio to receive 6 weekly SC infusions of rozanolixizumab 10 mg/kg, 7 mg/kg, or matching placebo. The recommended dosing under review by Health Canada is 7 mg/kg, and it is this dose that will be the focus of this review. The study spanned 81 sites across 17 countries with 4 sites in Canada. The total duration of study participation for all patients was up to approximately 18 weeks, including a Screening Period of up to 4 weeks, a 6-week Treatment Period, and an 8-week Observation Period. Patients who completed the 6-week Treatment Period and 8-week Observation Period had the opportunity to roll over into MG0004, an open label extension study where the long-term safety, tolerability, and efficacy of rozanolixizumab was measured in patients with gMG over 52-weeks of weekly chronic treatment. MG0004 was terminated in 2021 and replaced by MG0007, an ongoing open label extension study study which consists of 6-week treatment cycles based on MG worsening. Patients could roll over from MycarinG or MG0004 directly into MG0007.

Patients in the pivotal study were 52 years of age (standard deviation [SD]: 16 years) on average, and the majority (61%) were female. Most patients were MGFA Class IIa or IIb (39%) or Class IIIa or IIIb (57%) at baseline. The majority (83%) of patients were AChR-positive and 9% were MuSK-positive at baseline.

Efficacy Results

The outcomes determined to be of importance based on consultation with clinical experts, and input received from patient and clinician groups and public drug plans are discussed herein.

MG-ADL

The primary endpoint *was* change from Baseline to Day 43 in MG-ADL score (range 0 to 24 with higher scores indicating more severe symptoms). From a baseline mean (SD) ADL score of 8.4 (3.8) in the rozanolixizumab group and 8.4 (3.4) in the placebo group, the LS mean (SE) change from baseline was -3.22 (0.480) and -0.65 (0.363). The LS mean difference in change from baseline was -2.586 (95% CI: -4.091, -1.249; p<0.001), favouring rozanolixizumab. Results from the sensitivity analysis were consistent with those from the main analysis. Overall, compared with placebo, treatment with rozanolixizumab resulted in consistently greater decreases from baseline in MG-ADL score at Day 43 across all subgroups, except for the subgroups with a low number of patients. 45 patients (68.2%) in rozanolixizumab had MG-ADL response with at least a 2-point improvement at Day 43 versus 19 patients (28.4%) in the placebo group, with a between-group difference of 39.8% (95% CI: 24.2, 55.4).

The sponsor also reported data from a post hoc subgroup analysis for the [redacted] patients in the rozanolixizumab group and [redacted] patients in the placebo group who had 2 or more prior MG-specific therapies. From a mean (SD) baseline score of [redacted] in the rozanolixizumab group and [redacted] in the placebo group, the LS mean (SE) change from baseline to Day 43 in MG-ADL scores was [redacted] for rozanolixizumab and [redacted] for placebo, with a LS mean difference between groups of [redacted] In this subgroup, the number of responders with at least a 2-point improvement in MG-ADL at Day 43 was [redacted] and [redacted] in the rozanolixizumab and placebo groups, respectively.

QMG score

The QMG score ranges from 0 to 39 with higher scores indicating more severe impairment. From a mean (SD) baseline of 15.4 (3.7) in the rozanolixizumab group and 15.8 (3.5) in placebo, the LS mean change from baseline was –5.598 (SE, 0.679) with rozanolixizumab and –1.915 (SE, 0.685) with placebo. The LS mean between-group difference in change from baseline was –3.483 (95% CI: 5.614, –1.584; p<0.001), favouring rozanolixizumab. Results for various sensitivity analyses were consistent with the overall analysis of change from baseline to Day 43 in QMG score.

The sponsor also reported of subgroup analyses of QMG scores by baseline antibody status, for the 59 patients in rozanolixizumab and 51 patients in placebo who were AChR-positive, and the 4 patients in rozanolixizumab and 7 patients in placebo who were MUSK-positive. In the AChR-positive subgroup, the LS mean (SE) change from baseline to day 43 was –4.660 (1.605) with rozanolixizumab and –1.189 (1.575) for a LS mean difference between groups of –3.471 (97.5% CI; –5.433 to –1.510). In the MuSK–positive subgroup, the LS mean (SE) change from baseline to day 43 was –10.276 (3.490) with rozanolixizumab and –2.662 (2.710) with placebo, for a LS mean difference between groups of –7.614 (97.5% CI: –16.291 to 1.062).

The sponsor also reported data from a post hoc subgroup analysis of the [redacted] patients in the rozanolixizumab group and [redacted] patients in the placebo group who had 2 or more prior MG-specific therapies. From a mean (SD) baseline score of [redacted] in the rozanolixizumab group and [redacted] in the placebo group, the mean (SD) change from baseline to Day 43 in QMG scores with rozanolixizumab was [redacted] and for placebo [redacted] for a LS mean difference between groups of [redacted]

Revised 15-item Myasthenia Gravis Quality of Life questionnaire (MG-QoL 15r)

The MG-QoL 15r ranges from 0 to 30 with higher scores indicating a more severe impact of disease on HRQoL. From a mean (SD) baseline of 15.7 (7.7) in the rozanolixizumab group and 15.0 (6.4) with placebo, the LS mean change from baseline was –4.0 (SE, 6.1) with rozanolixizumab compared to –1.3 (4.3) with placebo. The LS mean between-group difference in change from baseline was –2.245 (95% CI, –4.096 to –0.394), favouring rozanolixizumab.

MG-C

The MG-C score ranges from 0 to 50 with higher scores indicating more severe impairment. The LS mean change from baseline was –5.23 (SE, 0.828) with rozanolixizumab and –1.47 (SE, 0.722) with placebo. The LS mean between group difference in change from baseline was –3.901 (95% CI, –6.634 to –1.245), p<0.001, favouring rozanolixizumab. Results of sensitivity analyses were consistent with the overall analysis.

Harms Results

Adverse Events

Overall, the number of study patients who experienced AEs was 52 (81.3%) with rozanolixizumab and 45 (67.2%) with the placebo group. The most common AEs (10% or more in either group) for rozanolixizumab versus placebo, respectively, were diarrhea (25.0 vs. 13.4%), pyrexia (12.5 vs. 1.5%), and headache (45.3 vs. 19.4%).

Serious Adverse Events

A comparable number of study patients in the rozanolixizumab and placebo groups reported SAEs (5 [7.8%]) and placebo (6 [9.0%]). The only SAEs reported in >1 study patient per treatment group was myasthenia gravis crisis, which occurred in no patients in the rozanolixizumab group and 2 (3.0%) in the placebo patients.

Withdrawals Due to Adverse Events

The incidence of AEs leading to permanent discontinuation of study drug was similar in rozanolixizumab 7mg/kg group (2 [3.1%], and the placebo group (2 [3.0%]).

Mortality

There were no deaths in the study.

Notable Harms

Infection was identified as a notable harm for this review, and ‘infections and infestations’ occurred in 10 patients (15.6%) in the rozanolixizumab group and 13 patients (19.4%) in placebo.

Critical Appraisal

- The MyCarinG trial was relatively well-conducted with adequate allocation concealment and steps taken to maintain blinding. With the exception of the MG-ADL responders and MG-QoL 15r outcomes, all efficacy outcomes were multiplicity controlled, reducing the risk of type 1 error. Although there were some imbalances in baseline characteristics between groups, the clinical expert did not believe these were of clinical relevance.
- With respect to external validity, the clinical expert believed that the population in MyCarinG was generalizable to the population of patients for whom he would expect to use the drug in Canada. Although the sponsor is seeking reimbursement for patients whose symptoms persist despite treatment with AChEIs, corticosteroids, and/or NSISTs, the pivotal did not restrict enrollment based on prior treatment. However, most patients (96%) had received at least 1 prior gMG-specific therapy before the trial. The sponsor provided data from a post hoc subgroup analysis of patients who had received 2 prior therapies, however limited conclusions can be drawn from this data because of the inherent limitations in post hoc analyses.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CDA-AMC expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of an important effect based on thresholds identified in the literature and supported by the clinical expert for the change from baseline to day 43 in MG-ADL and QMG scores; presence or absence of an important effect based on thresholds informed by the clinical expert consulted for this review for MG-ADL responders; and the presence or absence of any [non-null] effect for the change from baseline to day 43 in MG-QoL 15r scores and for notable harms (infections and infestations).

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- MG-ADL score (change from baseline to day 43; responders [patients at least a 2-point improvement from baseline in MG-ADL])
- QMG score (change from baseline to day 43)
- MG-QoL 15r score (change from baseline to day 43)
- Notable harms: Infections and infestations

Table 3: Summary of Findings for Rozanolixizumab Versus Placebo for Patients With gMG

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Rozanolixizumab	Difference		
Activities of Daily Living (MG-ADL)							
Change from baseline (Scale from 0 to 24, higher scores indicate more severe symptoms) Follow-up: day 43	127 (1 RCT)	NA	-0.65	-3.22 (0.480)	-2.586 (-4.091 to -1.249)	Moderate[a]	Rozanolixizumab likely results in a clinically important improvement in MG-ADL scores compared to placebo.
Patients achieving response, n (%) (response defined as at least a 2 point improvement in MG-ADL) Follow-up: day 43	133 (1 RCT)	OR = 5.765 (2.100, 14.882)	28 per 100	68 per 100	39.8 more per 100 (24.2 to 55.4 per 100 more)	Moderate[b]	Rozanolixizumab likely results in a clinically important increase in the number of MG-ADL responders compared to placebo.
Mysasthenia Gravis-Quality of life (MG-QoL)							
LS Mean change from Baseline to Day 43 in MG-QOL 15r score (Scale from 0 to 30, with higher scores indicating more severe impact of disease on HRQOL)	133 (1 RCT)	NA	-2.1	-4.4 (0.9)	-2.245 (-4.365 to -0.125)	Moderate[c]	Rozanolixizumab likely results in an improvement in MG-QoL scores compared to placebo. The clinical significance of this improvement is not known.
Quantitative Myasthenia Gravis (QMG)							
Mean change from Baseline to Day 43 in QMG score (Scale from 0 to 39 with higher scores indicating more severe impairment)	127 (1 RCT)	NA	-0.89	-4.22 (0.574)	-3.483 (-5.614 to -1.584)	Moderate[d]	Rozanolixizumab likely results in a clinically important improvement in QMG scores compared to placebo.
Harms							
Infections and infestations	133 (1 RCT)		19 per 100	16 per 100 (NR)	4 fewer per 100 (17 fewer to 9 more per 100)	Low[e]	Rozanolixizumab may result in little to no difference in the risk of infection compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Rozanolixizumab	Difference		
Follow-up: to 8 weeks after the final dose							

CI = confidence interval; gMG = generalized Myasthenia Gravis; LS=least square; MG-ADL = Myasthenia Gravis-Activities of Daily Living; MG-QoL15r = revised 15 item Myasthenia Gravis Quality of Life; MID=minimally important difference; QMG = Quantitative Myasthenia Gravis

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

Note: Results for the MG-ADL response and change from baseline in MG-QoL were not adjusted for multiplicity and should be considered as supportive evidence. The results for

[a] Rated down 1 level for serious imprecision; the point estimate suggests a clinically important benefit, while the upper bound of the 95% CI crossing the MID found in the literature. The literature-based MID was estimated for within-group effects; input from the clinical expert consulted by the review team considered that a between-group difference smaller than 2 points was not likely to be clinically important.

[b] Rated down 1 level for serious imprecision; there is a small sample size and number of events raising concern for prognostic imbalance and the potential that the effect may be overestimated.

[c] Rated down 1 level for serious imprecision; the null was used as the threshold and the point estimate suggests benefit, but the upper bound of the 95% CI includes a value that most reasonable individuals would agree is unimportant.

[d] Rated down 1 level for serious imprecision; the point estimate suggests a clinically important benefit, while the upper bound of the 95% CI crossing the MID found in the literature.

[e] Rated down 2 levels for very serious imprecision; the points estimate suggests little to no difference, but the 95% CI includes a potential for both benefit and harm.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence and from the sponsor's response to a request for information.

[redacted] Long-Term Extension Studies

Description of Studies

Results from two open label extension studies (OLE), MG0004 (NCT04124965; data cutoff date of September 1, 2021) and MG0007 (NCT04650854; data cutoff date of July 8, 2022) were reviewed. MG0007 was approximately ongoing for 1.5 years at the date of data cutoff for interim analysis. Results for the 7mg/kg group are only summarized to align with the reimbursement request.

MG0004

MG0004 was a phase 3, multicentre, randomized, OLE study of MyCarinG (MG0003) to investigate the long-term safety, tolerability, and efficacy of rozanolixizumab (weekly dosing regimen for 52 weeks) in adult patients with gMG who were experiencing moderate-to-severe symptoms and under consideration for IVIg or PLEX therapy, indicating they needed additional therapeutic intervention. Patients were randomized to two different treatment arms in a 1:1 ratio to receive SC rozanolixizumab either at 7 mg/kg or 10 mg/kg. The primary safety endpoints were occurrence of treatment-emergent adverse event and those leading to permanent withdrawal of study medication. Other safety endpoints included occurrence of adverse events of special monitoring (potential Hy's law – defined as AST or ALT > 3xULN and TBL > 2xULN and ALP <2xULN, with no other explanation for the biochemical abnormality), vital signs, ECG assessments, and clinical laboratory findings. Patients who experienced disease worsening (e.g., an increase of 2 points on the MG-ADL scale or 3 points on the QMG scale between two consecutive visits) were considered for rescue therapy, and if the patient received IVIg or PLEX during the study, treatment with rozanolixizumab was discontinued or paused for a minimum of two weeks but continued with visits as per the schedule of assessments, after which the patient continued to receive rozanolixizumab at the discretion of the Investigator. Following the temporary discontinuation of study medication, patients restarted at the same dose of rozanolixizumab as previously. Patients at a dose level of 7 mg/kg rozanolixizumab could have been restarted at 10 mg/kg rozanolixizumab at the discretion of the Investigator.

Of the 71 patients enrolled, 35 patients were randomized to 7 mg/kg rozanolixizumab group. The mean age was 50.6 (SD 14.2) years. More than half of all patients were female (54.3%). Most patients permanently discontinued the study during the COVID-19 pandemic (29 [82.9%]). One patient (2.9%) before the COVID-19 pandemic and two patients (5.7%) during the COVID-19 pandemic

permanently discontinued the study due to TEAE. Most of the patients permanently discontinued the study to transition to the MG0007 study (25 [71.4%] in the 7 mg/kg group).

The mean duration of the study medication by first dose received was 22.93 weeks. There was no treatment nonadherence or incorrect treatment or dosing. Beyond 18 weeks, the numbers of patients steadily decreased; this decrease was mainly due to the 53 (74.6%) patients who discontinued the study to transition to MG0007.

MG0007

MG0007 was a phase 3, two-arm, randomized, OLE study of MycarinG and replaced MG0004 to evaluate the long-term safety, tolerability, and efficacy of repeated six-week treatment cycles of rozanolixizumab based on MG worsening in adult patients with gMG. Worsening of disease was defined as the worsening of gMG symptoms (e.g., an increase of 2 points on the MG-ADL or 3 points on the QMG scale) between 2 consecutive visits. Patients were randomized to receive an initial fixed 6-week treatment cycle of rozanolixizumab either at 7 mg/kg or 10 mg/kg once weekly, followed by an observation period that began after the last dose of that treatment cycle. Eligible patients from MG0004 who completed at least six scheduled visits in the treatment period could move directly into the observation period in MG0007. In the case of worsening MG symptoms, patients underwent another six weeks of treatment followed by an observation period. Rescue therapy was given as per conventional therapy and at the discretion of the Investigator. Patients who continued to experience moderate-to-severe symptoms despite treatment with rozanolixizumab may have been treated with the following as rescue therapy: IVIg, SCIg, PLEX or plasmapheresis, or IV corticosteroids (at a higher dose than previous oral dose). Patients who were treated with rescue therapy were withdrawn from the study.

Of the 157 patients enrolled, 79 received 7 mg/kg rozanolixizumab. The mean age was 52.7 years (SD 15.7). More than half were female (55.7%). A total of 16 (20.3%) patients treated with rozanolixizumab permanently discontinued the study during the COVID-19 pandemic; the most common reason for study discontinuation was TEAEs (8 [10.1%]), followed by “withdrawal by patient” (5 [6.3%]).

Of the 79 patients who received 7 mg/kg rozanolixizumab in Cycle 1, 18 (22.8%) patients only had one treatment cycle, and 43 (54.4%) patients continued to receive rozanolixizumab 7 mg/kg in subsequent cycles. Sixteen (20.5%) patients switched to rozanolixizumab 7 mg/kg in subsequent cycles (five switched at Cycle 2, three at Cycle 4, two at Cycle 5, two at Cycle 7, three switched at Cycle 2 and switched back at Cycle 3, and one switched at Cycle 3 and switched back at Cycle 4). Five (6.3%) patients in the rozanolixizumab 7 mg/kg group received rescue medication (four received immunoglobulins [one of which continued treatment with efgartigimod alfa] and one received methylprednisolone sodium succinate); two (2.5%) patients required a rescue procedure (i.e., PLEX).

Efficacy Results

Change in MG-ADL

MG0004

Changes from baseline in MG-ADL score showed a stable trend up to Week 33; study participant numbers steadily declined over time. The maximum mean reduction from baseline up to week 33 was -3.1 (Week 13, n=30). When assessed by autoantibodies subgroup, a consistent reduction in MG-ADL scores was observed from baseline in MuSK-positive patients up to week 25. The greatest reduction (improvement) from baseline was -2.4 points which was observed at week 5 (n=5). The lowest reductions (improvement) from baseline were -1.6 points, observed at week 9 (n=5) and sustained at week 13 (n=5), and -1.3 points at week 21 (n=3). For AChR-positive patients, the greatest reduction (improvement) from baseline up to week 29 was -3.4 points (n=25, week 13). Between weeks 29 and 52, there was a consistent improvement in MG-ADL scores from baseline ranging from -4.2 points (week 37, n=5) to -2.0 points (week 49, n=3).

MG0007

Baseline MG-ADL scores and changes from baseline to Day 43 in MG-ADL scores for the 6 treatment cycles. Baseline values were defined as the last available value prior to or on the same date of first administration of IMP at each cycle (i.e., Baseline [Day 1]) value for that cycle. The number of participants declined across cycles from 79 at cycle 1 to 11 at cycle 6. Within each cycle, the mean change from baseline ranged from -3.0 to -4.3 points depending on the cycle. When assessed by antibodies subgroup, a consistent reduction (improvement) in MG-ADL scores was observed from baseline at Day 43, with repeated cyclic treatments for both MuSK-positive (n=8, cycles 1 to 4) and AChR-positive (n=62, cycles 1 to 6) patients; however, sample sizes steadily declined within each cycle. For MuSK-positive patients, the mean change from baseline ranged from -6.5 points (Cycle 1, n=8) to -3.8 points (Cycle 3, n=3). For AChR-positive patients, the mean change from baseline ranged from -4.0 points (Cycle 6, n=6) to -2.8 points (Cycle 2, n=41).

Change in QMG

MG0004

Changes from Baseline showed a stable trend over time to week 52; study participant numbers steadily declined over time. The maximum mean reduction from baseline up to Week 29 for the AChR-positive subgroup was -5.4 points (Week 29, n=11) and -6.0 points for the MuSK-positive subgroup (Week 25, n=3). The sample sizes in both groups steadily declined over time (n ≤ 10).

MG0007

Baseline QMG scores and changes from baseline at Day 43 in QMG scores for the 6 treatment cycles. The sample size declined from 79 at cycle 1 to 11 at cycle 6. The mean change from baseline ranged from -4.1 to -6.4 across cycles. A consistent improvement in QMG scores was observed with repeated cyclic treatment from baseline at Day 43 when assessed by MuSK-positive (from cycles 1 to 4) and AChR-positive participants (from cycles 1 to 5). However, sample sizes declined over time with ≤10 patients in any subgroup.

Change in MG-C

MG0004

Changes from baseline showed a consistent trend to week 52; study participant numbers declined steadily over time. A consistent change from baseline up to week 25 and 29 was observed when assessed by MuSK-positive and AChR-positive antibodies, respectively. The maximum mean reduction was -7.0 points (Week 25, n=15) from baseline up to Week 29 for AChR-positive subgroup (Week 25, n=15) and -3.6 points (Week 5, n=5) from baseline up to Week 25 for MuSK-positive subgroup. The sample sizes declined over time across the subgroups.

MG0007

Baseline MG-C scores and changes from baseline to Day 43 in MG-C scores for the 6 treatment cycles. The sample size declined over time, from 79 at cycle 1 to 11 at cycle 4. The mean change from baseline ranged from -6.1 to -9.6 across cycles. A consistent improvement in MG-C scores was observed from baseline at Day 43, with repeated cyclic treatment when assessed by antibody subgroups.

Change in MG-QoL 15r

MG0004

Baseline QMG scores and changes from baseline to Day 43 in QMG scores for the 6 treatment cycles. The mean MG-QoL 15r score at baseline was 14.4 points. An improvement in health-related quality was observed. The maximum mean reduction from baseline up to week 33 was –5.1 points (Week 21, n=20).

MG0007

Quality of life for MG patients was an exploratory outcome. The sample size declined over time, from 79 at cycle 1 to 11 at cycle 4. The mean change from baseline ranged from -2.2 to -6.1 across cycles.

Harms Results

Adverse events

MG0004

Seventy six percent of the patients in the 7mg/kg group experienced any TEAE. The most common AE (20% of patients or more) were nervous system disorders (36.0%), gastrointestinal disorders (26.0%), infections and infestations (26.0%), investigations (22.0%), and musculoskeletal and connective tissue disorders (20.0%).

MG0007

Sixty-eight patients (69.4%) in the 7mg/kg group experienced any TEAE. Nervous system disorders (36.7%), infections and infestations (34.7%), gastrointestinal (24.5%) and general site administration issues (27.6%) were the most reported.

Serious Adverse events

MG0004

Serious TEAEs were reported in 7 (14.0%) patients. The only SAE occurring in more than one patient was nervous system disorders (n = 3, 6.0%).

MG0007

Serious TEAEs were reported in 9 (9.2%) patients. The SAEs occurring in more than one patient were nervous system disorders (n = 3, 3.1%) and infections and infestations (n = 2, 2.0%).

Withdrawals due to adverse events

MG0004

A total of 4 (8.0%) patients experienced TEAEs that led them to discontinue from the study. Three (75.0%) of these patients experienced MG, while 1 (25.0%) patient experienced congestive cardiac failure. In patients who temporarily discontinued rozanolixizumab (n=12, 24.0%), the main reasons were decreased blood IgG and hypogammaglobulinemia.

MG0007

A total of 6 (6.1%) patients permanently discontinued the study. Two (33.3%) patients had TEAEs with preferred term MG, while one patient each reported TEAEs of adrenal disorder, pneumonia, tendon disorder, tenosynovitis, retroperitoneal neoplasm, thymoma, and subacute cutaneous lupus erythematosus. In patients who temporarily discontinued rozanolixizumab, the main reasons were decreased blood IgG, hypogammaglobulinemia and COVID-19.

Mortality

MG0004

There were no AEs leading to death in this study.

MG0007

One death was reported due to fatal TEAEs (pneumonia).

Critical Appraisal

Patients who were enrolled in the pivotal trial (MyCarinG), were the ones entering the OLE's (MG0004 and MG0007). MG0004 and MG0007 were limited by their non-comparative open-label study designs. A lack of a control group precludes causal statements about benefit and harm compared with any comparator. The open label and non-blinded nature of the study may increase the risk of bias in determining the magnitude of the subjective safety outcomes and all efficacy endpoints because these were subjective (e.g. MG-ADL, QMG, MG-QoL, MG-C scores) as the lack of blinding may impact patients' expectations of the treatment. The direction and magnitude of these potential biases remains unclear. Concomitant treatments were intended to remain stable within treatment cycles but could be adjusted between cycles. These additional treatments could confound the relationship between rozanolixizumab and the efficacy and harm outcomes, but the degree of impact on the results cannot be predicted. Efficacy results were assessed by MG-specific antibody subgroups; however, these results should be interpreted with caution due to the small sample sizes (especially in the MuSK-positive autoantibody subgroup). Baseline MG-ADL, QMG and MG-C scores indicated higher disease severity of patients entering MG0007, potentially suggesting that there is a selection bias. Patients in MG0007 were allowed to switch between the 7mg/kg and 10mg/kg groups, based on Investigator's discretion before the start of each subsequent cycle of treatment. Therefore, it is difficult to differentiate the effect of 7mg/kg dose (which is the focus of the reimbursement request) from that of the 10mg/kg dose on the efficacy outcomes. There is a high risk of attrition bias, as the number of patients contributing to the analyses declined steadily over time.

Indirect Comparisons

The submission included a NMA and a matching-adjusted indirect comparison (MAIC). The comparator treatments included in the NMAs were zilucoplan, efgartigimod alfa, eculizumab, IVIg, PLEX, rituximab, and ravulizumab; of these, results from the comparisons with efgartigimod, eculizumab, IVIg, PLEX and rituximab were included in the review. The comparator treatments included in the MAIC submission were efgartigimod and IVIg/PLEX.

Description of Studies

The study selection methods were the same for the NMA and the MAIC. Briefly, a clinical systematic literature review (SLR) based on studies identified from database searches from inception to May 1, 2023, was performed to inform both the NMA and MAIC. Results from the SLR were then filtered by distinct PICOs for the NMA or MAIC as part of the feasibility assessment.

Network Meta-Analysis Design

Homogeneity in the NMA network was assessed by visual inspection of the distribution of baseline characteristics for the trials comprising the network, as well as the timepoint at which study outcomes were reported. Plot digitization at 12 weeks was carried out to obtain data points from published figures. The NMAs were performed using a Bayesian approach with non-informative priors and fixed-effect models were used. Change from baseline outcomes were assessed at the 12 (± 2) week timepoint using only Phase III studies in the primary analysis, and the results were presented with estimates for treatment effects of each intervention relative to placebo as the reference treatment. Relative treatment effects (MG-ADL responders, defined as improvement of 3 points or more in score) were presented as odds ratios (ORs) and continuous treatment effects (change in baseline in MG-ADL score) were reported as mean differences (MD). Analysis was conducted in the overall population and refractory population (defined according to the RAISE trial). The sensitivity analyses were conducted assessing the inclusion of different timepoints of reporting outcomes, as well as differences in study design (i.e., Phase II vs Phase III studies).

Matching-Adjusted Indirect Comparison Design

Prior to carrying out a feasibility assessment, the relative importance of all the baseline characteristics based on their impact on the outcomes was ranked by 2 clinical experts. The feasibility assessment consisted of comparing the relevant trials for each comparison in terms of their baseline characteristics and inclusion/exclusion criteria. In cases of differences in the inclusion/exclusion criteria, a subset of patients from the rozanolixizumab trial (MycarinG) were used to match the comparator trial. If feasibility was confirmed, the two studies were matched using a propensity score weighting method. A comparison of all potential analysis scenarios was presented to knowledge opinion leaders, and the base case was selected based on specific criteria. The comparisons of rozanolixizumab vs efgartigimod (ADAPT trial) were modeled using an anchored MAIC, and the results for rozanolixizumab vs IVIg (Barth et al. 2011) were modeled using an unanchored MAIC. Continuous outcomes (change from baseline in MG-ADL, MGC, MG-

QoL and QMG scores) were modeling using linear regression, with results presented as mean differences. Binary outcomes (2- or 3-point improvements in MG-ADL or QMG) were modeled using logistic regression, with results presented as ORs.

Efficacy Results

Network Meta-Analysis

Heterogeneity was observed throughout the NMA network in disease severity, treatment history (where reported), trial eligibility criteria, placebo response, the definition of MG-ADL responders, the timing of endpoint evaluation, study designs, and baseline characteristics. The majority of patients enrolled in the trials were AChR-receptor positive, majority female, and had gMG Class II to IV. The duration of disease ranged from 6.9 to 10.3 years. MuSK antibody status was reported in 2 trials (MycarinG [12% of patients] and ADAPT [4% of patients]). Study duration ranged from 12 to 48 weeks. The study network for the primary analysis showed that all included studies compared treatments to placebo, and each node in the network consisted of a single study.

The NMA primary analysis results for rozanolixizumab 7mg/kg indicated [redacted] for treatment and comparators with [redacted]. Rozanolixizumab 7mg/kg [redacted] placebo for MG-ADL responders.

Matching-Adjusted Indirect Comparison

There were some differences identified between the MycarinG (rozanolixizumab) trial and the ADAPT (efgartigimod) trial. Most notably, there were differences in the minimum MG-ADL scores required for enrollment, and that ADAPT required patients to be on stable doses of gMG therapy while MycarinG required patients being considered for additional therapy. There were also differences noted between the inclusion criteria for MycarinG and the inclusion criteria for Barth et al. 2011 (IVIg), most notably that Barth et al. was an active-controlled trial which did not require specific MGFA class diagnosis or MG-ADL baseline score for enrollment, whereas MycarinG was placebo-controlled, required weight and MG-ADL thresholds as well as AChR or MuSK-positive antibody status.

Results of the primary analysis for rozanolixizumab vs. efgartigimod indicated that at 6 weeks, the results [redacted]. The [redacted] for the outcomes of 2 or 3-point improvements in MG-ADL at 4 weeks, or 3-point improvements in QMG at 4 weeks.

Results from the primary analysis for rozanolixizumab vs. IVIg indicated that at 2 and 4 [redacted]; the results for QMG responders [redacted].

Harms Results

Harms outcomes were not analyzed as part of the indirect comparisons.

Critical Appraisal

Some limitations of the SLR include the fact that the search was only run up until 2023, and therefore may miss more recent publications on comparators. In addition, the quality assessment was carried out at the level of the trial, which might not capture the fact that risks of some domains of bias (e.g., attrition bias) can vary by outcome. According to the clinical expert, the NMA included relevant comparators to the Canadian context and the outcome was of interest to clinicians. However, data from some relevant comparators such as IVIg and rituximab were not available in the primary analysis of the NMA, and additional limitations in the sensitivity analyses do not allow conclusions to be drawn regarding these comparators. Likewise, results from all comparators were not available in the submission for the MAIC.

There are important sources of heterogeneity in the NMA network which have clinical relevance and impact the certainty of the results. While all trials enrolled patients with gMG Class II to IV, there were differences between trials in the refractory status of the enrolled patients which were not accounted for in the analyses. For example, the trials for eculizumab and rituximab generally enrolled refractory patients and newly diagnosed patients, respectively, the trial for zilucoplan included refractory patients, and the trial for rozanolixizumab required patients to be under consideration for additional therapy. In addition, MuSK antibody status was only reported in 2 of the 6 included trials, and the trials in the network used MG-ADL thresholds ranging from 3 to 6 points. Sensitivity analyses were conducted, but they do not address the heterogeneity concerns. Taken together, these could represent clinically

meaningful differences in patient disease status and affect confidence that the transitivity assumption underpinning the NMA was met.

With regards to the MAICs, while the clinical expert consulted for the review noted that the list of known prognostic and/or effect modifying variables used for weighting in both MAICs was comprehensive, not all baseline characteristics were reported before and after weighting and therefore it is not known whether there were other potential sources of heterogeneity in the trial populations remaining after weighting. Weighting controlled for the differences in the reported baseline characteristics for the anchored MAIC comparing rozanolixizumab to efgartigimod. However, the effective sample size (ESS) was considerably smaller than the sample sizes of the two trials pre-matching, suggesting that a small proportion of the patient population may be driving the results, and the findings could be unstable. This suggests that there remains uncertainty in the results for the comparison of rozanolixizumab to efgartigimod. The comparison of rozanolixizumab to IVIg was carried out using an unanchored MAIC, which rely on the assumption that all possible prognostic factors and treatment effect modifiers are controlled for, an assumption that is largely considered impossible to meet. The scenario used in the current MAIC did not include all baseline characteristics in the weighting process, resulting in a high risk of residual confounding. Confidence in the results is therefore highly uncertain. Furthermore, there are important study differences which were not controlled for by the weighting process, such as the lack of placebo comparator in the Barth et al. trial, the timing of the primary endpoint, and the proportion of MuSK patients. Taken as a whole, conclusions on the efficacy of rozanolixizumab versus IVIg are challenging to draw.

The indirect evidence as a whole is also subject to some limitations impacting generalizability. Firstly, the study population of MycarinG included AChR-positive or MuSK-positive patients. To improve similarity to the efgartigimod trial population, only the MuSK-negative, AChR-positive patients from MyCarinG were included in the unanchored MAIC for rozanolixizumab vs. efgartigimod (i.e., a subset of the full trial population). This adversely impacts the generalizability of those results to the MuSK-positive gMG population. Furthermore, the results of the MAIC were assessed as early as 2 to 6 weeks, which the clinical expert noted is early to assess treatment response and which might not capture maximal treatment response. Lastly, long-term comparative efficacy and harms information is unavailable.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with AChR-Ab+ or MuSK-Ab+ gMG for whom symptoms persist despite conventional therapy with AChEIs, corticosteroids, and/or NSISTs.
Treatment	Rozanolixizumab (TBC) plus conventional therapy
Dose regimen	Dose weekly for 6 weeks. Subsequent treatment cycles are based on clinical evaluation and may vary by patient. Body weight ≥35 to <50 kg: 280 mg Body weight ≥50 kg to <70: 420 mg Body weight ≥70 to <100 kg: 560 mg Body weight ≥100 kg: 840 mg
Submitted price	Rozanolixizumab 280 mg/2 mL single-dose vial: $12,260
Submitted treatment cost	$436,956 per year, assuming a patient weighing ≥70 and <100 kg, and 2.97 treatment cycles per year
Comparators	• Conventional therapy (CT)[a] • Eculizumab plus CT • Efgartigimod alfa plus CT

Component	Description
	• IVIG/SCIG plus CT • PLEX plus CT • Rituximab plus CT
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (52.5 years)
Key data sources	• Sponsor-submitted NMA informed the comparative efficacy of rozanolixizumab, conventional therapy, eculizumab and efgartigimod alpha; individual trials informed the comparative efficacy of chronic IVIG/SCIG, chronic plasma exchange (Barth et al. 2011) and rituxumab (Nowak et al. 2021)
Submitted results	• Rozanolixizumab plus CT was associated with an ICER of $2,676,135 per QALY gained (incremental cost: $21,998, 0.01 incremental QALYs) compared to efgartigimod alfa plus CT. • CT alone and rituximab plus CT were also on the efficacy frontier but were less costly and less effective treatments.
Key limitations	• The modelled population reflects the MycarinG trial which is narrower than the proposed Health Canada indication of adults with gMG. The trial excluded patients with MGFA Class I, IVb, and V gMG, those who do not meet specific disease severity score cutoffs, and those who have not shown persistent symptoms despite CT. • Due to the lack of direct clinical evidence, limitations with the sponsor-submitted NMA (e.g., imprecision of estimates, heterogeneity in the patient and study characteristics), and the sponsor's use of naïve comparisons to inform the economic evaluation, conclusions regarding the comparative efficacy and safety of rozanolixizumab relative to its comparators largely cannot be drawn. • The relevance of some comparators varies by serotype as some comparators are currently only used for AChR-Ab+ gMG (e.g., efgartigimod alfa), while others are primarily used for MuSK-Ab+ gMG (i.e., rituximab). • The sponsor assumed maintenance of clinical effects beyond treatment discontinuation which is not appropriate, as this assumption underestimated treatment costs and overestimated benefits. • The sponsor-assumed reductions in corticosteroid use based on treatment response were not supported by the available clinical data. This likely overestimated the extent to which corticosteroid use may be reduced and overestimated the cost and HRQoL associated with reductions in use. • The model lacked transparency and reliability, limiting CADTH's ability to properly validate results within the time frame of this review.
CADTH reanalysis results	• Given the clinical limitations identified with the sponsor's economic submission, including uncertainty in comparative treatment effect, CADTH was unable to derive a more reliable estimate of the cost-effectiveness of rozanolixizumab as an add-on therapy to CT. • While the sponsor's base case suggested differences in treatment benefits between rozanolixizumab and other add-on therapies used for the treatment of adults with AChR-Ab+ or MuSK-Ab+ gMG whose symptoms persist despite CT, there is no robust evidence to support this claim. If the sponsor's claim of added benefit (0.008 QALYs, 3 quality-adjusted days) is realized, the probability that rozanolixizumab is cost-effective at a willingness-to-pay of $50,000 per QALY gained is 0%. • CADTH undertook several scenarios which suggested that the ICER for rozanolixizumab is likely higher than estimated by the sponsor, due to underestimation of drug acquisition costs. • A price reduction of at least 87.5% (from $12,260 to $1,533 per 280 mg vial) is required for rozanolixizumab to achieve an ICER of $50,000 per QALY gained.

AChR-Ab+ = anti-acetylcholine receptor antibody positive; AChEI = acetylcholinesterase inhibitor; CT = conventional therapy; gMG = generalized myasthenia gravis; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; IVIG = intravenous immunoglobulin; LY = life-year; MuSK-Ab+ = anti-muscle-specific

tyrosine kinase antibody positive; NMA = network meta-analysis; NSIST = non-steroidal immunosuppressive therapy; PLEX = plasma exchange; QALY= quality-adjusted life-year; SCIG = subcutaneous immunoglobulin.

[a] Conventional therapy is defined as consisting of 12.5% mix of each of the following: prednisone, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine, and cyclophosphamide.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- Reference scenario market shares are uncertain as the proportion of patients receiving PLEX is likely overestimated and eculizumab is not a funded comparator for the treatment of gMG.
- The analyses were not conducted from a drug plan payer perspective given the costs of blood products were included.
- The uptake of rozanolixizumab is underestimated when considering funding for its Health Canada indicated population (i.e., adult patients with gMG).
- Different body weight distributions were assumed when calculating the total treatment cost of rozanolixizumab and efgartigimod alfa.

CADTH reanalyses revised the sponsor's submitted analysis by assuming eculizumab has 0% of the public market, by redistributing half the market share assigned to chronic IVIG/SCIG to other comparators, by removing the cost of blood products from the analysis, and by revising the distribution of patient body weights used to estimate dosing for rozanolixizumab and efgartigimod alfa. In addition to the changes noted above, CADTH increased the uptake of rozanolixizumab in the analysis based on the Health Canada indicated population.

Results of CADTH reanalyses suggest that the reimbursement of rozanolixizumab in combination with conventional therapy for the treatment of adults with AChR-Ab+ or MuSK-Ab+ gMG whose symptoms persist despite conventional therapy may be associated with a 3-year incremental budgetary cost of $132,461,365 (year 1: $24,638,709, year 2: $42,950,784, year 3: $64,871,872).

CDEC Information

Members of the Committee:

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: January 22, 2025

Regrets:

Two expert committee members did not attend.

Conflicts of interest:

One expert committee member did not participate due to considerations of conflict of interest.