Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

EFGARTIGIMOD ALFA (VYVGART)

Indication: For the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.

Sponsor: argenx Canada Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that efgartigimod alfa be reimbursed for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from one phase 3, multicentre, double blind (DB), randomized, placebo-controlled trial (ADAPT) demonstrated that compared with placebo, treatment of efgartigimod alfa results in added clinical benefit in adult patients with gMG who are AChR antibody positive. ADAPT demonstrated that, after cycle 1 of treatment, efgartigimod alfa compared with placebo was associated with a statistically significant and clinically meaningful improvement in terms of the proportion of MG-ADL responder (the between group mean difference [EFG – PBO]: 38%, 95%CI, 22% to 56%; the odds ratio versus placebo (95% CI) was 4.951, 95% CI, 2.213 to 11.528, p <0.0001); the proportion of QMG responders (the between group mean difference [EFG – PBO]: 49.0%, 95%CI, 34.5% to 63.5%, the odds ratio versus placebo was 10.84, 95%CI 4.18 to 31.20, p = 0.0001); and the percentage of time with a meaningful MG-ADL improvement during 126 days follow-up (48.7% versus 26.6%, p = 0.0001). There were largely no notable differences in adverse events. In terms of MG-ADL, QMG and safety profile, evidence from the long-term open label extension (ADAPT+) trial appeared consistent.

Despite the available treatment options, there remains an unmet therapeutic need for effective treatment options for patients with this rare and chronic condition, specifically for patients with refractory gMG and patients with inadequately controlled gMG despite trial of conventional therapies (e.g., acetylcholinesterase inhibitors (AChEIs), corticosteroids (CSs), and/or non-steroidal immunosuppressants (NSISTs)). Patients expressed a need for treatments with sustained efficacy, reduced side effects that enhance independence (e.g., method, frequency, setting of delivery). Based on the evidence reviewed, CDEC concluded that efgartigimod alfa met some of the needs identified. Efficacy results from ADAPT demonstrated meaningful benefit (improvement in gMG daily activity, reduction in disease activity, and improvement health-related quality of life), suggesting sustained benefit for up to 14 cycles in the long-term open label extension (ADAPT+) trial. Efgartigimod alfa may offer more convenience in terms of fast onset (proportion of early MG-ADL responders) and longer period between infusions in a subpopulation (e.g., potentially compared to some IVIg regimens).

Using the sponsor submitted price for efgartigimod alfa and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for efgartigimod alfa plus conventional therapy was $1,764,628 per quality-adjusted life-year (QALY) compared with rituximab plus conventional therapy. At this ICER, efgartigimod alfa plus conventional therapy is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adults with AChR-Ab+ gMG. A price reduction is required for efgartigimod alfa to be considered cost-effective at a $50,000 per QALY threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with efgartigimod alfa should be reimbursed for adult patients with gMG who have all of the following: 1.1. positive serologic test for anti-acetylcholine receptor antibodies 1.2. a Myasthenia Gravis Activities of Daily Living (MG-ADL) score at baseline of ≥ 5 1.3. Myasthenia Gravis Foundation of America (MGFA) class II to IV disease 1.4. symptoms persist, despite a stable dose of standard of care with acetylcholinesterase inhibitors (AChEIs), corticosteroids (CSs), and/or non-steroidal immunosuppressants (NSISTs)	The results from one phase 3, multicentre, double blind (DB), randomized, placebo-controlled trial (ADAPT) demonstrated that compared with placebo, treatment of efgartigimod alfa results in added clinical benefit in adult patients with gMG who are AChR antibody positive. ADAPT enrolled adult patients (age ≥ 18 years) with gMG patients who tested positive for anti-acetylcholine receptor antibodies, had a MG-ADL score ≥ 5, MGFA class of II to IV and symptoms persist despite a stable dose of standard of care with AChEIs, CSs, and/or NSISTs at baseline.	Stable dose may be defined as adequate trial of at least one of AChEIs, CSs, and/or NSISTs in the previous 12 months. CDEC noted that rituximab may be available in some jurisdictions, however, CDEC heard from the clinical experts that access to rituximab remains a barrier for some patients.
2. Efgartigimod alfa should not be initiated: 2.1. during a gMG exacerbation or crisis, or 2.2. within 3 months of thymectomy	Patients with MGFA class of V and who had thymectomy less than 3 months prior to screening were excluded from ADAPT. The efficacy and harms of efgartigimod alfa in such patients are unknown.	
3. MG-ADL score must be measured and provided by the physician at baseline.	Baseline MG-ADL score was measured in ADAPT and was used to determine response to treatment.	
4. The maximum duration of initial authorization is 3 cycles	According to the clinical experts, approval for 3 cycles initially would be reasonable to assess response to treatment.	Considerations for maximum duration of initial authorization for approximately 6 months would be reasonable given that the treatment phase in ADAPT was a 26-week treatment period.
Renewal		
5. Reimbursement of treatment with efgartigimod alfa should be continued if, after the initial 3 cycles of treatment, there is documented improvement in the MG-ADL of two points or greater.	According to the clinical experts, clinically meaningful responses would be reflected by improvements in disease	Based on clinical expert opinion, after first initial 3 cycles of efgartigimod alfa, if a patient has responded, treatment would be given as long as the patient

Reimbursement condition	Reason	Implementation guidance
Reassessment should occur every 12 months thereafter.	symptoms (approximately 2 points for MG-ADL).	continues to have a clinically meaningful response. In terms of maximum duration of treatment, treatment with efgartigimod alfa would probably be given as long as efgartigimod alfa continued to be effective, or disease spontaneously remitted.
6. For subsequent renewal, the physician must provide proof of no worsening of MG-ADL.	To ensure patients are maintaining their response to treatment with efgartigimod alfa.	Based on clinical expert opinion, there is the possibility of efgartigimod alfa being used for one year or more years. If a patient had responded to efgartigimod alfa after the 3 initial cycles and was stable for a year, but worsens afterwards, the patient can reinitiate therapy, as long as, they met initiation criteria.
Prescribing		
7. Efgartigimod alfa 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 efgartigimod alfa is prescribed to appropriate patients.	
8. Efgartigimod alfa should not be used concomitantly with rituximab or complement inhibitors.	The efficacy and safety of efgartigimod alfa in combination with rituximab, eculizumab and/or ravulizumab is unknown.	
Pricing		
9. A reduction in price	The ICER for efgartigimod alfa plus conventional therapy is $1,764,628 per QALY when compared with rituximab plus conventional therapy. A price reduction of 84% would be required for efgartigimod alfa plus conventional therapy to achieve an ICER of $50,000 per QALY compared to rituximab plus conventional therapy.	
Feasibility of adoption		

Reimbursement condition	Reason	Implementation guidance
10. The feasibility of adoption of efgartigimod alfa must be addressed.	At the submitted price, the incremental budget impact of efgartigimod alfa is expected to be greater than $40 million per year.	

AChEIs = acetylcholinesterase inhibitors; CSs = corticosteroids; gMG = generalized Myasthenia Gravis; ICER = incremental cost-effectiveness ratio; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; NSISTs = non-steroidal immunosuppressants; QALY = quality-adjusted life year.

Discussion Points

- CDEC discussed the rarity of this condition and noted that despite its low incidence, treatment options are available for patients (e.g., azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, methotrexate, prednisone). However, CDEC acknowledged that not all treatment options may be available to every patient in every jurisdiction. CDEC acknowledged that there is an unmet need for effective therapy for patients with refractory gMG and patients with inadequately controlled gMG despite trial of conventional therapies (e.g., AChEIs, CSs, and/or NSISTs). CDEC noted that among the patients who were ACH-R AB seropositive in ADAPT, 63% patients had failed on prior gMG treatments and were considered refractory (i.e., prior exposure to ≥2 immunosuppressive therapies or treatment with ≥1 immunosuppressive therapy and requiring plasma exchange or intravenous immunoglobulin multiple times within 1 year prior to study inclusion).

- CDEC noted that according to the clinical experts, ~90% patients respond to current treatments and that response is often partial, resulting in the continuation of symptoms that affect quality of life and function. CDEC noted that the overall treatment gMG goal is to improve quality of life, followed by reduce treatment burden and treatment-related morbidities, and maintain adequate disease control. CDEC reviewed evidence from ADAPT and noted that while improvements in HRQoL were exploratory, the results were considered clinically meaningful.

- CDEC discussed needs identified by patients including for decreased intensity of exacerbations and less serious hospital admissions. CDEC acknowledged the ad-hoc analysis which report the incidence of MG-related hospitalizations and MG exacerbations to be low.

- CDEC also discussed patients' desire for fewer treatment related adverse effects. While ADAPT did not provide direct comparative evidence regarding the adverse effects of efgartigimod alfa versus other myasthenia gravis therapies, CDEC noted that TEAEs appeared similar in both efgartigimod alfa and placebo groups and that there were no treatment related deaths in either group. CDEC did, however, acknowledge that in terms of adverse events of special interest, infections and infestations events were higher in the efgartigimod alfa group, which was also acknowledged in the Health Canada product monograph.

- CDEC acknowledged the possibility of treatment burden being higher initially compared to conventional therapy given that efgartigimod alfa is an add-on therapy. While treatment burden may be impacted initially, CDEC noted that improvement in quality of life observed in ADAPT was clinically meaningful.

- While the proportion of early MG-ADL responders (i.e., responder within 2 weeks) during cycle 1 were descriptive in nature, the results were considered clinically meaningful. Moreover, while the meaningful benefits (improvement in gMG daily activity, reduction in disease activity, and improvement health-related quality of life) observed in ADAPT involved short 8-week cycles, and that longer comparative evidence were not available, nonetheless, evidence from the long-term open label extension (ADAPT+) trial suggests sustained benefit for up to 14 cycles, although interpretation of the long-term results was limited by the open label and descriptive nature of the extension study.

- CDEC discussed the results of the sponsor-submitted NMA, which suggested that relative to IVIg and ravulizumab, efgartigimod alfa may provide a benefit with respect to change in MG-ADL and QMG scores; however, the 95% CrIs for the effect estimates included the possibility of trivial effects (i.e., only small, non-clinically important differences between groups) and no difference (in the case of change in MG-ADL score relative to ravulizumab). No difference in efficacy in terms of change from baseline in MG-ADL and QMG could be concluded for efgartigimod alfa relative to rituximab due to wide 95% CrIs (which included the possibility of clinically important benefit favouring efgartigimod alfa), and methodological limitations.

Background

Myasthenia gravis (MG) is a rare, chronic, neuromuscular autoimmune disease mediated by pathogenic autoantibodies which target structural components of the neuromuscular junction (NMJ), impairing neuromuscular transmission, and leading to muscle weakness and fatigue. Many patients initially present with symptoms affecting only the eye muscles (i.e., ocular MG). Approximately 85% of patients go on to develop generalized weakness affecting the neck, trunk, limbs, bulbar and respiratory muscles (gMG). Patients with gMG experience symptoms which negatively impact health-related quality of life (HRQoL). The disease has a fluctuating natural history, MG exacerbation (an increase in symptoms in patients who were previously asymptomatic or minimally symptomatic, defined as a ≥3-point worsening in qualitative myasthenia gravis [QMG] score versus baseline) and myasthenic crisis (muscle weakness causing life-threatening difficulties with breathing and swallowing and requiring ventilator support) can occur gradually or without warning. Approximately 85% of patients with gMG are acetylcholine receptor antibody (AchR-Ab) seropositive (Ach-R AB+) and as many as 15% of patients with gMG are seronegative for AchR-Ab (Ach-R AB-). An estimated 1-10% of patients do not have AchR antibodies but do have autoantibodies against muscle-specific kinase antibody seropositive (MuSK-Ab+) or autoantibodies against lipoprotein receptor-related protein-4 seropositive (LRP4-Ab+), which also lead to a decrease in acetylcholine receptors (AchRs). The Myasthenia Gravis Foundation of America (MGFA) classification system is a tool used to categorize gMG based on clinical features and/or disease severity. The classification ranges from Class I (i.e., ocular weakness only); Class II, Class III and Class IV represents gMG patients with mild, moderate and severe muscle weakness respectively; to Class V (i.e., defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. myasthenic crisis). The incidence of MG in Canada is estimated at 23 cases per 1 million person-years, with a prevalence of 32 cases per 100,000 adults (0.032%) in Canada. Thus, there are approximately 8,121 patients with MG across CADTH- participating drug programs (0.032% × 25,376,703 adult patients in CADTH-participating drug programs in 2023). Approximately 85% of adults with MG are anticipated to have progressed to gMG, which corresponds to approximately 6,903 adult patients with gMG in Canada.

The clinical experts that CADTH consulted for this review indicated that the goal of treatment in patients with gMG is to reduce disease symptoms as well as adverse effects of MG therapy and to allow the patient to function and work normally with good HRQoL. Other goals of treatment include: avoiding MG exacerbations and myasthenic crisis, minimizing hospitalizations and ICU admissions, and reducing the numbers and doses of therapies (e.g., especially corticosteroid use) required for symptom control. The available main therapies of gMG include: AChEIs, corticosteroids, NSIST, rituximab, IVIg, PE/PP, terminal complement inhibitors (i.e., ravulizumab and eculizumab). According to the clinical experts consulted by CADTH for this review, the first line standard of care (i.e., the conventional therapy) for MG are acetylcholinesterase inhibitors (AChEIs), corticosteroids and non- steroid immunosuppressant (NSIST, e.g., azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, methotrexate). Mild to moderate gMG (Myasthenia Gravis Foundation of America [MGFA] class II or IIIa) is initially treated symptomatically with AChEIs (usually pyridostigmine); the onset of benefit occurs in hours to days. If this provides insufficient symptom relief, immunosuppressive therapy (IST) with corticosteroids (usually prednisone) is administered; maximal responses typically occur 2 to 6 months later, after which slow tapering of corticosteroids is begun. In patients who do not respond to corticosteroids, who have significant comorbidities such that long-term corticosteroid treatment is contraindicated, or in whom doses of corticosteroids cannot be tapered, treatment with a NSISTs [15] and/or immunomodulatory agents including rituximab may be initiated. The clinical experts stated that the onset of benefit from NSISTs occurs in months to years (approximately 9 to 18 months for azathioprine and mycophenolate). While rituximab has not been approved as a gMG treatment by Health Canada, it is considered a treatment option in Canada for refractory AChR-Ab seropositive patients according to surveys conducted with clinical experts. According to the clinical experts, in patients with moderate to severe gMG, especially those who have respiratory or bulbar weakness, intravenous immunoglobulin (IVIg), plasma exchange (PE) or plasmapheresis (PP) may be administered in addition to rituximab, either at the time of immunosuppressive therapy (IST) initiation or to treat MG exacerbation or myasthenic crisis. As MG symptoms improve, doses of AchEIs, steroids, NSIST are reduced and the frequency of IVIg, PE or PP is reduced until the minimal maintenance therapy required for remission is identified. Patients with refractory gMG who are AChR antibody positive may be candidates for the complement inhibitor eculizumab. While eculizumab received a recommendation for reimbursement with conditions in 2020, price negotiations concluded without an agreement in December 2022. A survey of 7 expert Canadian clinicians across 6 provinces indicated that ravulizumab would be a another option, if it were to be approved and funded. Ravulizumab would be a treatment option for patients who have an inadequate response to conventional therapy. In April 2023, CADTH issued a draft “do not reimburse” recommendation for ravulizumab in this indication. The clinical experts consulted by CADTH for this review emphasized that most patients with gMG (more than 80%) respond well to currently available treatments; although these cannot cure the

disease, excellent symptom control is achieved in most patients and prognosis is generally good in terms of muscle strength and function as well as HRQoL. Despite treatment with conventional therapy (AchEIs, CSs, and/or NSISTs), many patients continue to experience disease burden and symptoms that impact their HRQoL and suffer from treatment-related side effects which may be severe.

Efgartigimod alfa is a first-in-class human IgG1 antibody Fc-fragment that blocks neonatal Fc receptor (FcRn). Efgartigimod alfa is supplied as a 20 mg/ mL solution, 10 mg/kg administered as an intravenous (IV) infusion over 1 hour once weekly for 4 doses (i.e., Weeks 0 to 3). In patients weighing 120 kg or more, the recommended dose of efgartigimod alfa is 1200 mg (3 vials) per infusion. Efgartigimod alfa reduces the levels of pathogenic IgG autoantibodies. Efgartigimod alfa received a Health Canada Notice of Compliance for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody positive on September 19, 2023. The sponsor's reimbursement request is that efgartigimod alfa be reimbursed as an add-on therapy for acetylcholine receptor antibody positive (AChR-Ab+) gMG adult patients whose symptoms persist despite adequate treatment with acetylcholinesterase inhibitors (AChEIs), corticosteroids (CSs), and/or non-steroidal immunosuppressants (NSISTs), which is a subgroup of the approved Health Canada indication.

Sources of Information Used by the Committee

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

- a review of one phase 3, DB, placebo-controlled RCT (ADAPT) in adult patients with gMG whose symptoms persist despite a stable dose of standard of care (concomitant gMG treatment) treatment with acetylcholinesterase inhibitors (AChEIs), corticosteroids (CSs), and/or non-steroidal immunosuppressants (NSISTs).
- patient perspectives gathered by one patient group, Muscular Dystrophy Canada (MDC).
- input from public drug plans that participate in the CADTH review process
- two of clinical specialists with expertise diagnosing and treating patients with generalized myasthenia gravis (gMG).
- input from one clinician group, the Neuromuscular Disease Network for Canada (NMD4C).
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

CADTH received one patient group submission from the Muscular Dystrophy Canada (MDC).

MDC identified and contacted adults living with MG to participate in a survey and semi-structured interviews.

Respondents indicated that MG has a significant impact on productivity, feeling fatigue, energy levels, quality of sleep, respiratory health, mobility, strength, independence, relationships and social participation, eyes and vision, speech, and swallowing. They also explained that the impact of MG extends beyond physical symptoms, and affects their mental health, quality of life, and the wellbeing of their families.

Some of the respondents indicated they feel that their lungs are weaker, had to go on a ventilator in ICU, choking on food or saliva interferes with breathing, cannot even walk inside my house, always keep a walker or cane nearby because you never know when the MG will flare up, cannot sleep at night because it aches, unable to drive. Some indicated that they had slurred speech, frequently go cross eyed, double vision interferes with reading, and experienced multiple acute hospitalizations.

When asked about how MG is being managed with available treatments, 3 main themes emerged from the analysis: negative experiences with steroids (e.g., adverse effects; costs); the slow onset of medication effects; and a feeling of trial and error with

medications. Regarding the improved outcomes, the patient group identified 3 aspects of MG that they want better controlled, these included: decreased intensity of exacerbations and side effects, maintenance of independence, and less serious hospital admissions. The administering method, duration, frequency, and convenience of treatment, as well as the cost are very important to the patients and caregivers. They prefer less travel, less hospital visits, and less invasive method of treatment. Health related quality of life was noted as a key priority over convenience of a drug.

Respondents stated that they would be willing to deal with side effects of medications if these aspects of MG were better controlled. They also stated that although current medications decrease the number of exacerbations, they do not have an impact on overall quality of life. They expect new treatments to: help them to become independent, stop the myasthenic crises, address the respiratory and general weakness, be easier to swallow (for pills), reduce pain, not lead to diabetes, be target treatment for MG instead of general immunosuppression, be less expensive, work quickly, be a one daily dose in the morning.

One participant had received Vyvgart as a participant of a clinical trial and explained that this medication replaced the need for IVIg, the effects appeared quicker compared with other therapies, the infusion time was less than expected, treatment was received less frequently compared with other therapies, and they experienced less side effects compared with other therapies. This patient respondents highlighted that while diarrhea was a problem and not unique to Vyvgart, the diarrhea was manageable after the first cycle.

All the respondents had experienced diagnostic blood testing, and many had single fiber electromyography to confirm diagnosis. A total of 80% of the respondents reported difficulty getting diagnosed. MDC, based on early findings of the MG Journey Mapping Project, reported 7 years from time of first bothersome symptom to diagnosis, with the range up to 23 years. According to MDC, the majority of respondents found the process of testing and diagnosis cost-effective but lengthy with many missed opportunities, delayed diagnosis, misdiagnosis (such as stroke and Bell's palsy), and costs incurred. Those who were diagnosed during a crisis or hospitalization, reported a smooth diagnosis (25%).

Clinician Input

Input From Clinical Experts Consulted by CADTH

The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of generalized myasthenia gravis (gMG).

The clinical experts indicated ~90% of patients respond to current treatments; however, response is often partial, meaning that there are still symptoms that affect QoL and function. According to the clinical expert, besides prednisone and rescue treatments, ISTs take very long to act, for example azathioprine takes at least a year. The clinical expert explained that this means that patients may be exposed to higher doses of steroids for longer, and with persistent symptoms for long, before even knowing whether this medication will be effective or not. Current treatments are non-targeted, so overall cause more diffuse immunosuppression, and there is an increased risk of cancer on long term use. Also, the risk of all steroid-related AEs increases with prolonged doses. The clinical experts also indicated that the fraction of 'refractory' patients varies according to definition, however 10-20% of the total population considered to be "refractory" is a reasonable estimate. According to the clinical experts consulted by CADTH for this review, patients with gMG usually start with pyridostigmine, but most patients will need disease modifying treatment with immunosuppressant, most commonly prednisone. Depending on severity, age and co-morbidities, a NSIST (azathioprine, mycophenolate, tacrolimus, etc.) may be started early after diagnosis, or later (for example, unable to reduce dose of steroids). Some patients with severe disease at onset (e.g., crisis or severe symptoms) may receive a rescue treatment such as IVIG or plasma exchange early, to have fast improvement while immunosuppression begins. Few patients receive chronic IVIG or plasma exchange, and some of these patients are dependent on these treatments. According to the clinical experts, the treatment goals is to achieve minimal symptoms or remission, with the least amount of adverse events form treatments. Patients express a need to improve the ability to perform their daily life activities, reduce fatigue, and improve their ability to care for their family and work or home obligations.

The clinical experts stated that efgartigimod alfa has a specific mechanism of action related to the pathophysiology of MG (reduction of IgG levels, including AChR antibodies). Efgartigimod alfa reduces levels of IgG, but efgartigimod alfa does not affect the process producing AChR antibodies. The clinical experts indicated that they do not foresee efgartigimod alfa will be used as first line treatment, rather efgartigimod alfa would be suitable for individuals without adequate response to available treatments, or those dependent on IVIG/Plasma exchange or those with very severe disease to bridge gap of delayed action of standard ISTs. The clinical experts noted that patients should have received standard conventional treatments first, since standard conventional treatments will be satisfactory in a large number of patients. The clinical experts also stated that most treatments for patients with gMG are given off label given lack of RCT evidence (prednisone, azathioprine, mycophenolate, tacrolimus, rituximab etc.). The clinical experts noted that IVIG/PLEX used as a rescue treatment is different from IVIG /PE used chronically (I.e. maintenance therapies, once a month); and only a small number of patients use IVIG/PE chronically. According to the clinical experts, eculizumab or ravulizumab are used too rarely at present to include them as comparators. One clinical expert indicated that if cost was not an issue, one could argue that efgartigimod alfa could be tried as an initial therapy in patients in whom pyridostigmine alone was ineffective, however, noted that the cost is likely to be a major barrier. The clinical experts indicated that efgartigimod alfa will provide a new treatment for patients with gMG who are AChR-Ab seropositive and probably for patients with MuSK antibody positive. However, whether patients with gMG who seronegative would respond to efgartigimod alfa is unknown because few seronegative patients were included in ADAPT trial. The clinical experts indicated that in most clinics (not academic) patients do not have standardized assessments. In academic settings, clinician use validated measures. The clinical experts noted that MG-ADL used in trials is easy to use and can be easily incorporated to routine clinical practice and all settings (community, hospital and academic). The clinical experts recommended using MG-ADL for all visits in patients with active treatment, as this allows to follow clinical course. The clinical experts stated that an improvement (reduction) of 2 points is considered significant. Apart from symptom scores, overall function, and ability to return to work are also assessed. The clinical experts expressed that the ability to reduce or stop chronic use of corticosteroids, IVIg or PLEX is an important outcome when considering the use of efgartigimod alfa. They explained that some patients are dependent on chronic IVIG or plasma exchange, weaning of these treatments is important. Clinical experts also highlighted that reduction or avoidance of hospitalization due to MG is an important outcome. n. Frequency of assessments depends on symptoms and patient stability. Patients whose symptoms are well controlled typically seen by clinicians every 6 months, however, they can be seen more frequently (e.g., every 2-3 months) in case of worsening, new medications, etc.

For efgartigimod alfa, most responses were fast, however a small proportion of responders lagged, and response could be seen at the second cycle. Therefore, the clinical experts suggested 2-3 months may be needed to assess response to cycle 1 and/or to assess for need of new cycle. An assessment at 6 months may be needed to determine non responders. For responders, assessments could then be done every 3-6 months would be needed to determine if new cycles will be needed.

The clinical experts indicated that efgartigimod alfa should be discontinued if a patient has no response to treatment (i.e., no improvement in symptoms/function) occurs; if a patient experienced a severe adverse event (e.g., severe infusion reaction); if patients need rescue treatment (IVIG or plasma exchange, or increased dose of steroids), or there is an inability to reduce chronic use of corticosteroids, IVIg, or PLEX. The clinical experts indicated that patients should be under the care of a neurologist with experience in diagnosing and treating myasthenia gravis, usually a neuromuscular specialist. The infusion itself can be arranged at infusion clinics.

Clinician Group Input

CADTH received one clinician group submission from the Neuromuscular Disease Network for Canada (NMD4C).

NMD4C stated that conventional treatment options for gMG have been based on symptomatic therapy, short-term rescue immunotherapy and long-term immunosuppressive therapy. Moreover, non-specific immunosuppressants have been only partially effective and many patients do not attain stable remission, with 10–20% of patients not responding or intolerant to these agents.

According to the NMD4C, some of the unmet needs of the standard treatments are: side effects, not being effective for all patients, long period of treatment, and transient effectiveness. Another unmet need in this field is the lack of therapeutic options for seronegative patients.

The NMD4C noted that patients with acetylcholine receptor antibodies seropositive will most likely respond to the drug under review. Patient with MuSK antibodies and those who are double seronegative might respond. Patients who get worse quickly, particularly patients with MG crisis are most in need of an intervention that works quickly, but patients who have symptoms restricted to only ocular muscles are unlikely to require such rapid intervention with the drug under review. To identify the patients best suited for treatment with drug under review, clinician examination and judgement supplemented by assessment of MG activities of daily living, using scales that reflect severity of disease such as the quantitative myasthenia gravis score, the MG Impairment Index, and the single simple question. If not available, then antibody testing needs to be done, but according to the clinician group, can be delayed. There is nothing clear at this point to predict which patients are more likely to respond, except the presence of acetylcholine receptor antibodies.

The NMD4C indicates that diagnosis of double seronegative patients is an issue since cluster antibodies to both acetylcholine and MuSK may be present but need to be tested specifically, which can take weeks.

The clinician group believe that to determine patients' response to therapy, scales such as MG-ADL, QMGS, MGII, and single simple question (SSQ) at 2 and 4 weeks is required and after that the assessment should be based on the patient's status. The clinician noted that a clinically meaningful response to treatment used in the clinical trials is 2 or more points on the ADL and 3 or more points on the QMGS. For single simple question (SSQ), the clinician group suggested that levels above 72% indicate general satisfaction. In case of lack of response, discontinuation of treatment should be considered.

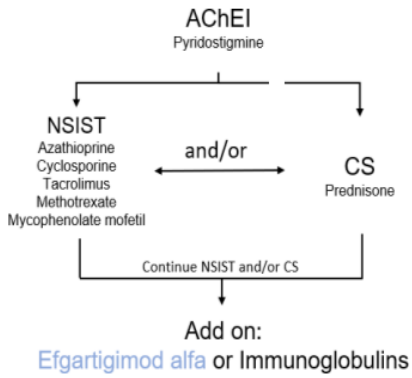
The clinician group mentioned that usual Ig treatment for MG can be effective but place a significant burden on the Canadian health care system and that supplies can be at risk in situations such as pandemic. They think the drug under review is likely to replace Ig therapies.

In summary, the clinician group's input is aligned with the input provided by the clinical experts consulted by CADTH.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 2.

Table 2: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
Issues with the choice of comparator in the submitted trial(s) • The comparator in the pivotal trial, ADAPT, is placebo. • This is a first-in-class human IgG1 antibody FC fragment. • There is no direct comparator for this novel drug. • That being said, ravulizumab received NOC from Health Canda earlier this year (January 2023) for the treatment of adult patients with AChR-AB+ gMG. It did receive a negative recommendation at CADTH and is awaiting reconsideration. Although it would have been a useful comparison to efgartigimod alfa, the pivotal trial for this submission enrolled patients between August 2018 and April 2020 and would not have aligned to allow comparison to ravulizumab. • The sponsor did not compare it to eculizumab.	According to the clinical experts, the complements inhibitors (eculizumab, ravulizumab) are mechanistically different from efgartigimod alfa, and would likely have a different role in therapy. The lack of direct comparison with these two is not really a problem. CDEC agreed with the clinical experts.
Considerations for initiation of therapy	
Prior therapies required for eligibility The requested indication for efgartigimod alfa is for add-on therapy to conventional therapy, which may include AChEIs, CSs, and/or NSISTs in patients who are AChR-Ab+. Although the sponsor included rituximab in the list of comparators it was not included in the studied indication because it is only used in patients who are not AChR-Ab+. Patients treated with either rituximab or eculizumab within 6 months of screening were also excluded from the study. The sponsor envisions the place in therapy of efgartigimod alfa to be considered as an add-on as an alternative to immunoglobulins after use of NSISTs and/or CSs as depicted below Figure 4. Anticipated Place in Therapy of Efgartigimod Alfa for AChR+ gMG  The indication is for addition of efgartigimod alfa to one or a combination of the three conventional therapy classes. The ADAPT trial allowed inclusion of patients on any combination of conventional gMG treatment, which was limited to AChEIs, steroids, and NSISTs and did not require the patients to have received or discontinued use of any specific treatment. It is unclear if a patient's eligibility for addition of efgartigimod alfa would require trials of medications from all three classes, or from one, or two classes?	According to the clinical experts, Figure 4 is a reasonable depiction of efgartigimod alfa's place in therapy, although the clinical expert suspect that cost will drive clinicians to use IVIg first. Unless efgartigimod alfa ends up being priced similar to current conventional therapies, it is likely that unsuccessful trials of all 3 classes (AChEI, corticosteroids, and NSIST) will be prerequisite to the use of efgartigimod alfa. The clinical experts stated that in addition, in ADAPT not all included patients were refractory, that was not all patients needed to have failed multiple therapies. So, technically from a data and mechanistical perspective, no need to have a failed trial of all conventional meds. Realistically, and mostly driven by price, it should not be offered as first line and rather after patient have tried conventional treatments. So, the diagram looks realistic. CDEC acknowledged the clinical expert's response and agreed that failure of all three conventional therapies would not be required, rather considering trial of at least one of AChEIs, CSs, and/or NSISTs in the previous 12 months.
Eligibility to re-treatment In the ADAPT trial, if a patient were an MG-ADL responder during a previous cycle and lost response, that patient could qualify for re-treatment. Loss of	The other clinical expert indicated that from an economic perspective, re-treatment with efgartigimod alfa on an as-need basis likely result

Drug program implementation questions	Clinical expert response
response was defined as a <2-point reduction in the MG-ADL total score during the cycle, compared to the baseline value for that cycle. Re-treatment in subsequent cycles was permitted if they met all of the following criteria: - Completed the prior TC (3-week treatment period and 5-week follow-up) - Had an MG-ADL total score of at least 5 points with >50% of the total score attributed to nonocular symptoms - The subsequent cycle did not start after day 127 and could be completed within the 26-week treatment period This allowed for a max. Of 3 TC's during the 26-week study. According to the sponsor and the product monograph, following cycle 1 (C1), treatment with efgartigimod alfa can be given on an as-needed basis, according to clinical assessment and thus would vary by patient. This poses a unique challenge for drug plans when instating an approval if there is no certainty on whether a patient will be re-treated and at what frequency.	in savings, as based on data some patients had relatively long stretches between cycles. However, it will pose an implementation difficulty for clinicians, based on need for more frequent monitoring to decided appropriate time for retreatment. Therefore, as a prescriber, approval for 3 cycles initially would be reasonable to assess response to treatment; further approvals conditional on demonstrating benefit. Clinician can then tailor cycles (e.g., some patients may take longer to use all cycles) CDEC agreed with the clinical expert that the above would be reasonable.
Special subtypes (not explicitly mentioned in the indication) to consider separately for eligibility Considering patients who had used eculizumab within 6 months of screening were excluded from the study, and there were no comparisons to ravulizumab, would patients who failed either one or both agents be considered for treatment with efgartigimod alfa?	Yes. Absolutely, failure to respond to rituximab or eculizumab (or ravulizumab) would not preclude consideration of efgartigimod alfa. They should be considered for efgartigimod alfa. CDEC agreed with the clinical expert that the above would be reasonable.
Considerations for continuation or renewal of therapy	
Challenges related to assessment and monitoring of therapeutic response • The primary endpoint utilized the MG-ADL scale which is an 8-item patient-reported outcome (PRO) tool. • In the ADAPT trial, patients were not re-treated with the IMP while their MG-ADL score remained below 5. • A clinically meaningful improvement on the MG-ADL is defined as a 2-point reduction in the total score (ranging from 0-24). • The primary endpoint was the percentage of patients in the AChR-Ab+ population who, after C1, had a reduction of at least 2 points on the MG-ADL total score (compared to baseline) for at least 4 consecutive weeks with the first of these decreases occurring within one week after the last infusion of IMP. Can the clinical expert(s) confirm if the MG-ADL reflective of best practices when treating gMG patients in Canada? If not, is there another tool or outcome that would better align with how patients are monitored in the Canadian practice setting?	One clinical expert indicated that he prefers a clinician-driven assessment (like the QMG). The other clinical expert indicated that most neurologists in Canada do not use standardized outcomes measurement in MG. The standard outcome measurements are mostly used in academic centres. The clinical expert uses MGII that combines PRO and examination. But the MG-ADL or equivalent is certainly acceptable. Both clinical experts agree MG-ADL is extremely easy to use and to implement. And both clinical experts agreed that regardless of outcome measurement tools, more important than the tools, patients should be assessed by neurologists with experience/expertise in the management of MG. CDEC noted the clinical expert response and suggested that MG-ADL would be reasonable given ease of use and that MG-ADL used in ADAPT.
Considerations for discontinuation of therapy	
Definition of loss of response, absence of clinical benefit, or disease progression Efgartigimod alfa is administered as-needed based on clinical response (physician assessment and patient-reported outcomes). How many times would a patient require re-treatment due to loss of response (as defined in Table 2.2.d.) before being considered for discontinuation? Likewise, if a patient has a need for increased frequency of dosing, would consideration be given to discontinuation of efgartigimod alfa?	One clinical expert stated that how many unsuccessful re-treatments would be needed before concluding that efgartigimod alfa does not work would vary from clinician to clinician, but I would probably stop it after two unsuccessful retreatments. There would not be a good rationale to give efgartigimod alfa at a frequency greater than every 1-2 weeks.

Drug program implementation questions	Clinical expert response
It would be helpful to have a clear definition of loss of response and disease progression that would indicate the need for discontinuation, defined according to MG-ADL parameters and/or frequency of dosing	The other clinical expert indicated that based on ADAPT, patients had no response after 2-3 cycles (no significant improvement or worsening) should discontinue the treatment. CDEC agreed with the clinical expert, it would be reasonable based on ADAPT, to discontinue the treatment if patients had no response after 3 cycles (no significant improvement or worsening).
Considerations for prescribing of therapy	
Dosing, schedule/frequency, dose intensity The medication is given as a one-hour infusion once weekly for 4 weeks (this being cycle 1). Following the initial dose, subsequent doses and frequency are dependent on clinical response, and thus may vary by patient. There is no further clarity provided in the product monograph regarding frequency of dosing. The sponsor estimates that AchR-Ab+ patients required a mean (SD) number of 4.72 cycles per year, with approximately 24% of patients requiring <3.5 cycles per year. Bearing in mind that each cycle consists of up to 4 weekly infusions, to a max of 3 vials per infusion, this would mean up to 48 vials annually if at max dose and with an average of 4 treatments per year. It is unclear if there is a minimum amount of time that should exist between cycles. Is there a minimum frequency before administering a subsequent dose? In the ADAPT trial, the median time between the last infusion of Cycle 1 and the start of Cycle 2 was 7 weeks (mean of 10 weeks). In a real-world study of utilization patterns, the sponsor noted an average gap of 50-58 days between the last infusion of Cycle 1 and the start of Cycle 2. In the long-term extension study, ADAPT+, subsequent cycles were only started if the patient completed the 4th infusion of the previous cycle at least 4 weeks prior. If consistent with this information, would re-treatments with efgartigimod alfa require a minimum of 4 weeks post-last infusion before initiating next cycle?	Both experts agreed that waiting at least 4 weeks before initiating a re-treatment cycle seems rational. CDEC agreed with the clinical experts.
Drug administration Administration is by intravenous infusion only and requires a trained healthcare professional. The sponsor expects the infusion to be most commonly administered in a patient's home and less commonly at an infusion clinic. Given this information, a trained healthcare professional would be required to make home visits to complete the administration.	Comment from the drug programs to inform CDEC deliberations.
Concerns related to accessing clinical specialists and/or special settings Administration will require in-home services or infusion clinics. Although the sponsor states a commitment to providing standardized access to all patients, including remote areas, it is a potential concern of how this accessibility will be provided.	Comment from the drug programs to inform CDEC deliberations.
Concerns related to combination usage Would there be any potential combination usage of efgartigimod alfa with eculizumab or ravulizumab, specifically considering that Health Canada issued a NOC for Ravulizumab + conventional therapy in the treatment of patients with AChR-Ab+ gMG?	One clinical expert indicated that efgartigimod alfa might be combined with either eculizumab or ravulizumab (as the mechanisms are different), but the cost would make this difficult to justify. The other expert stated that theoretically, efgartigimod alfa might be combined with either eculizumab or ravulizumab as they have different mechanisms. But hard to know if combination would be clinically superior to either alone as no data. I would not support concurrent use. Rather, I

Drug program implementation questions	Clinical expert response
	suspect they would be used sequentially if no response to one. CDEC acknowledged the clinical experts' response and noted that there was no evidence reviewed for this combination of efgartigimod alfa with eculizumab or ravulizumab.
Care provision issues	
Drug preparation, storage, administration or dispensing Administration is by intravenous infusion only. It requires reconstitution and administration by a trained healthcare professional, and up to 3 vials may be needed per dose, weight-dependent (10mg/kg).	Comment from the drug programs to inform CDEC deliberations.
System and economic issues	
Concerns regarding the anticipated budget impact and sustainability At the submitted price, efgartigimod alfa is significantly more expensive than conventional therapy and immunoglobulin/PLEX therapies but comparable to the cost of ravulizumab.	Comment from the drug programs to inform CDEC deliberations.
Presence of confidential negotiated prices for comparators At this time, ravulizumab has not received a positive funding recommendation for gMG or gone through pricing negotiations so it is difficult to make a comparison with these unknowns. It is awaiting CDEC reconsideration. Although not mentioned as a comparator by the sponsor, eculizumab is another treatment for gMG and its pricing negotiations ended without agreement. It is not publicly known the reimbursement status of eculizumab for gMG across the jurisdictions.	Comment from the drug programs to inform CDEC deliberations.

AChEI= acetylcholinesterase inhibitor; AChR = acetylcholine receptor; AChR-Ab = AChR autoantibodies; CDEC = Canadian Drug Expert Committee; MI = clinically meaningful improvement; CS =corticosteroids; gMG = generalized myasthenia gravis; IgG = immunoglobulin G; MGII = Myasthenia Gravis Impairment Index; NOC = notice of compliance; duct; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; NSIST = nonsteroidal immunosuppressive therapy; PLEX = plasma exchange; TC = treatment cycle.

Clinical Evidence

Systematic Review

Description of Studies

One phase 3, DB, placebo-controlled RCT (ADAPT, N=169)[30] is included in the systematic review. The objective of ADAPT trial was to evaluate the efficacy and safety of efgartigimod alfa added on to the conventional therapy versus placebo added to the conventional therapy in adult patients with gMG whose symptoms persist despite a stable dose of standard of care (concomitant gMG treatment) treatment with acetylcholinesterase inhibitors (AChEIs), corticosteroids (CSs), and/or non-steroidal immunosuppressants (NSISTs). All patients were MGFA class II to IV with a MG-ADL total score 5 or more. The mean age was 44.7 to 49.2 years, and most patients were white (83.1% to 87.5%). In the ACh-R AB seropositive population, 129 (100%) patients received one prior therapy, [redacted] patients receive two prior therapies and [redacted] patients received ≥3 prior therapies respectively. The majority had been previously pre-treated with ≥2 [redacted] or ≥3 [redacted] different classes of conventional therapy medication (any combination of acetylcholinesterase inhibitors [AChEIs], corticosteroids [CSs], and/or non-steroidal immunosuppressants [NSISTs] at the physician's discretion). In the patients who were ACH-R AB seropositive, patients who received three classes of prior therapy (steroid+NSIST+AChEI) were [redacted] in the efgartigimod alfa group and [redacted] in the placebo group. [redacted] patients in the efgartigimod alfa and [redacted] in the placebo group had received any two of the three prior therapies (i.e., steroid, NSIST, and/or AChEI). In addition, among the patients who were ACH-R AB seropositive, 63% patients had failed on prior gMG treatments (also known as refractory gMG patients) [31] and 37% had not failed on a prior treatment, but inadequately responded to the existing standard of gMG therapy.

Patients were randomized 1:1 to receive efgartigimod alfa or a matching placebo in cycle 1 (i.e., for first 8 weeks), followed by an individualized treat-as-needed regimen based on the patients MG-ADL response. All patients received a stable concomitant treatment during the trial. The primary outcome of the study was percentage of AChR-Ab seropositive patients who were MG-ADL responders in the first treatment cycle (an MG-ADL responder was defined as a patient with a ≥2-point improvement [reduction] in MG-ADL score). Key secondary outcomes included percentage of MG-ADL responders in cycle 1 in the overall population (i.e., AChR-Ab seropositive and AChR-Ab seronegative); percentage of time AChR-Ab seropositive patients showed a CMI in MG-ADL score (≥2-point reduction) up to day 126; time from week 4 to qualify for retreatment in the AChR-Ab seropositive population; percentage of early MG-ADL responders in cycle 1 in the AChR-Ab seropositive population (i.e., MG-ADL ≥2 points occurred by week 2); and change from cycle baseline in MG-ADL total score at cycle 1 and cycle 2. Change from cycle baseline in HRQoL (MG-QoL15r score, EQ-5D-VAS) at cycle 1 and cycle 2 were assessed as tertiary or exploratory outcomes. Post hoc analysis was performed for gMG hospitalization, gMG exacerbation, and gMG crisis. It should also be noted that, although the ADAPT trial duration was designed for 26 weeks, the primary, key secondary and the HRQoL outcomes at the end of the study (EOS, i.e., week 26) were not assessed. Instead, the outcomes were assessed at end of cycle 1 and cycle 2.

Efficacy Results

Patients with ACH-R AB seropositive

Myasthenia Gravis Activities of Daily Living (MG-ADL)

MG-ADL responder during cycle 1 and cycle 2: MG-ADL responders during cycle 1 in patients who were ACH-R AB seropositive was the primary outcomes in the ADAPT trial. Thirty-eight percent (95% CI, 22 to 56%) more patients in the efgartigimod alfa group (those with ACH-R AB seropositive randomized to receive efgartigimod alfa) than in the placebo group achieved ≥ 2 points of MG-ADL improvement during cycle 1. The between group difference was considered clinically meaningful by the clinical experts consulted by CADTH.

Various post hoc subgroup analyses were conducted for MG-ADL responder during cycle 1. Consistent with the primary analysis, these results demonstrate that efgartigimod alfa produces improvements in MG-ADL response compared to placebo, regardless of prior therapies, concomitant therapies, disease duration, thymectomy, and prior treatment failure; however, the trial was not powered to detect subgroup differences. In terms of the MG-ADL responders, similar benefit was observed in cycle 2.

Early MG-ADL Responders: Early MG-ADL Responders (responded at week 2 of the cycle 1) in the patients who were ACH-R AB seropositive was assessed as a fifth key secondary outcome. Because the statistical testing hierarchy was broken at the fourth secondary endpoint (i.e., time to quality re-treatment), the percentage of patients in the AChR-Ab+ population who were early MG-ADL responders was not statistically tested based on statistical plan in the protocol. Nevertheless, within the AChR-Ab seropositive population, a higher proportion of patients in efgartigimod alfa group achieved ≥ 2 points of MG-ADL improvement at week 2 than in placebo group (between group difference, 31.9%; 95% CI, NR) The between group difference was considered clinically meaningful by the clinical experts consulted by CADTH. The percentage of MG-ADL early Responders During cycle 2 was not assessed and not reported in the sponsor's evidence summary.

Percentage time of the MG-ADL Clinical meaningful improvement (CMI) up to day 126: Among patients who were AChR-Ab seropositive, the percentage of time with a CMI in the MG-ADL total score up to day 126 was assessed as a third key secondary outcome and was included hierarchy test to control the type 1 error. According to the clinical experts, the percentage of time with a CMI in the MG-ADL total score in efgartigimod alfa group was a clinically meaningfully longer (EFG-PBO: 22.07%, [redacted], p = 0.0001) than that in placebo group.

MG-ADL change from cycle baseline (CFCB). During cycle 1 and cycle 2, the change from cycle baseline of MG-ADL change from cycle baseline (CFCB) were assessed as the exploratory outcomes in patients who were ACH-R AB seropositive. At week 4 of cycle 1, the reduction (improvement) of MG-ADL total score in the efgartigimod alfa group was larger than that in the placebo group (EFG – placebo: -2.84, [redacted] p<0.0001). This was assessed as an exploratory outcome and with no multiplicity adjustment (no included in the hierarchy test), therefore, there is an increased risk of type 1 error; however, the findings were aligned with the responder analysis and were considered clinically meaningful by the clinical experts consulted by CADTH. It should be noted that the maximum MG-ADL change from cycle baseline with efgartigimod alfa appeared to occur at approximately week 4 of the cycle. The magnitude of the improvement and the comparative benefit of efgartigimod alfa compared with placebo tended to smaller at the end of the cycle. Similar results were observed in cycle 2.

Time to retreatment: Time to qualify for retreatment in the patients who were ACH-R AB seropositive was assessed as a fourth key secondary outcome. The median time to qualify for retreatment in the efgartigimod alfa group was numerically but not significantly greater than the time in the placebo group (median: 35 days, 95%CI, 29 days to 43 days, vs. 8 days, 95%CI, 1 day to 30 days, respectively, log-rank p=0.2604). The statistically hierarchy test was broken at this point. [redacted] The clinical expert CADTH consulted for this review indicated that the results likely showed that about half of the patients would need to get the retreatment around the week 6 of the treatment cycle.

Disease severity (assessed with QMG)

QMG responder during cycle 1: The percentage of QMG responders among patients who were ACH-R AB seropositive was assessed as the first key secondary outcome. It was reported that the 49.0% more patients (95%CI, 34.5% to 63.5%) in the efgartigimod alfa group achieved a QMG response compared with the placebo group (OR: 7.1, 95% CI: 3.24 to 16.49; p<0.0001). According to the clinical experts, this benefit of treatment with efgartigimod alfa compared with placebo was considered as clinically meaningful.

HRQoL

The HRQoL (i.e., MG-QOL-15 r and EQ-5D-VAS) was assessed with the as exploratory outcome among patients who were ACH-R AB seropositive. The change from cycle baseline (CFCB) of MG-QOL-15r and EQ-5D-VAS were assessed for cycle 1 and cycle 2. At week 4 of cycle 1, the reduction (improvement) of MG-QOL-15r in the efgartigimod alfa group was greater than that in placebo group (EFG – PBO: -5.45, 95%CI -7.221 to -3.685; p<0.0001). The increase (improvement) of EQ-5D-VAS score in efgartigimod alfa group was greater that in placebo group (EFG – PBO: 13.28, 95%CI, 8.32 to 18.24, p <0.0001). Since HRQOL was assessed as an exploratory outcome and with no multiplicity adjustment (not included in the hierarchy test), there is an increased risk of type 1 error; however, the results provide supportive evidence. Although there is no known MID for either the MG-QoL15r or EQ-5D VAS among patients with gMG, the clinical experts considered the results to be clinically meaningful. It should be noted that both maximum MG-QOL-15r and EQ-5D-VAS improvement with efgartigimod alfa occurred at approximately week 4 of the cycle. The magnitude of the

improvement and the comparative benefit of efgartigimod alfa compared with placebo tended to be smaller at the end of the cycle. Similar results were observed in cycle 2.

Other clinical outcomes (MG hospitalization, MG exacerbations and MG crisis)

In patients who were ACH-R AB seropositive, during the 26 weeks double blind period, the event rates for MG hospitalization and MG crisis were low in both groups. MG exacerbations were identified in 17 patients (26.2%) in the efgartigimod alfa group and 27 patients (44.3%) in the placebo group. The between group absolute risk difference (EFG – PBO) was -18.2, 95%CI, not reported. The results of MG hospitalization, MG exacerbations and MG crisis were based on post hoc analyses. Therefore, the results for these outcomes were inconclusive.

Harms Results

Reduction of side effects was identified in the patient input for this review as of interest for patients with gMG. The ADAPT trial, including its randomized controlled period and OL extension, provided relevant information regarding the safety profile of efgartigimod alfa in the treatment of gMG. However, it did not provide direct comparative evidence regarding the adverse effects of efgartigimod alfa versus other active gMG therapies. In the Ach-R AB seropositive l population, during the randomized controlled period, proportion of patients with TEAEs in the efgartigimod alfa group appeared similar to that in the placebo group (EFG vs. PBO: 75.4% vs. 84.4%) in the ADAPT trial. The proportion of patients with SAEs was low in both groups and appeared lower in efgartigimod alfa group than that in placebo group (4.6% vs. 9.4%) in the ADAPT trial. WDAEs occurred in similar proportions in both the efgartigimod alfa and placebo groups (3.1% vs. 4.7%) in the ADAPT trial. No death was reported during the double-blind period; however, the length of follow-up in the trial may not have been long enough to assess this outcome with certainty. The main notable harm (i.e., AEs of special interest for this review) in the system organ class was Infections and infestations, which was reported in higher proportion of patients in efgartigimod alfa than placebo group (44.6% vs. 34.4%). No meningococcal infections were reported. According to the clinical expert CADTH consulted for this review, the TEAE reported in the ADAPT trial were expected and commonly seen in existing immunosuppressive treatments, complement C5 inhibitor treatment in gMG.

Critical Appraisal

Appropriate methods of randomization, blinding and allocation concealment were reported. Outcomes were assessed using validated scales incorporating physician and patient assessment, and endpoints requiring a combination of clinically meaningful improvement and sustained effect. However, minimal important between group difference, that is the thresholds used for the GRADE for all outcomes are not available. Therefore, clinical expert opinion informed the thresholds to determine whether the between group difference observed for each outcome are clinically meaningful or not. Appropriate statistic method was used in the ADAPT trial. Multiplicity adjustment was used for the primary and 5 key secondary outcomes to control the family-wise type I error (probability of making more than one type 1 error). Overall, the ADAPT trial was relatively well designed, however, several potential key limitations of the ADAPT trial includes: some notable imbalance of baseline disease characteristics between groups were noted. For example, the proportion of patients had a MG-ADL score ≥10 MG-ADL total score, prior combination use of steroid+AChEI, the proportion of patients who underwent thymectomy were imbalanced between groups. Furthermore, the proportion of patients who used concomitant AChEi, concomitant “Steroid + AChEi” were also imbalanced between the two treatment groups. Whether these baseline imbalances may have introduced bias is uncertain. However, the clinical experts consulted by CADTH for this review indicated that, these observed imbalances were unlikely to significantly affect the study results. The efficacy outcome assessment for patients with ACH-R AB seronegative were assessed as sensitivity or subgroup analysis. In addition, the ADAPT trial was a placebo control trial. The comparative efficacy information comparing efgartigimod alfa with existing gMG therapies (e.g., ACHEIs, steroids, NSIST, IVIG, PE, C5-complement inhibitors) are unknown. Furthermore, MG-ADL total score change from cycle baseline, HRQOL, and all outcomes examined in cycle 2 were assessed as either tertiary or exploratory outcomes, which were not included in the hierarchy test and were not controlled for type 1 error. Therefore, the results of all those tertiary and exploratory analysis should interpreted with the consideration of the limitation of without controlled for the type 1 error. Finally, reduction of steroids uses and reduction of high dose of steroids use is one treatment goal with the efgartigimod alfa, however, these outcomes could not be assessed because of the study design, the concomitant treatments were not allowed to change unless it is used for rescue. The impact of efgartigimod alfa on changes in MG medications could not be evaluated because this was not allowed as per the study protocol.

According to clinical experts CADTH consulted for this review, population included in the ADAPT trial well reflects the patients who experience unmet needs in the treatment gMG in Canadian clinical settings. However, patients with MGFA I (ocular MG) and MGFA V were excluded in ADAPT trial. Whether the findings of ADAPT trial can be generalized to patients with MGFA I (ocular M) or MGFA

V are uncertain. The clinical experts CADTH consulted for this review indicated that efgartigimod alfa will provide a new treatment for patients with gMG who AChR-AB are positive and probably for patients with MuSK antibody positive. The clinician group input for this review also indicated that patient with MuSK antibodies might respond to efgartigimod alfa. It is uncertain, whether the findings derived from the ADAPT trial can be generalized to patients who were AChR-Ab seronegative, MuSK or double seronegative ACH-R AB seronegative and MuSK antibody seronegative). The number of patients with ACH-R AB seronegative were relatively small and the ADAPT trial was not powered for testing the statistically significant between group difference. Therefore, the comparative efficacy comparing efgartigimod alfa with placebo for patients with ACH-R AB seronegative were inconclusive. In addition, 6(3.6%) patients were MuSK-Ab seropositive, there was no sensitivity or subgroup analysis for patients who were MuSK-Ab seropositive. The comparative efficacy of efgartigimod alfa comparing with placebo for patients who were MuSK-Ab seropositive was unknown. Therefore, findings for overall population were mainly driven by the patients with ACH-R AB seropositive.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group: Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

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 (proportion of MG-ADL responders in cycle 1 and cycle 2; proportion of early MG-ADL responder in cycle 1; mean proportion of time with a clinically meaningful (≥2-point) improvement of MG-ADL (Follow-up: 126 days); time to qualify for retreatment (up to 168 days); MG-ADL total score change from cycle baseline at week 4 of cycle 1 and cycle 2; disease severity (measured with QMG); HRQOL (MG-QoL15r and EQ-5D-5L VAS) change from cycle baseline at week 4 in cycle 1 and cycle 2); and other clinical outcomes (MG hospitalization, MG exacerbation and MG crisis by week 26) and notable harms (i.e., infections and infestations).

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. For this review, the target of the certainty of evidence assessment was based on the presence of absence of a clinically important effect, as informed by MIDs suggested by the sponsor and agreed upon by the clinical experts consulted by CADTH for this review (for change from baseline in MG-ADL score and QMG score), or by thresholds suggested by the clinical experts (for all other outcomes).

Results of GRADE Assessment: Table 3 below presents summary of findings for efgartigimod alfa versus placebo for patients with Ach-R AB+

Table 3: Summary of Findings for Efgartigimod alfa versus Placebo For patients with Ach-R AB+

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Efgartigimod alfa	Difference		
Activities of daily living							
MG-ADL score (0 [best] to 24 [worst])							
Responders (≥2-point reduction for 4 consecutive weeks) during cycle 1 Follow-up: 8 weeks	129 (1 RCT)	OR = 4.95 (2.21 to 11.53)	30 per 100	68 per 100 (NR)	38 more per 100 (22 to 56 more per 100)	Moderate[a]	As an add-on to conventional therapy, efgartigimod alfa likely results in a clinically important increase in the proportion of MG-ADL responders during the first treatment cycle when compared with placebo.
Early responders (≥2-point reduction during first 2 weeks) during cycle 1 Follow-up: 2 weeks	129 (1 RCT)	[redacted]	25 per 100	57 per 100 (NR)	32 more per 100 (NR)[b]	Moderate[c]	As an add-on to conventional therapy, efgartigimod alfa likely results in a clinically important increase in the proportion of early MG-ADL responders during the first treatment cycle when compared with placebo.
LSM change from cycle baseline at week 4 of cycle 1, points Follow-up: 4 weeks	129 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Moderate[d]	As an add-on to conventional therapy, efgartigimod alfa likely results in a clinically important improvement in activities of daily living during the first treatment cycle when compared with placebo.
Responders (≥2-point reduction for 4 consecutive weeks) during cycle 2[e] Follow-up: 8 weeks of cycle 2	94 (1 RCT)	OR = [redacted]	26 per 100	71 per 100 (NR)	45 more per 100 (NR)[b]	Low[f]	As an add-on to conventional therapy, efgartigimod alfa may result in a clinically important increase in the proportion of MG-ADL responders during the second treatment cycle when compared with placebo.
LSM change from cycle baseline at week 4 of cycle 2, points[e] Follow-up: 8 weeks of cycle 2	98 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Moderate[g]	As an add-on to conventional therapy, efgartigimod alfa likely results in a clinically important improvement in activities of daily living during the second treatment cycle when compared with placebo.
Mean % time with a clinically meaningful (≥2-point) improvement Follow-up: 126 days	129 (1 RCT)	NA	26.7	48.7 ([redacted]	22.1 ([redacted])	Moderate[h]	As an add-on to conventional therapy, efgartigimod alfa likely results in a clinically important increase in the percentage of time with a clinically meaningful improvement in MG-ADL total score when compared with placebo.
Disease severity							
QMG responders (≥3 points reduction for 4	129 (1 RCT)	OR = 10.84 (4.18, 31.20)	14 per 100	63 per 100	49 more per 100 (35 to 65 more per 100)	Moderate[i]	As an add-on to conventional therapy, efgartigimod alfa likely

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Efgartigimod alfa	Difference		
consecutive weeks) during cycle 1 Follow-up: 8 weeks							results in a clinically important increase in the proportion of QMG responders during the first treatment cycle when compared with placebo.
Time to retreatment							
Qualified for retreatment Follow-up: 168 days	129 (1 RCT)	NA	89 per 100	88 per 100	1 less per 100 (NR)[b]	Moderate[j]	As an add-on to conventional therapy, efgartigimod alfa likely results in little to no difference in the proportion of patients who qualify for retreatment when compared with placebo.
HRQOL							
LSM change from baseline in MG-QoL15r score (0 [best] to 30 [worst]) at week 4 of cycle 1, points[e] Follow-up: 4 weeks	123 (1 RCT)	NA	[redacted]	[redacted]	-5.45 [redacted]	Moderate[k]	As an add-on to conventional therapy, efgartigimod alfa likely results in a clinically important improvement in HRQoL as measured by the MG-QoL15r during the first treatment cycle when compared with placebo.
Mean change from baseline in EQ-5D VAS (0 [worst] to 100 [best]) at week 4 of cycle 1, points[e] Follow-up: 4 weeks	123 (1 RCT)	NA	[redacted]	[redacted]	13.28 [redacted]	Moderate[l]	As an add-on to conventional therapy, efgartigimod alfa likely results in a clinically important improvement in HRQoL as measured by the EQ-5D VAS during the first treatment cycle when compared with placebo.
LSM change from baseline in MG-QoL15r score (0 [best] to 30 [worst]) at week 4 of cycle 2, points[e] Follow-up: 4 weeks of cycle 2	89 (1 RCT)	NA	[redacted]	[redacted]	-5.45 [redacted]	Low[m]	As an add-on to conventional therapy, efgartigimod alfa may result in a clinically important improvement in HRQoL as measured by the MG-QoL15r during the second treatment cycle when compared with placebo.
Mean change from baseline in EQ-5D-5L VAS (0 [worst] to 100 [best]) at week 4 of cycle 2, points[e] Follow-up: 4 weeks of cycle 2	89 (1 RCT)	NA	[redacted]	[redacted]	12.24 [redacted]	Low[n]	As an add-on to conventional therapy, efgartigimod alfa may result in a clinically important improvement in HRQoL as measured by the EQ-5D VAS during the second treatment cycle when compared with placebo.
Other clinical outcomes							
MG-related hospitalizations[e] Follow-up: 26 weeks	129 (1 RCT)	NR	5 per 100	0 (NR)	5 less per 100 (NR)[b]	Very low[o]	As an add-on to conventional therapy, the evidence is very uncertain about the effect of efgartigimod alfa on the number of hospitalizations when compared with placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Efgartigimod alfa	Difference		
MG exacerbations[e] Follow-up: 26 weeks	129 (1 RCT)	NR	44 per 100	26 per 100 (NR)	18 less per 100 (NR)[b]	Low[p]	As an add-on to conventional therapy, efgartigimod alfa may result in a clinically important reduction in MG exacerbations when compared with placebo.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events of special interest							
Infections Follow-up: 26 weeks	129 (1 RCT)	NR	34 per 100	45 per 100 (NR)	10 more per 100 (7 less to 27 more per 100)	Moderate[q]	As an add-on to conventional therapy efgartigimod alfa likely results in a clinically important increase in the proportion of patients experiencing 1 or more infection when compared with placebo.

AChR-Ab+ = AchR-Ab seropositive, seropositive for AchR autoantibodies; CI = confidence interval; HRQoL = health-related quality of life; LSM = least square mean; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QoL15r = Revised 15-Component Myasthenia Gravis Quality of Life; NR = not reported; OR = odds ratio; QMG = Quantitative Myasthenia Gravis; RCT = randomized controlled trial; VAS = Visual Analogue Scale.

[a] -1 level for serious imprecision. The 95% CI excludes the threshold of a 20% difference between groups, as informed by the clinical experts; however, the sample size and number of events does not meet the optimal information size.

[b] Upon request, the sponsor did not provide the 95% CI for the between-group difference (indicated that it was not calculable).

[c] -1 level for serious imprecision. No CI was available for judging the precision of the comparative effect estimate. The number of events does not meet the optimal information size.

[d] -1 level for serious imprecision. The 95% CI includes the possibility of a trivial effect, The 95% CI includes the possibility of a trivial effect, based on a suggested MID of 2 points, as defined in the trial and agreed upon by the clinical experts.

[e] In the trial, statistical testing for these efficacy outcomes was not adjusted for multiplicity. The results are considered as supportive evidence.

[f] -1 level for serious risk of bias. Not all patients completed the second treatment cycle, so prognostic balance between the groups cannot be ensured. -1 level for serious imprecision. No CI was available for judging precision of the comparative effect estimate. The number of events does not meet the optimal information size.

[g] -1 level for serious risk of bias. Not all patients completed the second treatment cycle, so prognostic balance between the groups cannot be ensured.

[h] -1 level for serious imprecision. The 95% CI includes the possibility of a trivial effect, based on a threshold of a 10 to 15% difference between groups, as informed by the clinical experts.

[i] -1 level for serious imprecision. The 95% CI excludes the threshold of a 20% difference between groups, as informed by the clinical experts; however, the sample size and number of events does not meet the optimal information size.

[j] -1 level for serious imprecision. No CI was available for judging the precision of the comparative effect estimate. The number of events does not meet the optimal information size.

[k] -1 level for serious imprecision. The 95% CI includes the possibility of a trivial effect, based on a threshold of a difference of 5 points between groups, as informed by the clinical experts.

[l] -1 level for serious imprecision. The 95% CI includes the possibility of a trivial effect, based on a threshold of a difference of 10 points between groups, as informed by the clinical experts.

[m] -1 level for serious risk of bias. Not all patients completed the second treatment cycle, so prognostic balance between the groups cannot be ensured. -1 level for serious imprecision. The 95% CI includes the possibility of a clinically important effect favouring efgartigimod alfa, based on a threshold of a difference of 5 points between groups, as informed by the clinical experts.

[n] -1 level for serious risk of bias. Not all patients completed the second treatment cycle, so prognostic balance between the groups cannot be ensured. -1 level for serious imprecision. The 95% CI includes the possibility of a trivial effect, based on a threshold of a difference of 10 points between groups, as informed by the clinical experts.

[o] -1 level for serious risk of bias. The analyses of these outcomes were undertaken post-hoc, so there is risk of bias in the selection of the reported result. -2 levels for very serious imprecision. No CI was available for judging the precision of the comparative effect estimate. The number of events does not meet the optimal information size; there were very few or no events in either group.

[p] -1 level for serious risk of bias. The analyses of these outcomes were undertaken post-hoc, so there is risk of bias in the selection of the reported result. -1 level for serious imprecision. No CI was available for judging the precision of the comparative effect estimate. The number of events does not meet the optimal information size.

[q] -1 level for serious imprecision. The 95% CI includes the possibility of a trivial effect, based on a threshold of a 10% difference between groups, as informed by the clinical experts.

Source: CSR [30] The sponsor's submission [1]; The sponsor provide additional information.[35,36] . Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

The ADAPT+ study (ARGX-113-1705) is a long-term, single-arm, open-label, multicenter, phase 3 follow-on study of patients who enrolled in the ADAPT study (ARGX-113-1704, NCT03669588). The primary objective was to evaluate the long-term safety and tolerability of efgartigimod alfa in the AChR-Ab seropositive subgroup and the secondary objective was to evaluate safety and tolerability in the overall population (AChR-Ab seropositive and seronegative). Efficacy data were collected as exploratory endpoints. The ADAPT+ study was conducted at 51 sites, including 41 sites in 14 countries/regions that had ≥1 patient roll over from the ADAPT study. Data were collected over a 3-year period in two sequential parts (Part A: 1 year, Part B: 2 years maximum). Part B was added as a protocol amendment to ensure accessibility to efgartigimod alfa until it became commercially available or available through an expanded access program. Results of the long-term extension phase up to 14 cycles (ADAPT+) are also presented in this report. The ADAPT+ trial was still ongoing at the time of this review. Therefore, the long-term efficacy and safety outcome of ADAPT+ was based on interim analysis IA4 and IA5. MG-ADL, QMG and safety outcomes were assessed in the long-term extension study. At the data cut-off (June 30, 2022), 151 patients had rolled over from ADAPT, regardless of treatment or placebo group, into ADAPT+ and 145 patients had received ≥1 partial or complete dose of efgartigimod alfa in ADAPT+.

Efficacy Results

In terms of MG-ADL (up to 14 cycles) and QMG response (up to 7 cycles), evidence from the long-term open label extension (ADAPT+) trial appeared consistent with those from the randomized controlled period. Patients who switched from placebo to efgartigimod alfa experienced numeric improvements from baseline in MG-ADL and QMG in each cycle. However, interpretation of these data was limited by the OL and descriptive nature of the extension study.

Harms Results

Safety data from the long-term extension phase appeared consistent with that observed in the double-blind phase with no new safety signals reported.

Critical Appraisal

Internal Validity

The ADAPT+ study was limited by its open-label and noncomparative design, since it was uncertain whether the results observed may be attributable to the effects of the drugs including other treatments or natural history of disease. Furthermore, the missing outcome data and small sample size towards the end of ADAPT+ led to difficulties to draw any firm conclusion on the efficacy and safety of efgartigimod alfa. Due to its open-label nature, the subjective outcomes, (e.g., rates of self- reported adverse events), were at risk of bias and potentially in favour of the intervention, (i.e., efgartigimod alfa). It is noteworthy that ADAPT+ had fewer scheduled visits for outcome assessments compared with ADAPT. ADAPT+ only collected MG-ADL data at week 3 of each study; however, the maximum clinical effect in ADAPT was observed at weeks 4 to 5 of a cycle. Furthermore, the longer-term safety and tolerability profile of efgartigimod alfa treatment was hard to determine due to the rates of adverse events and SAEs may be underestimated with less frequent assessment schedule. In ADAPT+, efficacy was assessed as an exploratory outcome using the patient-reported MG-ADL and physician- reported QMG scales patients were to remain on their stable dose and regimen of concomitant gMG treatment during Part A of ADAPT+. Given the presence of rollover effects, efficacy results related to Part B may be difficult to interpret due to that changes were permitted in Part B including changes in the type, dose, or regimen of the concomitant gMG treatment, as well as the additional use of other treatments. Therefore, the confounding effects of other therapies cannot be eliminated in Part B. In terms of outcome measures, some important long-term outcomes reported by patients and clinicians were not measured, e.g., HRQoL, exacerbations, in the ADAPT+.

External Validity

Because the patients who took part in the open-label long-term safety extension phase were originally from the pivotal ADAPT trial, it is reasonable to expect that the same limitations to generalizability are relevant to the open-label long-term safety extension phase. Given the nature of noncomparative study design, it is not possible to compare the effectiveness and tolerability of efgartigimod alfa as add-on treatment of gMG against others add-on treatments (e.g., IVIg).

Indirect Comparisons

Description of Studies

To date, there have been no clinical trials directly comparing the efficacy of efgartigimod alfa with other treatments in patients diagnosed with gMG. Due to this gap in evidence, the Sponsor submitted an indirect treatment comparison (ITC), including a systematic literature review (SLR) and a Network meta-analysis (NMA) that provide comparative evidence of the efficacy of efgartigimod alfa relative to ravulizumab and intravenous immunoglobulin (IVIg). The eligible interventions for the ITC were limited to those used in Canada for the treatment of gMG to ensure that the comparators were relevant to the Canadian settings. After feasibility assessment, the following 5 studies were considered eligible to be included in the NMA: 2 studies comparing efgartigimod alfa with placebo, 2 studies comparing IVIg with placebo, and 1 study comparing ravulizumab with placebo. All NMAs were performed using a Bayesian framework. Placebo was chosen as the reference treatment for all analyses, given its presence as an anchor treatment in all studies and the outcomes assessed in the network. The clinical endpoints used for ITC estimates included change from baseline in MG-ADL and QMG as these were the most consistently reported outcomes in all studies included in the NMA. Primary analyses were performed at the primary assessment timepoints for all included studies, ranging from 4 to 26 weeks, and sensitivity analyses were performed at or within ± 2 weeks of Week 4, which was the primary assessment timepoint in ADAPT.

As the Sponsor's reimbursement request is limited to AChR-Ab seropositive subpopulation, comparators relevant to that group were used in the primary ITC analysis.

Efficacy

Primary analyses

The mean differences for change from baseline in MG-ADL were –2.64 (95% CrI, –4.16 to –1.12) for efgartigimod alfa versus IVIg, and –0.91 (95% CrI, –2.25 to 0.39) for efgartigimod alfa versus ravulizumab. The mean differences for change from baseline in QMG were –4.39 (95% CrI, –6.95 to –1.81) for efgartigimod alfa versus IVIg, and –2.89 (95% CrI, –4.72 to –1.12) for efgartigimod alfa versus ravulizumab. A change of 2 points in the MG-ADL score and 3 points in the QMG score was estimated to be the threshold of clinical significance in patients with MG.

Sensitivity analyses results for change from baseline in MG-ADL and QMG at or within of Week 4 were consistent with results of the primary analyses.

Additional analyses

The mean differences for change from baseline in MG-ADL were –2.64 (95% CrI, –4.18 to –1.12) for efgartigimod alfa versus IVIg, –0.92 (95% CrI, –2.25 to 0.43) for efgartigimod alfa versus ravulizumab, and –1.93 (95% CrI, –3.87 to 0.07) for efgartigimod alfa versus rituximab. The mean differences for change from baseline in QMG were –4.39 (95% CrI, –7.01 to –1.83) for efgartigimod alfa versus IVIg, –2.89 (95% CrI, –4.72 to –1.06) for efgartigimod alfa versus ravulizumab, and –2.71 (95% CrI, – 5.56 to –0.2) for efgartigimod alfa versus rituximab.

Harms

No analysis of harms was reported in the Sponsor-submitted ITC report.

Critical Appraisal

The SLR used to identify relevant studies was methodologically sound in terms of the sponsor using a comprehensive literature search strategy as well as performing study selection, data extraction, risk of bias assessment in duplicate, and providing a list of

excluded studies and justifying the exclusions. However, it was unclear in the ITC report whether the feasibility assessment was carried out by a single or multiple assessors. By conducting a feasibility assessment, the Sponsor excluded all head-to-head trials, including those comparing efficacy of IVIg treatment versus PLEX, which may have reduced the information to inform the NMA. The risk of bias of included studies in the SLR was assessed per individual study; however, it may be different depending on the study outcomes. Analyses were run using a Bayesian framework with placebo as the reference treatment, which deemed appropriate. Change from baseline in MG-ADL and QMG scores were considered the best source of comparative efficacy data for this NMA, although these outcomes were not primary or secondary endpoints for ADAPT. The studies that did not report on MG-MDL or QMG were excluded even if they reported other relevant outcomes, which may have biased the results, although the extent of bias is uncertain. All trials included in the ITC had sufficiently similar study designs and a common comparison group (placebo). However, there were some important differences between the trials included in the NMA that increase the uncertainty of the analyses. All included studies employed a dosing schedule involving spaced infusions, but only ADAPT used individual patient response to determine subsequent cycles of treatment. The studies included in the ITC analyses ranged in follow-up time from 4 to 26 weeks. All studies allowed the use of concomitant standard of care treatments (e.g., CSs, NSISTs), but detailed information on the breakdown of actual concomitant medications used was not available. In many studies, baseline data were not reported consistently, such as for MGFA at baseline, use of steroids or NSISTs at baseline, disease duration, and history of thymectomy. The primary analyses conducted at the primary assessment timepoint for all trials could be biased against ADAPT, as they could exclude the best responders to efgartigimod alfa, whereas ITCs conducted at Week 4 only could be biased against any treatments that demonstrated improved responses over time. Therefore, sensitivity analyses were performed at or within ± 2 weeks of Week 4 to improve the robustness of the indirect treatment comparisons and align with the primary assessment timepoint of the ADAPT trial.

The results were reported as mean differences and 95% credible intervals. The evidence is imprecise in the effect estimates from the NMA due to the sparseness of data, with wide credible intervals. Additionally, heterogeneity between the included studies would be expected to introduce bias into the study estimates observed between the comparators. Since all comparator studies were performed in exclusively AChR-Ab seropositive patients, all ITC analyses included only patients from the AChR-Ab seropositive subpopulation, which aligns with the reimbursement request submitted by the Sponsor and the approved Health Canada indication. Another important limitation of the presented ITC is the lack of safety and health-related quality of life (HRQoL) data. The results of this ITC are highly uncertain given the inconsistency between trials with respect to dosing regimen (individualized dosing for efgartigimod alfa versus continuous dosing for the comparators), variability in eligibility criteria, and study follow-up times. The ITC estimates were too imprecise to draw a conclusion about the comparative effect of efgartigimod alfa relative to alternative treatments on change from baseline in MG-ADL and QMG.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with gMG who are AChR-Ab+
Treatment	Efgartigimod alfa plus CT (conventional therapy, consisting of AChEIs, CSs, and/or NSISTs)
Dose regimen	10mg/kg of body weight administered once weekly for four weeks, with subsequent cycles based on clinical evaluation, varying by patient.
Submitted price	$7,900 per 400 mg vial
Treatment cost	$63,200 to $94,800 per patient per course or 298,304 to $447,456 per patient per year, depending on patient weight and assuming 4.72 courses per year.
Comparators	Blood products (chronic immunoglobulin/PLEX) plus CT; CT alone.
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (53 years)

Component	Description
Key data source	ADAPT, a randomized multicenter, double blind, placebo-controlled trial; ADAPT+ extension study; sponsor-submitted NMA.
Key limitations	• Participants in the ADAPT trial, used to populate the economic model, were MGFA class II to IV gMG with an MG-ADL score of ≥ 5. There is no clinical information for patients with MGFA I and V gMG or patients with MG-ADL scores less than 5. Therefore, the clinical efficacy and cost-effectiveness of efgartigimod alfa in these patients is unknown. Additionally, as the proportion of people enrolled in ADAPT who whose symptoms persist despite adequate treatment with AChEIs, CSs, and/or NSISTs is uncertain, the clinical efficacy and cost-effectiveness of efgartigimod alfa plus CT in the reimbursement request population is also unknown. • Rituximab should have been included as a comparator, based on clinical expert feedback, international guidelines, and jurisdictional funding. • The efficacy of efgartigimod alfa relative to active comparators was highly uncertain. Transition probabilities for active comparators were hardcoded in the model and could not be validated by CADTH. The model also did not consider the wide credible intervals observed in the NMA. • Assumptions leading to large reductions in myasthenic crises, CS use, and mortality for patients receiving efgartigimod alfa were inappropriate and not supported by clinical evidence. • Utility values of MG-ADL health states were likely underestimated and were not based on Canadian values. • The sponsor assumed that all patients who experience a myasthenic crisis enter the MG-ADL 10+ health state following their cycle in crisis, which was not reflective of clinical practice as experts indicated that patients would most likely to return to the health state they occupied prior to experiencing crisis, or improve their health state upon crisis recovery. Most patients also remained in the MG-ADL 10+ health state upon crisis recovery for the remainder of the model time horizon unless receiving efgartigimod alfa, which was also deemed to not be reflective of the natural history of gMG. Assumptions regarding treatment discontinuation were highly uncertain. Discontinuation and non-response were informed by heterogenous trials for the various comparators, and subsequent therapies were not considered after discontinuation. • The sponsor's economic model was complex and transition probabilities were difficult to trace, poorly labelled, and inadequately described, which compounded the issue of the lack of transparency in the non-trial comparator transition probabilities. CADTH was unable to conduct a full validation.
CADTH reanalysis results	CADTH undertook reanalyses to address several key limitations, including: adding rituximab plus CT as a comparator; equalizing risk of crisis as well as dose of CS used across health states; using health state utilities derived from the ADAPT trial; and, adjusting the distribution of health states for patients exiting a crisis. In the CADTH base case, compared with rituximab plus CT, efgartigimod alfa was associated with an ICER of $1,764,628 per QALY gained (inc. costs: $1,195,367; inc. QALYs: 0.68). A price reduction of 84% (from $7,900 to $1,264 per 400 mg vial) would be needed for efgartigimod alfa to be cost-effective at a WTP of $50,000 per QALY gained compared to rituximab.

AChR-Ab+ = acetylcholine receptor-antibody positive; AChEI = acetylcholinesterase inhibitors; CS = corticosteroid; CT = conventional therapy; gMG = generalized myasthenia gravis; ICER = incremental cost-effectiveness ratio; inc = incremental; IVIG = intravenous immunoglobulin; LY = life year; MFGA = Myasthenia Gravis Foundation of America; MG-ADL = Myasthenia Gravis Activities of Daily Living; NMA = network meta-analysis; NMA = network meta-analysis; NSIST = non-steroidal immunosuppressants; PLEX = plasma exchange; QALY = quality-adjusted life year; WTP = willingness-to-pay.

Budget Impact

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

- Market uptake and comparator displacement do not reflect the Health Canada indication.
- The sponsor's derivation of the Non-Insured Health Benefits (NIHB) population was inappropriately calculated.

- Rituximab was excluded as a comparator.
- The proportion of patients eligible for public reimbursement is uncertain and likely differs by comparator.
- 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 who receive PLEX was underestimated.

CADTH reanalyses corrected the double-counting of the NIHB population, included rituximab as a comparator in both populations, assumed 100% of patients would be publicly reimbursed, and considered both a drug plan payer perspective excluding the cost of blood products, as well as a healthcare system perspective, where administration costs were included and the cost of blood products was adjusted to reflect PLEX usage.

CADTH reanalyses suggest that:

- For the Health Canada indicated population, reimbursement of efgartigimod alfa plus CT for adults with gMG may be associated with a budgetary increase of $378,513,999 over three years (Year 1: $85,010,539; Year 2: $133,312,812; Year 3: $160,190,648). This estimate does not consider the likelihood that gMG patients beyond those meeting the reimbursement request criteria would access efgartigimod alfa, and thus may be an underestimation of the cost of reimbursing efgartigimod alfa for the full, indicated population.
- For the reimbursement request population, reimbursement of efgartigimod alfa plus CT for adults with AChR-AB+ gMG whose symptoms persist despite adequate treatment with CT, efgartigimod alfa may be associated with a budgetary increase of $378,137,376 over three years (Year 1: $84,925,953; Year 2: $133,180,165; Year 3: $160,031,258).

The estimated budget impact of reimbursing efgartigimod alfa, in combination with CT, is sensitive to the perspective taken (drug plan versus healthcare system), the price of efgartigimod alfa, the proportion of patients who are publicly reimbursed, and the number of additional patients who might receive efgartigimod alfa if funding is not limited to the reimbursement request.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: Oct 25, 2023

Regrets:

3 of expert committee members did not attend.

Conflicts of interest:

None