

Reimbursement Recommendation

Zilucoplan (Zilbrysq)

Indication: For the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. Patients continued to receive standard therapy throughout the pivotal trial.

Sponsor: UCB Canada Inc.

Final recommendation: Reimburse with conditions

Note: This document was initially published on February 11, 2025, and subsequently revised on June 13, 2025, to correct an error with the submitted price.

Summary

What Is the Reimbursement Recommendation for Zilbrysq?

Canada's Drug Agency (CDA-AMC) recommends that Zilbrysq be reimbursed by public drug plans for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive and who continue to receive standard therapy if certain conditions are met.

Which Patients Are Eligible for Coverage?

Zilbrysq should only be covered to treat adult patients who have received treatment for at least 1 year with 2 or more immunosuppressant therapies; or who have a history of treatment with at least 1 immunosuppressant for 1 year or more, and chronic plasma exchange, IV immunoglobulin, or subcutaneous immunoglobulin at least every 3 months for 12 months. Eligible patients should test positive for AChR antibodies, have a Myasthenia Gravis Activities of Daily Living (MG-ADL) score (which estimates patients' ability to perform activities of daily living; score ranges from 0 to 24, with higher scores indicating more impairment) of 6 or greater, and meet the Myasthenia Gravis Foundation of America (MGFA) classification (which categorizes clinical features by increasing severity) of II (mild weakness affecting body muscles and may also include weakness in the eye muscles) to IV (severe weakness affecting body muscles and may also include weakness in the eye muscles).

What Are the Conditions for Reimbursement?

Zilbrysq should not be given during a gMG exacerbation (moment when patient experiences weakness in some or all muscles, without needing assistance to breath) or crisis (moment when respiratory muscles are too weak, limiting air flow in and out of lungs, as a result patient is unable to breathe), or within 12 months of thymectomy (surgical removal of thymus gland). Zilbrysq should only be reimbursed if prescribed by or in consultation with a neurologist with expertise in managing patients with gMG and the cost of Zilbrysq is reduced. Zilbrysq should not be used concomitantly with rituximab, efgartigimod alfa, or complement inhibitors, such as eculizumab.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial (RAISE) demonstrated that compared with placebo, treatment with Zilbrysq was associated with meaningful improvements in patients' ability to perform activities of daily living and

Summary

health-related quality of life (HRQoL), as well as a reduction in gMG symptom severity.

- Zilbrysq met some of the identified patient needs as it improves the ability to perform activities of daily living and HRQoL, as well as reduces gMG symptom severity. It may also offer a faster onset of action and a subcutaneous drug option that can be administered in a patient's home.
- Based on the CDA-AMC assessment of the health economic evidence, Zilbrysq does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Zilbrysq is estimated to cost the public drug plans approximately \$82 million over the next 3 years.

Additional Information

What Is gMG?

Myasthenia gravis (MG) is a condition that causes muscle weakness. In some patients, symptoms remain exclusively to the eyes (ocular MG); however, most patients either are diagnosed with or progress within a few years to gMG, which affects the head and neck and other muscles. Symptoms of gMG include eyelid drooping and double vision, altered facial expression, difficulty chewing and swallowing food, difficulty speaking, and, in patients with more severe disease, problems with limb movement and breathing. When patients are unable to control their symptoms with conventional therapies, they are considered to have refractory gMG. In Canada, the incidence of MG is estimated at approximately 23 cases per 1 million population annually.

Unmet Needs in gMG

Patients with refractory gMG whose symptoms persist despite adequate treatment with conventional therapies have few treatment options.

How Much Does Zilbrysq Cost?

Treatment with Zilbrysq is expected to cost approximately \$237,512 to \$463,577 per patient per year, depending on patient weight.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that zilucoplan be reimbursed for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive and who continue to receive standard therapy if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

One phase III, double-blind, placebo-controlled trial (RAISE; N = 174) demonstrated that, compared with placebo, treatment with zilucoplan results in added clinical benefit in adult patients with AChR antibody-positive gMG. The RAISE trial showed that, after 12 weeks of treatment, zilucoplan resulted in statistically significant and clinically meaningful improvements in the primary outcome — change from baseline in the Myasthenia Gravis Activities of Daily Living (MG-ADL) score — and key secondary outcomes: the Quantitative Myasthenia Gravis (QMG) score, the Myasthenia Gravis Composite (MGC) scale, and the Myasthenia Gravis Quality of Life 15-item (MG-QoL15r) instrument. Results in the subgroup of patients with refractory gMG (n = 88) were consistent with results in the overall trial population suggesting that zilucoplan was favoured over placebo in change from baseline in the MG-ADL score (mean difference between groups = -3.11 points; 95% confidence interval [CI], -4.69 to -1.52 points), QMG score (mean difference between groups = -3.32 points; 95% CI, -5.42 to -1.23 points), MGC score (mean difference between groups = -3.68 points; 95% CI, -6.65 to -0.72 points), and MG-QoL15r score (mean difference between groups = -3.28, 95% CI; -5.89 to -0.67). CDEC considered the zilucoplan safety profile, noting that infections were more common in the zilucoplan group, most were low grade, and treatment discontinuation as a consequence was relatively rare. Findings on long-term efficacy and safety based on the open-label extension trial (RAISE-XT) appeared consistent with the RAISE trial and suggested ongoing benefit of zilucoplan.

The patient input received for this review identified a need for treatment options with a more rapid onset of action, which maintain patients' independence in daily activities, enhance disease control, have fewer side effects, provide improved administration (method, frequency, setting of delivery), and decrease the number of exacerbations, hospital admissions, and the dependency on corticosteroids. Based on the evidence reviewed, CDEC concluded that zilucoplan met some of the needs identified. Efficacy results in the RAISE trial suggested meaningful benefits in activities of daily living, gMG symptom severity, and health-related quality of life (HRQoL) compared with placebo, although the impact of zilucoplan relative to other comparators remains uncertain. Zilucoplan may offer a faster onset of action and provide a subcutaneous drug option that can be administered in a patient's home. The impact of zilucoplan on MG exacerbations, hospitalizations, and doses of corticosteroid treatment was not assessed in the RAISE trial.

The committee considered analyses conducted by Canada's Drug Agency (CDA-AMC) that considered the cost-effectiveness of zilucoplan plus standard of care (SOC) relative to SOC alone, efgartigimod alfa plus SOC, chronic IV immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) plus SOC, chronic plasma exchange (PLEX) plus SOC, and rituximab plus SOC based on data from the submitted indirect treatment comparison as well as naive comparisons. Based on the sponsor's submitted price for zilucoplan and

publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) was \$6,024,388 per quality-adjusted life-year (QALY) gained compared with PLEX plus SOC. Based on that analysis, a price reduction of approximately 95% would be required for zilucoplan to achieve an ICER of \$50,000 per QALY gained.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with refractory gMG, defined as not achieving symptom control after 1 of the following criteria: 1.1. treatment for at least 1 year with 2 or more of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, other corticosteroids for gMG, or other ISTs 1.2. history of treatment with at least 1 IST for 1 year or more and chronic PLEX, IVIg, or SCIg at least every 3 months for 12 months. 2. Patients have all the following: 2.1. positive serologic test for AChR antibodies 2.2. MG-ADL score at baseline of 6 or greater 2.3. MGFA class II to IV disease 2.4. vaccination against meningococcal infection.	Subgroup analyses of the RAISE trial for patients with refractory gMG (reflecting 51% of patients in the overall trial population) demonstrated that, compared with placebo, treatment with zilucoplan resulted in clinical benefit in patients with refractory gMG who did not achieve symptom control after treatment with conventional therapies (defined in points 1.1 and 1.2). The eligibility criteria for the RAISE trial included adult patients (≥ 18 years and < 75 years) with gMG who tested positive for AChR antibodies, an MG-ADL score of 6 or greater, MGFA class of II to IV, and vaccination against meningococcal infections.	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. Refractory gMG could be defined in a similar way as other advanced therapies for gMG (e.g., efgartigimod alfa, ravulizumab) based on the reimbursement criteria for each public drug plan.
3. Zilucoplan should not be initiated: 3.1. during a gMG exacerbation or crisis 3.2. within 12 months of thymectomy.	Patients who had a thymectomy within 12 months before screening or received treatment with IVIg or PLEX 4 weeks before baseline were excluded from the RAISE trial. The efficacy and harms of zilucoplan in these populations of patients are unknown.	—
4. MG-ADL score must be measured and provided by the physician at baseline.	Baseline MG-ADL score was measured in the RAISE trial and was used to determine response to treatment.	—

Reimbursement condition	Reason	Implementation guidance
5. The maximum duration of initial authorization is 6 months.	According to the clinical experts, approval for 6 months initially would be reasonable to assess response to treatment.	—
Renewal		
6. Reimbursement of zilucoplan treatment should be continued if, after the initial 6 months of treatment, there is documented improvement in the MG-ADL score of 2 points or greater.	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. Clinical experts propose a 2-point reduction in the MG-ADL score as a minimal clinically meaningful measure of response to treatment.	Based on clinical expert opinion, after the initial 6 months of treatment with zilucoplan, if a patient has responded, treatment would continue as long as the patient has a clinically meaningful response. In terms of maximum duration of treatment, treatment with zilucoplan would probably be given as long as zilucoplan continued to be effective or the disease spontaneously remitted.
7. For subsequent renewal, the treating clinician must provide proof that the initial response achieved after the first 6 months of therapy with zilucoplan for the MG-ADL score has been maintained. Reassessment for renewal should occur every 6 months.	To ensure patients are maintaining their response to treatment with zilucoplan.	Based on clinical expert opinion, there is the possibility of zilucoplan being used for 1 or more years. A patient who had initially responded to zilucoplan (after the initial 6 months) and was stable for a year but worsened afterward (while no longer receiving zilucoplan), could reinstitute therapy as long as the initiation criteria are met. The patient would not be expected to try standard care (AChEIs, corticosteroids, and/or NSiSTs) again.
Discontinuation		
8. Treatment with zilucoplan should be discontinued in case of serious adverse events related to zilucoplan or secondary infection, such as meningococcal infection.	As per the protocol of the RAISE trial, zilucoplan was discontinued in cases of severe uncontrolled infection.	—
Prescribing		
9. Zilucoplan 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 is important to ensure that zilucoplan is prescribed to appropriate patients.	—
10. Zilucoplan should not be used concomitantly with rituximab or complement inhibitors.	The efficacy and safety of zilucoplan in combination with rituximab, eculizumab and/or efgartigimod alfa is unknown.	—
Pricing		
11. A reduction in price.	The cost-effectiveness of zilucoplan plus SOC is highly uncertain. The ICER for zilucoplan plus SOC was estimated to be \$6,024,388 per QALY gained compared to PLEX plus SOC. A price reduction of 95.5% would be required for zilucoplan to achieve an ICER	—

Reimbursement condition	Reason	Implementation guidance
	of \$50,000 per QALY gained compared to SOC alone. Cost-effectiveness relative to other advanced treatments (i.e., efgartigimod alfa, rituximab, IVIg, PLEX, and ravulizumab) for AChR antibody-positive gMG is uncertain given the lack of head-to-head evidence and limitations with the indirect comparison. To ensure cost-effectiveness, zilucoplan should also be priced no more than the lowest cost advanced treatment reimbursed for AChR antibody-positive gMG.	
Feasibility of adoption		
12. The economic feasibility of adoption of zilucoplan must be addressed.	At the submitted price, the incremental budget impact of zilucoplan is expected to be greater than \$40 million in year 3.	—

AChEI = acetylcholine inhibitor; AChR = acetylcholine receptor; CDEC = Canadian Drug Expert Committee; gMG = generalized myasthenia gravis; ICER = incremental cost-effectiveness ratio; IST = immunosuppressive therapy; IVIg = IV immunoglobulin; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MID = minimal important difference; NSIST = nonsteroidal immunosuppressive therapy; PLEX = plasma exchange; QALY = quality-adjusted life-year; SCIg = subcutaneous immunoglobulin; SOC = standard of care.

Discussion Points

- Significant unmet need:** CDEC deliberated on zilucoplan considering the criteria for significant unmet need that are described in section 9.3.1 of the [Procedures for Reimbursement Reviews](#). CDEC noted that gMG is a rare, chronic, and progressive autoimmune disease with significant impact on patient functioning. Approximately 15% of patients with gMG are considered to have refractory gMG, which is the focus of the reimbursement request. The committee agreed with the clinical experts that there is a significant unmet need for effective treatment options in patients with refractory gMG who do not achieve symptom control after treatment with conventional therapies (e.g., acetylcholine inhibitors [AChEIs], corticosteroids, and/or nonsteroidal immunosuppressant therapies [NSISTs]). CDEC considered that the subgroup results of the RAISE trial reasonably suggest that zilucoplan results in meaningful benefits in activities of daily living, gMG symptom severity, and HRQoL compared with placebo. CDEC concluded that the available evidence supports the use of zilucoplan in patients with refractory gMG and, therefore, recommended to reimburse with conditions in this population.
- Efficacy:** CDEC considered that the RAISE trial did not conduct a calculation to determine the sample size needed to detect statistically significant differences in effect estimates in the subgroup of patients with refractory gMG. However, the committee discussed that the consistent effects of zilucoplan in this subgroup compared with the overall trial population across all main end points indicated the likelihood that zilucoplan has a beneficial clinical effect in patients with refractory gMG compared with placebo. Effect estimates for the absolute differences exceeded the suggested

thresholds of importance. The evidence was rated as being of moderate certainty using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. CDEC noted that confidence in the between-group differences for the primary and key secondary outcomes in both the overall trial and the gMG refractory subgroup populations was limited due to imprecision (i.e., associated CIs included effects close to the null).

- Adverse effects:** CDEC discussed patients' desire for treatments with fewer adverse effects. Although the RAISE trial did not provide direct comparative evidence regarding the adverse effects of zilucoplan versus other advanced gMG therapies (e.g., eculizumab, efgartigimod, IVIg), CDEC noted that overall treatment-emergent adverse events (TEAEs) appeared more frequent in patients treated with zilucoplan compared with placebo. The most common TEAEs included injection site reactions, infections, diarrhea, and headache in the zilucoplan group. CDEC noted that infections were higher in the zilucoplan group, which was acknowledged in the Health Canada product monograph. The majority of infections were low grade, and treatment discontinuation as a consequence was relatively rare. No meningococcal infections were reported in the RAISE trial, which required patients to be vaccinated. The incidence of TEAEs and serious adverse events (SAEs) in the subgroup of patients with refractory gMG were overall consistent with the harm results in the overall trial population.
- Indirect evidence:** CDEC discussed the uncertainty of the comparative efficacy and safety of zilucoplan due to the absence of direct comparative evidence. CDEC considered 1 sponsor-submitted network meta-analysis (NMA) assessing zilucoplan relative to eculizumab, efgartigimod alfa, IVIg, PLEX, and rituximab. The committee noted several limitations with the submitted comparative analysis, notably heterogeneity across study designs and populations, sparse evidence networks, short-term data, and imprecision of estimates. CDEC concluded that the comparative evidence was insufficient to draw a definitive conclusion on the relative efficacy (i.e., change from baseline in MG-ADL and at least 3-point MG-ADL response) of zilucoplan versus comparator therapies.
- Long-term extension study:** CDEC considered the data from the long-term extension study, RAISE-XT, which suggested a sustained benefit up to 1.5 years and a long-term adverse effects profile in patients receiving zilucoplan that was consistent with the RAISE trial. However, interpretation of the long-term results was limited by the small sample size and the open-label and descriptive nature of the extension study, so it was considered supportive evidence by CDEC.
- Treatment administration:** CDEC discussed patients' desire for improved treatment administration (e.g., method, frequency, setting of delivery). CDEC noted that zilucoplan may offer more convenience in terms of a faster onset of action (the typical treatment duration for NSISTs to maximize response is approximately 9 to 18 months), and by providing a subcutaneous drug option that can be administered in a patient's home as opposed to hospital or specialized clinical settings for IV therapies, such as IVIg regimens. However, CDEC noted that no evidence was available assessing the impact of zilucoplan's route of administration on HRQoL outcomes.
- Cost-effectiveness of zilucoplan:** CDEC discussed the cost-effectiveness of zilucoplan for the treatment of gMG in adult patients with AChR antibody-positive gMG and who continued to receive standard therapy. Based on the sponsor's analysis, the ICER for zilucoplan plus SOC is \$1,611,347

per QALY gained compared to PLEX plus SOC. CDA-AMC identified several limitations with the sponsor's submission, including uncertainty associated with the indirect comparisons to relevant comparators, inappropriate treatment discontinuation assumptions, assumptions for the reductions in corticosteroid use that were not supported by clinical data and likely overestimated the extent to which corticosteroid use may be reduced, and the model lacking transparency and reliability, which limited the ability of CDA-AMC to properly validate results within the time frame of this review. CDA-AMC undertook reanalyses to address some of the limitations identified, which suggested that the ICER for zilucoplan could be \$6,024,388 per QALY gained. CDEC considered the ICER from the CDA-AMC combined scenario analysis to be a reasonable estimate of the ICER for zilucoplan. CDEC also discussed that if other recently recommended treatments for refractory gMG are reimbursed by the CDA-AMC participating drug plans, there is no robust comparative clinical evidence for zilucoplan to be priced more than the lowest cost advanced treatment reimbursed for AChR antibody-positive refractory gMG.

Background

Myasthenia gravis (MG) is a rare, chronic, progressive autoimmune neuromuscular disease in which antibodies against the neuromuscular junction disrupt nerve impulse conduction, resulting in localized or generalized skeletal muscle weakness. In most patients, MG initially affects the extraocular muscles (ocular MG) and then progresses to other muscle groups, including the bulbar and proximal limb skeletal muscles. When the disease progresses to other muscle groups, it is referred to as gMG. Diagnosis of gMG is based on clinical presentation; serological tests to detect antibodies against AChR (80% to 90% of patients with gMG), muscle-specific tyrosine kinase (MuSK), and lipoprotein receptor-related protein 4 (LRP4); and electrodiagnostic tests for evaluation of neuromuscular transmission. Approximately 80% of all patients with MG have gMG. In Canada, the incidence and prevalence of gMG are estimated at 23 cases per 1 million person-years and 32 cases per 100,000 people, respectively. In 2021, the incidence of MG in the US was estimated as 3.2 per 100,000 people and the total prevalence estimated as 37.0 per 100,000 people using population estimates from the US Census. The Myasthenia Gravis Foundation of America (MGFA) classification system groups patients with MG according to severity and localization of symptoms into 5 functional classes: I (ocular manifestations only), II (mild), III (moderate), IV (severe generalized), and V (intubation or myasthenic crisis). 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. The symptoms of gMG occur unpredictably and fluctuate in nature, intensity, and severity on a day-to-day basis and throughout a patient's life. Patients can also experience exacerbation, which can deteriorate into a myasthenic crisis in which patients experience sudden respiratory failure requiring emergency intubation or ventilation. Almost 15% of patients with gMG have been classified as having refractory gMG. According to the clinical expert consulted for this review, the goals of treatment for patients with gMG are to reduce MG-related morbidity and mortality, minimize treatment-associated morbidity and mortality, reduce weakness (ocular, bulbar, respiratory, axial, and extremity) associated with gMG, prevent disease exacerbations or a gMG crisis, and improve HRQoL.

The initial symptomatic treatment for most patients with gMG is an AChEI, such as pyridostigmine. Many patients need treatment with corticosteroids and/or NSISTs when they do not reach their treatment goals with AChEIs. Other treatment options include immunomodulating therapies, PLEX, and IVIg. Novel biologic treatments include efgartigimod alfa, eculizumab, and rituximab. Patients with gMG experience disease morbidity while awaiting the beneficial effects of prolonged treatments, which often have intolerable side effects. Therefore, the clinical expert consulted by CDA-AMC highlighted the need for new treatments that provide faster onset of action (particularly among patients with any bulbar or respiratory involvement) and are more effective with reduced significant adverse effects and greater durability compared with current treatment options.

Per the sponsor's request, this review focused on the indication in patients with refractory gMG: zilucoplan as an add-on therapy for the treatment of adult patients with AChR antibody–positive refractory gMG, defined as not achieving symptom control after either:

- treatment for at least 1 year with 2 or more of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, other corticosteroids for gMG, or other ISTs
- history of treatment with at least 1 of these therapies for 1 year or more and required chronic PLEX, IVIg, or SCIg at least every 3 months for the 12 months before treatment with zilucoplan.

The recommended dose of zilucoplan for adult patients with gMG is 0.3 mg/kg as a subcutaneous injection once daily, administered about the same time every day, according to the patient's body weight (i.e., total daily dose: 16.6 mg for body weight < 56 kg, 23.0 mg for body weight ≥ 56 kg to < 77 kg, and 32.4 mg for body weight ≥ 77 kg). Zilucoplan received a Notice of Compliance from Health Canada on July 11, 2024, for the treatment of gMG in adult patients who are anti-AChR antibody positive. Patients continued to receive standard therapy throughout the pivotal trial. Zilucoplan has not been previously reviewed by CDA-AMC.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized controlled trial (RCT) (RAISE) in patients with AChR antibody–positive gMG, 1 long-term extension study, and 1 sponsor-submitted indirect treatment comparison
- patients' perspectives gathered by 1 patient group, Muscular Dystrophy Canada (MDC)
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 1 clinical specialist with expertise diagnosing and treating patients with gMG
- input from 1 clinician group, Neuromuscular Disease Network for Canada (NMD4C)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to the CDA-AMC call for input and from a clinical expert consulted by CDA-AMC for the purpose of this review.

Patient Input

CDA-AMC received 1 patient group submission from the MDC, a health charity that supports people affected by muscular dystrophies and related muscle diseases (neuromuscular disorders) in Canada, which included a survey (via e-blasts, personalized invites, and online patient groups) and semistructured virtual interviews of adults living with MG. MDC also conducted an MG Canadian Journey Mapping project among adults living with MG via virtual interviews, round table sessions, surveys, and the completion of HRQoL measures. A total of 127 participants (84 females and 43 males) aged 22 years to 78 years from all provinces in Canada contributed to MDC's group submission, the majority of whom reported having gMG. Additionally, 47 people living in Canada (33 females, 14 males) with MG provided input on their hopes and expectations for zilucoplan and their everyday experiences with MG. None of the respondents included in the MDC's patient input had experience with zilucoplan.

Respondents indicated that MG has a significant impact on productivity, fatigue and energy levels, quality of sleep, respiratory health, mobility, strength, independence, relationships and social participation, eyes and vision, speech, and swallowing. In addition to physical and mental health, quality of life, and the wellbeing of their families, respondents reported available treatments for MG to provide positive impact on health outcomes but also negative experiences (adverse events [AEs] with steroids, slow onset of medication effects, and a feeling of trial and error with medications).

Patients with MG sought improved outcomes with new treatments, including decreased intensity of exacerbations and side effects, maintenance of independence, and fewer hospital admissions for serious MG disease-related circumstances. Patients were willing to tolerate side effects of medications if they would achieve improved MG outcomes. In addition, respondents stated that although current medications appeared to decrease the number of exacerbations, they did not have an impact on patients' overall quality of life. Moreover, MDC noted that patients, families, and caregivers value the following factors when evaluating MG therapies: treatment method and delivery (e.g., invasiveness, duration, frequency of administration), potential side effects (e.g., low risk of side effects, number of side effects), HRQoL, convenience of treatment (e.g., administration at home or community centre, perceived control and flexibility, time to travel to clinic, access to parking for clinic visits), financial impact (e.g., treatment coverage by public or private insurance), and access to treatment. According to MDC, HRQoL was noted as a key priority versus convenience of a drug. MDC stated that beyond accessing treatments, patients with MG need improved treatment options with enhanced effectiveness and tolerance over the long term.

Patients and caregivers reported varied experiences in diagnostic testing for MG. Although some respondents experienced minimal problems with testing and diagnosis, especially in cases of MG crisis or hospitalization due to MG, the majority reported significant difficulties getting diagnosed, including a lengthy

process with many missed opportunities, delayed diagnosis, misdiagnosis (such as stroke and Bell's palsy), and costs incurred. According to early findings of the MG Journey Mapping Project, time of first bothersome symptom to diagnosis ranged from 7 years to 23 years. All the respondents had diagnostic blood testing, and many had single-fibre electromyography to confirm diagnosis.

Clinician Input

Input From the Clinical Expert Consulted by CDA-AMC

The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of MG.

The clinical expert expressed that while there has been significant improvement in the management of patients with MG over the past few decades, there remains significant treatment gaps among patients with gMG. Given that patients with gMG experience disease morbidity while awaiting the beneficial effects of prolonged treatments that often have intolerable side effects, the expert highlighted the need for new treatments that provide faster onset of action (particularly among patients with any bulbar or respiratory involvement) and are more effective with reduced significant adverse effects and greater durability over current treatment options. Additionally, the clinical expert noted that patients would benefit from new treatments that are least invasive (e.g., oral preferred over subcutaneous or IV route of administration), are less frequent (e.g., weekly or monthly preferred over daily administration), allow for reduced doses of other immunosuppressive drugs, and may be used in combination with existing or future treatments which have differing mechanisms of action (e.g., combination of a peptide complement inhibitor plus a neonatal Fc receptor [FcRn] inhibitor among patients with severe or refractory MG). Overall, the expert outlined that goals of treatment for patients with MG are to reduce MG-related morbidity and mortality, minimize treatment-associated morbidity and mortality, reduce weakness (ocular, bulbar, respiratory, axial and extremity) associated with MG and prevent disease exacerbations or an MG crisis, and improve HRQoL.

The expert noted that depending on how refractory disease is defined, approximately 10% to 15% of patients do not respond to conventional treatment and, therefore, require more aggressive treatments, including IVIg or PLEX. These patients are considered to be the target population of complement inhibitors such as zilucoplan. The expert expressed that patients who were identified as refractory in the RAISE trial were aligned with how refractory disease would be defined in clinical practice, particularly with reference to an adequate trial of prednisone in addition to another IST.

The clinical expert outlined that patients are initially identified as having MG through clinical suspicion, with diagnosis confirmed via electrophysiology (i.e., repetitive nerve stimulation for assessment of "decrement") and serology (e.g., confirmation of antibodies for AChR, MuSK, and LRP4), adding that the presence of AChR antibodies is a reliable diagnostic finding with high specificity such that the identification of patients with MG using AChR antibody testing is straightforward. Nevertheless, given the rarity of disease and that the initial identification of patients with MG is based on clinical suspicion, the clinical expert considered that MG is likely underdiagnosed in the population. The expert noted that the availability and timeliness of AChR antibody assays varies across Canada.

According to the expert consulted, patients who are most likely to benefit from treatment with zilucoplan are aligned with patients who were enrolled in the RAISE trial on the following criteria: AChR antibody–positive gMG, disease class MGFA II to IV, and an MG-ADL score of 6 or greater. The exception was the criterion of a QMG score of 12 or greater in the study, which was reportedly not used commonly in clinical practice. The expert weighed in that patients who have had an adequate trial (including both dose and duration) of both a prednisone and at least 1 NSIST, or those who demonstrated intolerance to the combination of prednisone and NSIST(s), should be eligible for treatment with zilucoplan. Such criteria limits inclusion to patients who have been on conventional treatment for at least 6 months (commonly 12 months), reflecting the duration needed for corticosteroids (3 to 6 months), mycophenolate mofetil, and azathioprine (likely 12 to 18 months) to produce an optimal benefit.

The MG-ADL scale is a patient-reported outcome deemed by the expert consulted to be clinically relevant (a 2-point change as minimum clinically meaningful improvement) for evaluating response to treatment. According to the clinical expert for this review, the MG-ADL can be self-administered within minutes (by patients, with supervision of a neuromuscular neurologist) and should be used as an eligibility criterion for treatment with zilucoplan and as monitoring of efficacy throughout treatment. A clear lack of response (i.e., no reduction in MG-ADL after approximately 6 months) to treatment with zilucoplan, intolerance due to significant AEs requiring discontinuation of treatment, and the requirement for additional ongoing treatments with IVIg or PLEX despite an adequate trial of zilucoplan were reasons to discontinue treatment with zilucoplan according to the clinical expert.

The clinical expert expressed that because MG is a rare disorder requiring nuanced management, patients with gMG should be diagnosed, treated, and monitored by a neuromuscular neurologist with experience in gMG. This is especially important when considering the role for more advanced treatment options in gMG due to the resource utilization associated with their use in the management of gMG.

Clinician Group Input

CDA-AMC received 1 clinician group submission from the NMD4C comprising 8 clinicians with experience in treating gMG. The clinician group agreed with the clinical experts about unmet treatment needs, goals of treatment, treatment response evaluations, and care management for patients with MG. NMD4C identified additional treatment outcomes (emergency department visits, hospitalizations, and intensive care unit admissions). The ability to self-administer zilucoplan at home was noted to provide patients with greater autonomy of their care management. Both the clinician group and the clinical expert consulted for this review indicated that patients with AChR antibody–positive gMG would most likely benefit from treatment from zilucoplan, with the clinician group noting that evidence on the efficacy of zilucoplan has not been confirmed for patients with seronegative MG.

Drug Program Input

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

Implementation issues	Response
Relevant comparators	
Placebo was the comparator in the RAISE study. Patients received either zilucoplan 0.3 mg/kg or placebo as subcutaneous injection once daily.	The clinical expert noted there is currently no robust direct or indirect evidence of zilucoplan compared with other active treatments in patients with gMG whose symptoms persist despite treatment with conventional therapies. The expert considered that the most relevant comparators for zilucoplan among patients with refractory gMG include other complement inhibitors (i.e., eculizumab, ravulizumab), neonatal FcRn inhibitors (e.g., efgartigimod alfa), chronic IVIg, and chronic PLEX. Rituximab as a comparator is less applicable due to limited access by patients with gMG in Canada, its use off-label, lack of rigorous clinical trial evidence among patients with AChR antibody–positive MG, and some evidence of improved benefit among patients with MuSK-positive MG. CDEC acknowledged the expert's response.
At baseline, the majority of patients had received prior gMG-specific medications, including cholinesterase inhibitors (84.0% of patients), corticosteroids (63.2% of patients), and NSISTs (52.9% of patients). This follows the prerequisite drugs for the ADAPT trial for Vyvgart for adult patients with AChR antibody–positive gMG. Do these proportions align with clinical practice for adult patients with AChR antibody–positive gMG who have refractory disease?	In the RAISE trial, prior gMG medications were defined as any medications started before the first administration of study drug. The majority of patients in both study groups had received prior AChEIs (approximately 95% of patients), steroids (approximately 85% of patients), and NSISTs (approximately 70% of patients). In the RAISE trial, gMG-specific baseline medications were defined as medications started before and continued after receiving the study drug, including cholinesterase inhibitors (84.5%), corticosteroids (63.2%), mycophenolate mofetil (19.5%), azathioprine (17.8%), cyclosporin (7.5%), tacrolimus (5.7%), and methotrexate (2.3%). The clinical expert reported that a higher proportion of patients would be expected to be receiving both corticosteroids and NSISTs among those with refractory disease at baseline. Therefore, if the RAISE trial defined patients with refractory disease as those who previously (i.e., historically) experienced lack of response to these gMG medications and, therefore, were no longer on those drugs, it may be reasonable to observe lower proportions of patients with these medications at baseline. CDEC acknowledged the expert's response.
Considerations for initiation of therapy	
In the RAISE trial, patients were adults (18 to 74 years of age) with AChR antibody–positive gMG disease class II to IV (both of which match Vyvgart initiation criteria). Patients required a score of ≥ 6 on the MG-ADL in the RAISE trial; patients required a score of ≥ 5 on the MG-ADL for Vyvgart.	The clinical expert outlined that patients who were identified as having AChR antibody–positive gMG, MGFA disease class II to IV, and an MG-ADL score of ≥ 6 were included in the RAISE trial and, as such, are the patients most likely to benefit from treatment with zilucoplan. The expert noted that patients were not required to have severe disease to be defined as having refractory disease. Only 5% of patients in the RAISE trial had MGFA disease class IV (severe disease); 26% were classified as MGFA disease class of II (26%) and III (70%). The MG-ADL total score cut-off value was ≥ 6 points as an inclusion criterion in the RAISE and other clinical trials for gMG, such as the CHAMPION-MG trial for ravulizumab and REGAIN

Implementation issues	Response
	trial for eculizumab. However, the review team noticed that the inclusion criteria for recruiting patients in the ADAPT trial was ≥ 5 points for MG-ADL total score. Patients in the ADAPT trial who had a 5 point MG-ADL total score at baseline were relatively few. The clinical expert consulted for this review indicated that a subset of patients with MG-ADL scores less than 6 could potentially be suitable for treatment. Specifically, the clinical expert indicated that patients with ocular MG or mild symptoms can still be refractory to other therapies. However, whether the results of the RAISE trial can be generalized to patients who have an MG-ADL total score of less than 6 despite conventional therapies remains uncertain. CDEC noted that there is currently insufficient evidence to guide a recommendation for zilucoplan in patients who have an MG-ADL total score of less than 6 despite conventional therapies.
- Should patients who have tried other “advanced therapies” be able to transition to zilucoplan? - This could include reasons such as ease of convenience as zilucoplan can be given at home as SC injections. Do you perceive any issues with this?	The expert considered that patients who have tried other advanced therapies to be eligible for treatment with zilucoplan, including for reasons related to ease of treatment administration. CDEC acknowledged the input of the clinical expert but noted that there is currently insufficient evidence to guide a decision on switching to zilucoplan in patients who receive a comparator advanced therapy.
From previous reviews for this indication, rituximab may not be available in some jurisdictions. Are you aware of variable access to rituximab across jurisdictions?	The expert agreed that there is a wide variation in access to rituximab, which is used off-label for patients with gMG, across jurisdictions in Canada (e.g., relatively easy access in Quebec but nearly impossible in Ontario). CDEC acknowledged the expert’s feedback on the wide variation in access to rituximab.
Considerations for continuation or renewal of therapy	
There should be no challenges as the renewal criteria is based on a scoring system.	This is a comment from the drug plans to inform CDEC deliberations.
Consider alignment with Vyvgart.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for discontinuation of therapy	
Consider alignment with Vyvgart.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for prescribing of therapy	
Dosing is based on actual body weight as follows: < 56 kg: 16.6 mg SC once daily ≥ 56 kg to < 77 kg: 23 mg SC once daily ≥ 77 kg: 32.4 mg SC once daily	This is a comment from the drug plans to inform CDEC deliberations.
There may be concerns with accessing neurologists in remote locations. Vyvgart prescribing states: prescribed by or in consultation with a neurologist with expertise in managing patients with gMG.	According to the clinical expert consulted for this review, prescribing of biologics should be made by or on the advice of a neuromuscular neurologist with experience in the management of MG. CDEC agreed with the clinical expert’s feedback.

Implementation issues	Response
- Is there any evidence for combination use of zilucoplan with other advanced therapies (e.g., Vyvgart)? - If other C5 inhibitors become available in the future (e.g., Soliris), can zilucoplan be used in combination or, if treatment fails with other C5 inhibitors, can zilucoplan be considered?	The expert indicated that there is an absence of empirical evidence to support the use of zilucoplan in combination with other treatments in the same patient. The expert expressed that zilucoplan in combination with other C5 inhibitors would be potentially dangerous, resulting from the combined effect of drugs with similar mechanisms of action. For example, a patient who does not experience response to treatment with a single complement inhibitor (e.g., eculizumab, ravulizumab) could subsequently be tried on zilucoplan monotherapy, according to the expert, despite a lack of evidence to support whether a patient who experienced lack of treatment response with a complement inhibitor would then respond to treatment with a different complement inhibitor. Instead, the expert expressed that it would be preferable to switch a patient who experienced treatment failure with a complement inhibitor to a drug of a different mechanism of action (e.g., efgartigimod alfa). CDEC noted that there is currently insufficient evidence of zilucoplan in combination with rituximab, ravulizumab, eculizumab, and/or efgartigimod alfa to guide a decision on combining zilucoplan with these advanced treatments. CDEC agreed with the clinical expert that patients who have tried other advanced therapies should be eligible for treatment with zilucoplan.
System and economic issues	
It would seem as though zilucoplan would displace other therapies in this space as this can be given at home instead of an IV infusion clinic.	This is a comment from the drug plans to inform CDEC deliberations.
- The unit prices of zilucoplan for the 16.6 mg/syringe, 23.0 mg/syringe, and 32.4 mg/syringe is \$650.2718, \$900.9790, and \$1,269.2052, respectively. - Year 1: \$25,582,701 - Year 2: \$36,524,794 - Year 3 total: \$75,033,053	This is a comment from the drug plans to inform CDEC deliberations.
Vyvgart is still under consideration for negotiation at the pCPA. Soliris concluded without an agreement at the pCPA.	This is a comment from the drug plans to inform CDEC deliberations.

ACHR = acetylcholine receptor; CDEC = Canadian Drug Expert Committee; C5 = complement protein 5; FcRn = Fc receptor; gMG = generalized myasthenia gravis; IVIg = IV immunoglobulin; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MuSK = muscle-specific tyrosine kinase; NSIST = nonsteroidal immunosuppressive therapy; pCPA = pan-Canadian Pharmaceutical Alliance; PLEX = plasma exchange; SC = subcutaneous.

Clinical Evidence

Systematic Review

Description of Studies

One phase III, multicentre, double-blind trial (RAISE) compared the efficacy and safety of zilucoplan with placebo. The RAISE trial enrolled 174 patients aged 18 years to 74 years with AChR antibody-positive gMG. The primary objective was to evaluate the change from baseline to week 12 in the MG-ADL score. Key secondary end points included change from baseline to week 12 in QMG score, MGC score, and MG-QoL15r score. Additional secondary end points included achieving minimal symptom expression (MSE) at week 12 without rescue therapy, MG-ADL responder rate at week 12 without rescue therapy, QMG responder rate at week 12 without rescue therapy, and time to first administration of rescue therapy. Achieving Minimal Manifestation Status per MGFA – Post-Intervention Status (MGFA-PIS) at week 12 without rescue therapy was an exploratory end point in the RAISE study. Patients with refractory AChR antibody-positive gMG were included in the exploratory subgroup analyses. Outcomes reported for patients with refractory gMG included change from baseline to week 12 in the MG-ADL score; change from baseline to week 12 for the QMG score, the MGC score, and the MG-QoL15r score; achieving MSE at week 12 without rescue therapy; MG-ADL responder rate at week 12 without rescue therapy; and QMG responder rate at week 12 without rescue therapy.

In the overall population, 56.9% of patients were female and 43.1% were male, and the mean age was 53.0 years (standard deviation [SD] = 15.1 years). Most patients had a diagnosis of MGFA Class III at screening (67.2%) and generalized symptoms at disease onset (64.4%); mean age of disease onset was 43.8 years (SD = 18.0 years) and mean disease duration was 9.2 years (SD = 9.9 years). More patients had higher scores in the stratified randomization for the MG-ADL (62.1% of patients had a score ≥ 10) and the QMG (56.3% of patients had a score ≥ 18). Patients were similar between treatment groups on most disease characteristics and history, except for a higher proportion of patients with prior thymectomy in the zilucoplan group (52.3%) compared with the placebo group (42.0%). Patients had similar between-group mean baseline scores in the MG-ADL and the QMG. Patients were considered to have refractory gMG in the RAISE trial if they had treatment for at least 1 year with 2 or more of the following: prednisone, azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, or other ISTs, or they had a history of treatment with at least 1 of the aforementioned therapies for 1 year or more and required chronic PLEX, IVIg, or SCIg at least every 3 months for the 12 months before enrolment. No patients in the RAISE trial had received eculizumab as a past or baseline gMG therapy, and 1 patient who had received rituximab within 12 months before baseline was excluded.

Efficacy Results

Efficacy results were summarized using the data cut-off date of December 30, 2021, for the following outcomes: change from baseline to week 12 in the MG-ADL score, the QMG score, and the MG-QoL15r score; achieving MSE at week 12 without rescue therapy; MG-ADL responder rate at week 12 without rescue

therapy; QMG responder rate at week 12 without rescue therapy; and Minimal Manifestation Status per MGFA-PIS at week 12 without rescue therapy.

Change From Baseline to Week 12 in MG-ADL Score

In the overall population, the least squares (LS) mean change from baseline to week 12 in the MG-ADL score was -4.39 points (standard error [SE] = 0.45) in the zilucoplan group and -2.30 points (SE = 0.44) in the placebo group (LS mean difference = -2.09; 95% CI, -3.24 to -0.95; $P < 0.001$), favouring the zilucoplan group. In the refractory subpopulation, the LS mean change from baseline to week 12 in the MG-ADL score was -4.72 points (SE = 0.58) in the zilucoplan group and -1.62 points (SE = 0.58) in the placebo group (LS mean difference = -3.11; 95% CI, -4.69 to -1.52; nominal $P < 0.001$).

Change From Baseline to Week 12 in QMG Score

In the overall population, the LS mean change from baseline to week 12 in the QMG score was -6.19 points (SE = 0.56) in the zilucoplan group and -3.25 points (SE = 0.55) in the placebo group (LS mean difference = -2.94; 95% CI, -4.39 to -1.49; $P < 0.001$), favouring the zilucoplan group. In the refractory subpopulation, the LS mean change from baseline to week 12 in the QMG score was -6.08 points (SE = 0.76) in the zilucoplan group and -2.76 points (SE = 0.75) in the placebo group (LS mean difference = -3.32; 95% CI, -5.42 to -1.23; nominal $P < 0.001$).

Change From Baseline to Week 12 in MGC Score

In the overall population, the LS mean change from baseline to week 12 in the MGC score was -8.62 points (SE = 0.81) in the zilucoplan group and -5.42 points (SE = 0.79) in the placebo group (LS mean difference = -3.20; 95% CI, -5.24 to -1.16; $P = 0.0023$), favouring the zilucoplan group. In the refractory subpopulation, the LS mean change from baseline to week 12 in the MGC score was -7.85 points (SE = 1.09) in the zilucoplan group and -4.17 points (SE = 1.07) in the placebo group (LS mean difference = -3.68; 95% CI, -6.65 to -0.72; nominal $P = 0.0156$).

Change From Baseline to Week 12 in MG-QoL15r Score

In the overall population, the LS mean change from baseline to week 12 in the MG-QoL15r score was -5.65 points (SE = 0.77) in the zilucoplan group and -3.16 points (SE = 0.76) in the placebo group (LS mean difference = -2.49; 95% CI, -4.45 to -0.54; $P = 0.0128$), favouring the zilucoplan group. In the refractory subpopulation, the LS mean change from baseline to week 12 in the MG-QoL15r score was -5.63 points (SE = 0.96) in the zilucoplan group and -2.36 points (SE = 0.95) in the placebo group (LS mean difference = -3.28; 95% CI, -5.89 to -0.67; nominal $P = 0.0145$).

Achieving MSE at Week 12 Without Rescue Therapy

In the overall population, the percentage of patients who achieved MSE (MG-ADL score of 0 or 1) at week 12 without rescue therapy was 14.0% in the zilucoplan group and 5.8% in the placebo group (between-group difference = 8.2%; 95% CI, -0.6% to 17.0%). In the refractory subpopulation, the number of patients who achieved MSE at week 12 without rescue therapy was 7 of 44 patients (15.9%) and 1 of 42 patients (2.4%) in the zilucoplan and placebo groups, respectively.

Achieving at Least a 3-Point Reduction in MG-ADL Score at Week 12 Without Rescue Therapy

In the overall population, the percentage of patients who were MG-ADL responders (achieved at least a 3-point decrease in the MG-ADL score) at week 12 without rescue therapy was 73.1% in the zilucoplan group and 46.1% in the placebo group (between-group difference = 27.0%; 95% CI, 12.9% to 41.1%). In the refractory subpopulation, the number of patients who were MG-ADL responders at week 12 without rescue therapy was 33 of 44 patients (75.0%) and 17 of 42 patients (40.5%) in the zilucoplan and placebo groups, respectively.

Achieving at Least a 5-Point Reduction in QMG Score at Week 12 Without Rescue Therapy

In the overall population, the percentage of patients who were QMG responders (achieved at least a 5-point decrease in the QMG score) at week 12 without rescue therapy was 58.0% in the zilucoplan group and 33.0% in the placebo group (between-group difference = 25.0%; 95% CI, 10.5% to 39.5%). In the refractory subpopulation, the number of patients who were QMG responders at week 12 without rescue therapy was 24 of 43 in the zilucoplan group (55.8%) and 11 of 41 (26.8%) in the placebo group.

Minimal Manifestation Status per MGFA-PIS at Week 12 Without Rescue Therapy

In the overall population, the number of patients who achieved Minimal Manifestation Status per MGFA-PIS at week 12 without rescue therapy was 22 of 78 (28.2%) in the zilucoplan group and 16 of 83 (19.3%) in the placebo group (between-group difference = 10.9%; 95% CI, -1.5% to 23.2%). The number of patients who achieved Minimal Manifestation Status per MGFA-PIS at week 12 without rescue therapy was not reported in the refractory subpopulation.

Harms Results

The analysis population for harms included all patients who received at least 1 dose of study drug, with patients grouped according to the treatment received, using data from the data cut-off date of December 30, 2021.

The number of patients in the overall gMG population with at least 1 TEAE was 66 of 86 (76.7%) in the zilucoplan group and 62 of 88 (70.5%) in the placebo group. The most common TEAEs occurring in greater than 5% of patients in either the zilucoplan group or the placebo group, respectively, were headache (15.1% versus 15.9%), injection site bruising (16.3% versus 9.1%), MG (10.5% versus 9.1%), diarrhea (10.5% versus 2.3%), injection site pain (9.3% versus 3.4%), urinary tract infection (8.1% versus 4.5%), contusion (8.1% versus 3.4%), increased lipase (8.1% versus 1.1%), nasopharyngitis (5.8% versus 3.4%), vomiting (3.5% versus 5.7%), rash (3.5% versus 5.7%), and increased amylase (5.8% versus 2.3%).

In the refractory subpopulation, the number of patients with at least 1 TEAE was 39 (88.6%) in the zilucoplan group and 34 (77.3%) in the placebo group. The most common TEAEs occurring in greater than 10% of patients in either the zilucoplan group or the placebo group, respectively, were headache (20.5% versus 15.9%), MG (13.6% versus 13.6%), injection site bruising (15.9% versus 11.4%), diarrhea (15.9% versus 2.3%), and vomiting (4.5% versus 11.4%).

The number of patients in the overall gMG population with at least 1 SAE was 11 (12.8%) in the zilucoplan group and 13 (14.8%) in the placebo group. The most common SAEs reported in at least 2% of patients in the zilucoplan group and the placebo group, respectively, were MG (2.3% and 5.7%), COVID-19 (1.2% and 2.3%), and COVID-19 pneumonia (1.2% and 2.3%).

In the refractory subpopulation, the number of patients with at least 1 SAE was 6 (13.6%) in the zilucoplan group and 8 (18.2%) in the placebo group. SAEs specified by system organ class were not reported for the refractory subpopulation.

The number of patients in the overall gMG population who stopped study treatment due to AEs was 4 (4.7%) in the zilucoplan group and 2 (2.3%) in the placebo group. Withdrawals due to AEs in the zilucoplan group were due to aphthous ulcer, mouth ulceration, COVID-19, and increased hepatic enzyme (1 patient [1.2%] each); the TEAEs aphthous ulcer and COVID-19 were considered serious, with the latter having had a fatal outcome. Withdrawals due to AEs in the placebo group were due to cerebral hemorrhage and hyperemesis gravidarum (1 patient [1.1%] each); both TEAEs were considered serious and the TEAE of cerebral hemorrhage had a fatal outcome. The number of patients in the overall gMG population who died was 1 (1.2%) in the zilucoplan group (SAE leading to death due to COVID-19 and COVID-19 pneumonia) and 1 (1.1%) in the placebo group (SAE leading to death due to cerebral hemorrhage).

In the refractory subpopulation, 1 patient (2.3%) stopped study treatment in the zilucoplan group, and no patients stopped study treatment in the placebo group. Reasons for withdrawals due to AEs were not reported for the refractory subpopulation.

Notable Harms

Infections occurred in 23 patients (26.7%) in the zilucoplan group compared with 16 patients (18.2%) in the placebo group (between-group difference = 8.6%; 95% CI, -3.8% to 20.9%). Of these, 4 patients (4.7%) in the zilucoplan group and 4 patients (4.5%) in the placebo group had serious infections. AEs of special interest were not reported for the refractory subpopulation.

Critical Appraisal

Randomization appeared to be adequate in the RAISE trial; treatment groups were balanced overall on demographics and disease characteristics indicating randomization was likely successful and risk of selection bias was low. Randomization was stratified by baseline MG-ADL score (≤ 9 versus ≥ 10), QMG score (≤ 17 versus ≥ 18), and geographical region (North America, Europe, and East Asia). The instruments used to evaluate the primary and secondary efficacy outcomes (MG-ADL, QMG, MGC, MG-QoL15r) were appropriate and their psychometric properties have been investigated in patients with MG, although no minimal important differences (MIDs) have been estimated for the MG-QoL15r. Minimal Manifestation Status per MGFA-PIS without rescue therapy was based on clinician-assessed patient symptoms of MG after initiating MG-specific therapy, intended to capture patients who may not meet the definition of complete stable remission or pharmacologic remission but who have muscle weakness based on careful examination. This was an exploratory end point and no MID has been validated in the indicated population. Results for Minimal Manifestation Status per MGFA-PIS at week 12 were not reported for the refractory subpopulation.

There was low risk of bias for allocation concealment because patients and study staff were blinded to treatment assignment, both treatments were identical, and unblinding of treatment assignment was not permitted before initiation of rescue therapy.

Patients with refractory disease represented approximately half of the enrolled patients with gMG. The selection criteria for the refractory subgroup were specified a priori and were similar to the criteria used to define patients with refractory gMG in other RCTs (e.g., the REGAIN trial for eculizumab). Baseline characteristics were overall similar between treatment groups with low concerns regarding prognostic imbalance in the refractory subpopulation. The population included in the refractory subgroup was adequately reflective of the patients with refractory gMG in the Canadian clinical setting, according to the clinical expert consulted by the review team. Although subgroup analyses were not adjusted for multiplicity and not powered to detect treatment effect differences between study groups, results from the refractory subgroup can be interpreted for consistency with analyses of the overall trial population in the RAISE trial and share the same limitations of those analyses. Results for the refractory subgroup showed consistency with the overall trial population across all outcomes.

There was a notable proportion of patients with important protocol deviations in both the zilucoplan group (38.4%) and the placebo group (36.4%). Deviations included prohibited concomitant medication use in 24.7% of patients (changes to gMG conventional medications, use of prohibited concomitant medications, and changes to cholinesterase inhibitor dosing less than 10 hours before evaluation) and those related to inclusion criteria in 7.5% of patients (not withholding acetylcholinesterase inhibitor therapy for at least 10 hours before the QMG assessment, not meeting the no change in corticosteroid for at least 30 days before baseline, and having received inpatient treatment with IVIg that was not reported as rescue therapy). The proportion of patients with deviations during the study were balanced between groups. Multiple imputation methods were used to account for missing data in the primary and secondary end points based on assumptions of missing not at random (assumed missingness may be related to the study drug or having received rescue medication) and missing at random. Based on the specified approach, each of these were imputed with either their baseline value or the last observed value (whichever was worse). Because the rate of intercurrent event 1 (received rescue therapy with IVIg, PLEX, or eculizumab) was higher in the placebo group (11%) than in the zilucoplan group (5%), this appeared to be an overly pessimistic approach and possibly introduce bias in favour of zilucoplan; however, the imbalance was not large to raise serious concerns of biased treatment effects. Sensitivity analyses to account for censoring of patients who experienced treatment failure were also conducted. Although the supplemental analyses and sensitivity analyses of the primary analysis did not adequately assess the potential bias related to missing data, there were low concerns for losses to follow-up because approximately 95% of patients with gMG in the overall population and the refractory subpopulation completed the RAISE study, with balanced proportions between treatment arms.

External Validity

Per sponsor request, the focus of this review was on the sponsor's reimbursement request, which was narrower than the Health Canada indication. The reimbursement request aligned with the criteria for

the refractory subgroup of the RAISE trial, which was zilucoplan as add-on therapy for the treatment of adult patients with AChR antibody–positive refractory gMG — defined as not achieving symptom control after treatment for at least 1 year with 2 or more of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, other corticosteroids for gMG, or other ISTs — or a history of treatment with at least 1 of these therapies for 1 year or more and required chronic PLEX, IVIg, or SCIg at least every 3 months for the 12 months before treatment with zilucoplan. The requested reimbursement criteria were similar to the reimbursement criteria for the comparator therapy, eculizumab, which received a positive final recommendation from CADTH in 2020.

Patients in the RAISE trial who did not have refractory gMG (49% of patients in the RAISE trial) were not included in the reimbursement request. While the clinical expert consulted for this review agreed that there is also a current unmet need in patients with nonrefractory gMG who have responded inadequately to the existing standard of gMG therapies, this population was not the focus of this review.

According to the experts, stratifying patients during randomization by baseline scores on the MG-ADL and the QMG appeared to be appropriate for ensuring equal distributions of patients according to disease severity. The expert noted that no specific patient populations were missing from eligibility in the trial who might otherwise be considered eligible in clinical practice. The expert emphasized that, in line with patients who were excluded for eligibility in the RAISE trial, patients with MuSK-positive MG should not be treated with a complement inhibitor such as zilucoplan based on its mechanism of action; rather, patients with MuSK-positive MG would benefit from treatment with a neonatal FcRn inhibitor (e.g., efgartigimod alfa).

Looking at the types and duration of prior conventional treatments received by patients in the RAISE trial, the clinical expert agreed that all patients in the RAISE trial were adequately managed on conventional therapy for gMG at the time of enrolment into the trial and were reflective of patients who experience an unmet need in Canadian clinical settings.

Moreover, the RAISE trial did not provide evidence for the comparisons between zilucoplan and other currently available active treatments for gMG. The expert considered that the most relevant comparators for zilucoplan among patients with refractory gMG include other complement inhibitors (i.e., eculizumab, ravulizumab), neonatal FcRn inhibitors (e.g., efgartigimod alfa), chronic IVIg, and chronic PLEX. Rituximab as a comparator is less applicable due to its limited access by patients with gMG in Canada, its off-label use, the lack of rigorous clinical trial evidence among patients with AChR antibody–positive MG, and some evidence of improved benefit among patients with MuSK-positive MG.

The expert agreed that the primary end point of change from baseline in MG-ADL score was an important outcome for evaluating treatment response and aligned with clinical practice, including the threshold used in the RAISE trial. MID scores used for the QMG and MGC scores were also noted by the expert to align with literature for thresholds validated in patients with MG. According to the experts, most patients with gMG would be assessed at approximately 12 weeks to evaluate treatment response as was done for all end points in the RAISE trial, with additional assessments at the 3- or 4-month time point to assess responsiveness or maintenance of response.

GRADE Summary of Findings and Certainty of the Evidence

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: activities of daily living (MG-ADL score), disease severity (QMG score), treatment response (MGC score), HRQoL (MG-QoL15r), and harms (infections).

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect for change from baseline to week 12 scores in the MG-ADL, the QMG, and the MGC based on thresholds identified in the literature. The certainty of evidence assessments for change from baseline to week 12 in the MG-QoL15r score, number of patients achieving MSE at week 12 without rescue therapy, MG-ADL responder rate at week 12 without rescue therapy, QMG responder rate at week 12 without rescue therapy, number of patients with Minimal Manifestation Status per MGFA-PIS at week 12 without rescue therapy, and infections were based on the presence or absence of any (non-null) effect.

Results of GRADE Assessments

[Table 3](#) presents the GRADE summary of findings for zilucoplan versus placebo in patients with AChR antibody-positive gMG.

Table 3: Summary of Findings for Zilucoplan Versus Placebo for Adult Patients With AChR Antibody–Positive gMG

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	Zilucoplan (95% CI)	Difference (95% CI)		
Activities of daily living							
MG-ADL (0 to 24; higher indicates more severe symptoms), mITT							
LSM change from baseline in the MG-ADL score Follow-up: 12 weeks	174 (1 RCT)	NR	−2.30	− 4.39 (− 5.28 to −3.50)	−2.09 (−3.24 to −0.95)	Moderate ^a	Zilucoplan likely results in a clinically important decrease (improvement) in the MG-ADL score at 12 weeks compared with placebo.
Number of patients achieving MSE (MG-ADL score of 0 or 1) without rescue therapy Follow-up: 12 weeks	174 (1 RCT)	OR = 2.608 (0.739 to 9.209 ^b)	58 per 1,000	140 per 1,000 (NR)	82 more per 1,000 (19 fewer to 183 more ^b) ^c	Low ^d	Zilucoplan may result in an increase in the number of patients achieving MSE at 12 weeks without rescue therapy compared with placebo. There is some uncertainty in the clinical importance of the estimates.
Number of patients with a ≥ 3-point decrease in the MG-ADL score without rescue therapy Follow-up: 12 weeks	174 (1 RCT)	OR = 3.184 (1.391 to 7.293 ^b)	461 per 1,000	731 per 1,000 (NR)	270 more per 1,000 (90 to 449 more ^b) ^c	Moderate ^e	Zilucoplan likely results in an increase in the number of patients with a ≥ 3-point decrease (improvement) in the MG-ADL score at 12 weeks without rescue therapy compared with placebo. There is some uncertainty in the clinical importance of the estimates.
Disease severity							
QMG (0 to 39; higher indicates more severe impairment), mITT							
LSM change from baseline in the QMG score Follow-up: 12 weeks	174 (1 RCT)	NR	−3.25	−6.19 (−7.29 to −5.08)	−2.94 (−4.39 to −1.49)	Moderate ^f	Zilucoplan likely results in a clinically important decrease (improvement) in the QMG score at 12 weeks compared with placebo.
Number of patients with a ≥ 5-point decrease in the QMG score without rescue therapy Follow-up: 12 weeks	174 (1 RCT)	OR = 2.865 (1.319 to 6.225 ^b)	330 per 1,000	580 per 1,000 (NR)	250 per 1,000 (73 to 427 more ^b) ^c	Moderate ^g	Zilucoplan likely results in an increase in the number of patients with a ≥ 5-point decrease (improvement) in the QMG score at 12 weeks without rescue therapy compared with placebo. There is some

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	Zilucoplan (95% CI)	Difference (95% CI)		
							uncertainty in the clinical importance of the estimates.
Treatment response							
MGC (0 to 50; higher indicates more severe impairment), mITT							
LSM change from baseline in MGC score Follow-up: 12 weeks	174 (1 RCT)	NR	-5.42	-8.62 (-10.22 to -7.01)	-3.20 (-5.24 to -1.16)	Moderate ^h	Zilucoplan likely results in a clinically important decrease (improvement) in the QMG score at 12 weeks compared with placebo.
Other efficacy end point							
Number of patients with Minimal Manifestation Status per MGFA-PIS without rescue therapy Follow-up: 12 weeks	151 (1 RCT)	OR = 1.834 (0.847 to 3.969)	193 per 1,000	282 per 1,000 (NR)	109 more per 1,000 (15 fewer to 232 more) ^c	Low ⁱ	Zilucoplan may result in an increase in the number of patients with Minimal Manifestation Status per MGFA-PIS at 12 weeks without rescue therapy compared with placebo. There is some uncertainty in the clinical importance of the estimates.
Health-related quality of life							
MG-QoL15r (0 to 30; higher indicates greater severe impact), mITT							
LSM change from baseline in the MG-QoL15r score Follow-up: 12 weeks	174 (1 RCT)	NR	-3.16	-5.65 (-7.17 to -4.12)	-2.49 (-4.45 to -0.54)	Moderate ^j	Zilucoplan likely results in a reduction (improvement) in the MG-QoL15r score at 12 weeks compared with placebo. There is some uncertainty in the clinical importance of the estimates.
Harms							
Adverse events, safety set							
Number of patients with infections Follow-up: 12 weeks	174 (1 RCT)	NR	182 per 1,000	267 per 1,000 (NR)	86 more per 1,000 (38 fewer to 209 more) ^c	Low ^k	Zilucoplan may result in an increase in infections compared with placebo. There is some uncertainty in the clinical importance of the estimates.

AChR = acetylcholine receptor; CI = confidence interval; LSM = least squares mean; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MG-QoL15r = Myasthenia Gravis Quality of Life 15-item revised; mITT = modified intent to treat; MSE = Minimal Symptom Expression; NA = not applicable; NR = not reported; OR = odds ratio; QMG = Quantitative Myasthenia Gravis; RCT = randomized controlled trial.

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

^aRated down 1 level for serious imprecision. Based on a 2-point MID identified in the literature, the 95% CI included the possibility of little to no difference and clinically important benefit. The 2 point MID has been estimated for change within an individual patient and was applied in the absence of an estimate of a between-group MID.

^bBased on the testing procedure used for the secondary end points, the CI was 98.75% for MG-ADL responder, 98.3% for QMG responder, and 97.5% for achieving MSE in the statistical hierarchy using the Holm's procedure. The associated CI was generated using a post hoc analysis upon request by the review team.

^cRisk difference (95% CI) was not included in the sponsor's planned analyses; the absolute risk difference was requested by the review team for interpretation purposes.

^dRated down 2 levels for very serious imprecision. In the absence of an identified threshold in the literature or by the clinical expert consulted by CDA-AMC for the review, the null was used as the threshold. The 95% CI included the null. The CDA-AMC review team judged the effect estimate to be large and the number of events to be small, raising concern for prognostic balance and potential overestimation of the true effect.

^eRated down 1 level for serious imprecision. In the absence of an identified threshold in the literature or by the clinical expert consulted by CDA-AMC for the review, the null was used as the threshold. The point estimate and the entire CI suggested potential benefit. The CDA-AMC review team judged the effect estimate to be large and the sample size to be small, raising concern for prognostic balance and potential overestimation of the true effect.

^fRated down 1 level for serious imprecision. Based on a MID ranging from 2 to 3 identified in the literature, the 95% CI included the possibility of little to no difference and clinically important benefit. This MID has been estimated for change within an individual patient and was applied in the absence of an estimate of a between-group MID.

^gRated down 1 level for serious imprecision. In the absence of an identified threshold in the literature or by the clinical expert consulted by CDA-AMC for the review, the null was used as the threshold. The CDA-AMC review team judged the effect estimate to be large and the sample size to be small, raising concern for prognostic balance and potential overestimation of the true effect.

^hRated down 1 level for serious imprecision. Based on a 3-point MID identified in the literature, the 95% CI included the possibility of little to no difference and clinically important benefit. This MID has been estimated for change within an individual patient and was applied in the absence of an estimate of a between-group MID.

ⁱRated down 2 levels for very serious imprecision. In the absence of an identified threshold in the literature or by the clinical expert consulted by CDA-AMC for the review, the null was used as the threshold. The 95% CI included the null. The effect estimate was based on a small sample size. This analysis was not adjusted for multiplicity and the results should be considered as supportive evidence.

^jRated down 1 level for serious imprecision. In the absence of an identified threshold in the literature or by the clinical expert consulted by CDA-AMC for the review, the null was used as the threshold. The effect estimate was based on a small sample size.

^kRated down 2 levels for very serious imprecision. In the absence of an identified threshold in the literature or by the clinical expert consulted by CDA-AMC for the review, the null was used as the threshold. The 95% CI included the null. The effect estimate was based on a small sample size.

Source: RAISE Clinical Study Report.

Long-Term Extension Study

Description of Studies

The sponsor included 1 ongoing, phase III, multicentre, open-label extension study (RAISE-XT) of adult patients with AChR antibody–positive gMG (overall gMG population and refractory subpopulation) who had previously participated in a double-blind trial of zilucoplan 0.3 mg/kg or placebo to evaluate the long-term efficacy and safety of zilucoplan. The primary outcome of the RAISE-XT study was the incidence of TEAEs, defined as an AE starting on or after the time of first administration of the study drug and up to and including 40 days after the final dose (or last contact). Secondary efficacy outcomes included change from baseline to RAISE-XT week E12 in the MG-ADL score, the QMG score, the MGC score, and the MG-QoL15r score. Exploratory outcomes in the RAISE-XT study included minimal manifestation per MGFA-PIS at week E12 without rescue therapy; responder rates for the MG-ADL, QMG, and MGC scores at week E12 without rescue therapy; and achieving MSE (MG-ADL score of 0 or 1) at week E12 without rescue therapy. In the overall gMG population, the 93 patients in the zilucoplan 0.3 mg/kg and zilucoplan 0.3 mg/kg (zilucoplan-zilucoplan) group and 90 patients in the placebo and zilucoplan 0.3 mg/kg (placebo-zilucoplan) group were similar in mean age (53 years and 54 years), the percentage who were female (56% and 53%) and male (44% and 47%), the percentage enrolled from North America (57% and 54%), the percentage enrolled from Europe (35.5% and 35.6), and the percentage enrolled from East Asia (7.5% and 10.0%).

Efficacy Results

Secondary efficacy end points in the RAISE-XT study were reported for the data cut-off date of November 11, 2023.

Change From Parent Study Baseline to Week E12 in MG-ADL Score

In the overall population, the LS mean change from parent study baseline to week E12 in the MG-ADL score was –5.90 (SE = 0.47) in the zilucoplan-zilucoplan group and –6.17 (SE = 0.59) in the placebo-zilucoplan group. In the refractory subpopulation, the mean change from parent study baseline to week E12 in the MG-ADL score was –6.61 (SE = 0.63) in the zilucoplan-zilucoplan group and –6.24 (SE = 0.71) in the placebo-zilucoplan group.

Change From Parent Study Baseline to Week E12 in QMG Score

In the overall population, the LS mean change from parent study baseline to week E12 in the QMG score was –8.78 (SE = 0.66) in the zilucoplan-zilucoplan group and –8.53 (SE = 0.79) in the placebo-zilucoplan group. In the refractory subpopulation, the mean change from parent study baseline to week E12 in the QMG score was –8.18 (SE = 0.71) in the zilucoplan-zilucoplan group and –8.34 (SE = 1.09) in the placebo-zilucoplan group.

Change From Parent Study Baseline to Week E12 in MGC Score

In the overall population, the LS mean change from parent study baseline to week E12 in the MGC score was –11.77 (SE = 0.86) in the zilucoplan-zilucoplan group and –12.30 (SE = 1.12) in the placebo-zilucoplan group. In the refractory subpopulation, the mean change from parent study baseline to week E12 in the MGC

score was -11.83 (SE = 1.17) in the zilucoplan-zilucoplan group and -13.34 (SE = 1.35) in the placebo-zilucoplan group.

Change From Parent Study Baseline to Week E12 in MG-QoL15r Score

In the overall population, the LS mean change from parent study baseline to week E12 in the MG-QoL15r score was -9.92 (SE = 0.95) in the zilucoplan-zilucoplan group and -8.07 (SE = 1.08) in the placebo-zilucoplan group. In the refractory subpopulation, the mean change from parent study baseline to week E12 in the MG-QoL15r score was -9.46 (SE = 1.15) in the zilucoplan-zilucoplan group and -9.34 (SE = 1.32) in the placebo-zilucoplan group.

Updated results at week E84 were consistent with those observed as week E12.

Exploratory End Points

Exploratory end points in the RAISE-XT study were reported at the data cut-off date of November 11, 2023.

In the overall population, the number of patients who achieved MSE (MG-ADL score of 0 or 1) at week E12 without rescue therapy was 18 (19.4%) in the zilucoplan-zilucoplan group and 7 (7.8%) in the placebo-zilucoplan group. In the refractory subpopulation, the number of patients who achieved MSE at week E12 without rescue therapy was 8 (18.6%) in the zilucoplan-zilucoplan group and 1 (2.4%) in the placebo-zilucoplan group.

In the overall population, the number of patients who were MG-ADL responders at week E12 without rescue therapy was 71 (84.5%) in the zilucoplan-zilucoplan group and 68 (81.9%) in the placebo-zilucoplan group. In the refractory subpopulation, the number of patients who were MG-ADL responders at week E12 without rescue therapy was 34 (87.2%) in the zilucoplan-zilucoplan group and 27 (75.0%) in the placebo-zilucoplan group.

In the overall population, the number of patients who were QMG responders at week E12 without rescue therapy was 66 (80.5%) in the zilucoplan-zilucoplan group and 59 (72.0%) in the placebo-zilucoplan group. In the refractory subpopulation, the number of patients who were QMG responders at week E12 without rescue therapy was 28 (73.7%) in the zilucoplan-zilucoplan group and 25 (69.4%) in the placebo-zilucoplan group.

In the overall population, the number of patients who achieved Minimal Manifestation Status per MGFA-PIS at week E12 without rescue therapy was 29 (37.7%) in the zilucoplan-zilucoplan group and 29 (37.2%) in the placebo-zilucoplan group. In the refractory subpopulation, the number of patients who achieved Minimal Manifestation Status per MGFA-PIS at week E12 without rescue therapy was not reported.

Updated results at week E84 were consistent with those observed as week E12.

Harms Results

Harms data in the RAISE-XT study are reported for the data cut-off date of November 11, 2023.

The number of patients in the overall population who experienced at least 1 TEAE was 89 of 93 (95.7%) in the zilucoplan-zilucoplan group and 86 of 90 (95.6%) in the placebo-zilucoplan group. The most common

TEAEs occurring in 10% of patients or greater in any group (the zilucoplan-zilucoplan group and the placebo-zilucoplan group, respectively) were MG (29% and 29%), COVID-19 (39% and 31%), headache (19% and 22%), nasopharyngitis (23% and 17%), arthralgia (20% and 13%), diarrhea (19% and 13%), fatigue (18% and 13%), nausea (15% and 17%), upper respiratory tract infection (14% and 18%), urinary tract infection (16% and 14%), pain in extremity (16% and 10%), cough (12% and 12%), fall (11% and 10%), back pain (11% and 10%), rash (10% and 10%), vomiting (11% and 6%), injection site bruising (4% and 11%), and oropharyngeal pain (1% and 10%).

The number of patients in the refractory subpopulation who experienced at least 1 TEAE was 82 of 85 (96.5%) in the zilucoplan 0.3 mg/kg group (zilucoplan-zilucoplan and placebo-zilucoplan groups combined). The most common TEAEs occurring in 10% of patients or greater in the refractory subpopulation in any group (the zilucoplan-zilucoplan group and the placebo-zilucoplan, respectively) were MG (42% and 38%), COVID-19 (44% and 24%), headache (21% and 21%), arthralgia (26% and 10%), nasopharyngitis (16% and 19%), urinary tract infection (19% and 12%), upper respiratory tract infection (19% and 12%), diarrhea (16% and 12%), nausea (12% and 17%), fall (14% and 12%), back pain (14% and 12%), and pain in extremity (16% and 10%).

The number of patients in the overall population who experienced at least 1 serious TEAE was 35 (37.6%) in the zilucoplan-zilucoplan group and 29 (32.2%) in the placebo-zilucoplan group. Serious TEAEs occurring in 2% of patients or greater in any group (the zilucoplan-zilucoplan group and the placebo-zilucoplan group, respectively) were MG (9.7% and 11.1%), COVID-19 pneumonia (4.3% and 1.1%), myocardial infarction (4.3% and 0%), pneumonia (3.2% and 1.1%), cholecystitis (2.2% and 1.1%), staphylococcus bacteremia (2.2% and 0%), atrial fibrillation (2.2% and 0%), cardiac arrest (2.2% and 0%), cellulitis (2.2% and 2.2%), and large intestine polyp (0 and 2.2%).

The number of patients in the refractory subpopulation who experienced at least 1 serious TEAE was 20 of 43 (46.5%) in the zilucoplan-zilucoplan group and 15 of 42 (35.7%) in the placebo-zilucoplan group.

TEAEs resulting in permanent withdrawal from the study drug in the overall population were reported in 21 patients (11.4%), with 9 patients (9.7%) in the zilucoplan-zilucoplan group and 12 patients (13.3%) in the placebo-zilucoplan group. The most common TEAE resulting in permanent withdrawal from study drug was MG (6 patients [3.0%]).

The number of patients in the refractory subpopulation who experienced at least 1 serious TEAE was 11 of 85 (12.9%), with 2 patients (4.7%) in the zilucoplan-zilucoplan group and 9 (21.4%) in the placebo-zilucoplan group.

A total of 6 patients died during the RAISE-XT study. The number of patients who experienced a TEAE leading to death was 3 (3.2%) in the zilucoplan-zilucoplan group and 1 (1.1%) in the placebo-zilucoplan group. In the zilucoplan-zilucoplan group, the TEAEs leading to death were cardiac arrest (2 patients [2.2%]) and head injury (1 patient [1.1%]). In the placebo-zilucoplan group, the TEAE leading to death was death (1 patient [1.1%]).

Two patients (2.5%) in the refractory subpopulation died during the study; 1 patient in the zilucoplan-zilucoplan group had a TEAE leading to death. No details were reported for the deaths in the refractory subpopulation.

The number of patients who experienced any infection was 67 (72.0%) in the zilucoplan-zilucoplan group and 65 (72.2%) in the placebo-zilucoplan group. Of these, the number of patients who experienced serious infections was 16 (17.2%) in the zilucoplan-zilucoplan group and 11 (12.2%) in the placebo-zilucoplan group.

The number of patients in the refractory subpopulation who experienced any infections was 34 (79.1%) in the zilucoplan-zilucoplan group and 33 (78.6%) in the placebo-zilucoplan group.

Critical Appraisal

The RAISE-XT study was an open-label, noncomparative extension of the RAISE parent study. The key limitation of the absence of a comparator group is that patients were not randomized to treatment groups (while patients in the parent study were randomized to zilucoplan or placebo, all patients in the extension study received zilucoplan), precluding inferences of any observed differences as being due to treatments received. Importantly, treatment efficacy and harms for patients with longer follow-up should be interpreted cautiously because it cannot be determined if the findings are due to the natural history of the disease, study treatments including concomitant therapies, or other unknown factors. The number of patients with missing data in the secondary end points of change from parent study baseline to week E12 of the RAISE-XT study was similar in the zilucoplan-zilucoplan and the placebo-zilucoplan groups, and was low overall for scores on the MG-ADL (4%), QMG and the MGC (6%), and MG-QoL15r (7%) despite lack of imputation. Similar proportions of patients with missing data for change from parent study baseline to week E12 in the refractory subpopulation ranged from 7% (MG-ADL score) to 8% (QMG and MGC scores) and 9% (MG-QoL15r score). At week E84, missing data were higher (ranging from approximately 22% to 28% of patients for the MG-ADL, QMG, MGC, and MG-QoL 15r outcomes, and spanning from approximately 28% to 38% of patients across MSE, MG-ADL, and QMG responder rates). Although the proportions of missing patients were similar across groups, the missing data may increase concerns related to interpretation of findings that may not be generalizable to the full population.

The clinical experts consulted for the review anticipated that zilucoplan would be used as long as the patient was responding to treatment and any AEs were manageable, so it would be reasonable for patients to continue treatment for at least the 12 weeks as was evaluated in the RAISE-XT study. No concerns were raised by the expert based on the AEs observed with longer treatment with zilucoplan.

Indirect Comparisons

Description of Studies

The sponsor submitted an indirect comparison that evaluated the short-term efficacy of zilucoplan compared with other treatments used for the management of patients with AChR antibody-positive gMG in the overall gMG population, as well as those with refractory gMG (subgroup analysis). The indirect comparison was based on a systematic literature review. Bayesian NMA methods were used to estimate the comparative efficacy in the proportion of patients who met MG-ADL response criteria at the end of the primary studies

and the change from baseline for the MG-ADL score at 12 weeks (± 2 weeks). The treatments included in the NMAs were zilucoplan, eculizumab, efgartigimod alfa, IVIg, PLEX, rituximab, ravulizumab, and rozanolixizumab.

A total of 12 double-blind, placebo-controlled RCTs were included in the NMA, but the primary analyses were based on phase III studies only (5 RCTs).

Efficacy Results

In the overall gMG population, the proportion of patients with a 3-point or greater improvement in MG-ADL score at the end of the studies (week 6 to 26) was analyzed based on data from 5 RCTs (793 patients). Four of the 5 studies reported the proportion of patients with at least a 3-point improvement in MG-ADL and 1 study (rozanolixizumab) was based on at least a 2-point improvement. The odds ratio (OR) for the proportion of responders was [REDACTED] for zilucoplan versus eculizumab and [REDACTED] for zilucoplan versus efgartigimod.

The subgroup analysis in patients with refractory gMG reported an OR of [REDACTED] and [REDACTED] for zilucoplan versus eculizumab and efgartigimod, respectively. Of note, only 2 of 5 studies in this sensitivity analysis included exclusively patients with refractory gMG. The other studies included either a mixed population (1 study with 63% patients with refractory gMG) or 2 studies with an unknown proportion of patients with refractory disease.

The primary analysis for the change from baseline in MG-ADL score included 5 studies with 755 patients and was based on outcomes reported at 10 weeks (2 studies) or 12 weeks (3 studies). The mean difference for the change from baseline in the MG-ADL score for zilucoplan was [REDACTED] versus eculizumab, and [REDACTED] versus efgartigimod. For the refractory subgroup, the mean difference in the change from baseline in the MG-ADL score was [REDACTED] for zilucoplan versus eculizumab and [REDACTED] for zilucoplan versus efgartigimod.

The sensitivity analysis that included 6 to 12 phase II and III studies (depending on the analysis), showed similar results for zilucoplan versus eculizumab or efgartigimod in the overall and refractory populations, as compared with the primary analyses in these populations.

Harms Results

No safety outcomes were included in the NMA.

Critical Appraisal

The indirect treatment comparison (ITC) report provided insufficient detail to describe the methods used to select studies for inclusion in the ITC, thus it is unclear if all potentially relevant studies were considered. In addition, the ITC report did not describe the findings from a feasibility assessment, which was used to inform the conduct of the NMA. No information was provided on the characteristics of the studies included in the analyses, which was a major limitation.

Based on the data available, several important sources of heterogeneity were identified, including differences in outcome definitions and the timing of assessments, the placebo MG-ADL response rate, and in terms of disease severity and MG treatment history of the patients enrolled. Specifically, the trials had different proportions of patients rated as having mild, moderate, severe, and/or refractory gMG. The clinical expert stated that patients with refractory gMG or more severe disease may be less likely to respond to therapy, thus differences in the distribution of these patients across trials may bias the findings. Both the overall population analyses and the refractory subgroup analyses contain a varying mix of patients with and without refractory gMG, which is a key source of heterogeneity. Moreover, the refractory subgroup analyses cannot be considered a true comparative assessment of patients with refractory gMG as not all studies were limited to patients with refractory disease.

A major limitation of the ITC methods was due to issues with the timing of outcomes. The responder analyses used each study's primary outcome time point, which varied from 6 to 26 weeks. The change from baseline analyses assessed outcomes at week 10 or 12 in the primary analyses but included other time points in the sensitivity analyses (from 4 to 52 weeks). The CDA-AMC reviewer considered the differences in the timing of outcomes to be a significant source of heterogeneity that was not controlled for in the analyses. Restricting the outcome to those reported at 10 or 12 weeks also had serious limitations, related in part to the differences in dosing schedules (intermittent versus continuous), which could bias the results. The response definition also varied, with 4 of the 5 studies in the primary analysis reporting the proportion of patients with at least a 3-point improvement in the MG-ADL score, however 1 of the key studies used a 2-point threshold.

Overall, the evidence networks were sparse, with the primary analysis based on 1 trial per comparator. Generally, the duration of follow-up in the source studies was limited (up to 26 weeks for the primary analyses), thus comparative estimates were based on short-term data. The NMA results lacked precision, as shown by the wide 95% CrI. Considering the heterogeneity in the patient and study characteristics that was identified based on a limited assessment, there is likely substantial risk of bias for the comparisons in the network. As a result, no conclusions could be drawn on the comparative efficacy of zilucoplan. No harms outcomes were assessed in the NMA, thus the comparative safety of zilucoplan is unknown.

Studies Addressing Gaps in the Evidence From the Systematic Review

No additional studies addressing important gaps in the systematic review were identified.

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	Patients with AChR antibody–positive gMG that is uncontrolled on high-dose corticosteroids and nonsteroidal ISTs, consistent with patients in the refractory group included in the RAISE trial ^a
Treatment	Zilucoplan plus SOC ^b
Dose regimen	Body weight < 56 kg: 16.6 mg SC once daily Body weight ≥ 56 to < 77 kg: 23.0 mg SC once daily Body weight ≥ 77 kg: 32.4 mg SC once daily
Submitted prices	Zilucoplan 16.6 mg/0.416 mL prefilled syringe: \$650.27 Zilucoplan 23.0 mg/0.574 mL prefilled syringe: \$900.98 Zilucoplan 32.4 mg/0.810 mL prefilled syringe: \$1,269.21
Submitted treatment cost	\$461,990 per year (364 days), assuming a patient weighing more than 77 kg
Comparators	• Refractory SOC^b • Eculizumab plus SOC • Efgartigimod alfa plus SOC • Chronic IVIg or SCIg plus SOC • Chronic PLEX plus SOC • Rituximab plus SOC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (48.2 years)
Key data sources	Sponsor-submitted NMA report comparing zilucoplan, efgartigimod, SOC, and eculizumab. Naive comparisons using data from the RAISE trial (SOC), Barth et al. (2011) (chronic IVIg and SCIg and chronic PLEX), Nowak et al. (2021) (rituximab)
Submitted results	• Zilucoplan was associated with an ICER of \$1,611,347 per QALY gained compared to PLEX (incremental costs: \$815,770; incremental QALYs: 0.1661) • SOC and rituximab plus SOC were also on the efficiency frontier but were less costly and less effective treatments.
Key limitations	• Due to the lack of direct evidence, limitations with the sponsor-submitted NMA, and the sponsor's use of naive comparisons to inform the economic evaluation, the relative treatment effects of zilucoplan to its comparators are highly uncertain. • The sponsor's assumptions regarding the impact of treatment discontinuation were inappropriate because they underestimated costs or overestimated benefits by assuming maintenance of effect beyond treatment discontinuation. • The sponsor assumed reductions in corticosteroid use based on treatment response, which were not supported by clinical data and likely overestimated the extent to which corticosteroid use may be

Component	Description
	reduced. This overestimated the cost and HRQoL impacts of such reductions in use. The model lacked transparency and reliability, limiting the ability of CDA-AMC to properly validate results within the time frame of this review.
CDA-AMC reanalysis results	- Given the clinical limitations identified with the sponsor's economic submission, including uncertainty in comparative treatment effect, CDA-AMC was unable to derive a more reliable estimate of the cost-effectiveness of zilucoplan as an add-on therapy to SOC. - While the sponsor's base case suggests differences in treatment benefits between zilucoplan and other add-on therapies used for the treatment of adults with refractory AChR antibody-positive gMG, there is no robust evidence to support this claim. If the sponsor's claim of added benefit (0.166 QALYs) is maintained, the probability that zilucoplan is cost-effective at a willingness-to-pay of \$50,000 per QALY is 0%. - CDA-AMC undertook several scenarios, the combination of which suggested that the ICER for zilucoplan is likely higher than estimated by the sponsor (\$6,024,388 per QALY gained relative to PLEX), mainly due to underestimation of drug acquisition costs. - A price reduction of at least 83% (from \$1,269 to \$216 per 32.4 mg vial) is required for zilucoplan to achieve an ICER of \$50,000 per QALY gained. Under the CDA-AMC combined scenario analysis, a price reduction of 95.5% (\$57 per 32.4 mg vial) would be required to achieve an ICER of \$50,000 per QALY gained.

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; IVIg = IV immunoglobulin; LY = life-year; PLEX = plasma exchange; QALY = quality-adjusted life-year; SC = subcutaneous; SCIg = subcutaneous immunoglobulin; SOC = standard of care.

*CDA-AMC accepted a request for deviation from the sponsor to limit the economic submission to the sponsor's reimbursement request.

^bRefractory SOC 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

CDA-AMC identified the following key limitations with the sponsor's analysis:

- The sponsor's derivation of the Non-Insured Health Benefits (NIHB) population was inappropriately calculated.
- Eculizumab is not a publicly funded comparator for the treatment of gMG.
- Assumptions around the comparators displaced as efgartigimod alfa expands into the public market are uncertain.
- The relative cost of zilucoplan and efgartigimod alfa within the same patient population is uncertain.
- The analyses were not conducted from a drug plan payer perspective as blood products are not funded by drug plan programs.
- The proportion of patients eligible for public funding was not estimated by jurisdiction.

CDA-AMC reanalyses revised the sponsor's submitted analysis by assuming eculizumab has 0% of the public market, assuming efgartigimod alfa displaces all comparators as it enters the market, and by removing the cost of blood products from the analysis.

Results of CDA-AMC reanalyses suggest that the reimbursement of zilucoplan plus SOC for the treatment of adults with refractory AChR antibody-positive gMG may be associated with a budgetary increase of \$82,030,716 (year 1: \$13,946,524; year 2: \$27,772,856; year 3: \$40,311,336).

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, 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: November 27, 2024

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.



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