


Original Article

Cost-Effectiveness Analysis of Efgartigimod vs Chronic Immunoglobulin for the Treatment of Myasthenia Gravis in Canada

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ABSTRACT: Introduction: Generalized myasthenia gravis (gMG) is a chronic neuromuscular disease that causes muscle weakness and fatigue, severely impairing quality of life. Efgartigimod is a novel drug that is recently approved for treatment of acetylcholine receptor antibody-positive (AChR-Ab+) gMG patients in Canada. In clinical practice, it is expected to be used in AChR-Ab+ gMG patients who continue to experience symptoms despite conventional therapy and primarily replace chronic immunoglobulins. **Methods:** A Markov model was developed to estimate costs and benefits (measured as quality-adjusted life years [QALYs]) of efgartigimod and chronic immunoglobulins for AChR-Ab+ gMG patients. The analysis was conducted from the perspective of the Canadian publicly funded healthcare system over a lifetime horizon. The model comprised six health states based on Myasthenia Gravis Activities of Daily Living (MG-ADL) scores: MG-ADL < 5, MG-ADL 5–7, MG-ADL 8–9, MG-ADL ≥ 10, myasthenic crisis or death. Health state transition probabilities were estimated from the ADAPT and ADAPT+ studies, plus a network meta-analysis that compared efgartigimod against chronic immunoglobulins. The MyRealWorld MG study informed utility values. Modeled costs included treatment and administration, disease monitoring, complications from chronic corticosteroid use, exacerbation/crisis management, adverse events and end-of-life care. **Results:** Over a lifetime horizon, efgartigimod and chronic immunoglobulins were predicted to have total discounted QALYs of 16.80 and 13.35 and total discounted costs of \$1,913,294 and \$2,170,315, respectively. Efgartigimod dominated chronic immunoglobulins with incremental QALYs of 3.45 and cost savings of \$257,020. **Conclusions:** Efgartigimod provides greater benefit in terms of lower costs than chronic immunoglobulins for AChR-Ab+ gMG patients in Canada.

RÉSUMÉ: Analyse coût-efficacité de l'efgartigimod par rapport aux immunoglobulines pour le traitement de la myasthénie grave au Canada. Introduction: La myasthénie grave généralisée (MGG) est une maladie neuromusculaire chronique qui provoque une faiblesse musculaire et de la fatigue, altérant considérablement la qualité de vie des patients. L'efgartigimod est un nouveau médicament récemment approuvé au Canada pour le traitement des patients atteints de MGG positive aux anticorps anti-récepteurs de l'acétylcholine (AChR-Ab+). Dans la pratique clinique, il devrait être utilisé chez les patients atteints de MGG positive aux AChR-Ab+ qui continuent de présenter des symptômes malgré un traitement conventionnel et remplacer principalement les immunoglobulines destinées au traitement des maladies chroniques. **Méthodes:** Un modèle de Markov a été développé pour estimer les coûts et les bénéfices, mesurés en années de vie ajustées en fonction de l'indicateur QALY, de l'efgartigimod et des immunoglobulines destinées au traitement des maladies chroniques pour les patients atteints de MGG positive aux AChR-Ab+. L'analyse a été menée du point de vue du système de santé public canadien sur une période couvrant toute la durée de vie. Le modèle comprenait six états de santé basés sur les scores à l'échelle *Myasthenia Gravis Activities of Daily Living* (MG-ADL) : MG-ADL < 5, MG-ADL 5-7, MG-ADL 8-9, MG-ADL ≥ 10, crise myasthénique ou décès. Les probabilités de transition entre les états de santé ont été estimées à partir des études ADAPT et ADAPT+ ainsi qu'à partir d'une méta-analyse en réseau comparant l'efgartigimod aux immunoglobulines destinées au traitement des maladies chroniques. L'étude MyRealWorld-MG a fourni des renseignements sur les valeurs d'utilité. Les coûts modélisés comprenaient le traitement et l'administration, la surveillance de la maladie, les complications liées à l'utilisation chronique de corticostéroïdes, la prise en charge des exacerbations et des crises, les événements indésirables et les soins de fin de vie. **Résultats:** Sur une durée de vie, l'efgartigimod et les immunoglobulines destinées au traitement des maladies chroniques devraient donner à voir respectivement un QALY total actualisé de 16,80 et 13,35, et des coûts totaux actualisés de 1 913 294 \$ et 2 170 315 \$. L'efgartigimod a dominé les immunoglobulines destinées au traitement des maladies chroniques avec des QALY incrémentiels de 3,45 et des économies de coûts de 257 020 \$. **Conclusions:** L'efgartigimod offre au Canada un avantage supérieur en termes de coûts réduits par rapport aux immunoglobulines destinées au traitement des maladies chroniques pour les patients atteints de MGG positive aux AChR-Ab+.

Keywords: cost-effectiveness; economic model; efgartigimod; immunoglobulin; myasthenia gravis

(Received 19 February 2025; final revisions submitted 3 September 2025; date of acceptance 29 September 2025)

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Cite this article: Siddiqi ZA, Qi CZ, Zhou A, Kaprielian R, Locklin J, Garcia D, Hughes T, and Genge A. Cost-Effectiveness Analysis of Efgartigimod vs Chronic Immunoglobulin for the Treatment of Myasthenia Gravis in Canada. *The Canadian Journal of Neurological Sciences*, <https://doi.org/10.1017/cjn.2025.10449>

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Highlights

- Efgartigimod is a novel therapy for the treatment of patients with acetylcholine receptor antibody-positive (AChR-Ab+) generalized myasthenia gravis.
- Costs and benefits (as quality-adjusted life years [QALYs]) for efgartigimod versus chronic immunoglobulins in Canada were compared using an economic model.
- Efgartigimod had lower total healthcare costs and higher QALYs than chronic immunoglobulins.

Introduction

Generalized myasthenia gravis (gMG) is a rare chronic neuromuscular disease that causes muscle weakness and fatigue.¹ It has been estimated that there are 32 cases of MG per 100,000 adults in Canada, with an incidence of 23 cases per 1 million person-years.²⁻⁴ Typical symptoms associated with this autoimmune condition include drooping of eyelids, double vision, difficulty swallowing and breathing, limb weakness and fatigue, among others.⁵ These symptoms result in poorer health-related quality of life (HRQoL) as patients experience worsening muscle weakness and greater physical impairments. About 80% of patients with gMG exhibit elevated levels of serum acetylcholine receptor antibodies (AChR-Abs) and are routinely tested to confirm the diagnosis.^{6,7} In clinical practice, disease prognosis and treatment decisions are influenced by the presence of these AChR-Abs.⁸

The objective of treating gMG is to alleviate symptoms or functional limitations while minimizing adverse events (AEs) from the medication. Current standard treatments for gMG include acetylcholinesterase inhibitors (AChEIs), corticosteroids (CSs) and non-steroidal immunosuppressants (NSISTs).^{4,9-12} In cases where the disease is inadequately controlled by standard therapy, chronic immunoglobulins are administered either intravenously (IVIg) or subcutaneously (SCIg) as an off-label treatment option for gMG.⁸ Many of these conventional medications are limited by a lack of strong clinical evidence supporting their use and potential safety concerns or are not yet approved in Canada for treating gMG (i.e., off-label use). Furthermore, patients who receive these treatments often experience suboptimal response or clinically meaningful toxicity, which can worsen the negative impact of gMG on their physical and mental well-being, HRQoL, work capacity and daily activities.¹³⁻¹⁶ Therefore, there is a clear need for additional treatments for gMG that are fast-acting, effective, targeted and well-tolerated.

Efgartigimod (Vyvgart[®]) is an immunoglobulin G1 (IgG1) antibody fragment (Fc) engineered for increased affinity to Fc receptor (FcRn) and has proven to be an effective and well-tolerated treatment for gMG, as evaluated in the ADAPT and

ADAPT+ clinical trials.^{17,18} It was approved by Health Canada in 2023 for the treatment of adult patients with gMG who are AChR-Ab+,¹⁹ intended as an add-on treatment for those who continue to experience symptoms of gMG despite conventional therapy of AChEIs, CSs and/or NSISTs.²⁰

The objective of this study is to evaluate the economic value of efgartigimod from the Canadian public healthcare system perspective. To inform public reimbursement decisions, such an analysis must focus on a comparison against the most relevant, publicly funded treatment alternatives. Figure 1 illustrates the intended treatment algorithm for AChR-Ab+gMG in Canada based on feedback from Canadian clinical experts and Canada's Drug Agency (CDA), the country's national health technology assessment (HTA) agency.²⁰ This algorithm, which represents a realistic treatment pathway within the Canadian public system, positions efgartigimod as an option for patients who remain symptomatic following conventional therapy. In this context, chronic immunoglobulins were identified as the primary and most relevant clinical comparator for efgartigimod, leading to a positive reimbursement recommendation from CDA.²⁰

It is important to clarify the deliberate and focused scope of this study, which necessitates the exclusion of other therapies as comparators. While conventional medications including chronic CSs are the mainstay for gMG management, efgartigimod is not intended to be a replacement for them but rather an add-on treatment for patients whose disease is not adequately managed by them. As the specified treatment pathway for efgartigimod stipulates that patients would have already been treated with conventional therapies, a direct comparison is not appropriate for its intended place in therapy. Other immunomodulatory agents, such as eculizumab and ravulizumab, were also considered. Although approved by Health Canada, they were not funded by Canadian public payers at the time of this study and were therefore not deemed relevant comparators by CDA in its reimbursement review.²⁰ While a subset of patients may access these therapies through private coverage, that is outside the public payer perspective of this study. Conversely, rituximab was excluded due to its lack of a Health Canada indication for treatment of gMG²¹ and the limited high-quality evidence supporting its clinical benefit and usage in AChR-Ab+ MG.^{9,11}

Given this specific policy and funding context, this study aims to address a critical knowledge gap by conducting a cost-utility analysis (CUA) to determine the economic value of efgartigimod relative to chronic immunoglobulin therapy. By adhering to the treatment algorithm endorsed by Canadian clinical and HTA experts, these analyses seek to provide a realistic assessment of the total costs and health outcomes of introducing efgartigimod into its intended place in therapy over a lifetime horizon.²⁰ The purpose of

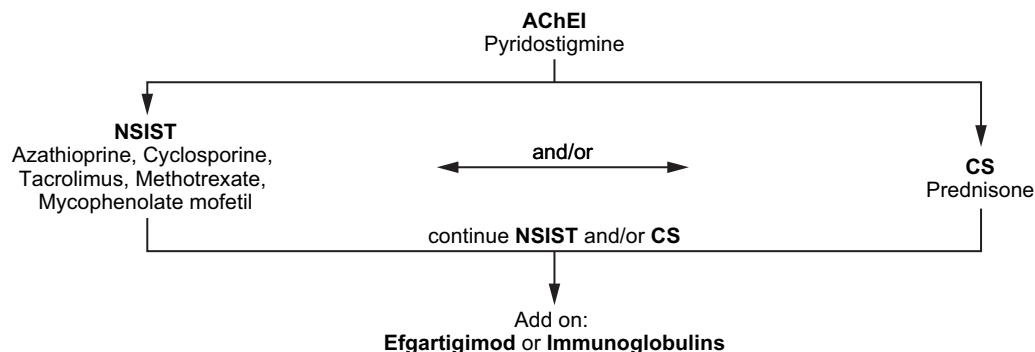


Figure 1. Anticipated place in therapy for efgartigimod. Source: CDA 2024.²⁰ AChEI = acetylcholinesterase inhibitor; CDA = Canada's Drug Agency; CS = corticosteroids; NSIST = non-steroidal immunosuppressive therapy.

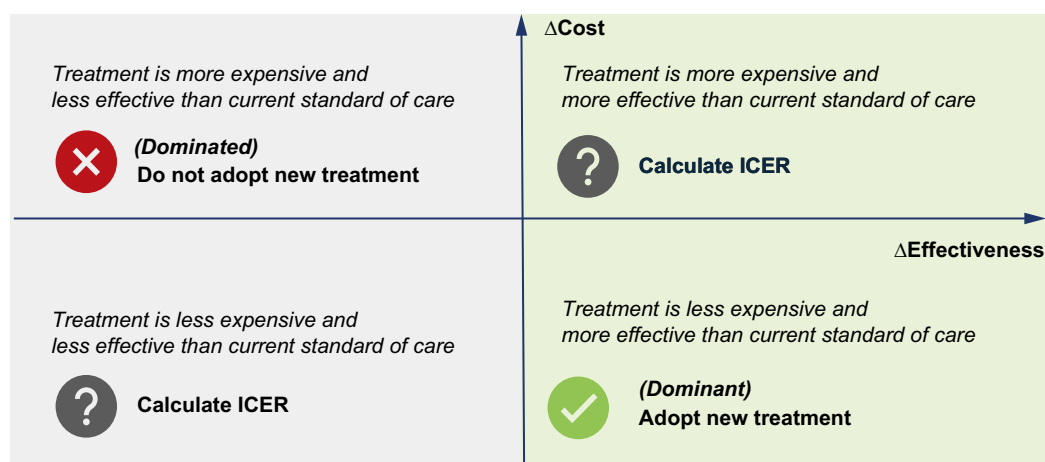


Figure 2. Interpretation of cost-utility analysis results. ICER = incremental cost-effectiveness ratio.

this assessment is not to evaluate all possible treatment sequences but to supplement CDA's reimbursement recommendation by focusing on the specific comparison that reflects the most likely access scenario for patients within Canada's public healthcare system.

Methods

Model overview

A Markov model was developed to simulate the treatment of adult AChR-Ab+ patients with gMG whose symptoms persist despite adequate treatment with AChEIs, CSs and/or NSiSTs. Patients in the model received either efgartigimod or chronic immunoglobulins (IVIg/SCIg) as their therapy, both as an add-on to standard care (AChEIs, CSs and/or NSiSTs). A lifetime horizon was selected for the analysis given that gMG is a chronic disease, and treatments were expected to have an impact on costs and health outcomes over a patient's lifetime.

In this CUA, total costs included any relevant costs for the public payer, such as product acquisition and disease monitoring, and the health benefit was measured in quality-adjusted life years (QALYs).²² The incremental cost-effectiveness ratio (ICER) in this model was calculated by dividing the difference in costs by the difference in QALYs between efgartigimod and IVIg/SCIg therapy, as a measure of the cost-effectiveness of efgartigimod. When the intervention is less costly and more effective than the comparator, the intervention is considered dominant (i.e., no numerical ICER) and should logically be adopted; in the opposite situation, the intervention is considered dominated. Figure 2 presents a visual summary of interpreting ICER calculations.

The model was developed using a core structure and set of assumptions that were validated by seven Canadian clinical experts from academic centers across six provinces. These clinical experts were identified using a thorough solicitation process, ensuring that a significant proportion of Canadian patients with gMG were under their care, making their input broadly representative. Specifically, each clinical expert provided care for an average of 300 adult patients with gMG, representing 30% of the estimated 7000 patients in Canada.²⁰ Key validation questions and responses can be found in the supplemental material. In alignment with CDA's requirements, the model was parameterized with inputs that accurately represented the gMG treatment landscape in Canada and analyzed under multiple scenarios to confirm its robustness. Published literature was the primary source of model inputs, and

key inputs were validated with the Canadian experts to confirm applicability to the Canadian treatment landscape. If literature could not be identified for informing an input, feedback from the clinical experts was used to address the data gap. Upon completion, the model was provided to CDA for an independent appraisal by the organization. The results reflecting the scenario based on CDA's appraisal were also presented as one of the scenario analyses.

Model structure

The Myasthenia Gravis Activities of Daily Living (MG-ADL) scale was used to define the health states. The MG-ADL scale was the primary endpoint of the ADAPT trial and has been considered in other CUA models in Canada, including the eculizumab and ravulizumab reimbursement submissions to CDA.^{23,24} The model comprised six health states: controlled (MG-ADL < 5), mild (MG-ADL 5–7), moderate (MG-ADL 8–9), severe (MG-ADL ≥ 10), myasthenic crisis and death. Each health state was associated with differences in exacerbations (increased risk with more severe disease), as well as the impact of chronic corticosteroid use on mortality, HRQoL and costs. The overall model structure is shown in Figure 3.

Patients entered the model in the mild, moderate or severe health state based on the distribution of MG-ADL scores of gMG patients at baseline in the ADAPT trial. Transitions between health states were informed based on patient-level data from the ADAPT and ADAPT+ trials for efgartigimod and indirect treatment comparison for chronic immunoglobulin therapy. The model had a cycle length of 4 weeks, in alignment with the duration of the treatment cycles used in ADAPT¹⁷ and the duration of time expected to observe a reduction in MG-ADL scores in treated patients. During each cycle, patients within the cohort could either transition to another health state or remain in the same health state as the previous cycle.

Model inputs

A summary of the model inputs is provided in Table 1, with further details described in the following sections.

Efficacy

The efficacy of efgartigimod was modeled using pooled data from both the ADAPT (data cut-off: April 2020) and ADAPT+ clinical trials (data cut-off: January 2022) to achieve a greater sample

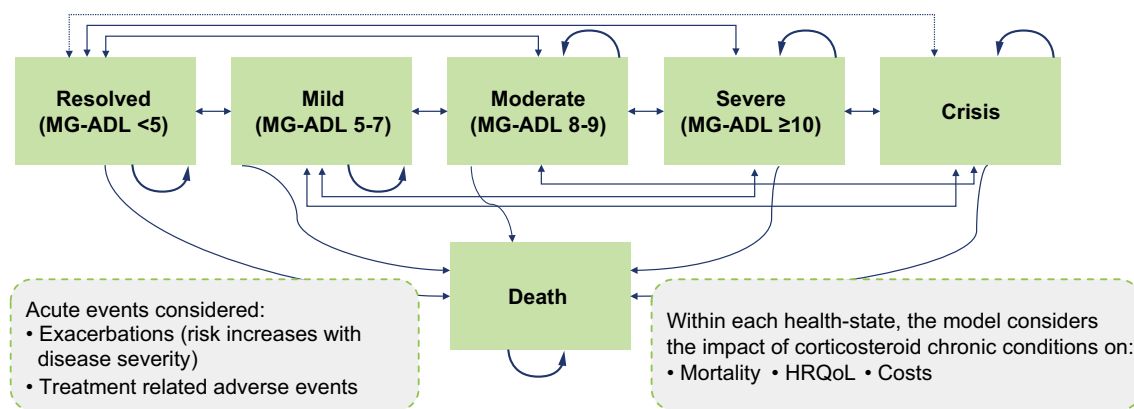


Figure 3. Model structure featuring six health states. HRQoL = health-related quality of life; MG-ADL = Myasthenia Gravis Activities of Daily Living.

Table 1. Overview of model inputs

Parameter	Value	Source/details
Baseline disease severity		
Controlled (MG-ADL < 5)	0%	ADAPT ¹⁷
Mild (MG-ADL 5–7)	26%	ADAPT ¹⁷
Moderate (MG-ADL 8–9)	42%	ADAPT ¹⁷
Severe (MG-ADL ≥ 10)	32%	ADAPT ¹⁷
Efgartigimod non-responders	18%	ADAPT ¹⁷
Transition probability to crisis (per cycle, only applicable to MG-ADL ≥ 5)	0.09%	Ramos-Fransi et al. ⁵⁶
Exacerbation probability (per cycle)		
Controlled (MG-ADL < 5)	1%	Derived from CDA (eculizumab submission) ²³
Mild (MG-ADL 5–7)	2%	Derived from CDA (eculizumab submission) ²³
Moderate (MG-ADL 8–9)	4%	Derived from CDA (eculizumab submission) ²³
Severe (MG-ADL ≥ 10)	16%	Derived from CDA (eculizumab submission) ²³
Probability of death in crisis	5%	CDA ²³
Hazard ratio for mortality with high-dose CS	3.48	Systematic literature review
Hazard ratio for mortality with low-dose CS	1.6	Systematic literature review
Health state utilities		
Controlled (MG-ADL < 5)	0.84	MyRealWorld MG ³⁴
Mild (MG-ADL 5–7)	0.69	MyRealWorld MG ³⁴
Moderate (MG-ADL 8–9)	0.63	MyRealWorld MG ³⁴
Severe (MG-ADL ≥ 10)	0.46	MyRealWorld MG ³⁴
Utility impacts		
Per exacerbation	–0.20	CDA ²³
On high-dose CS	–0.18	Sullivan et al. and Bexelius et al. ^{47,48}
On low-dose CS	–0.07	Sullivan et al. and Bexelius et al. ^{47,48}
Proportion of concomitant therapy		
Corticosteroid	75.2%	ADAPT ¹⁷
Acetylcholinesterase inhibitor	88.4%	ADAPT ¹⁷
Non-steroidal immunosuppressant	59.7%	ADAPT ¹⁷
Product costs (Canadian dollars)		
Efgartigimod	\$7,9000.00 per 400 mg vial	argenx
Immunoglobulin	\$73.88 per 1000 mg	Blackhouse et al. ³⁰

(Continued)

Table 1. Overview of model inputs (Continued)

Parameter	Value	Source/details
Administration cost per hour of intravenous infusion (Canadian dollars)	\$211.50	Tam et al. ³¹
Duration per intravenous infusion		
Efgartigimod	1 hour	argenx
IVIg	4 hours	Canadian clinical experts
Cost per exacerbation (Canadian dollars)	\$25,547.91	Derived from CDA (eculizumab submission) ²³
Cost per crisis (Canadian dollars)	\$114,903.01	Derived from CDA (eculizumab submission) ²³
Healthcare resource use costs (Canadian dollars)		
General practitioner	\$84.45	Ontario Schedule of Benefits and Fees ³⁵
Outpatient hospital visit	\$81.25	Ontario Schedule of Benefits and Fees ³⁵
Nurse at hospital	\$40.00	Government of Canada Job Bank ³⁶
Physiotherapist	\$41.03	Government of Canada Job Bank ³⁷
Neurologist outpatient visit	\$178.60	Ontario Schedule of Benefits and Fees ³⁵
End-of-life costs (Canadian dollars)	\$12,976.68	Tanuseputro et al. ⁴¹

CDA = Canada's Drug Agency; CS = corticosteroid; IVIg = intravenous immunoglobulin; MG-ADL = Myasthenia Gravis Activities of Daily Living.

Table 2. Network meta-analysis input data

Study ID	Treatment	N	Change from baseline MG-ADL		
			Mean	SE	Timepoint (weeks)
ADAPT	Efgartigimod	65	-4.60	0.4	4
	Placebo	64	-1.80	0.31	4
Howard 2019	Efgartigimod	12	-3.50	1.10	11
	Placebo	12	-1.80	1.20	11
NCT02473952	IVIg	30	-3.31	0.58	24
	Placebo	32	-2.22	0.58	24
Wolfe 2002	IVIg	6	-0.30	0.82	6
	Placebo	9	-2.60	0.80	6
CHAMPION MG	Ravulizumab	86	-3.12	0.38	26
	Placebo	89	-1.42	0.35	26

MG-ADL = Myasthenia Gravis Activities of Daily Living; IVIg = intravenous immunoglobulin; N = number; SE = standard error.

size.^{17, 18} The ADAPT and ADAPT+ trial protocols specified 5 and 4 weeks, respectively, as the minimum time off treatment between treatment cycles of efgartigimod,^{17, 18} although patients could have remained off treatment for even longer and thus incurred lower drug costs. To account for this individualized dosing schedule of efgartigimod, the model assumed a conservative treatment period wherein patients received one cycle of efgartigimod treatment consisting of four weekly infusions and then remained off treatment for 4 weeks prior to initiating the next cycle of treatment. It was also assumed that patients with MG-ADL < 5 would remain off efgartigimod until their MG-ADL score became 5 or above, in alignment with the ADAPT trial protocol.¹⁷

Health state transition probabilities were calculated for patients while on treatment with efgartigimod, as well as during off-treatment periods, to accurately simulate the individualized dosing schedule of efgartigimod. While on treatment, these probabilities were derived from patient-level data on weekly MG-ADL scores collected between baseline and week 4 of each treatment cycle in the ADAPT and ADAPT+ trials. During off-treatment periods, transition probabilities were based on the same weekly patient-

level data but also included scores collected from the placebo arm of the ADAPT trial on the basis that patients in either arm were not receiving efgartigimod during this time.

Due to the lack of clinical evidence directly comparing efgartigimod to chronic immunoglobulins, an indirect treatment comparison was required. A Bayesian network meta-analysis (NMA) was performed to determine the comparative mean difference in change from baseline MG-ADL between the available treatments for the AChR-Ab+ population. Inputs for the NMA included the ADAPT trial and the Phase 2 study for efgartigimod,²⁵ as well as two studies for IVIg.^{26, 27} Studies that assessed non-chronic usage of gMG treatments, such as IVIg for gMG crisis, were not included. A summary of inputs is provided in Table 2. Placebo was chosen as the reference treatment for the NMA due to its presence as the anchor treatment across all studies and outcomes assessed in the network. Results from the NMA (Figure 4) indicated that treating a patient with efgartigimod would result in an average lower MG-ADL score by 2.64 compared to treating that patient with IVIg instead. Further details on the NMA methodology and results can be found in the supplemental material.

Health state transition probabilities for patients receiving chronic immunoglobulins were derived by applying those NMA results (i.e., a relative increase in MG-ADL score of 2.64 with IVIg) to patient-level data from the efgartigimod arm of ADAPT for the first 4 weeks. It was assumed that the NMA results for chronic IVIg would broadly apply to chronic immunoglobulins in the absence of clinical data specifically for SCIG. Because long-term efficacy data for chronic immunoglobulins were limited (one study only evaluated 42 days),²⁶ it was assumed that patients would remain in the same health states (neither improving nor worsening) after the first model cycle except for death and to/from crisis. Additional details on the methodology for transition probabilities can be found in the supplementary material.

The ADAPT study did not gather exacerbation/crisis event data associated with efgartigimod treatment during trial follow-up. Instead, the probability of gMG exacerbations in each health state was based on data from the Phase III REGAIN clinical trial (ClinicalTrials.gov identifier: NCT01997229) for eculizumab in the treatment of gMG, which established the relationship between

EFG							
	-0.91 (-2.25 to 0.39)	RAV					
	-2.61 (-3.53 to -1.73)	-1.70 (-2.68 to -0.68)	PBO				
	-2.64 (-4.16 to -1.12)	-1.73 (-3.28 to -0.10)	-0.02 (-1.24 to 1.21)	IVIG			

Figure 4. Mean difference in change from baseline MG-ADL from network meta-analysis. EFG = efgartigimod; IVIG = intravenous immunoglobulin; PBO = placebo; RAV = ravulizumab.

MG-ADL score and the risk of exacerbation/crisis event, as used in its submission to CDA.²³

Costs

The following costs were considered for the analysis: product acquisition, product administration, cost of patient monitoring, cost of complications associated with the chronic use of CSs, cost of exacerbation/crisis management, cost of treatment-emergent AEs and terminal care costs. All costs were inflated to 2023 Canadian dollars (for alignment with CDA's appraisal) using the Consumer Price Index for Canada, where appropriate.²⁸ Efgartigimod was administered at a dose of 10 mg/kg in cycles of four weekly infusions. Chronic IVIg was administered with an initial 2000 mg/kg induction dose, followed by maintenance doses of 1000 mg/kg every 3 weeks (with every 4 weeks explored in a scenario analysis).^{29,30} Following the same initial induction dose, chronic SCIG was administered in maintenance doses of 400 mg/kg weekly. The cost of efgartigimod was \$7900 per vial. The product acquisition cost per 1000 mg of immunoglobulin was \$73,8826 (same unit cost for both IVIg and SCIG).³⁰ The analysis assumed that vial sharing was not permitted.

Intravenous treatment administration was assumed to carry a cost of \$211.50 per hour.³¹ Administering one dose of efgartigimod was assumed to require 1 hour,³² whereas 4 hours were estimated for IVIg.³³ No administration costs were applied to SCIG, as it was assumed to be self-administered by the patient.

Estimates for the frequency of healthcare resource use related to routine patient monitoring were obtained from the MyRealWorld MG (MRW-MG) study, including visits to healthcare providers, but not emergency or in-hospital visits.³⁴ Healthcare resource unit costs were obtained from the Ontario Schedule of Benefits for Physician Services³⁵ and Government of Canada job bank.^{36,37}

Additional costs associated with chronic CS use were applied to patients receiving CS as part of their conventional therapy. Separate costs were applied depending on whether patients were on low-dose or high-dose CS, as these costs have been found to be higher in patients taking higher doses of CS.^{38,39}

The costs of gMG exacerbations and crises were obtained from the CDA review for eculizumab, with all acute care and post-acute care costs considered.²³ Per CDA's recommendation, the duration of the hospital stay without ICU for exacerbations was reduced from 31.1 days to 14 days, with a proportional reduction in the cost of the hospital stay.

The one-time cost of each treatment-emergent grade ≥ 3 AE was applied to the proportion of the cohort having each AE. The

costs were informed by the Canadian Institute for Health Information Patient Cost Estimator tool.⁴⁰

A one-time terminal care cost of \$12,976.68 (inflated from 2013 to 2023) was applied upon death.⁴¹

Utilities

Utility values for the controlled, mild, moderate and severe health states were available from two sets of data: one based on the MRW-MG study³⁴ and another treatment-specific set based on the ADAPT trial. To adhere to CDA guideline requirements, the utility values in the current analysis were obtained from the MRW-MG study, as treatment-specific utility values are not accepted.²² However, because the ADAPT trial showed strong evidence that the utility value varies significantly between both treatment arms, its input was evaluated in an additional scenario analysis. Notably, lower MG-ADL scores among patients with gMG were significantly associated with higher utility values in a recent analysis.⁴²

Patients who experienced disease exacerbation were assumed to incur a disutility of -0.20 , based on analysis of data from the REGAIN trial, obtained from CDA's eculizumab review.²³ Utility decrements from AEs were sourced from literature⁴³ and were applied to the proportion of patients experiencing the AE. The average duration of all AEs was assumed to be 14 days. Patients receiving high- and low-dose CSs incurred disutilities of -0.18 and -0.07 , respectively, based on two studies of the impact of CS use on HRQoL.^{44,45}

Assumptions

Several assumptions were required to adequately model the treatment of Canadian gMG patients within the framework of the cohort model structure. In the ADAPT/ADAPT+ trials, efgartigimod treatment followed an individualized dosing schedule where the subsequent treatment cycles were initiated based on clinical evaluation. In the model, it was assumed that patients would remain off treatment for 4 weeks before starting the next on-treatment cycle, as a conservative assumption because this was the minimum duration between cycles in the ADAPT/ADAPT+ trial; an exception was that patients would remain off treatment if their MG-ADL score remained below 5, in alignment with the ADAPT trial protocol.¹⁷ The same MG-ADL < 5 assumption was applied to patients treated with chronic immunoglobulins, for consistency, due to it also having response-based dosing.

Assumptions were made around treatment discontinuation. For efgartigimod treatment, the cohort not responding to two consecutive treatment cycles was assumed to discontinue.

Table 3. Base case results

	Efgartigimod	Chronic immunoglobulin Mean over 1000 iterations (SD)
Total Costs (Canadian dollars)	\$1,913,294 (\$155,780)	\$2,263,906 (\$211,108)
Drug costs	\$1,432,893 (\$133,355)	\$1,385,182 (\$103,423)
Administration costs	\$15,376 (\$4,763)	\$133,658 (\$40,865)
Disease monitoring	\$25,114 (\$2997)	\$29,501 (\$3565)
Exacerbations	\$261,708 (\$67,381)	\$510,617 (\$143,075)
CS-related complications	\$130,926 (\$20,525)	\$150,243 (\$24,741)
Crises	\$13,434 (\$3416)	\$23,465 (\$5810)
Adverse events	\$25,671 (\$2913)	\$22,879 (\$2878)
End of life (palliative care)	\$8172 (\$1649)	\$8362 (\$1686)
Total QALY	16.80 (0.69)	13.35 (0.77)
Total LY	25.08 (0.71)	24.20 (0.74)
ICER (Efgartigimod vs comparator)	-	Dominant

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year; SD = standard deviation.

Discontinuation of chronic immunoglobulins was assumed to be 33% after 1 month of treatment based on limited data available from the literature.²⁶ Patients who discontinued the treatment were assumed to incur the same costs and efficacy as conventional therapy. Patients who did not discontinue the treatment would continue to take it until the end of the time horizon.

Limited data from the literature on chronic immunoglobulin use also necessitated other assumptions. Efficacy of IVIg and SCiG was assumed to be equivalent, with patients having no worsening or improvement of disease after the first model cycle for the rest of the time horizon (except crisis or death). Studies on patients with gMG who switched from IVIg to SCiG demonstrated non-inferiority of SCiG.^{46,47} Furthermore, although direct comparative data for IVIg and SCiG in gMG could not be identified, the equivalency of IVIg's and SCiG's efficacy and HRQoL has been observed in studies of neurological diseases.^{48,49} Canadian clinicians from seven academic centers indicated that a distribution of 75% IVIg and 25% SCiG usage would be representative of Canada as a whole. Chronic IVIg administration, although variable, was assumed to be once every 3 weeks based on the literature.²⁹ Lastly, the safety of chronic immunoglobulins was assumed to be equivalent to the placebo arm of the ADAPT study; patients in that arm received background gMG medications but not immunoglobulins, though this was a conservative assumption with the paucity of data for immunoglobulin safety in gMG.¹⁷

Because steroid tapering data while on efgartigimod was not available at the time of model development, the impact of reducing CS use was conservatively measured using health state transition

probabilities instead. Literature has demonstrated that chronic CS use is associated with additional mortality, utility decrement and additional healthcare resource costs.^{38,39} Therefore, among the 75.2% of the cohort using CS, it was assumed that patients with MG-ADL < 5 would receive low-dose CS, whereas for other health states, 43.3% of patients would receive low-dose CS, and the remainder would receive high-dose CS based on the ADAPT trial.

Analyses

All analyses were probabilistic to account for uncertainty in model inputs, in alignment with CDA guidelines.²² Additional details can be found in the supplementary material. The number of iterations for each analysis was 1000.

Several scenario analyses were conducted to test the robustness of the model and analysis assumptions by comparing results against those of the base case analysis. Three scenarios involved adjustments to assumptions around chronic immunoglobulins. The first changed the administration frequency of IVIg from every 3 weeks to every 4 weeks to address potential variability in IVIg dosing (though remaining off treatment if MG-ADL < 5). The other two explored 100% usage of IVIg every 3 weeks and 0% SCiG versus 100% SCiG weekly and 0% IVIg, such that mixed usage within a cohort would yield results in between. Given uncertainty around efficacy of IVIg/SCiG resulting from limited clinical data, two scenario analyses explored alternative NMA results for the CUA model inputs: one excluded the much smaller IVIg study that indicated it was less efficacious than placebo, whereas the other used updated data for one of the IVIg studies published after the initial NMA and CDA review.⁵⁰ Another scenario analysis explored the use of recent real-world data for informing CS usage inputs for efgartigimod; the real-world study compared CS dosing prior to receiving efgartigimod and up to 1 year following efgartigimod initiation and showed substantial reduction in CS dosing.⁵¹ A scenario analysis was also conducted, evaluating the impact of informing health state utilities with the ADAPT trial instead of the MRW-MG study, while respecting the observed differences in utility values between arms. The final scenario analysis considered additional granularity for the MG-ADL < 5 health state. Further details and rationale for these scenario analyses can be found in the supplemental material.

In CDA's appraisal of the CUA model for efgartigimod, there were several adjustments to the assumptions in CDA's re-analysis. Changes included not associating MG-ADL < 5 scores with reduced CS use, using alternative health state utility values informed by ADAPT trial data and allowing patients to transition to any health state after a crisis instead of only severe (MG-ADL ≥ 10), among other adjustments.²⁰ The direct results from CDA's re-analysis were included as a scenario analysis in this study.

A deterministic sensitivity analysis (DSA) was conducted to assess the impact of individual inputs on model results and to determine key model drivers. One by one, each model input was decreased by 20% from the base value and then increased by 20%, with results recorded each time.

Results

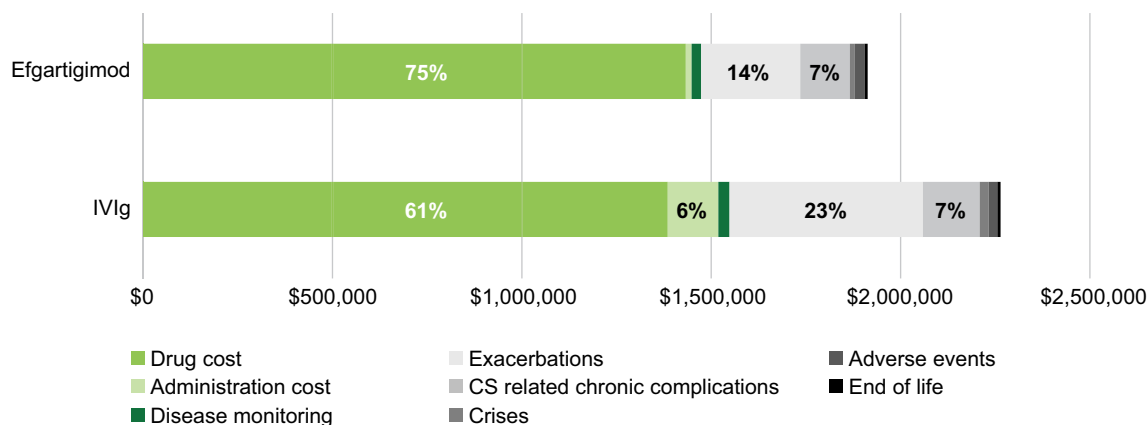
Base case results

Over a lifetime horizon, efgartigimod dominated chronic immunoglobulins as treatment for Canadian patients with AChR-Ab+ gMG, with higher total QALYs and lower total costs in Canadian dollars (Table 3). For both treatments, the largest contributor to total treatment costs was product acquisition costs

Table 4. Scenario analysis results

Scenario	Efgartigimod cost (Canadian dollars) mean over 1000 iterations (SD)	Chronic immunoglobulin cost (Canadian dollars) mean over 1000 iterations (SD)	Efgartigimod QALYs mean over 1000 iterations (SD)	Chronic immunoglobulin QALYs mean over 1000 iterations (SD)	ICER
IVIg every 4 weeks	\$1,913,294 (\$155,780)	\$1,992,976 (\$196,022)	16.80 (0.69)	13.35 (0.77)	Dominant
100% IVIg every 3 weeks	\$1,913,294 (\$155,780)	\$2,238,148 (\$212,541)	16.80 (0.69)	13.35 (0.77)	Dominant
100% SCIg weekly	\$1,913,294 (\$155,780)	\$2,340,630 (\$212,764)	16.80 (0.69)	13.35 (0.77)	Dominant
Exclude one IVIg study from NMA (showed worse efficacy than placebo)	\$1,913,294 (\$155,780)	\$1,935,524 (\$193,853)	16.80 (0.69)	14.49 (0.77)	Dominant
Updated data for one IVIg study in NMA	\$1,913,294 (\$155,780)	\$2,263,906 (\$211,108)	16.80 (0.69)	13.35 (0.77)	Dominant
Real-world data for steroid usage (pre- and post-efgartigimod)	\$1,913,644 (\$156,662)	\$2,284,748 (\$207,459)	17.06 (0.66)	13.60 (0.72)	Dominant
Utility scores from ADAPT	\$1,913,294 (\$155,780)	\$2,263,906 (\$211,108)	17.60 (0.79)	15.22 (0.77)	Dominant
MG-ADL < 5 separated into 0–2 and 3–4	\$1,913,294 (\$155,780)	\$2,263,906 (\$211,108)	16.99 (0.68)	13.42 (0.77)	Dominant
CDA re-analysis	\$1,969,893	\$2,210,045	16.38	15.47	Dominant

CDA = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; IVIg = intravenous immunoglobulin; MG-ADL = Myasthenia Gravis Activities of Daily Living; NMA = network meta-analysis; QALY = quality-adjusted life year; SCIg = subcutaneous immunoglobulin; SD = standard deviation.

**Figure 5.** Cost results by cost category (in Canadian dollars). CS = corticosteroid; IVIg = intravenous immunoglobulin.

(Figure 5). Although efgartigimod treatment incurred slightly higher product acquisition costs relative to chronic immunoglobulins (75% vs 61%, respectively), it was also associated with comparatively lower exacerbation and product administration costs. All other cost types were comparable between the two treatments. The scatter plot and cost-effectiveness acceptability curve for the base case analysis can be found in the supplementary material.

Scenario analysis results

Probabilistic scenario analysis results are presented in Table 4. Efgartigimod remained dominant in all scenario analyses, with most of the costs and QALYs for each treatment not deviating greatly from the base case results. Dosing IVIg every 4 weeks instead of 3 weeks decreased costs for chronic immunoglobulins, as

did using 100% IVIg (less expensive per year than SCIg due to lower total amount of blood product used). Results from the ADAPT trial utilities scenario analysis demonstrated no deviation in costs and some deviation in QALYs from the base case analysis. The real-world CS usage scenario analysis results were also not drastically different from the base case, demonstrating the robustness of the modeling methodology. CDA's re-analysis had the smallest difference in QALYs between efgartigimod and chronic immunoglobulins out of all analyses, though QALYs were still higher with efgartigimod, and it was still dominant over chronic immunoglobulins.

Efgartigimod dominated chronic immunoglobulins in all analyses of the DSA except for a 20% increase in the cohort's initial age (from 47 to 56 years), which had an ICER of \$7323 per QALY gained.

Discussion

Currently, standard therapies for gMG in Canada include AChEIs, CSs and NSiSTs,^{4,9–12} but in cases where the disease is poorly controlled with standard treatment options, patients may receive off-label medications, such as IVIg/SCiG.⁸ However, the use of these conventional therapies is not supported by a strong evidence base, and they are not formally approved in Canada for treating gMG, constituting their widespread off-label use. Furthermore, many patients experience suboptimal response or clinically meaningful toxicity from these standard treatments, further exacerbating the negative impact of gMG on their mental and physical well-being, HRQoL, work productivity and daily living.^{13–16} The limitations of existing conventional therapies highlight the Canadian healthcare system's need for additional gMG treatments that are fast-acting, effective, targeted and well-tolerated.

Efgartigimod is a new, effective and well-tolerated treatment for AChR-Ab+ gMG as demonstrated in the ADAPT and ADAPT+ trials.^{17,18} This novel FcRn-targeting immunomodulator was approved by Health Canada in 2023 as an add-on treatment for adult patients with gMG who are AChR-Ab+ and continue to experience symptoms of gMG despite conventional therapy.¹⁹ As observed in its pivotal clinical trials, treatment with efgartigimod may offer significant improvements in MG-ADL score and patient quality of life, underscoring the need to evaluate its cost-effectiveness for treating gMG.^{17,18}

Economic evaluation is a core component of HTA in Canada that supports payers with informed decision-making on which drugs should be funded and at what price to ensure efficient healthcare resource allocations. CDA is the HTA body responsible for considering economic evidence in the formulation of health technology policies, practices and reimbursement decisions within Canada's public healthcare system.⁵² Fundamentally, these evaluations assess the health technology of interest by conducting a series of computational simulations on a hypothetical cohort of patients from the disease population. The findings are then compared with those of one or more selected comparators to determine the relative potential economic benefits of the health technology and inform payer decision-making.

This economic analysis demonstrated that therapy with efgartigimod is cost-effective relative to chronic immunoglobulins, the primary comparator based on efgartigimod's anticipated place in therapy as determined by Canadian clinicians and CDA.²⁰ Efgartigimod was dominant in the base case and all scenario analyses, representing more efficient use of Canada's healthcare resources at lower cost with efgartigimod compared to chronic immunoglobulins (savings of \$350,612 per patient over a lifetime horizon in the base case), as well as an improvement in key clinical parameters for gMG (MG-ADL) and consequently better quality of life. Despite product acquisition costs over the time horizon being slightly higher for efgartigimod relative to chronic immunoglobulins, efgartigimod resulted in cost savings in product administration and exacerbation management owing to its shorter infusion time and improved efficacy profile. Specifically, efgartigimod was predicted to incur nearly half as much in exacerbation costs as chronic immunoglobulins with savings of \$248,909 over a lifetime horizon. This is consistent with observations from recent real-world data, which observed a 68% reduction in exacerbation events following efgartigimod treatment.⁵³ Notably, dominant results are highly uncommon in Canada, particularly for rare diseases like gMG. A recent review of CDA reimbursement submissions of rare disease products found that the average ICERs

from sponsor-submitted models ranged from \$136,377 for more common conditions to \$2,158,454 for ultra-rare conditions.⁵⁴ In all of the 59 submissions reviewed, the treatment had higher total costs than the comparators.⁵⁴

In CDA's re-analysis of the CUA model as part of the drug reimbursement submission process, several model assumptions were changed to reflect what CDA considered to be more appropriate.²⁰ Nonetheless, results from CDA's re-analysis still indicated that efgartigimod is dominant over chronic immunoglobulins in terms of cost-effectiveness.²⁰ CDA added rituximab as a comparator in their re-analysis, based on clinical expert feedback, international guidelines and jurisdictional funding in select regions.²⁰ However, CDA acknowledged that rituximab is not funded in all Canadian jurisdictions and its usage in patients with gMG is lower compared to chronic immunoglobulins, and thus, they conducted a scenario analysis without rituximab as a comparator.²⁰ In the current study, chronic immunoglobulin was the only comparator because the objective was to compare efgartigimod against the treatment that it would capture most of its market share from, which CDA and Canadian clinicians indicated would be IVIg/SCiG.²⁰ The CDA re-analysis also equalized the dose of CS used across health states.²⁰ This addressed a limitation of the initial model, where the benefits of CS tapering were based on assumptions (i.e., all patients in the MG-ADL < 5 health state would have reduced CS dosing) rather than actual data. Notably, steroid tapering data for efgartigimod has become available recently, which demonstrated a significant reduction in CS utilization within 6 months and 1 year of initiating efgartigimod therapy for gMG.⁵¹ This recent data was incorporated and evaluated in a scenario analysis in this study and resulted in a higher overall quality of life for the efgartigimod arm than the base case model. Another key modification in CDA's re-analysis was to use the same health state utility values for efgartigimod and IVIg derived from the ADAPT trial instead of the MRW-MG study.²⁰ The MRW-MG study was used for the initial model because it contained a much larger sample of gMG patients and may provide estimates more applicable to real-world settings. In addition, EQ-5D data from the ADAPT trial demonstrated substantial heterogeneity between the two treatment arms for the same health state, with the efgartigimod arm having higher utility benefit even for the same MG-ADL score.⁴² Two factors may have contributed: one being that some MG-ADL components had higher impact on quality of life than others and the second being that some benefits were captured through EQ-5D but not MG-ADL.⁴² This distinction between the two trial arms was not captured in either this study's base case analysis or CDA's re-analysis, suggesting limitations with these conservative approaches. A scenario analysis explored treatment arm-specific EQ-5D from the ADAPT trial to inform utilities to address this limitation. Although total QALYs for both treatments were higher than the base case because of generally higher health state utility scores with ADAPT versus MRW-MG, the difference in QALYs between the treatment arms was greater than CDA's re-analysis, where pooled arm utility scores were used per CDA's guidelines.²² The inability to account for observed differences in quality of life for the same health state between trial arms suggests a limitation with HTA review procedures and that there may be situations where using treatment arm-specific utilities might better reflect the trial data.

The current analysis only included the most clinically relevant comparator from which efgartigimod would capture the majority of its market share from a Canadian public healthcare payer perspective. Other potential comparators that were not publicly

reimbursed or had limited usage among the target population were excluded. This was different from CDA's approach, which included all possible accessible treatment options regardless of clinical relevance. Specifically, eculizumab and ravulizumab were excluded from this study because they were not publicly reimbursed in Canada at the time of model development despite approval by Health Canada for gMG, which CDA was aligned with in their re-analysis base case.²⁰ Rituximab was excluded because it is predominantly used among anti-MuSK+ gMG patients and has limited usage for AChR-Ab+ gMG patients in Canada.^{9,20,21} Based on CDA's own estimate, only 5% of the target population for efgartigimod was expected to come from rituximab (vs over 70% of the population from chronic immunoglobulin).²⁰ However, it should be noted that rituximab was included as a comparator in CDA's economic evaluation report despite its limited clinical relevance because it is accessible in some but not all Canadian jurisdictions.²⁰ Zilucoplan was recently approved for AChR-Ab+ gMG patients in Canada and received a draft positive reimbursement recommendation from CDA,⁵⁵ however, this occurred after the current analysis, and thus, zilucoplan was not a comparator in this study. Rozanolixizumab is another upcoming drug that was not included as a comparator because it currently does not have an indication for gMG in Canada.

The analysis had several strengths. A key strength of this analysis was the validation of the model and assumptions by Canadian experts from seven academic centers across six provinces. Collectively, these physicians treated approximately 30% of the estimated 7000 adult patients with gMG in Canada,²⁰ ensuring broad representation of the Canadian treatment landscape. This added credible support to the structure and parameters that were selected for this model and ensured that literature-derived inputs were applied to Canada. Another strength was that conservative modeling assumptions were made wherever possible, to avoid biasing results in favor of efgartigimod. An example was the assumption that patients with MG-ADL ≥ 5 would initiate a new treatment cycle at 4 weeks, despite 4+ weeks being the minimum time off treatment between treatment cycles in the ADAPT and ADAPT+ trials and patients were able to postpone treatment for additional weeks if they continued to have meaningful clinical benefit.^{17,18} Long-term results from ADAPT/ADAPT+ showed that 37% of patients had ≥ 9 weeks between treatment cycles, 27% had 6 to < 9 weeks between cycles and the remaining 36% had < 6 weeks between cycles.¹⁸ The mean number of treatment cycles was 4.7, equating to approximately 8 weeks between cycles.¹⁸ Allowing for a longer time off treatment than 4 weeks for model patients without MG-ADL < 5 would have resulted in fewer drug and administration costs for efgartigimod. A scenario analysis explored stratification of the MG-ADL < 5 health state into MG-ADL 0–2 and 3–4, to represent potential differences in disability among patients with scores from 0 to 4. In the ADAPT trial, patients who received efgartigimod were more likely to have an MG-ADL score of 0–2 instead of 3–4, which translated to a higher gain in QALYs and indicated that the singular MG-ADL < 5 health state was a conservative approach. Moreover, the current model was designed to comprehensively capture key clinical events as consequences of the disease and the associated treatment. These included clinical and cost consequences associated with disease exacerbation/crisis, as well as high-dose steroid treatment. An analysis of the ADAPT trial demonstrated that fewer patients treated with efgartigimod experienced exacerbations during the 26-week follow-up compared with placebo (21% vs 44%).⁵³ The study also

found that hospitalization events were lower for patients treated with efgartigimod than placebo (4 vs 10).⁵³ These clinical benefits were reflected in the analysis, with efgartigimod being associated with much lower exacerbation-related costs and disease monitoring costs. Further, given the extensive literature supporting the detrimental consequences of chronic CS use,^{38,39} including additional mortality, utility decrement and additional healthcare resource costs,^{38,39} steroid tapering is an important clinical practice to consider. Accordingly, the current analysis assumed that patients with MG-ADL < 5 received low-dose CS rather than higher-dose CS based on Canadian clinical expert feedback, and a scenario analysis was conducted using recently available real-world steroid tapering data, which highlight the negative consequences of prolonged CS utilization.⁵¹

There were several limitations of this analysis to note. First, while the dosing frequency of IVIg was set to be every 3 weeks in the base case analysis, real-world dosing was expected to vary and, in some cases, may occur less frequently. To address this limitation, a scenario was tested where IVIg dosing occurred every 4 weeks instead, which yielded very similar results to the base case analysis. Uncertainty around the efficacy and safety of chronic immunoglobulins also represents a limitation of this analysis. There is limited evidence available on efficacy, utilization and AEs associated with chronic immunoglobulins for gMG patients, where it is generally used off-label including in Canada. This limitation was mitigated by conducting a robust NMA that used the best evidence available for the efficacy of chronic immunoglobulins. Two scenario analyses explored alternative NMA results. The first, which excluded one of the IVIg studies, resulted in IVIg having better relative efficacy that translated into higher total QALYs; however, efgartigimod was still dominant. The second alternative NMA used updated data for one of the IVIg studies,⁵⁰ although this did not alter transition probabilities enough to impact CUA results. A direct comparative trial involving the two treatments would alleviate this current large uncertainty. Another limitation of the study is that the scope only included chronic immunoglobulins as the comparator; however, this comparison is of most interest to Canadian public payers. Efgartigimod is an add-on to conventional medication rather than a replacement in the treatment pathway. Other therapies either did not have public payer funding or had very limited usage in Canada.²⁰ Lastly, while the analysis pooled efficacy data from ADAPT and ADAPT+ to increase sample size, it should be noted that there were some differences in trial design. For example, the minimum off-treatment period was 5 weeks for the ADAPT trial, while it was 4 weeks for the ADAPT+ trial. This specific example had limited impact on the analysis because the conservative assumption of a 4 weeks off-treatment period was considered for all patients with MG-ADL ≥ 5 .

Conclusion

Efgartigimod provides greater benefit at lower costs than chronic immunoglobulins for AChR-Ab+ gMG patients who remain symptomatic despite treatment with conventional therapy in Canada. It represents a more efficient use of healthcare resources than chronic immunoglobulins and has the potential to bring substantial clinical benefit to gMG patients with a reasonable cost profile.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/cjn.2025.10449>.

Acknowledgments. The authors thank Radia Kamal of CRG-EVERSANA Inc. for support with writing the manuscript and Elizabeth Willis of CRG-EVERSANA Inc. for graphic design.

Author contributions. ZAS, CZQ, AZ, RK, JL, DG and AG contributed to the study design and validation. CZQ, AZ, RK, JL and DG contributed to model execution. ZAS, CZQ, AZ, DG and TH contributed to data analysis and interpretation. ZAS, CZQ, AZ, RK, JL, TH and AG contributed to manuscript development.

Funding statement. This study was funded by argenx.

Competing interests. ZAS and AG have received compensation for consulting services provided to argenx. ZAS has also received honoraria for consulting services provided to Alexion, UCB, and Janssen and a grant to his institution from Takeda. AZ and DG are employees of CRG-EVERSANA Inc., which has provided compensated consulting services to argenx. CZQ, RK, JL and TH are employees of argenx and have stock and/or stock options with the company.

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