CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

ECULIZUMAB (SOLIRIS)

Alexion Pharma Canada Corporation

Indication: Adult patients with generalized myasthenia gravis

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Table of Contents

Tables

Figures

Abbreviations

AChR	acetylcholine receptor
ANCOVA	analysis of covariance
CDR	CADTH Common Drug Review
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
EQ-5D	Euro-Quality of Life 5-Dimensions questionnaire
FAS	full analysis set
gMG	generalized myasthenia gravis
ICU	intensive care unit
IST	immunosuppressive therapy
ITC	indirect treatment comparison
IV	intravenous
IVIG	intravenous immunoglobulin
LOCF	last observation carried forward
LRP4	lipoprotein receptor–related protein 4
LS	least squares
MDC	Muscular Dystrophy Canada
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post-Intervention Status
MG-QoL 15	Myasthenia Gravis Quality of Life
MID	minimally important difference
MuSK	muscle-specific kinase
NMA	network meta-analysis
PLEX	plasma exchange
PP	per-protocol
QMG	Quantitative Myasthenia Gravis
RCT	randomized controlled trial
rgMG	refractory generalized myasthenia gravis
SD	standard deviation
SEM	standard error of the mean
SLR	systematic literature review

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Eculizumab (Soliris), 30 mL parenteral solution (10 mg/mL), intravenous injection.
Indication	Adult patients with generalized myasthenia gravis. Eculizumab was studied in clinical trials in patients who were anti-acetylcholine receptor(s)-antibody–positive and refractory, defined as failure of treatment with two or more immunosuppressive therapies (ISTs), either in combination or as monotherapy, or failed at least one IST and required chronic plasmapheresis, plasma exchange (PLEX), or intravenous immunoglobulin (IVIg) to control symptoms. Patients continued to receive standard therapy throughout the pivotal clinical trial.
Reimbursement request	As per indication
Health Canada Approval Status	NOC
Health Canada Review Pathway	Standard
NOC date	August 20, 2018
Sponsor	As per application overview

NOC = Notice of Compliance.

Introduction

Myasthenia gravis (MG) is a rare, chronic, autoimmune condition in which antibodies to acetylcholine receptors (AChRs) bind at the neuromuscular junction, resulting in localized or generalized weakness of the skeletal muscles.[1,2] Symptoms include impaired mobility, speaking, swallowing, vision, shortness of breath, pulmonary failure, and fatigue, which could significantly impact the patient's activities of daily living. Diagnosis is made or clinically confirmed by a physician on the basis of signs and symptoms in patients with a positive test for specific autoantibodies against AChRs, muscle-specific kinase (MuSK), and lipoprotein receptor–related protein 4 (LRP4). Two-thirds of MG patients have generalized MG (gMG). The majority of patients (> 80%) with gMG are positive for AChR autoantibodies. MG has an incidence ranging from 1.7 to 21.3 per 1 million person-years and a prevalence of 150 to 250 per 1 million population. In Canada, the incidence has been stable through the last decades, estimated at 23 per 1 million person-years, with a prevalence at 263 per 1 million population.[3,4] Refractory generalized MG (rgMG) occurs in 10% to 15% of patients with MG[5,6] but can vary according to the definition. The proportion of patients with rgMG who are AChR-antibody–positive is reported at 53%, lower than the proportion of patients with nonrefractory MG (75%).[5] Given these proportions, AChR-antibody–positive rgMG is seen in approximately 5% to 7% of all MG patients.

The prognosis is generally good in terms of muscle strength, function, quality of life, and survival with current supportive treatments, symptomatic (acetylcholinesterase inhibitors) and immune-active approaches (immunosuppressive therapies [ISTs] such as prednisone, azathioprine, and mycophenolate), as well as immunomodulatory treatments such as intravenous immunoglobulin (IVIG) and plasma exchange (PLEX).[1] However, a proportion of patients still have a refractory condition that might need additional therapy beyond the current standard of care. The main goal of treatment is achieving remission — that is,

reducing severity of MG to mild or minimal disease — and staying in remission for as long as possible while improving quality of life and performance of daily activities. Goals also include reducing the number and severity of relapses, shortening the duration of hospital visits, and using the lowest possible medication dosage and duration in order to minimize adverse effects.

Eculizumab is a humanized monoclonal antibody that specifically binds with high affinity to human terminal complement protein C5, inhibiting enzymatic cleavage to the proteins C5a and C5b and preventing C5a-induced chemotaxis of proinflammatory cells and the formation of C5b-induced membrane attack complex.

The objective of this report is to perform a systematic review of the beneficial and harmful effects of eculizumab for the treatment of adult patients who are AChR-antibody–positive and have rgMG, defined as having failed treatment with at least two ISTs, either in combination or as monotherapy, or having failed at least one IST and requiring chronic PLEX or IVIG to control symptoms.

Stakeholder Engagement

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

Patient Input

Muscular Dystrophy Canada (MDC), a patient group of 15,000 members advocating for patients with neuromuscular conditions, collected and provided information for this review by interviewing 120 patients with gMG and 70 caregivers. In its report, patients describe how a debilitating condition such as MG affects their daily lives, commonly characterized by weakness and fatigue of muscles, with more than 75% reporting debilitating chronic progression, including choking, slurred speech, impaired swallowing, and even breathing difficulties. Eye movements can also be affected in 25% of the patients. Approximately 35% of the responders reported being hospitalized at least on one occasion to the intensive care unit (ICU) for respiratory support.

MG has an impact on patients' daily living in many ways, from the need for ventilatory support at home, to effects on employment (in as many as 75% of patients) and housing. Many patients have young children and are no longer able to function as a parent or caregiver. The disruptive nature of the disease and the burden on patients' families and the health care system make patients living with MG feeling depressed and apprehensive. Caregivers also are affected by the disease because their lives are disrupted by the continuing need for care in their relatives with MG, leading to effects ranging from caregiver burnout to financial burden.

Almost half of the patients interviewed reported trying several medications throughout their life with MG because previous medications had periods of ineffectiveness. They found that medications could decrease exacerbations yet had no lasting impact on quality of life or on their ability to work. Also, they reported common side effects, such as nausea, fatigue, and diarrhea. Furthermore, chronic use of corticosteroids can produce adverse effects such as diabetes.

Overall, patients and caregivers interviewed agreed that better options of treatment are needed, especially those that could improve quality of life (independence in daily activities), decrease exacerbations, and result in fewer and shorter hospital admissions.

Clinician Input

The CADTH review team convened a panel of seven clinical experts from across Canada to characterize unmet therapeutic needs, identify gaps in the evidence, identify potential implementation challenges, gain further insight into the clinical management of patients living with the condition, and explore the drug's potential place in therapy.

According to the clinical experts, treatment goals include achieving a meaningful remission and staying in remission for as long as possible, while increasing the patient's quality of life and improving their daily activities. In refractory MG, these goals also include reducing the quantity and severity of relapses, shortening the duration of hospital visits, using the lowest possible medication dosage, and minimizing adverse effects. Patients with refractory MG would have failed at least two ISTs, with a persistent need for more and different strategies. Hence, the experts currently observe an unmet need for a cost-effective in patients with refractory MG, one that would allow patients to be weaned off corticosteroids and other therapies that have adverse effects with long-term use. Although eculizumab is not expected to cause a major shift in the current treatment paradigm, it would be useful in patients with refractory MG as an adjunct to other therapies or as a last line of treatment. Patients with refractory MG who are candidates for this indication would have failed at least two ISTs or either require chronic IVIG or PLEX or have failed these therapies as well.

A meaningful response to treatment is defined as an adequate reduction in clinical scales, such as a two-point reduction in the Myasthenia Gravis Activities of Daily Living (MG-ADL) score or more than three-point reduction in the Quantitative Myasthenia Gravis (QMG) score. Also, patients would have to show a reduction in the frequency of attacks and in the dosages of medications. Such patients also require a close clinical assessment from an expert in neurological diseases.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

One double-blind, placebo-controlled, multi-centre, randomized trial was included in this review. The trial was conducted in 76 sites across 17 countries in North America (including three sites in Canada), Latin America, Europe, and Asia during 2014 to 2016. The pivotal ECU-MG-301 (REGAIN) study evaluated the efficacy and safety of eculizumab in patients with rgMG who were positive to AChR antibodies, had an MG-ADL score at baseline of 6 or higher, and Myasthenia Gravis Foundation of America (MGFA) class II to IV disease. Patients included those who received at least two ISTs, or at least one IST with IVIG or PLEX at least four times per year, for 12 months, without symptom control. The study excluded those patients with a history of thymoma or thymic neoplasms, thymectomy within 12 months before screening, or use of IVIG or PLEX within four weeks before randomization, or rituximab within six months before screening.

Patients were randomized (1:1) to either intravenous eculizumab (N = 62) or placebo (N = 63) for 26 weeks, stratified by MGFA classification. Patients received eculizumab 900 mg or

matching placebo on day 1 and at weeks 1, 2, and 3; 1,200 mg at week 4; and 1,200 mg every second week thereafter as maintenance treatment. During the study, patients were allowed to use existing MG therapies and rescue medications at the physician's discretion. The primary efficacy outcome was the change from baseline to week 26 in MG-ADL total score, as analyzed by worst-rank analysis of covariance (ANCOVA). Secondary efficacy end points included changes from baseline in mean QMG, Myasthenia Gravis Composite (MGC) score, and Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15) total scores over time, and the proportion of patients achieving clinically meaningful responses to eculizumab, defined as improvements from baseline of at least three points in MG-ADL total score or at least five points in QMG total score.

ECU-MG-302 was a phase III, open-label extension of the REGAIN study to evaluate the safety and efficacy of eculizumab. The study enrolled 117 patients between November 2014 and January 2019 to evaluate the long-term efficacy of eculizumab and to characterize the effect of eculizumab on quality-of-life measures. It was composed of three phases: a blind induction phase (to preserve blinding), an open-label maintenance phase, and a safety follow-up phase. Randomization from REGAIN (61 patients had received blinded placebo and 56 had received blinded eculizumab) defined the treatment arms.

One pilot, phase II, randomized trial used a crossover design to determine frequency of adverse events and proportion of patients with a three-point reduction from baseline in the QMG score and MG-ADL score, including 14 patients with the same eligibility criteria as in the REGAIN study.

Efficacy Results

The REGAIN study showed no statistically significant difference in its primary end point, the change from baseline to week 26 in MG-ADL score between eculizumab and placebo (least squares [LS] mean worst-rank treatment difference −11.7; 95% confidence interval [CI], −24.3 to 0.96; P = 0.0698). When measuring the proportion of patients reaching an improvement of three-point reduction in MG-ADL score, 59.7% (37 patients) in the eculizumab group versus 39.7% (25 patients) in the placebo arm improved by at least a three-point reduction, a difference in proportions of 20.0 percentage points (95% CI, 2.8 to 37.2 percentage points; P = 0.0229).

The differences from baseline in the actual scores of the MG-ADL reached statistical significance in the ANCOVA sensitivity analysis, with a difference in LS means (95% CI) of –1.4 (–2.77 to –0.07; P = 0.039).

For disease severity, the QMG worst-rank score was lower in the eculizumab group than in the placebo group (LS mean rank-based treatment difference −16.0; 95% CI, −28.48 to –3.43; P = 0.0129). The proportion of patients with at least a five-point reduction in QMG score was 45.2% (28 patients) in the eculizumab group versus 19.0% (12 patients) in the placebo arm, a difference in proportions of 26.2 percentage points (95% CI, 10.4 to 41.8 percentage points; P = 0.0018).

MG exacerbations were reported by six (10%) patients in the eculizumab group and 15 (24%) in the placebo group. Six (10%) patients in the eculizumab group and 12 (19%) in the placebo group required rescue therapy; also, fewer patients in the eculizumab group (9 [14.5%]) required hospitalization as compared to placebo (18 [28.6%]). These data, however, were not compared statistically.

Although quality-of-life measures (MG-QoL 15 total score) showed greater improvements in the eculizumab group than in the placebo group, the results were uninterpretable because a higher-order comparison for the MGC score was not statistically significant, per the pre-specified hierarchical analysis plan.

The open-label long-term extension study showed continued improvements with eculizumab, observed in the REGAIN study, in activities of daily living, muscle strength, functional ability, and quality of life throughout three years of follow-up (i.e., reductions in the MG-ADL, QMG, MGC, and MG-QoL15 scores).

Harms Results

The most common adverse events in the REGAIN study were headache and upper respiratory tract infection (10 [16%] for both events in the eculizumab group and 12 [19%] in the placebo group). No deaths or cases of meningococcal infection occurred during the study. No difference in the number of serious infections was noted.

The open-label extension study had similar findings, and the safety profile of eculizumab was consistent with REGAIN. Notably, three patients died during the long-term study, one due to pulmonary embolism, another due to liver cirrhosis, and the third due to lymphohistiocytosis associated with cytomegalovirus, although none of the deaths were reported as related to eculizumab or MG.

A phase II pilot study adds a total of 139 patients observed for more than three years regarding adverse events, serious adverse events, or harms of special interest, such as meningococcal or other serious infections due to the administration of eculizumab. The frequency of adverse events was consistent with REGAIN and the extension study, although the dosage used in the phase II study was less than the one recommended by Health Canada.

Table 2: Summary of Key Results From Pivotal and Protocol-Selected Studies

	REGAIN STUDY (ECU-MG-301)	
	Eculizumab N = 62	**Placebo N = 63**
Activities of daily living		
MG-ADL score — FAS		
Change from baseline to week 26 in MG-ADL total score for patients not needing rescue therapy or dropping out of the study — mean (SD)	–4.7 (4.32) N = 52	–2.8 (3.07) N = 51
Worst-rank change from baseline, ranked score LS mean (95% CI)	56.6 (47.66 to 65.61) N = 62	68.3 (59.43 to 77.20) N = 63
Difference in LS means and 95% CI[a]	–11.7 (–24.33 to 0.96)	
P value	0.0698	
Proportion of patients with at least a 3-point reduction in MG-ADL score[b]		
Overall, n (%)	37 (59.7)	25 (39.7)
Difference in proportions, % (95% CI)	20.0 (2.8 to 37.2)	
P value[c]	0.0229	
Disease severity		
QMG score — FAS		
Change from baseline to week 26 in QMG total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	–5.4 (4.80)	–2.4 (3.70)
Worst-rank change from baseline, ranked score LS mean (95% CI)	54.7 (45.82 to 63.64)	70.7 (61.85 to 79.51)

	REGAIN STUDY (ECU-MG-301)	
	Eculizumab N = 62	Placebo N = 63
Difference in LS means and 95% CI	–16.0 (–28.48 to –3.43)	
P value	0.0129	
Proportion of patients with at least a 5-point reduction in QMG score[b]		
Overall, n (%)	28/62 (45.2)	12/63 (19.0)
Difference in proportions, % (95% CI)	26.2 (10.4 to 41.8)	
P value[c]	0.0018	
MGC score — FAS		
Change from baseline to week 26 in MGC total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	–9.2 (8.08)	–6.0 (6.19)
Worst-rank change from baseline, ranked score LS mean (95% CI)	57.3 (48.32 to 66.21)	67.7 (58.89 to 76.57)
Difference in LS means and 95% CI	–10.5 (–23.07 to 2.13)	
P value [d]	0.1026	
Hospital admission and clinical outcomes		
Total number of patients hospitalized, n (%)	9 (14.5)	18 (28.6)
Total number of reported hospitalizations, n	10	37
Duration of each hospitalization, days, mean (SD)	9.4 (7.57)	6.1 (6.48)
Total number of patients requiring an ICU admission, n (%)	1 (1.6)	0 (0.0)
Days on ventilatory support	NR	NR
Total number of patients requiring rescue therapy, n (%)	6 (9.7)	12 (19.0)
Total number of patients experiencing a MG crisis, n (%)	1 (1.6)	0 (0.0)
Patient reports of myasthenia gravis exacerbations, n (%)	6 (9.67)	15 (23.80)
Total number of patients reporting clinical deterioration as defined and based on protocol criteria, n (%)	6 (9.67)	15 (23.8)
Quality of life		
MG-QoL15 — FAS		
Change from baseline to week 26 in MG-QoL15 total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	–13.5 (14.07) N = 52	–6.5 (9.40) N = 51
Worst-rank change from baseline, ranked score LS mean (95% CI)	55.5 (46.43 to 64.47)	69.7 (60.79 to 78.66)
Difference in LS means (95% CI)	–14.3 (–26.98 to –1.56)	
P value[e]	0.0281	
Neuro-QoL Fatigue score — FAS		
Change from baseline to week 26 in Neuro-QoL Fatigue total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	–18.2 (19.60) N = 51	–9.1 (14.58) N = 49
Worst-rank change from baseline, ranked score LS mean (95% CI)	53.5 (44.68 to 62.28)	68.7 (59.92 to 77.51)
Difference in LS means (95% CI)	–15.2 (–27.68 to –2.79)	
P value[f]	0.0168	
EuroQol (EQ-5D) index score — FAS		
Change from baseline to week 26 in EQ-5D index score for patients not needing rescue therapy or dropping out of the study, mean (SD)	0.07 (0.180) N = 52	0.05 (0.171) N = 51
Worst-rank change from baseline, ranked score LS mean (95% CI)	63.1 (54.99 to 71.18)	63.2 (55.19 to 71.24)
Difference in LS means (95% CI)	–0.1 (–11.51 to 11.24)	
P value[f]	0.981	
Patients with ≥ 1 adverse event		
n (%)	53 (85.5)	56 (88.9)

	REGAIN STUDY (ECU-MG-301)	
	Eculizumab N = 62	Placebo N = 63
Most common events,[g] n (%)		
Headache	10 (16.1)	12 (19.0)
Upper respiratory tract infection	10 (16.1)	12 (19.0)
Nasopharyngitis	9 (14.5)	10 (15.9)
Myasthenia gravis	6 (9.7)	11 (17.5)
Patients with ≥ 1 serious adverse event		
n (%) [h]	9 (14.5)	18 (28.6)
Myasthenia gravis	5 (8.1)	8 (12.7)
Pyrexia	2 (3.2)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	2 (3.2)
Patients withdrawal due to adverse events		
n (%)	4 (6.5)	0 (0.0)
Bacteremia/endocarditis	1 (1.61)	0 (0.0)
Diverticulitis/intestinal perforation	1 (1.61)	0 (0.0)
Myasthenia gravis crisis	1 (1.61)	0 (0.0)
Prostate cancer	1 (1.61)	0 (0.0)
Deaths		
n (%)	0 (0.0)	0 (0.0)
Notable harms, n of patients (%)		
Infusion reactions	0 (0.0)	2 (3.2)
Bacteremia	1 (1.6)	0 0 (0.0)
Meningococcal infections	0 (0.0)	0 (0.0)
Low hemoglobin at week 26	16 (28.6)	14 (23.3)

CI = confidence interval; EuroQol (EQ-5D) = European Quality of Life 5-Dimensions questionnaire; FAS = full analysis set; ICU = intensive care unit; LS = least squares; MGC = Myasthenia Gravis Composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; Neuro-QoL = Quality of Life in Neurological Disorders; SD = standard deviation; QMG = Quantitative Myasthenia Gravis score; NR = not reported; MG-QoL 15 = Myasthenia Gravis Quality of Life 15-item scale.

[a] LS means are from ANCOVA model.
[b] Score from baseline to week 26 and no rescue therapy using Cochran–Mantel–Haenszel (CMH) test.
[c] P value is from a CMH test, testing for a difference in proportions between treatments, adjusting for the pooled MGFA randomization stratification variable.
[d] The hierarchy failed at this level.
[e] The P value is uninterpretable because a higher-order test failed (i.e., the MGC score).
[f] P value is outside the hierarchy and not adjusted for type I error.
[g] Frequency > 5%.
[h] Frequency > 1%.
Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Critical Appraisal

The trial failed to achieve a statistically significant difference in the primary end point, a pre-specified worst-rank analysis of the MG-ADL, although there was a difference in the mean change from baseline to week 26 in MG-ADL total score, eculizumab versus placebo, of –4.7 (standard deviation [SD] 4.3) versus –2.8 (SD 3.1), respectively. Sensitivity analyses using less conservative techniques showed statistically significant differences in favour of eculizumab versus placebo, although none of the differences between groups in these analyses were considered clinically meaningful, based on a reported minimally important difference (MID) of two points for the MG-ADL. The large SD relative to the mean change from baseline indicates a substantial variation in the data, particularly in the active

treatment arm. The normal distribution assumption, required for the analysis of continuous data with mean and SD, may not be met.

The investigators decided to use the worst-rank approach for the primary and certain secondary analyses following input from regulatory agencies. This analysis is conservative, enabling patients who needed rescue medication to be included in the efficacy analysis by treating rescue medication use or discontinuation for any reason as a negative outcome. Sensitivity analyses using the change from baseline in MG-ADL and repeated-measures methods suggested that the results were sensitive to the methods used to handle rescue therapy use and premature study discontinuation.

An analysis of the percentage of patients who had achieved a pre-specified response threshold of at least three points in MG-ADL showed a statistically significant difference (20.0%; 95% CI, 2.8 to 37.2). The selected individual patient-level threshold is greater than the two-point threshold, which was recognized as the optimal cut point in terms of best sensitivity and specificity in indicating clinical important change.[24] The benefit was confirmed by using various thresholds in responder analysis, as recommended by the FDA guidance on interpretation of patient-reported outcomes.

Twenty-four (38.1%) patients in the placebo arm and 38 (60.3%) patients in the eculizumab arm had documented protocol deviations, which may signal the quality in conduct of the trial, although only a small percentage of patients had major protocol deviations that may have affected the validity of the results. The tools used for evaluating outcomes are appropriate and validated. The processes to carry out outcome measurements were well-described and assessed in a blinded fashion. There was a differential of dropouts in the study arms (9% versus 3%).

The populations, interventions, outcomes, and outcomes measures included in the REGAIN study generally reflect the population of interest for this review and CADTH application, with the potential exception that MG patients with a thymoma were excluded. Approximately 10% to 15% of patients with AChR-antibody–positive MG also have a thymoma, and there is no known biological reason why MG with thymoma should respond any differently to eculizumab. This applies to the population commonly seen in practice, within the limitations of a controlled setting from a clinical trial, according the members of the expert panel consulted by CADTH.

Other Relevant Evidence

Description of Studies

Two studies were included. One study, ECU-MG-302, was a phase III, open-label extension of ECU-MG-301 (REGAIN) to evaluate the safety and efficacy of eculizumab in patients with rgMG. This was a multi-centre study that enrolled 117 patients from 72 sites across 17 countries. The extension study took place between November 12, 2014, and January 15, 2019. The primary objective was to evaluate the long-term safety of eculizumab in patients with rgMG. Secondary objectives were to evaluate the long-term efficacy of eculizumab, as measured by the improvement or maintenance of the MG-ADL total score, QMG total score, and MGC total score, and to characterize the effect of eculizumab on quality-of-life measures. Patients were eligible to enter the extension study within two weeks of completing the 26-week REGAIN study. The extension study was composed of three phases: a blind induction phase (to preserve blinding in REGAIN), an open-label maintenance phase, and a safety follow-up phase. In the blind induction phase of the

extension study, patients who had received eculizumab in REGAIN were treated with eculizumab 1,200 mg on day 1 and week 2, and placebo at weeks 1 and 3. Patients who had received placebo in REGAIN were treated with eculizumab (900 mg) plus placebo on day 1 and weeks 1 through 3. In the open-label maintenance phase, all patients were treated with eculizumab 1,200 mg every two weeks until the end of the study.

The second study was a pilot phase II study of eculizumab in patients with rgMG identified in the literature. This exploratory study was a randomized, double-blind, placebo-controlled, crossover trial involving 14 patients with severe, refractory generalized MG to designed to study the efficacy and safety of treatment with eculizumab. Patients were recruited across 24 sites in the US, Canada, and the UK. After a screening period of two to four weeks, patients were randomized in a 1:1 ratio to receive treatment with eculizumab or placebo for 16 weeks, followed by a five-week washout period, and then crossed over to receive the other treatment for an additional 16 weeks.

Efficacy Results

The primary efficacy end point of the extension study was continuing observation of change in the MG-ADL total score from the extension study baseline to study end. As this was not a comparative study, authors present the difference from baseline, which was –2.7 (95% CI, –3.8 to –1.6) in the placebo/eculizumab arm and 0.0 (95% CI, –1.1 to 1.0) in the eculizumab/eculizumab arm. The proportion of patients in the placebo/eculizumab arm with at least a three-point reduction in MG-ADL total score from the extension study baseline to study end was 36.1% (95% CI, 24.2 to 49.4). Results were not reported for the eculizumab/eculizumab arm.

Similarly, the change in the QMG total score from the extension study baseline to study end was –3.1 (95% CI, –4.7 to –1.6) in the placebo/eculizumab arm and –0.4 (95% CI, –1.6 to 0.9) in the eculizumab/eculizumab arm. The proportion of patients in the placebo/eculizumab arm with at least a five-point reduction in QMG total score from the extension study baseline to study end was 31.1% (95% CI, 19.9 to 44.3).The change in the MGC total score from the extension study baseline to study end was –6.4 (95% CI, –7.89 to –4.82; P < 0.0001) in the placebo/eculizumab arm and –0.2 (95% CI, –2.77 to 2.47; P = 0.9066) in the eculizumab/eculizumab arm. The change in the MG-QoL 15 total score from the extension study baseline to study end was –7.0 (95% CI, –9.74 to –4.27; P < 0.0001) in the placebo/eculizumab arm and –0.2 (95% CI, –4.12 to 3.68; P = 0.9097) in the eculizumab/eculizumab arm.

A subset of patients with a recent history of IVIG use before study entry (received IVIG at least four times in one year, with at least one IVIG treatment cycle during the six months before the first REGAIN study dose) showed similar clinical improvements at week 52 of the extension study, based on descriptive results for MG-ADL, QMG, MGC, and MG-QoL15, but statistical analyses were not performed.

The pilot study did not evaluate clinical efficacy as a primary objective. The primary end point was the percentage of patients with a three-point reduction from baseline in the QMG total score; this was achieved by 86% of eculizumab-treated patients compared with 57% of placebo-treated patients.

Harms Results

Adverse events occurred in 96.7% in the placebo/eculizumab arm and 98.2% in the eculizumab/eculizumab arm. The most common adverse events were headache,

nasopharyngitis, diarrhea, and worsening of MG. Serious adverse events occurred in 49.2% of patients the placebo/eculizumab arm and 53.6% of patients in the eculizumab/eculizumab arm. There were three deaths in the extension trial, one in the placebo/eculizumab arm, and two in the eculizumab/eculizumab arm. The sponsor and investigator considered all deaths unrelated to eculizumab. One patient in the eculizumab/eculizumab arm experienced an infection with meningococcal meningitis on January 23, 2018, despite have been vaccinated before the study (July 24, 2015) and revaccinated on November 17, 2016. The event was considered resolved on January 31, 2018, and the patient was discharged from the hospital.

These results agreed with data from the pilot study, in which all patients treated with eculizumab had at least one adverse event, compared to 84.6% of patients treated with placebo. In both arms, most adverse events were mild or moderate in severity. Common adverse events were nausea, back pain, nasopharyngitis, and headache.

Critical Appraisal

The extension study was limited by its open-label design. Generally, the study population was representative of the patients who would be treated in clinic; however, its inclusion of patients who completed REGAIN created an enriched population that may not accurately reflect real-world practice. The blinded induction phase of the extension study was useful in maintaining blinding status of REGAIN. Missing data were not imputed in the extension study. Although the open-label design limits the certainty in the efficacy results, this concern is mitigated by the observation that treatment efficacy is continuous in both arms.

The pilot study was also at high risk of bias because of its design and purpose as an exploratory analysis, rather than evaluating efficacy outcomes.

Conclusions

The single reviewed randomized controlled trial (RCT), REGAIN, suggested that eculizumab at the maintenance dose of 1,200 mg given intravenously (IV) every two weeks improves activities of daily living (measured using the change from baseline in the MG-ADL score) versus placebo after 26 weeks of treatment. The treatment effect for this outcome, however, is uncertain because the results were sensitive to the statistical methods used for the analysis. Eculizumab did demonstrate benefit, as observed by a greater proportion of patients achieving improvement of at least three points in the MG-ADL score with the drug than with placebo. This was also seen in other disease-severity measures, such as the QMG score. The effects of eculizumab on health-related quality of life and exacerbations of MG are uncertain. The sustainability of the treatment effect may be maintained beyond 26-week period, yet the longer-term data are not robust.

The safety profile from the current evidence appears similar to that reported in the product monograph for eculizumab. However, due to the relatively small sample size and limited long-term evaluation for rare and serious adverse events, there is uncertainty about the balance between the longer-term benefit and harms of eculizumab in the gMG patient population. The study excluded patients with previous history of thymoma or thymectomy, pregnancy or breastfeeding, or patients with MGFA class V. The generalizability of the findings to those patients is limited.

Introduction

Disease Background

MG is an autoimmune condition in which antibodies to AChRs or to functionally associated molecules in the post-synaptic membrane bind at the neuromuscular junction, resulting in localized or generalized weakness of the skeletal muscles.[1] The muscle weakness fluctuates throughout the day, worsening with exertion and improving with rest. Around two-thirds of patients have symptoms involving the extraocular muscles that progresses to include other bulbar muscles and limb musculature, resulting in a generalized MG (gMG). Approximately 10% to 20% of patients remain exclusively symptomatic from extraocular muscle involvement, without developing more generalized weakness — also called ocular MG. MG affects muscle power symmetrically in most cases, except for eye involvement, where there can be a marked asymmetry with involvement of any individual or group of extraocular muscles.[2]

MG has an incidence of eight to 10 cases per 1 million persons annually, and a prevalence of 150 to 250 cases per 1 million population, worldwide.[3,4] In Canada, the incidence has been stable through the last decades, at close to 23 cases per 1 million per year, with a prevalence similar to the worldwide population at 263 cases per 1 million population.[3,4]

Diagnosis is made or clinically confirmed by a physician, based on signs and symptoms in persons with a positive test for specific autoantibodies against AChRs, MuSK, and LRP4. Serologic tests for AChR antibodies have a sensitivity of approximately 85% and a specificity greater than 99% for diagnosing gMG. In patients with mild symptoms (e.g., unilateral ptosis), it is most difficult to detect gMG, which is likely underdiagnosed in such patients. Both serologic and electrophysiological testing are available to neuromuscular neurologists in Canada.

There are subgroups of MG patients, classified according to autoimmune and antibody disease mechanisms, target molecules of skeletal muscle, thymic status, genetic characteristics, response to therapy, and disease phenotype. Overall, two-thirds of patients have generalized early- or generalized late-onset MG, without thymoma. Late-onset MG is defined when first symptoms occur on or after 50 years of age, is more common among men, is characterized by a higher chance of associated thymic atrophy or thymoma, and has fewer coexisting autoimmune conditions. Another subgroup includes ocular MG, which commonly starts with ptosis and diplopia and occurs in 15% of MG cases.[8] Most (60% to 70%) of ocular MG cases convert to gMG, usually within the first three years after initial ocular symptom onset. Approximately one-half of patients with ocular MG have detectable AChR antibodies, but their presence is associated with an increase in the risk of subsequent generalized disease. Thymoma is present in 10% to 15% of MG patients, and it can be detected at any age, although it is more prevalent in late-onset MG than in early-onset MG. Thymoma is a risk factor (together with late-onset disease and MuSK antibodies) for more severe disease. AChR antibodies are detected in approximately 80% of patients with MG. Antibodies to MuSK account for 1% to 10% of cases, and about 1% to 3% of MG patients have anti-LRP4 antibody.[9] The last subgroup are patients with MG that remain seronegative (about 10% to 15%).

Refractory generalized MG (rgMG) — the focus of this review — is defined as those patients who cannot lower their immunotherapy without clinical relapse, are not clinically controlled on their immunotherapy regimen, or have severe side effects from IST. rgMG has

been reported in 10% to 15% of patients with MG seen at tertiary care neuromuscular facilities (a highly selected population),[5,6] but the percentage can vary according to the definition. The proportion of patients with rgMG who are AChR-positive is reported at 53%, lower than the 75% in patients with nonrefractory MG.[5] Given these proportions, 8% to 10% of all MG patients have rgMG that is AChR-positive.

MG has a fluctuating natural history. Exacerbations, defined as an increase in symptoms (with or without signs) in patients who were previously minimally symptomatic or asymptomatic, are usually treated by modifying the patient's IST. In severe exacerbations, known as myasthenic crisis, muscle weakness causes life-threatening difficulties with breathing and swallowing, requiring hospitalization or ICU stays.

With current supportive treatments, and the use of symptomatic and immune-active approaches, the prognosis is generally good in terms of muscle strength, function, quality of life, and survival.[1] However, patients have fears and concerns related to the burden of MG on themselves and caregivers, including concern about limitations on ability to work and need for support with activities of daily living.

Standards of Therapy

This information is jointly based on input from clinicians consulted by CADTH and a review of the medical literature.

Treatment is individualized according to patient characteristics, type of MG (ocular or generalized), and severity of MG. There are two broad approaches: one aiming at increasing the amount of acetylcholine available to bind with post-synaptic receptors, and the second aiming at immunosuppression to decrease the binding of antibodies to the AChRs. The former is also called symptomatic therapy, while the latter is immunosuppressive, based on the pathophysiology of the disease that it targets. Other management options include immunomodulating treatments (i.e., PLEX and IVIG), which have a relatively rapid onset but produce only temporary improvement and have no long-term effect on the course of MG. Finally, surgery (thymectomy) is an option, under selected circumstances, to increase the chances of remission or improvement in the subsequent course of MG.[1,2]

Symptomatic Therapy

Treatment can be considered symptomatic when it is aimed at increasing the release of acetylcholine at the pre-synaptic nerve terminal. Patients in all MG subgroups may respond to acetylcholinesterase inhibitors; among these, pyridostigmine is the first choice. Other medications, such as neostigmine and ambenonium, are not used as much because of their lower effectiveness and/or adverse effects.[2] Symptomatic treatments do not address the underlying immunopathogenesis and are not effective in many patients in the long term.

Immunosuppressive and Immunomodulatory Therapies

Short-term immunomodulating therapies include PLEX and IVIG. These are regarded as equally effective in treating severe MG, and the choice between them depends on local availability, individual patient factors, feasibility, and acceptability of the intervention. IVIG is often viewed as more appropriate, with less severe side effects, and is a more common first step in immunomodulatory treatment.[10] Either is a treatment option in rgMG, but neither is considered an optimal long-term approach.

ISTs have the goal of inducing remission or near-remission of symptoms and maintaining this remission for as long as possible. This group of interventions includes corticosteroids (e.g., oral prednisone), one of the first and most common MG therapies, usually introduced if cholinesterase inhibitors do not control symptoms. Nonsteroidal ISTs belonging to this group include drugs such as azathioprine, mycophenolate mofetil or mycophenolic acid, cyclophosphamide, cyclosporine, tacrolimus, and rituximab.

Thymectomy has beneficial effects in patients in selected circumstances. Guidelines, consensus groups, and the results of one international RCT suggest that early thymectomy be performed in patients with early-onset MG who have generalized disease, are AChR-antibody–positive, and have disease duration of less than five years.[11] Bone marrow transplantation has been described,[12] although it is usually reserved for young patients on chronic IVIG or PLEX.

Treatment Goals

Treatment aims to achieve remission by reducing severity of MG to mild or minimal disease and staying in remission for as long as possible while increasing quality of life and performance of daily activities. Goals also include reducing the quantity and severity of relapses, shortening hospital admissions and decreasing need for ICU stays with ventilatory support, using the lowest possible medication dose, and minimizing adverse effects.

Physicians usually start with symptomatic therapy (pyridostigmine) followed by immunosuppression if there is no response within two to three weeks. Patients with more severe presentations often receive both from the outset. It is fairly common for clinicians to try an IST for a specific time and either increase the dosage or add or substitute another IST if the first IST tried is insufficient to achieve remission (for example, prednisone plus azathioprine). One concern from physicians and patients is the time to effect of drugs; for instance, it can take six to nine months for mycophenolate, three to six months for prednisone, and 12 to 18 months for azathioprine to produce a clinically relevant effect. Some patients can experience exacerbations while waiting. Higher doses or a different IST can be tried if there is no response. For severe exacerbations of gMG, patients are admitted to the hospital and sometimes ICU to receive ventilatory support and IVIG, and they are generally treated with IVIG or PLEX while adjusting or adding ISTs.

Drug

Eculizumab is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, inhibiting its cleavage into C5a and C5b and preventing the generation of the terminal complement complex C5b-9 and free C5a. The exact mechanism resulting in therapeutic effect is unknown; however, the role of complement activation in the neuromuscular junction is well recognized as part of the pathophysiology of MG through destruction of the post-synaptic structure.[13] Importantly, one of the major pathogenic mechanisms of MG-associated anti-AChR antibodies (generally either IgG1 or IgG3 subtypes) is complement binding, destroying the muscle endplate. MuSK antibodies, of the IgG4 subtype, do not bind complement. There is a biologic rationale for eculizumab, as it can inhibit terminal complement activation to prevent damage in patients with rgMG who are seropositive for anti-AChR antibodies.

Eculizumab has been approved by Health Canada for the treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and neuromyelitis optica spectrum disorder. For this submission, the indication is for adult patients with gMG.

Eculizumab was studied in clinical trials in patients who were AChR-positive and refractory to treatment — refractory defined as having failed treatment with at least two ISTs, either in combination or as monotherapy, or having failed at least one IST and requiring chronic plasmapheresis (PLEX), or IVIG to control symptoms.

Eculizumab has not been reviewed by CADTH for this indication. However, CADTH Common Drug Review (CDR) reviewed the drug for the indication of paroxysmal nocturnal hemoglobinuria in February 19, 2010, for which it issued a recommendation of "do not list [reimburse]."[14] In July 18, 2013, CDR assessed eculizumab for the indication of atypical hemolytic uremic syndrome and gave a recommendation of "do not list."[15] Eculizumab is being reviewed by CDR for the indication of neuromyelitis optica spectrum disorder at the time of drafting this report.

For the indication in this submission, the recommended dosage for patients 18 years of age and older consists of:

- 900 mg weekly for the first four weeks, followed by
- 1,200 mg for the fifth dose one week later, then
- 1,200 mg every two weeks thereafter.

Eculizumab comes in a 30 mL (10 mg/mL) vial with parenteral solution (300 mg single-use vial). The final admixture, at a concentration of 5 mg/mL, should be administered by slow IV infusion (over 35 minutes).[13]

Table 3 presents the main characteristics of eculizumab and its major comparators for this submission.

Table 3: Key Characteristics of Eculizumab, Rituximab, Azathioprine, Mycophenolate, Intravenous Immunoglobulin, and Tacrolimus

	Eculizumab	Rituximab	Azathioprine	Mycophenolate	IVIG	Tacrolimus
Mechanism of action	Monoclonal antibody that specifically binds to the complement protein C5	Chimeric monoclonal antibody that binds specifically to the transmembrane antigen CD20	Immunosuppressant by suppression of B and T cells	Immunosuppressant by suppression of B and T cells	Immunosuppressant by suppression of B and T cells	Immunosuppressant by suppression of T cells and natural killer cells
Indication[a]	Adult patients with gMG who are AChR-antibody–positive and refractory to treatment	Not indicated by HC for the treatment of MG Indicated for NHL, CLL, RA, GPA	Not indicated by HC for the treatment of MG Indicated for the treatment of RA, renal homo-transplantation	Not indicated by HC for the treatment of MG Indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids	Not indicated by HC for the treatment of MG Indicated for primary immunodeficiency, hypo-gamma-globulinemia, Guillain-Barré syndrome, immune thrombocytopenia	Not indicated by HC for the treatment of MG Indicated for transplantation and RA
Route of administration	IV	IV infusion	IV, oral	Oral	IV	Oral
Recommended dose	900 mg weekly for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter	NHL: 375 mg/m^2 weekly for 4 doses. CLL: 375 mg/m^2 body surface area RA: 1,000 mg by IV infusion followed two weeks later by the second 1,000 mg IV	For RA: initial dose should be approximately 1.0 mg/kg (50 mg to 100 mg) given as a single dose or on a twice daily schedule May be increased, beginning at six to eight weeks and thereafter by steps at four-week intervals	Myfortic: 720 mg (four 180 mg or two 360 mg tablets) administered twice daily (1.440 g total daily dose) Sandoz mycophenolate mofetil: For renal transplantation, 1 g twice a day (2 g daily)	Dose and regimen depend on the indication. For Guillain-Barré syndrome: 2 g/kg	Kidney transplant: 0.2 to 0.3 mg/kg/day as initial oral dose; two divided doses every 12 hours RA: 3 mg once a day

	Eculizumab	Rituximab	Azathioprine	Mycophenolate	IVIG	Tacrolimus
			Dose increments should be 0.5 mg/kg daily, up to a maximum dose of 2.5 mg/kg/day			
Serious adverse effects or safety issues	Serious meningococcal infections that may become rapidly life-threatening or fatal if not recognized and treated early	Bacterial and, viral infections; cytopenias; precipitation of additional autoimmune disorders; progressive multifocal leuko-encephalopathy reactions; angioedema	Hepatotoxicity; severe leukopenia and/or thrombocytopenia; macrophage activation syndrome; infection; fetal harm	Infection, lymphoma; neoplasms	Thromboembolic events; allergic reactions; contraindicated in IgA deficiency	Increased susceptibility to infections and lymphoma; other carcinogenesis reported To be administered only by experienced physicians

AChR = acetylcholine receptor; CLL = chronic lymphocytic leukemia; GPA = granulomatosis with polyangiitis; HC = Health Canada; IV = intravenous; IVIG = intravenous immunoglobulin; MG = myasthenia gravis; NHL = non-Hodgkin's lymphoma; RA = rheumatoid arthritis.

[a] Health Canada–approved indication.

Source: Product monographs for Soliris;[13] Rituxan;[16] Imuran[17], Myfortic[18], Sandoz Tacrolimus,[19] IVIG (Octagam).[20]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Groups and Information Gathered

One patient input submission was received for this review; it was from MDC. MDC aims to enhance the lives of those affected by neuromuscular disorders by continually working to provide ongoing support and resources while relentlessly searching for a cure through well-funded research. Services provided by MDC include education, referrals, equipment funding, advocacy, and ongoing peer support for those affected by neuromuscular disorders. MDC has between 10,000 to 15,000 members, with new chapters opening up across the country every year. MDC collected information from 120 patients (118 from Canada and two from the US) with gMG and 70 caregivers via interviews.

Disease Experience

Of the patients interviewed by MDC, 75% reported debilitating chronic progression, which included choking, slurred speech, impaired swallowing, breathing issues, and disabling fatigue. Eye movement difficulty and speech issues were reported in 25% of patients.

Patients with debilitating chronic progression of MG reported that they had at least five hospital admissions within the last five years, with an average of two weeks' admission for swallowing issues, while 35% of patients reported at least one admission to the ICU for respiratory failure. For example, one said, "A hospital stay for me is admission to ICU at least three times in the last year." Another noted, "I need very specialized help, 24-hour care for my frequent respiratory failures episodes."

All patients surveyed reported that they had experienced complications and explained that "there are frequent exacerbations that they have no control over." Patients described crisis events associated with MG as causing considerable anxiety and coming on without warning and without any triggers.

MG affects lives of patients in many ways. About 45% of patients reported that they required in-home support for all activities of daily living. The impact on employment was highlighted; 75% of patients reported that they were forced to leave their employment owing to progression of their muscle weakness, and 35% reported that they were forced to sell their home and move into subsidized rental housing. Furthermore,15% of patients reported that they were no longer able to take care of their children due to progression of muscle weakness; to care for the children, the partner or parent of the patient needed to leave their employment, leading to financial hardship. Patients expressed concern not only about their own overall quality of life but also about the financial burden placed on provincial health care systems.

The burden of MG affects both the patients' lives and the lives of their loved ones and caregivers, with 15% of caregivers reporting that they have had to leave employment to become full-time caregivers for their partner or adult child affected by MG. One caregiver stated, "I have watched my daughter's health decline from losing muscle in her eyes to not being able to hold head and now needed to quit her job as she experiences constant crisis with her breathing. We, in our 70s, are raising her children."

Caregivers expressed challenges, including those associated with “caregiver burnout” (25%), frequent visits to primary health care practitioners related to caregiver stress (25%), and admission to hospital due to caregiver stress (12%). Caregivers reported that the patients live in constant fear and are “uncertain of their future, fearful of losing their independence.”

Experience With Treatment

Patients interviewed reported current use of corticosteroids and immunosuppressants such as cyclosporine (in 20% of patients interviewed) and azathioprine (in 15%). Forty-five percent reported that the medication they have tried has not been totally effective; that is, patients reported that these medications decreased exacerbations but had no impact on their ability to work or live independently. Side effects associated with azathioprine and cyclosporine were reported by 65% of patients using these drugs. These side effects included nausea, fatigue, and diarrhea. A secondary health concern was hypertension and diabetes, reported in 55% of patients using corticosteroids. About 25% of patients declared that the medication they are receiving is paid for by their provincial funding program, while 15% of respondents reported paying out of pocket.

In this survey, two patients were interviewed in the US, where eculizumab has been available since the FDA approved it in 2017. These two individuals reported that eculizumab decreased the intensity of exacerbations, with better outcomes and fewer hospital admissions compared to other medications these patients had tried. Patients also reported seeing an improvement in their muscle strength and overall well-being, as well as being more independent in their activities of daily living and requiring a lower level of support.

Although some patients had similar overall experiences with treatments, each patient’s experience with symptoms was very different. There was consensus that new options are needed for patients who have not experienced positive outcomes with current treatments. As one commented, “I need another option — current treatments are not helping me.”

Improved Outcomes

Patients identified three aspects of MG that they want better controlled. These included decreased intensity of exacerbations, maintenance of independence, and fewer hospital admissions. Patients stated that they would be willing to deal with side effects of medications if these aspects of MG were better controlled.

Patients stated that current medications seem to be decreasing the number of exacerbations but not the impact on overall quality of life. These are some of the comments: “With each exacerbation our health declines.” “Every day, I am fearful of going into crisis.”

The patients emphasized the importance of being able to maintain their independence, being able to stay home longer, and not having to move to an institution to accommodate personal care needs. “I don’t want to live in long-term care. I am willing to deal with side effects. Staying in my home is my priority.”

“It breaks my heart to see my daughter living away from her children, she is dependent on all of her needs.”

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). In addition, as part of the eculizumab review, a panel of seven clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy of the drug (e.g., potential reimbursement conditions). A summary of this panel discussion is presented below.

Unmet Needs

Treatment goals for the clinical experts and their patients include achieving a meaningful remission; that is, reducing severity of MG to mild or minimal disease, and staying in remission for as long as possible while improving the patient's quality of life, improving the performance of their daily activities, and minimizing treatment-related adverse effects. In patients with refractory MG, these goals also include reducing the quantity and severity of exacerbations, reducing the frequency and duration of hospital visits, and using the lowest possible medication dosage to minimize adverse effects. Patients with refractory MG would have failed two or more ISTs, with a persistent need for more and different strategies. Hence, there is an unmet need for a cost-effective therapy in patients with refractory MG — one that would allow patients to be weaned off corticosteroids and other therapies that have adverse effects due to their long-term use. This includes patients with thymoma.

Place in Therapy

According to experts, although eculizumab is not expected to cause a major shift in the current treatment paradigm, it would be useful in patients with severe and refractory MG as an additional therapy. It can also be considered as a last-line treatment in the specialist's armamentarium. Currently, there is uncertainty about the safety of adding eculizumab to other medications in the long term.

Patient Population

Patients with refractory MG would have tried and failed at least two ISTs or either have required chronic IVIG or PLEX or have failed these therapies as well. Some experts suggest that it is common to add another IST, such as azathioprine or mycophenolate, to prednisone and, if the patient does not respond to the first or second IST, to switch to a different IST (e.g., from azathioprine to mycophenolate). In this sense, eculizumab could be indicated and fill a gap in this subpopulation of patients still presenting symptoms despite optimal dosages and durations of ISTs. The expert panel discussed the following points regarding subpopulations who could also be candidates to receive eculizumab:

- Patients with a diagnosis of MG of more than 30 years that has been refractory to treatment for the last 25 years could be considered candidates for a new treatment like eculizumab. Cases of "burned out" MG may, in some instances, result from chronic

complement-mediated damage to the neuromuscular junction. By stopping complement-mediated damage, eculizumab may allow AChRs at the neuromuscular junction to regenerate and restore responsiveness to previously ineffective ISTs.

- Seronegative patients were mentioned as possible candidates; however, this was considered a point of discussion for future research because there is disagreement and uncertainty in this area, especially as some seronegative patients may not even have MG.
- The clinical experts agreed that the recommendation will have to include confirmed clinically relevant intolerance to other ISTs if this is the reason for failure to try at least two ISTs.
- Patients with thymoma were excluded from the REGAIN study, but some experts believe that this subgroup of patients should be considered, although the evidence for efficacy of eculizumab in this subgroup is scarce.
- Clinical experts from the panel agreed that eculizumab should not be used in patients with solely ocular MG (MGFA class I) or mild gMG (MGFA class II).
- Also, eculizumab would not be considered for patients in a MG crisis. However, patients who have gone into crisis after initial treatment and had been on corticosteroids, IVIG or PLEX, and ISTs would be eligible for treatment with eculizumab.
- The clinical experts felt that, as a last management step before beginning eculizumab, rituximab should be tried. Response rates in MG are reasonably high (based on non-RCT data) and response to rituximab (which usually takes three to six months) would obviate the need for eculizumab, at a vastly lower cost to the health care system overall.

Assessing Response to Treatment

A meaningful clinical response to treatment would be considered the following.

1. Reduction in clinical scales
    a) Experts propose a two-point reduction in the MG-ADL score as a minimal clinically meaningful measure of response to treatment. The REGAIN study also categorized patients (responder analysis of the MG-ADL score) with a response of three or more points' improvement, which the experts thought was clinically meaningful. One clinical expert noted that an MID of 3 should be used, since that is what was used in the REGAIN study.

    b) The QMG score with a three-point reduction can be used, as this score has a validated MID (if QMG ≥ 11, the MID is 3; if QMG < 11, MID is 2).

    c) The experts suggested that the Myasthenia Gravis Impairment Index, with a cut-off of eight points' improvement, should also be considered.
2. Reduction in frequency and severity of symptoms
3. A response to treatment with eculizumab can also be used when reducing the dosage and number of other medications.
    a) Reduction in the dosage of other medications or reduction in IVIG (some experts suggested elimination of IVIG, while others suggested a 50% reduction in dosage) would be appropriate measures of clinical response.

    b) There was uncertainty about a precise number that could be used to indicate that the patient is getting better or worse. Experts did agree that, whichever change in points is chosen as indicating improvement, the same point change in the opposite direction would show that MG is getting worse. However, clinicians often take patients off treatment based on improvement according to validated scales,

following which MG may worsen. Thus, there must be criteria for putting those patients back on treatment.

Treatment should be reassessed at least four weeks after eculizumab is started and then every three months. If there is some improvement by six months, but this improvement does not reach the MID, patients can be monitored for another three months. If the patient shows no improvement at all by six months, it is unlikely they will respond at nine months. Last, if there is no improvement with eculizumab by nine months, all experts considered that this be deemed treatment failure.

Discontinuing Treatment

Deciding to discontinue the treatment with eculizumab would involve the following:

1. Lack of effect: This should be determined on a clinical basis, as no MG biomarkers are available. (AChR antibody levels and electrophysiology are not helpful.) Evidence of failure includes an increase in IVIG, PLEX, and other treatments (e.g., prednisone dose) to control symptoms.
2. Worsening of MG: Evidence of worsening includes ongoing attacks, progression, and bulbar/respiratory involvement.
3. Treatment failure: A treatment trial with eculizumab of at least six months is recommended before concluding the treatment is not working.
4. Increasing drug use: The panel voiced some concerns that treatment with both IVIG and eculizumab increases the risk of thrombosis, although more research on this is needed.
5. Adverse events: Adverse events, such as meningococcal infections or other common infections, should be taken into consideration when deciding to suspend treatment with eculizumab.

There was some uncertainty about when eculizumab should be discontinued if patients have responded properly to the drug. The panel judged that the drug should be discontinued within two years to determine the need for ongoing treatment with eculizumab. Discontinuing eculizumab requires careful monitoring, especially during periods of high complement activity (pregnancy, surgery, or infection).

Prescribing Conditions

Eculizumab should be administered in a specialized infusion centre with experienced staff. Patients should be assessed and managed by a neuromuscular neurologist with significant experience in the management of MG (e.g., who follows at least 50 MG patients actively).

Patients in rural communities need access to neuromuscular neurologists. Patients need to be assessed at least once in person; follow-up visits can be over the telephone or by web conference. Alternatively, these patients may be assessed by their local neurologists, with oversight by a neuromuscular neurologist.

Additional Considerations

The panel considered that more research is needed on the safety of using IVIG and eculizumab together, especially because of concern that IVIG may lower eculizumab levels and that treatment with both can increase the risk of thrombosis.

Clinical Evidence

The clinical evidence included in the review of eculizumab is presented in three sections. Section 1, Systematic Review, includes pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of eculizumab for the treatment of adult patients with gMG that is AChR-antibody–positive and refractory, defined as having failed treatment with at least two ISTs, in combination or as monotherapy, or having failed at least one IST and requiring chronic plasmapheresis (PLEX) or IVIG to control symptoms. Patients continued to receive standard therapy throughout the pivotal clinical trial.

Methods

Studies selected for inclusion in the systematic review include pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adult patients with gMG that is AChR-antibody–positive and refractory, defined as having failed treatment with at least two ISTs, in combination or as monotherapy, or having failed at least one IST and requiring chronic plasmapheresis/plasma exchange or intravenous immunoglobulin to control symptoms Subgroups: • thymoma (yes, no) • baseline disease severity • rescue therapy — plasmapheresis/plasma exchange or IVIG use — (yes, no) • previous therapies
Intervention	Eculizumab 30 mL parenteral solution (10 mg/mL), alone or in combination with other treatments, with the following dosage regimen: • induction phase: 900 mg by IV infusion over approximately 35 minutes every week for 4 weeks • maintenance phase: 1,200 mg IV infusion every other week starting with week 5
Comparators	The following, administered alone or in combination: • rituximab • chronic IV immunoglobulin • chronic plasmapheresis/plasma exchange • standard care (systemic corticosteroids, ISTs [e.g., azathioprine, mycophenolate mofetil, tacrolimus] any, alone, or in combination) • placebo

Outcomes	**Efficacy outcomes:** • activities of daily living[a] (e.g., MG-ADL total score) • hospital admissions (includes ICU admissions due to MG crisis/exacerbations)[a] • disease severity[a] (e.g., QMG total score) • dose reduction and number of existing medications (e.g., prednisone) • need for rescue therapy[a] • quality of life[a] (e.g., MG-QoL 15 total score) **Harms outcomes:** AEs, SAEs, WDAEs, mortality Notable harms and harms of special interest: serious infections (e.g., meningococcal and respiratory), serious infusion reactions, hemolysis, or low hemoglobin
Study design	Published and unpublished phase III and IV RCTs

AChR = acetylcholine receptor; AE = adverse event; gMG = generalized myasthenia gravis; ICU = intensive care unit; IST = immunosuppressive therapy; IV = intravenous; IVIG = intravenous immunoglobulin; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QoL = Myasthenia Gravis Quality of Life; QMG = Quantitative Myasthenia Gravis score; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[21]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Soliris (eculizumab) and myasthenia gravis. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on April 30, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on August 19, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[22] Health Technology Assessment (HTA) Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with the panel of experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer was acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings from the Literature

A total of one unique study (from nine reports) was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 5. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

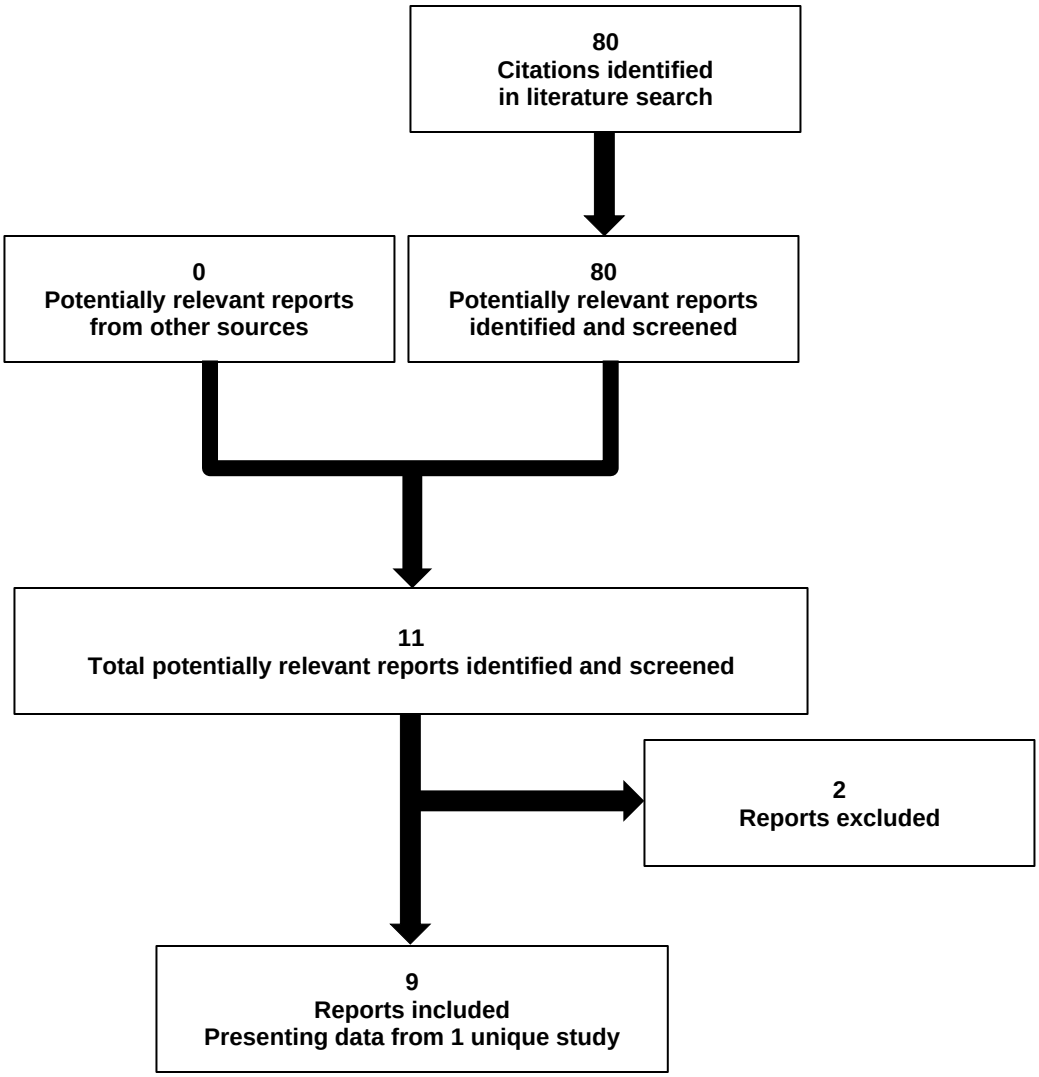


Table 5: Details of Included Study

		REGAIN Study (ECU-MG-301)
Designs and Populations	**Study design**	Double-blind, placebo-controlled randomized trial
	Locations	North America, Latin America, Europe, and Asia
	Randomized (N)	125
	Inclusion criteria	1. Patients ≥ 18 years of age with a diagnosis of MG by positive serologic test for anti-acetylcholine receptor antibodies as confirmed at screening, and one of the following: history of abnormal neuromuscular transmission test demonstrated by single-fibre electromyography or repetitive nerve stimulation; history of positive anticholinesterase test (e.g., edrophonium chloride test); or patient demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating physician 2. MGFA clinical classification class II to IV at screening 3. MG-ADL total score ≥ 6 at screening and at randomization (day 1) 4. Patients who had (a) failed treatment over 1 year or more with at least 2 ISTs, either in combination or as monotherapy (i.e., continued to have impairment of activities of daily living [persistent weakness, experienced crisis, or unable to tolerate IST]); or (b) failed at least 1 IST and had required chronic plasmapheresis (PLEX) or IVIG to control symptoms (i.e., patients who required PLEX or IVIG regularly for the management of muscle weakness at least every 3 months over the previous 12 months)[a] 5. If patients who entered the study were receiving AZA, they were required to have been on AZA for ≥ 6 months and on a stable dose for ≥ 2 months before screening 6. If patients who entered the study were receiving other ISTs (i.e., MMF, MTX, CYC, TAC, or cyclophosphamide), they were required to have been on the IST for ≥ 3 months and to have been on a stable dose for ≥ 1 month before screening 7. If patients who entered the study were receiving oral corticosteroids, they were required to have been on a stable dose for ≥ 4 weeks (i.e., 28 days) before screening 8. If patients who entered the study were receiving a cholinesterase inhibitor, they were required to be on a stable dose for ≥ 2 weeks before screening
	Exclusion criteria	1. History of thymoma or other neoplasms of the thymus 2. History of thymectomy within 12 months before screening 3. Weakness affecting only ocular or periocular muscles (MGFA class I) 4. Myasthenic crisis at screening (MGFA class V) 5. Pregnancy or lactation 6. Any systemic bacterial or other infection that was clinically significant in the opinion of the investigator and had not been treated with appropriate antibiotics 7. Unresolved meningococcal infection 8. Use of IVIG within 4 weeks before randomization (day 1) 9. Use of PLEX within 4 weeks before randomization (day 1) 10. Use of rituximab within 6 months before screening
Drugs	**Intervention**	Eculizumab, vial containing 30 mL (10 mg/mL) of eculizumab. Patients received eculizumab according to the following regimens: **Induction period:** Either eculizumab 900 mg or matching placebo via IV infusion every 7 (± 2) days for 4 weeks followed by eculizumab 1,200 mg or matching placebo for the fifth dose **Maintenance period:** Either eculizumab 1,200 mg or matching placebo via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose onwards **Supplemental doses:** If plasmapheresis (PLEX) was administered as rescue therapy because of clinical deterioration, supplemental study drug (2 vials, equivalent to 600 mg of eculizumab or matching placebo) was administered within 60 minutes after the end of each plasmapheresis (PLEX) session
	Comparator(s)	Placebo: Each vial of placebo contained the same buffer components as the eculizumab vials, but without active ingredient. Patients received placebo according to the same schedule as patients who received eculizumab.

		REGAIN Study (ECU-MG-301)
Duration	**Phase**	
	Run-in	Screening 2 to 4 weeks
	Double-blind	Study period 26 weeks
	Follow-up	Safety follow-up 8 weeks
Outcomes	**Primary end point**	Primary end point: • Change from baseline in the MG-ADL total score at week 26 of the study period for eculizumab compared with placebo
	Secondary and exploratory end points	Secondary end points: • Change from baseline in the QMG total score at week 26 • Proportion of patients with ≥ 3-point reduction in the MG-ADL total score from baseline to week 26 and with no rescue therapy • Proportion of patients with ≥ 5-point reduction in the QMG total score from baseline to week 26 and with no rescue therapy • Change from baseline in the MGC scale total score at week 26 • Change from baseline in the Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15) at week 26 Tertiary end points: • Time to response as measured by the reduction in the MG-ADL total score (3-point reduction from baseline) • Change from baseline in Quality of Life in Neurological Disorders Fatigue at week 26 • Change from baseline in the European Quality of Life Health Questionnaire at week 26 • Change from baseline in negative inspiratory force (NIF) at week 26 in patients with abnormal NIF at baseline • Change from baseline in FVC at week 26 in patients with abnormal FVC at baseline • Change from baseline in the MG-ADL individual items and changes from baseline in the bulbar (items 1, 2, and 3), respiratory (item 4), limb (items 5 and 6), and ocular (items 7 and 8) MG-ADL subcategories at week 26 in patients with an abnormal baseline score for the particular item or subcategory • Change from baseline in the MGFA Post-Intervention Status at week 26 • Safety and tolerability of eculizumab compared to placebo
Notes	**Publications**	Howard et al. (2017)[23]

AZA = azathioprine; CYC = cyclosporine; FVC = forced vital capacity; IST = immunosuppressive therapy; IV = intravenous; IVIG = intravenous immunoglobulin; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; MMF = mycophenolate mofetil; MTX = methotrexate; NIF = negative inspiratory force; PLEX = plasma exchange; TAC = tacrolimus.

[a] ISTs included, but were not limited to, corticosteroids, AZA, MMF, MTX, CYC, TAC, or cyclophosphamide.

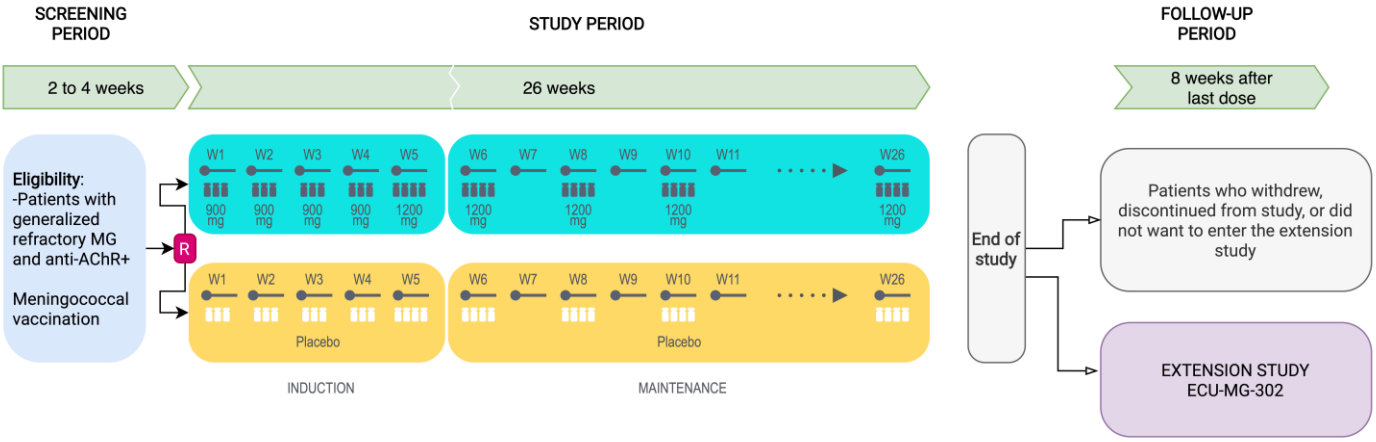
Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Description of Studies

The REGAIN trial was the only included study. It is a phase III, randomized, double-blind, placebo-controlled, multi-centre study to evaluate the efficacy and safety of eculizumab in patients with rgMG. The study was conducted in 17 countries from North America (including three sites from Canada), Latin America, Europe, and Asia from April 2014 to February 2016.[7,23]

The overall design of the study is depicted in Table 5 and Figure 2.

Figure 2: Study Design for the REGAIN Trial



AChR = acetylcholine receptor; MG = myasthenia gravis; R = randomization; W = week.

Each dark vial represents 300 mg of eculizumab. White vials represent placebo. Randomization is stratified by MGFA class (see text).

Source: Clinical Study Report of the REGAIN study (ECU-MG-301).[7]

After a screening period of two to four weeks, a total of 125 patients were randomly assigned on day 1 in a 1:1 ratio to one of two treatment arms: eculizumab infusion or placebo infusion. Patients were assessed through three periods: screening, study, and follow-up (for patients who withdrew from this study or who did not enter the extension study). The overall study duration for an individual patient was up to 38 weeks, including screening and follow-up. Patients were provided the opportunity to participate in an open-label extension, ECU-MG-302, to receive eculizumab after completion of this study. The results of ECU-MG-302 are described in the section of other relevant evidence of this report.

The randomization was across centres and stratified based on the assessment of clinical classification by the MGFA performed at the screening visit according to the following groups:

a) MGFA class IIa and IIIa

b) MGFA class IVa

c) MGFA class IIb and IIIb

d) MGFA class IVb

During the screening period, if all inclusion criteria were met and none of the exclusion criteria were present, the patient was vaccinated against *Neisseria meningitidis* at least 14 days before receiving the first dose of study drug or was vaccinated and received treatment with appropriate antibiotics until 14 days after the vaccination. The washout period for IVIG and for PLEX was four weeks before randomization, per the amended protocol.

Populations

Inclusion and Exclusion Criteria

The REGAIN study included patients ≥ 18 years of age with a diagnosis of MG and AChR-antibody–positive who met a diagnostic test criterion, including electromyograph or anticholinesterase test, or physician's assessment of response to oral cholinesterase (Table 5).

The study included only patients with MGFA class II to IV and a MG-ADL total score of 6 or more, indicating moderate-to-severe MG disease. Moreover, the study patients were required to have MG refractory to existing therapies according to a pre-specified set of criteria. For instance, they should have failed treatment for more than one year with at least two ISTs (either in combination or as monotherapy) or have failed treatment with at least one IST and have required chronic plasmapheresis (PLEX), or IVIG to control the symptoms.

Patients with thymoma or other neoplasms of the thymus were excluded, as well as those with history of thymectomy within 12 months before screening. Also, patients were excluded if they had myasthenic crisis at screening, unresolved meningococcal infections, use of IVIG or PLEX within four weeks, or use of rituximab within six months before screening.

Baseline Characteristics

A total of 125 patients were included in the full analysis set (Table 6). Of these, 62 were in the eculizumab group and 63 in the placebo group. Age and sex were similar between treatment groups, but there was a higher proportion of Asians in the placebo arm (4.8% versus 25.4%, eculizumab versus placebo, respectively). This difference was likely due to the stratification randomization by MGFA classes, rather than by study sites, leading to imbalance by regions (Europe and North America) along with an imbalance in ethnic groups (white and Asian).

Baseline disease characteristics were generally similar between groups, including MG-ADL (10.5% versus 9.9%), QMG (17.3% versus 16.9%), and MGC (20.4% versus 18.9%) scores; previous ISTs, including chronic IVIG; as well as history of hospitalizations for MG and MG crises (Table 7). Of note, the eculizumab group had a higher proportion of patients with MGFA severity moderate weakness categories of IIIa or IIIb (59.7%) than the placebo group (46.0%). Previous thymectomy was higher in the eculizumab group than the placebo group (59.7% versus 49.2%), while a greater percentage of patients in the placebo group had had prior chronic PLEX treatment (6.5% versus 15.9%).

Table 6: Summary of Baseline Characteristics — Full Analysis Set

Characteristics	Eculizumab N = 62	Placebo N = 63
Age at first dose, years, mean (SD)	47.5 (15.66)	46.9 (17.98)
Sex, female, n (%)	41 (66.1)	41 (65.1)
Weight, kg, mean (SD)	87.67 (28.19)	86.24 (28.07)
Ethnicity, n (%)		
White	53 (85.5)	42 (66.7)
Asian	3 (4.8)	16 (25.4)
Black or African-American	0 (0.0)	3 (4.8)
Multiple	1 (1.6)	0 (0)
Unknown	1. (1.6)	0 (0)
Other	4 (6.5)	2 (3.2)
Region, n (%)		
North America	21 (33.9)	25 (39.7)
South America	5 (8.1)	7 (11.1)
Europe	33 (53.2)	18 (28.6)
Asia-Pacific	0 (0.0)	5 (7.9)
Japan	3 (4.8)	8 (12.7)
MGFA class at screening, n (%)		
Class IIa	10 (16.1)	15 (23.8)
Class IIb	8 (12.9)	14 (22.2)
Class IIIa	20 (32.3)	16 (25.4)
Class IIIb	17 (27.4)	13 (20.6)
Class IVa	4 (6.5)	2 (3.2)
Class IVb	3 (4.8)	3 (4.8)
MGFA class by randomization stratification		
Class IIa or IIIa	30 (48.4)	32 (50.8)
Class IVa	4 (6.5)	2 (3.2)
Class IIb or IIIb	25 (40.3)	26 (41.3)
Class IVb	3 (4.8)	3 (4.8)

MGFA = Myasthenia Gravis Foundation of America; SD = standard deviation.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Table 7: Myasthenia Gravis History — Full Analysis Set

Characteristics	Eculizumab N = 62	Placebo N = 63
Myasthenia gravis duration, years, mean (SD)	9.87 (8.10)	9.23 (8.40)
Age at MG diagnosis, years, mean (SD)	38.02 (17.83)	38.12 (19.55)
MG-ADL score at baseline, mean (SD)	10.5 (3.1)	9.9 (2.6)
QMG score at baseline, mean (SD)	17.3 (5.10)	16.9 (5.56)
MGC score at baseline, mean (SD)	20.4 (6.13)	18.9 (5.95)
MG-QoL15 score at baseline, mean (SD)	33.6 (12.21)	30.7 (12.72)
ISTs, IVIG, and PLEX used before screening, n (%)		
Corticosteroids	58 (93.5)	62 (98.4)
Azathioprine	47 (75.8)	47 (74.6)
Mycophenolate mofetil	27 (43.5)	29 (46.0)
Cyclosporine	18 (29.0)	18 (28.6)
Tacrolimus	9 (14.5)	11 (17.5)
Methotrexate	6 (9.7)	8 (12.7)
Rituximab	7 (11.3)	7 (11.1)
Cyclophosphamide	3 (4.8)	3 (4.8)
Patients using only 2 ISTs	30 (48.4)	28 (44.4)
Patients using only 3 ISTs	20 (32.3)	19 (30.2)
Patients using 4 or more ISTs	11 (17.7)	15 (23.8)
IVIG	51 (82.3)	48 (76.2)
IVIG (chronic)	18 (29)	17 (27)
PLEX	31 (50.0)	29 (46.0)
PLEX (chronic)	4 (6.5)	10 (15.9)
Previous thymectomy, n (%)	37 (59.7)	31 (49.2)
Required ventilatory support (ever), n (%)	15 (24.2)	14 (22.2)
Patients reporting MG exacerbation including crisis (ever), n (%)	52 (83.9)	53 (84.1)
Patients reporting at least one MG crisis (ever), n (%)	13 (21.0)	10 (15.9)
Patients reporting at least one MG exacerbation (ever), n (%)	46 (74.2)	52 (82.5)
Any hospitalization for MG since diagnosis, n (%)	47 (75.8)	48 (76.2)
Any hospital admission for MG in the last 2 years, n (%)	30 (48.4)	29 (46.0)
Any ICU admission in the last 2 years, n (%)	9 (15)	7 (11)

ICU = intensive care unit; IST = immunosuppressive therapies; IVIG = intravenous immunoglobulin; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MG-QoL15 = 15-item Myasthenia Gravis Quality of Life questionnaire; PLEX = plasma exchange; QMG = Quantitative Myasthenia Gravis score; SD = standard deviation.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Interventions

Eculizumab was administered in an induction phase consisting of 900 mg (three vials) starting on visit 2 (week 1) that was repeated every 7(± 2) days for three more weeks (i.e., weeks 2, 3, and 4). At week 5, a fifth dose of 1,200 mg (four vials) was administered. After this, eculizumab was administered in the maintenance phase at 1,200 mg every other week (every 14 [± 2] days) from the sixth dose up to week 26 (Figure 2). All doses were

administered following pre-specified procedures by specialized health professionals in a slow IV infusion.

Patients in the placebo group received the same schedule of administration using a matching sterile, clear, colourless solution with the same buffer components but without the active ingredient, in an identical 30 mL vial. All administration procedures were blinded to investigators, patients, and clinicians.

Concomitant medications were allowed, including cholinesterase inhibitors, ISTs (including corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, and cyclophosphamide). All patients continued their palliative and supportive care without restrictions. Oral corticosteroid dosage or schedule could not be changed during the double-blind study period unless it was deemed medically necessary. If the dosage had to be increased subsequently, the increase could not have been above the dosage level reported at baseline. For other ISTs (azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, cyclosporine, or tacrolimus), the dosage regimen of the IST could not be changed during the entire double-blind study period. If a change was needed, the sponsor had to approve it.

Plasmapheresis/PLEX and IVIG were allowed for those patients experiencing clinical deterioration, as specified in the study protocol. If plasmapheresis/PLEX was administered as a rescue therapy, supplemental eculizumab or placebo (two vials) was administered within 60 minutes after the end of each plasmapheresis/PLEX session.

Only rituximab was not allowed as a concomitant medication during the study.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 8. These end points are further summarized below. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Table 8: Summary of Outcomes of Interest Identified in the CADTH Review Protocol That Were Measured in the Study

Outcome Measure	REGAIN — ECU-MG-301
Change from baseline in MG-ADL score	Primary
Change from baseline in QMG score	Secondary
Change from baseline in MGC score	Secondary
MG-QoL 15	Secondary
MGFA-PIS	Exploratory (tertiary)
Neuro-QoL Fatigue Scale	Exploratory (tertiary)
EuroQol (EQ-5D)	Exploratory (tertiary)

EuroQol (EQ-5D) = European Quality of Life 5-Dimensions questionnaire; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MG-QoL 15 = Myasthenia Gravis Quality of Life 15-item scale; Neuro-QoL = Quality of Life in Neurological Disorders; QMG = Quantitative Myasthenia Gravis score.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

The primary objective of the study was to evaluate the efficacy of eculizumab in patients with rgMG based on the improvement in MG-ADL scores. Secondary objectives included evaluating safety and tolerability and assessing other efficacy outcome measures with

various scales. In Appendix 4, there is an in-depth evaluation about the validity and reliability of these outcome measures and their MID, when available.

Activities of Daily Living (MG-ADL Score)

The MG-ADL score is an eight-item, patient-reported scale that assesses relevant MG symptoms and their functional impact on the patient.[24] Patients assess their functional disability secondary to ocular, bulbar, respiratory, and gross motor or limb impairment; each item is scored between 0 and 3 (normal, mild, moderate, and severe), and total scores range from 0 to 24, where higher scores indicate more severe disease. The MG-ADL is based on patient recall (over the previous seven days). The MG-ADL has been validated, and it has good test–retest reliability and responsiveness. A two-point improvement from baseline in MG-ADL score is a recognized response threshold that optimally (in terms of best sensitivity and specificity when referenced to MG-QoL15) indicates clinical improvement at the level of the individual for patients with MG.[24] No MID study was found in the literature. In the REGAIN study, given that the MG-ADL score is based on patient recall, the MG-ADL was assessed by a trained and certified clinical evaluator using a recall period of seven days or since the last visit.

Disease Severity

In REGAIN, disease severity was measured using several scales:

- The QMG score was assessed as a secondary outcome in the REGAIN study. It is a validated direct physician assessment scoring system that contains 13 items: ocular (two items), facial (one item), bulbar (two items), gross motor (six items), axial (one item), and respiratory (one item). These items are objectively and quantitatively assessed and each graded from 0 to 3, with 3 being the most severe, providing a total QMG score ranging from 0 to 39 points. This score has been established as a standard tool in MG clinical research,[25] with a 3.5-point difference correlating with a clinically meaningful change, as used in previous studies.[10,26] An MID of 2.6 points in patients with MG was determined in the original QMG publication.[20,27] In the REGAIN study, an improvement of five points or more in QMG total score from baseline at week 26 was selected as a clinically significant threshold for defining response to treatment.
- The MGC score was also assessed as a secondary outcome in the REGAIN study. It is a validated outcome measure for evaluating severity of MG.[28] As its name implies, it combines items from three other MG scales: the QMG, the MG-ADL, and the Manual Muscle Test. It is a hybrid of physician- and patient-reported test items and is weighted to account for the potential clinical impact of MG signs and symptoms ranging from 0 to 50, with higher scores representing greater morbidity. A three-point improvement in score from baseline indicates clinical improvement that is meaningful to the patient.[29]
- The MGFA Post-Intervention Status (MGFA-PIS) was measured as a tertiary (exploratory) outcome in the REGAIN study. MGFA has a disease-specific classification system that provides the physician's global assessment of the patient's clinical status following initiation of MG treatment. The MGFA does not have an evaluative purpose, as it is aimed at splitting groups based on disease severity and localization of symptoms.[20] The MGFA classes are:
  - Class I: pure ocular muscle weakness
  - Class II: mild generalized
  - Class III: moderate generalized
  - Class IV: severe generalized
  - Class V: intubation/myasthenic crisis.

- Patients with class II, III, and IV MG may be subclassified as class A if their symptoms are predominantly generalized, or class B if their symptoms are predominantly bulbar. The MGFA-PIS includes remission, defined as one year or longer without signs or symptoms and without any symptomatic (pyridostigmine) treatment, and which can be subdivided into complete remission (no pharmacologic treatment at all) or pharmacologic remission. Minimal manifestation status is defined as minimal signs or symptoms (no specific time frame was defined), and pyridostigmine use may be accepted.

  To assess hospital admission and related outcomes, the REGAIN study included days of hospitalization, but ICU days and days of ventilatory support were not available (only one patient was admitted to the ICU). The REGAIN study uses the term "clinical deterioration" (which is used interchangeably with "exacerbation" or "worsening"), which is defined as:

  - an MG crisis, defined as weakness from MG severe enough to necessitate intubation or to delay extubation following surgery, and respiratory failure due to weakness of respiratory muscles; severe bulbar (oropharyngeal) muscle weakness may accompany the respiratory muscle weakness or may be the predominant feature in some patients
  - significant symptomatic worsening to a score of 3 or a two-point worsening on any of the individual MG-ADL items other than double vision or eyelid droop
  - emergent situation in which the investigator believes that the patient's health is in jeopardy if rescue therapy is not given.

Dose Reduction, Reduction in Existing Medications, and Need for Rescue Therapy

Changes in concomitant MG therapy from baseline to the end of study by treatment group were evaluated. For this review, the focus was on cholinesterase inhibitors, corticosteroids (e.g., prednisone), other ISTs, acute and chronic PLEX, and acute and chronic IVIG.

Health-Related Quality of Life

Three scales were used in REGAIN to measure health-related quality of life:

- The Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15) is a validated disease-specific questionnaire[30] that can be applied by the clinician or completed by the patient; it consists of 15 questions, with responses to each question scored from 0 (not at all) to 4 (quite a bit), with a possible total score ranging from 0 to 60. Higher scores represent worse quality of life, as assessed over a recall period of the previous four weeks. Previous studies[31] have suggested that a seven- to eight-point improvement in the MG-QoL15 score indicates treatment impact.
- The Quality of Life in Neurological Disorders Fatigue scale (Neuro-QoL Fatigue) is a validated 19-item survey of fatigue, completed by the patient.[32] The items are scored from 1 (never) to 5 (sometimes). Total scores range from 19 to 95, where higher scores indicate greater fatigue and greater impact of MG on activities. Of note, in another autoimmune neurologic disorder (multiple sclerosis), cut-off points have been established, with less than 45 meaning no problem, 45 to 55 indicating mild problems, 55 to 65 meaning moderate problems, and more than 65 indicating severe problems with fatigue, as assessed by an MS patient expert panel.[33] No MID was given for this measurement scale.
- The European Quality of Life Health 5-Dimensions (EQ-5D) questionnaire consists of a generic 5-item questionnaire and visual analogue scale (EQ-VAS) and is a validated patient-reported survey of current health status. The five questions pertain to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[34] Each question, or dimension, has three levels: no problems, some problems, or extreme problems. The

set of responses provided by each patient represents a health state that can be converted into a single index value, where 0.0 represents death and 1.0 represents perfect health. The EQ-VAS records the patient's perceptions of their current, overall health status on a vertical, 20 cm VAS on which the high and low end points are labelled "Best imaginable health state," marked as 100, and "Worst imaginable health state," marked as 0, respectively. No MID has been identified for patients with MG. However, reported minimal clinically important differences for this scale in the general population have ranged from 0.033 to 0.074.[35]

Harms

Treatment-emergent adverse events in REGAIN were defined using the standard definitions for RCTs.

Statistical Analysis

The sample size was calculated to detect a mean-ranked difference of three points between the eculizumab and placebo groups based on a two-sided type I error of 5% and 90% power, assuming a common SD of four. A sample size of approximately 92 patients (46 per treatment group) was required after adjusting for 15% of patients dropping out.

The mean-ranked difference of 3 (SD 4) was based on mean changes from baseline to week 26 of four points on the MG-ADL scale for eculizumab and 1.5 points for placebo (SD 3.25); and seven points on the QMG for eculizumab and three points for placebo (SD 6), based on the results of the MG pilot phase II study.[36] All hypothesis testing was two-sided and performed at the 0.05 level of significance, unless otherwise specified. Estimates of treatment effect were reported with 95% CIs.

Worst-Rank Analysis (ANCOVA With Ranks)

The worst-rank ANCOVA analysis was used on the change from baseline to week 26 for the primary (MG-ADL) and relevant secondary (QMG, MGC, and MG-QoL15) and tertiary (e.g., Neuro-QoL Fatigue) outcomes. Worst-rank analysis was intended to adjust for the influence of rescue medication on subsequent efficacy assessments. Patients were ranked in the following order, with worst-rank first:

- Patients who died, calculated using time from first dose of the study drug to date of death (worst rank)
- Patients who experienced MG crisis, calculated using time from first dose of the study drug to start date of MG crisis
- Patients who received rescue therapy for "the other types of clinical deterioration" and patients who discontinued the study (regardless of whether they needed rescue therapy), calculated using time from first dose of the study drug to date of rescue therapy or dropout date
- All other patients who did not require rescue therapy and did not discontinue the study; rank calculated using changes from baseline to week 26 (or last observation carried forward [LOCF] if week 26 was missing)

The actual changes from baseline to week 26 were ranked from highest (best improvement in MG-ADL score) to worst (least improvement or most worsening in MG-ADL score) across all patients who did not withdraw from the study, needed rescue therapy, experienced MG crisis, or died from any cause. In this sense, patients were ranked from 1 (best outcome) to 125 (worst outcome). For each category of poor outcome type, patients were ranked on the basis of the time to that event. For the remaining patients, rank was assigned based on

change from baseline to week 26 (with rank 1 equivalent to the largest improvement). A similar approach was followed to assess QMG, MGC, and MG-QoL15.

Efficacy Analyses

For the primary efficacy analysis, the worst-rank analysis model was used and adjusted for baseline MG-ADL total score and randomization stratification.

Hypothesis testing for the secondary efficacy analyses was performed using a closed hierarchical testing procedure to address the issues of *multiplicity* — by using the following hierarchical order:

- change from baseline in the QMG total score at week 26
- proportion of patients with three-point or greater reduction in the MG-ADL total score from baseline to week 26 and with no rescue therapy
- proportion of patients with five-point or greater reduction in the QMG total score from baseline to week 26 and with no rescue therapy
- change from baseline in the MGC scale total score at week 26
- change from baseline in MG-QoL15 at week 26.

The hypothesis-testing procedure proceeds until statistical significance (0.05 level of significance) is not achieved at an end point. Once a comparison does not meet the threshold for significance, the end points of lower rank are not considered statistically significant.

A responder analysis was performed in the proportion of patients with a three-point or greater reduction in the MG-ADL total score with no rescue therapy, as well as the proportion of patients with a five-point or greater reduction in the QMG total score with no rescue therapy. For this, the Cochran–Mantel–Haenszel (CMH) test stratified by pooled randomization stratification variable was applied. The following were provided:

- summaries of the proportion of patients with different thresholds of reductions (e.g., two-, three-, four-, five-, six-, seven-, and eight-point reductions) in the MG-ADL total score from baseline to week 26, with and without rescue therapy
- summaries of the proportion of patients' different thresholds of reductions (e.g., three-, four-, five-, six-, seven-, eight-, nine-, and 10-point) in the QMG total score, with and without rescue therapy
- 95% CIs and P values, which were not pre-specified.

Subgroup Analyses

Pre-specified subgroup analysis for the primary outcome (i.e., the MG-ADL) was performed based on MGFA classifications and MG-ADL total score groups (up to seven, eight to nine, 10 to 12, or 13 to 18), thymectomy (yes versus no), and rescue therapy (yes versus no). A subgroup based on patients who had failed treatment for more than one year with two or more ISTs versus those who had failed treatment with one or more IST and required chronic PLEX or IVIG was also examined. Similarly, a subgroup analysis was performed for the secondary outcomes, by MGFA classifications, thymectomy (yes versus no), rescue therapy (yes versus no), and IST failure group. No tests for interaction were performed.

Sensitivity Analyses

Sensitivity analysis was performed based on the actual change from baseline to week 26 in the MG-ADL total score for all patients who completed 26 weeks on study treatment without rescue therapy. For patients who received rescue therapy or discontinued the study, the LOCF was used before rescue medication use or time of discontinuation.

Sensitivity analyses (MG-ADL, QMG, MGC, and MG-QoL15) also included repeated-measures analyses (using a restricted maximum likelihood–based model) with observed changes from baseline at each visit, with and without adjusting for IST use as a covariate.

Finally, modelling assumptions for both the primary and sensitivity analyses were assessed. All worst-rank ANCOVA and repeated-measures models included treatment, baseline values, and the randomization stratification by MGFA (pooled the categories of classes II, III, and IVa or II, III, and IVb due to the small numbers of patients in classes IVa and IVb). ANCOVA analyses used LOCF for missing assessments at week 26. No missing data were imputed for the repeated-measures analyses.

Analysis Populations

There were three main analysis populations sets. First, the full analysis set (FAS) is the population on which primary, secondary, and tertiary efficacy analyses were performed, and consists of all patients who were randomly assigned to study drug and who received at least one dose of study drug (eculizumab or placebo treatment), had a valid baseline assessment in the MG-ADL total score, and had at least one efficacy assessment after infusion of the study drug. Patients were compared for efficacy according to the treatment they were randomly assigned to receive, irrespective of the treatment they actually received.

Second, the per-protocol (PP) set was a subset of the FAS population, excluding patients with major protocol deviations. The PP set included all patients who had no major protocol deviations or inclusion/exclusion criteria deviations that might have affected efficacy, who took at least 80% of the required doses and remained enrolled in the study for 26 weeks, or took at least 80% of the required doses up to the time of being discontinued for clinical deterioration (e.g., MG crisis/exacerbation) or any other reason.

Third, the safety-analyses set included all patients who received at least one dose of study drug (eculizumab or placebo). Patients were assessed for safety according to the treatment they actually received. Patients who signed informed consent but were not treated in the study were not included in the safety set.

Results

Patient Disposition

In the REGAIN study, a total of 170 patients were screened for eligibility, and, of these, 44 (26%) failed because they did not fulfill the inclusion criteria (n = 24), they fulfilled the exclusion criteria (n = 23), or both (n = 3) (Table 9). The remaining 126 patients were randomly assigned to treatment, and 125 patients were treated; one patient was randomly assigned to the eculizumab arm but was randomized in error and never received the study drug. A total of eight patients discontinued, and 118 completed the study. The reasons for discontinuation were adverse events (four [6.3%] patients in the eculizumab arm),

withdrawal by patient (two [3.2%] patients in the placebo arm; one [1.6%] patient in the eculizumab arm), and other (one [1.6%] patient, who was randomized in error and never received study drug, in the eculizumab arm).

Major protocol deviations were defined as not meeting all of the inclusion/exclusion criteria; taking a prohibited medication (i.e., rituximab) during the double-blind treatment period; taking a cholinesterase inhibitor within 10 hours before the QMG and MGC tests at baseline, week 26, or the LOCF assessment; changes in dosage or addition of an IST or change in dosage of a background MG treatment (e.g., cholinesterase inhibitor) during the treatment phase that was not in accordance with the protocol; emergency unblinding by the investigator during the study; or any other protocol deviation that was considered to have a major effect on the assessment of efficacy. These were determined by medical and statistical review of all protocol deviations before database lock and unblinding.

Critical deviations occurred in one patient from each treatment arm. One (1.6%) patient from the placebo arm experienced a study procedure deviation, and one (1.6%) patient from the eculizumab arm experienced an eligibility and entry criteria deviation. Major protocol deviations occurred in 62 (49.2%) patients overall (24 [38.1%] patients in the placebo arm and 38 [60.3%] patients in the eculizumab arm). Major protocol deviations that occurred in more than five patients overall included the following:

- study procedure deviations (9 [14.3%] patients in the placebo arm; 16 [25.4%] patients in the eculizumab arm)
- informed consent deviations (10 [15.9%] patients in the placebo arm; 14 [22.2%] patients in the eculizumab arm)
- concomitant medication deviations (3 [4.8%] patients in the placebo arm; 6 [9.5%] patients in the eculizumab arm)
- safety reporting deviations (3 [4.8%] patients in the placebo arm; 2 [3.2%] deviations in the eculizumab arm)
- source document deviations (3 [4.8%] patients in the placebo arm; 2 [3.2%] deviations in the eculizumab arm).

Only patients who had major protocol deviations that could impact efficacy assessments were excluded from the PP set. Fifteen patients from the FAS were not included in the PP set, including seven patients from the placebo arm and eight patients from the eculizumab arm. The most common reason for exclusion from the PP set was not having a stable dosage of IST therapy at the time of enrolment and/or having a change in IST status during the study (five patients from the placebo arm and seven patients from the eculizumab arm).

Table 9: Patient Disposition

	REGAIN Study (ECU-MG-301)	
	Eculizumab	**Placebo**
Screened, N	170	
Randomized, N (%)	63 (100)	63 (100)
Discontinued from study, N (%)	6 (9.5)	2 (3.2)
Reason for discontinuation, N (%)		
Adverse events	4 (6.3)	0 (0)
Lost to follow-up	0 (0)	0 (0)

	REGAIN Study (ECU-MG-301)	
Death	0 (0)	0 (0)
Withdrawal by patient	1 (1.6)	2 (3.2)
Other[a]	1 (1.6)	0 (0)
ITT, N	62	63
PP, N	54	56
Safety, N	62	63

ITT = intention-to-treat; PP = per-protocol.

[a] Missing the MG-ADL assessments.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Exposure to Study Treatments

Measures of extent of exposure to the study drug, including study duration, treatment duration, number of infusions per patient, total actual volume of study drug infused per patient, and full adherence, were similar in the two treatment arms (Table 10).

Table 10: Exposure to Study Treatments — Safety Set REGAIN

	REGAIN Study (ECU-MG-301)	
	Eculizumab N = 62	**Placebo N = 63**
Study duration, days, mean (SD)[a]	204.8 (33.04)	214.4 (37.82)
Treatment duration, days, mean (SD)[b]	174.5 (33.44)	180.5 (26.37)
Number of infusions per patient, mean (SD)	15.4 (2.45)	15.9 (2.47)
Total infusions, N	955	999
Number of supplemental infusions per patient, mean (SD)	0.1 (0.59)	0.3 (1.54)
Total infusions, N	8	18
Total number of patients with a dose interrupted during the study, N (%)	5 (8.1)	11 (17.5)
Total actual volume of study drug infused per patient (mL), mean (SD)	3,441.98 (585.01)	3,537.30 (496.93)
Total amount of study drug infused per patient (mg), mean (SD)[c]	17,205.08 (2,923.99)	0.0 (0.00)
Full adherence (100%) during study duration,[d] N (%)	55 (88.7)	56 (88.9)
Patients reaching 90% to 100% adherence during study duration, N (%)	61 (98.4)	60 (95.4)

SD = standard deviation.

[a] Study duration = date of completion/discontinuation (or death) from the study period - date of informed consent + 1.

[b] Duration of treatment = last investigation product dose date - first investigation product dose date + 1.

[c] Total amount of study drug infused = total actual volume of eculizumab infused (mL) × 5 + total actual volume of placebo infused (mL) × 0.

[d] Compliance = (total amount of study drug infused [mL]/total amount of study drug expected [mL]) × 100.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

The number of supplemental infusions of the study drug was higher in the placebo arm (18) than in the eculizumab arm (eight), and the number of patients with an interruption of dose or infusion of study drug was higher in the placebo arm (11) than in the eculizumab arm (five). Adherence to treatment was similar between treatment groups, with more than 88% of patients achieving 100% adherence and more than 95% reaching a 90% to100% adherence during study duration (61 [98.4%] patients in the eculizumab group and in 60 [95.4%] patients in the placebo arm) (Table 10).

All patients in both treatment arms used concomitant medications while on the study. The most commonly used classes of concomitant medications were anticholinesterases, corticosteroids, and proton pump inhibitors. ISTs other than prednisone were used during the study by 52 (82.5%) patients in the placebo arm and 55 (88.7%) patients in the eculizumab arm (Table 11).

Table 11: Concomitant Medications Used During the Study — Safety Set REGAIN

	REGAIN Study (ECU-MG-301)	
	Eculizumab N = 62	Placebo N = 63
Anticholinesterases, patients, N (%)	58 (93.5)	53 (84.1)
Glucocorticoids, N (%)	47 (75.8)	51 (81.0)
Prednisone	26 (41.9)	26 (41.3)
Prednisolone	8 (12.9)	17 (27.0)
Methylprednisolone	6 (9.7)	6 (9.5)
Other	10 (16.1)	13 (20.6)
Azathioprine, N (%)	20 (32.3)	21 (33.3)
Methotrexate, N (%)	4 (6.5)	4 (6.3)
Mycophenolate mofetil, N (%)	18 (29.0)	16 (25.4)
Cyclosporine, N (%)	8 (12.9)	9 (14.3)
Tacrolimus, N (%)	3 (4.8)	4 (6.3)
Tacrolimus monohydrate, N (%)	2 (3.2)	2 (3.2)
Immunoglobulins, N (%)	3 (4.8)	5 (7.9)
Cyclophosphamide, N (%)	2 (3.2)	0 (0.0)
Proton pump inhibitors, N (%)	33 (53.2)	33 (52.4)

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Overall, the total number of concomitant medications taken and the proportion of patients who took at least one concomitant medication were similar between treatment arms.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below.

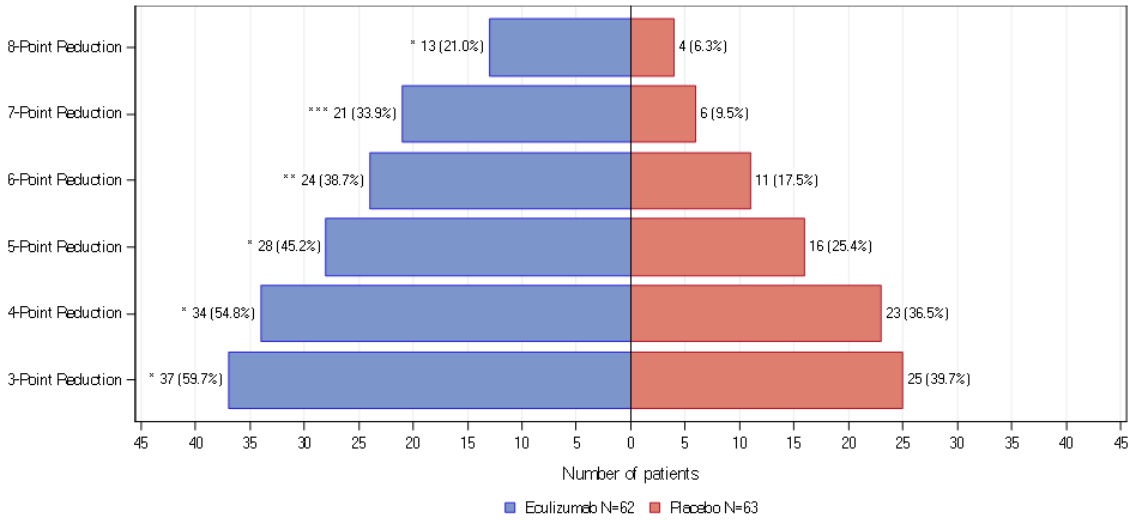
Activities of Daily Living (MG-ADL Score)

In patients who completed the study without rescue therapy, the improvement in MG-ADL total score at week 26 was greater in patients who received eculizumab than in patients who received placebo. When assessed with the worst-rank ANCOVA, the eculizumab group had a lower (better) ranked score (LS mean [95% CI]) than the placebo group (56.6 [47.66 to 65.61] versus 68.3 [59.43 to 77.20]). This difference in LS means of –11.7 (–24.33 to 0.96) was not statistically significant (P = 0.0698) (Table 12).

A greater proportion of patients in the eculizumab group showed a three-point or greater improvement in the change from baseline to week 26 in MG-ADL (59.7% versus 39.7% in eculizumab and placebo groups, respectively). The difference in proportions was 20.0%

(95% CI, 2.8 to 37.2; P = 0.0229). The results of differences were consistently in favour of eculizumab at various responder thresholds (Figure 3).

Figure 3: Proportion of Patients with Different Responder Threshold Reductions in MG-ADL Total Score (No Rescue Therapy) Assessed at Week 26 – Full Analysis Set



MG-ADL = Myasthenia Gravis Activities of Daily Living score.
* P < 0.05. All P values two-sided, CMH test.
** P < 0.01.
*** P < 0.001.
Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

The pre-specified ANCOVA sensitivity analysis and the change from baseline in MG-ADL total score at week 26 using the pre-specified sensitivity analysis based on a repeated-measures model are shown in Appendix 3.

In both the eculizumab and placebo arms, there was improvement in MG-ADL in patients with a higher baseline MG-ADL total score. However, all subgroups showed a greater improvement in the eculizumab arm than the placebo arm at week 26. The difference between treatment arms in the change from baseline to week 26 in MG-ADL was similar in patients with or without previous thymectomy. Mean changes from baseline in MG-ADL total score at week 26 by treatment arm are summarized by randomization stratification group for the FAS (Appendix 3).

Table 12: Efficacy Outcomes — REGAIN

	REGAIN Study (ECU-MG-301)	
	Eculizumab N = 62	Placebo N = 63
Activities of daily living		
MG-ADL score — FAS		
Baseline MG-ADL total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	10.1 (3.00) N = 52	9.9 (2.64) N = 51
Week 26 MG-ADL total score (LOCF) for patients not needing rescue therapy or dropping out of the study, mean (SD)	5.4 (4.05) N = 52	7.0 (3.36) N = 51
Change from baseline to week 26 in MG-ADL total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	–4.7 (4.32) N = 52	–2.8 (3.07) N = 51
Worst-rank change from baseline, ranked score LS mean[a] (95% CI)	56.6 (47.66 to 65.61) N = 62	68.3 (59.43 to 77.20) N = 63
Difference in LS means (95% CI)	–11.7 (–24.33 to 0.96)	
P value	0.0698	
Proportion of patients with at least a 3-point reduction in MG-ADL score[b]		
Overall, n (%)	37 (59.7)	25 (39.7)
Difference in proportions, % (95% CI)	20.0 (2.8 to 37.2)	
P value[c]	0.0229	
Disease severity		
QMG score —FAS		
Baseline QMG total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	17.1 (4.96) N = 52	16.4 (5.76) N = 51
Week 26 QMG total score (LOCF) for patients not needing rescue therapy or dropping out of the study, mean (SD)	11.7 (5.83) N = 52	14.1 (5.40) N = 51
Change from baseline to week 26 in QMG total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	–5.4 (4.80)	–2.4 (3.70)
Worst-rank change from baseline, ranked score LS mean (95% CI)	54.7 (45.82 to 63.64)	70.7 (61.85, to79.51)
Difference in LS means (95% CI)	–16.0 (–28.48 to –3.43)	
P value	0.0129	
Proportion of patients with at least a 5-point reduction in QMG score[b]		
Overall, n (%)	28/62 (45.2)	12/63 (19.0)
Difference in proportions, % (95% CI)	26.2 (10.4 to 41.8)	
P value[c]	0.0018	
MGC score —FAS		
Baseline MGC total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	19.4 (5.97) N = 52	19.0 (6.19) N = 51
Week 26 MGC total score (LOCF) for patients not needing rescue therapy or dropping out of the study, mean (SD)	10.3 (7.00)	13.0 (6.96)
Change from baseline to week 26 in MGC total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	–9.2 (8.08)	–6.0 (6.19)

	REGAIN Study (ECU-MG-301)	
	Eculizumab N = 62	Placebo N = 63
Worst-rank change from baseline, ranked score LS mean (95% CI)	57.3 (48.32 to 66.21)	67.7 (58.89 to 76.57)
Difference in LS means (95% CI)	–10.5 (–23.07 to 2.13)	
P value[d]	0.1026	
Hospital admission and clinical outcomes		
Total number of patients hospitalized, n (%)	9 (14.5)	18 (28.6)
Total number of reported hospitalizations, n	10	37
Duration of each hospitalization, days, mean (SD)	9.4 (7.57)	6.1 (6.48)
Total number of patients requiring an ICU admission, n (%)	1 (1.6)	0 (0.0)
Days on ventilatory support	NR	NR
Total number of patients requiring rescue therapy, n (%)	6 (9.7)	12 (19.0)
Total number of patients experiencing a MG crisis, n (%)	1 (1.6)	0 (0.0)
Patient reports of MG exacerbations, n (%)	6 (9.67)	15 (23.80)
Total number of patients reporting clinical deterioration as defined and based on protocol criteria, n (%)	6 (9.67)	15 (23.8)
Quality of life		
MG-QoL15 — FAS		
Baseline MG-QoL15 total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	31.5 (11.82) N = 52	30.2 (13.10) N = 51
Week 26 MG-QoL15 total score (LOCF) for patients not needing rescue therapy or dropping out of the study, mean (SD)	18.0 (14.37) N = 52	23.7 (13.38) N = 51
Change from baseline to week 26 in MG-QoL15 total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	–13.5 (14.07) N = 52	–6.5 (9.40) N = 51
Worst-rank change from baseline, ranked score LS mean (95% CI)	55.5 (46.43 to 64.47)	69.7 (60.79 to 78.66)
Difference in LS means (95% CI)	–14.3 (–26.98 to–1.56)	
P value [e]	0.0281	
Neuro-QoL Fatigue Score — FAS		
Baseline Neuro-QoL Fatigue total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	61.8 (13.57) N = 51	61.7 (15.36) N = 49
Week 26 Neuro-QoL Fatigue total score (LOCF) for patients not needing rescue therapy or dropping out of the study, mean (SD)	43.6 (19.44) N = 51	52.6 (18.66) N = 49
Change from baseline to week 26 in Neuro-QoL Fatigue total score for patients not needing rescue therapy or dropping out of the study, mean (SD)	–18.2 (19.60) N = 51	–9.1 (14.58) N = 49
Worst-rank change from baseline, ranked score LS mean (95% CI)	53.5 (44.68 to 62.28)	68.7 (59.92 to 77.51)
Difference in LS means (95% CI)	–15.2 (–27.68 to –2.79)	
P value	0.0168	
EuroQol (EQ-5D) index score— FAS		
Baseline EQ-5D index score for patients not needing rescue therapy or dropping out of the study, mean (SD)	0.70 (0.133) N = 52	0.69 (0.184) N = 51

	REGAIN Study (ECU-MG-301)	
	Eculizumab N = 62	Placebo N = 63
Week 26 EQ-5D index score (LOCF) for patients not needing rescue therapy or dropping out of the study, mean (SD)	0.77 (0.175) N = 52	0.74 (0.170) N = 51
Change from baseline to week 26 in EQ-5D index score for patients not needing rescue therapy or dropping out of the study, mean (SD)	0.07 (0.180) N = 52	0.05 (0.171) N = 51
Worst-rank change from baseline, ranked score LS mean (95% CI)	63.1 (54.99 to 71.18)	63.2 (55.19 to 71.24)
Difference in LS means (95% CI)	–0.1 (–11.51 to 11.24)	
P value	0.981	

CI = confidence interval; EuroQol (EQ-5D) = European Quality of Life 5-Dimensions questionnaire; FAS = full analysis set; ICU = intensive care unit; LOCF = last observation carried forward; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MG-QoL 15 = Myasthenia Gravis Quality of Life 15-item scale; Neuro-QoL = Quality of Life in Neurological Disorders; NR = not reported; SD = standard deviation; QMG = Quantitative Myasthenia Gravis score.

[a] LS means are from ANCOVA model.

[b] Score from baseline to week 26 (no rescue therapy), analyzed using CMH.

[c] P value is from a CMH test a difference in proportions between treatments, adjusting for the pooled MGFA randomization stratification variable.

[d] P value failed hierarchy significance analysis.

[e] P value not interpretable because a higher-order comparison in the hierarchy (change in MGC) was not significant at the P < 0.05 level.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

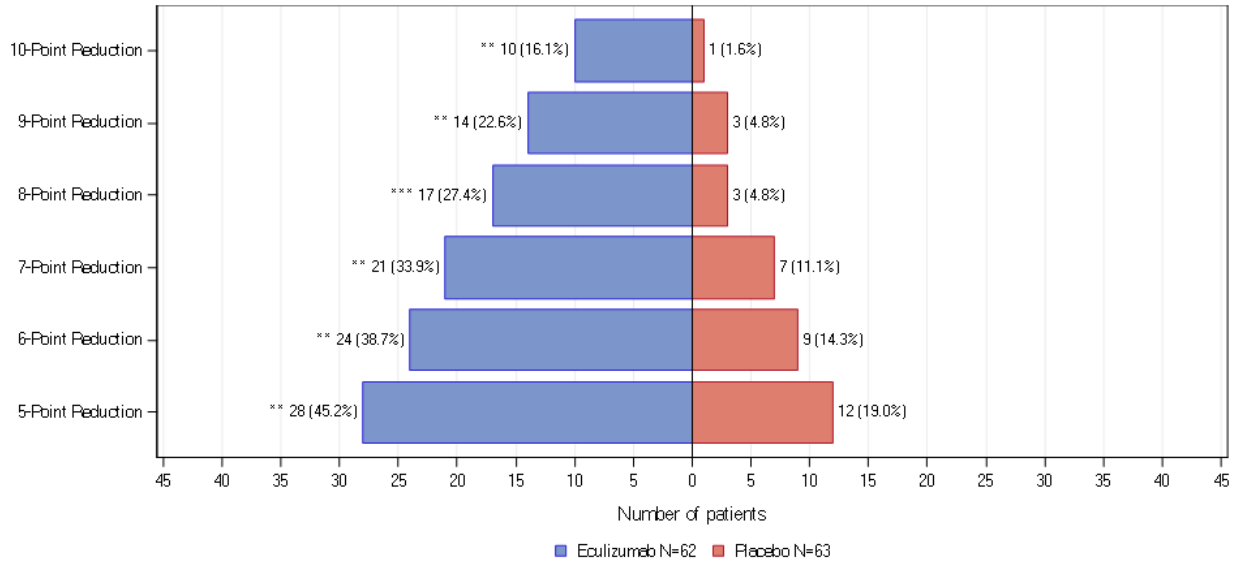
Disease Severity

Quantitative Myasthenia Gravis Score

This was a secondary end point in the REGAIN study. For patients who completed 26 weeks without rescue therapy, the mean (SD) change from baseline to week 26 in QMG total score was greater in patients who received eculizumab (–5.4 [4.80]) than in patients who received placebo (–2.4 [3.70]) (Table 12). Using the worst-rank change from baseline, the ranked score LS mean (95% CI) was higher in the placebo group (70.7 [61.85 to 79.51]) when compared to the eculizumab group (54.7 [45.82 to 63.64]), a difference in LS means of –16.0 (–28.48 to –3.43), P = 0.0129.

Responder analysis assessed the proportion of patients with a five-point or greater reduction in the QMG total score from baseline to week 26 and no rescue therapy using the CMH test adjusting for pooled MGFA randomization stratification. A larger proportion of patients in the eculizumab arm (28 [45.2%] patients) than the placebo arm (12 [19.0%] patients) had a five-point or greater reduction in the QMG total score from baseline to week 26 and no rescue therapy (P = 0.0018). The difference between treatment arms was similar when comparing patients in each pooled MGFA stratification group. In both treatment arms, more patients in the MGFA class IIb/IIIb/IVb group had a five-point or greater reduction in the MG-ADL total score in change from baseline to week 26 and no rescue therapy than patients in the MGFA class IIa/IIIa/IVa group.

Figure 4: Proportion of Patients with Different Point Reductions in QMG Total Score (No Rescue Therapy) Assessed at Week 26 — Full Analysis Set



QMG = Quantitative Myasthenia Gravis score.

* P < 0.05. All P values two-sided, CMH test.
** P < 0.01.

*** P < 0.001.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

In the sensitivity analysis (described in more detail in Appendix 3) using the ANCOVA, the LS mean (standard error of the mean [SEM]) change from baseline was greater for the eculizumab arm than the placebo arm (P = 0.0032). For the sensitivity analysis based on a repeated-measures model, at week 26, the LS mean (SEM) change from baseline in QMG total score was also greater in the eculizumab arm (P = 0.0006). Subgroup analyses of QMG total score were consistent with those for MG-ADL total score.

Myasthenia Gravis Composite Score

For patients who completed 26 weeks without rescue therapy, the mean (SD) change from baseline to week 26 in MGC total score was greater in patients who received eculizumab (–9.2 [8.08]) than in patients who received placebo (–6.0 [6.19]) (Table 12). When analyzing the worst-rank ANCOVA in change from baseline, patients in the eculizumab group had lower LS mean (95% CI) rank (57.3 [48.32 to 66.21]) than those in the placebo group (67.7 [58.89 to 76.57]), although the difference between groups in LS means of –10.5 (95% CI, –23.07 to 2.13; P = 0.102) was not statistically significant. Failure to show a statistically significant difference at this level of the hierarchical analysis plan precludes declaring subsequent comparisons (i.e., for the change from baseline in the MG-QoL15 total score) as statistically significant even if the P value is less than 0.05.

The sensitivity analysis using ANCOVA on the change from baseline to week 26 in the MGC total score at week 26 demonstrated a LS mean (SEM) of –5.0 (0.94) for the placebo arm and –7.8 (0.95) for the eculizumab arm (P = 0.0406). The sensitivity analysis using repeated measures including IST as a covariate demonstrated a similar difference between

arms (P = 0.0134) (Appendix 3). Results from subgroup analyses of MGC total score were consistent with those observed for MG-ADL total score and QMG total score.

Myasthenia Gravis Foundation of America Post-Intervention Status

A statistically significantly greater proportion of patients in the eculizumab arm than the placebo arm experienced improvement in the MGFA-PIS from baseline to week 4 (P = 0.0006), week 12 (P = 0.0361), and week 26 (P = 0.0178), using the CMH test and adjusting for the pooled MGFA randomization stratification variable (data shown in Appendix 3). These were consistent with the improvements observed in responder analyses for MG-ADL total score, QMG total score, MGC total score, and MG-QoL15 total score. There were no sensitivity or subgroup analysis based on this measurement.

Hospital Admission and Clinical Outcomes

These data are descriptive only; no statistical comparisons were performed for these outcomes.

Over the 26-week study period, both the total number of reported hospitalizations (10 versus 37) and the percentage of patients hospitalized (14.5% versus 28.6%) were lower in the eculizumab group than in the placebo group (Table 12). The percentage of patients requiring rescue therapy was also lower for the eculizumab group versus the placebo group (9.7% versus 19.0%). No difference was observed on the duration of each hospitalization. Only one patient was reported requiring an ICU in the eculizumab group. Days on ventilatory support were not reported. Clinical deterioration was reported on 15 (23.8%) patients in the placebo arm and 6 (9.7%) patients in the eculizumab arm (Table 12). Some patients experienced more than one event of clinical deterioration. One patient in the eculizumab treatment arm experienced an MG crisis.

Dose Reduction, Reduction in Existing Medications, and Need for Rescue Therapy

These data are descriptive, with no statistical comparisons performed for these outcomes between groups. The crude numbers are shown in Table 13. Patients in both groups had reductions in the use of concomitant medications, particularly in both chronic and acute use of IVIG and PLEX.

Table 13: Change in Medications Used Before Screening and at the End of the Study — REGAIN

Medication	REGAIN — ECU-MG-301			
	Eculizumab N = 62		Placebo N = 63	
	Before Screening n (%)	End of Study n (%)	Before Screening n (%)	End of Study n (%)
Cholinesterase inhibitors	62 (100.0)	57 (91.9)	61 (96.8)	52 (82.5)
Prednisone	58 (93.5)	45 (72.6)	62 (98.4)	49 (77.8)
IST other than prednisone	61 (98.4)	55 (88.7)	63 (100)	52 (82.5)
Acute PLEX	29 (46.8)	3 (4.8)	25 (39.7)	4 (6.3)
Chronic PLEX	4 (6.5)	0 (0.0)	10 (15.9)	0 (0.0)
IVIG therapy (acute)	42 (67.7)	4 (6.5)	37 (58.7)	6 (9.5)

Medication	REGAIN — ECU-MG-301			
	Eculizumab N = 62		Placebo N = 63	
	Before Screening n (%)	End of Study n (%)	Before Screening n (%)	End of Study n (%)
IVIG therapy (chronic)	18 (29.0)	1 (1.6)	17 (27.0)	0 (0.0)

IST = immunosuppressive therapy; IVIG = intravenous immunoglobulin; PLEX = plasma exchange.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Quality of Life

Myasthenia Gravis Quality of Life 15-Item Scale

When assessing the worst-rank change from baseline, patients in the eculizumab group had a lower worst-rank score (LS mean 55.5; 95% CI, 46.43 to 64.47) when compared to placebo patients (LS mean 69.7; 95% CI, 60.79 to 78.66) (Table 12). The difference in LS means was –14.3 (95% CI, –26.98 to –1.56) The difference achieved statistical significance (P = 0.0281).

The LS mean (SEM) change from baseline to week 26 in MG-QoL15 total score using the ANCOVA sensitivity analysis was –6.0 (1.49) for the placebo arm and –11.3 (1.50) for the eculizumab arm (P = 0.0152) (Appendix 3). Using the pre-specified sensitivity analysis based on a repeated-measures model, the LS mean (SEM) was –5.4 (1.49) for the placebo arm and –12.6 (1.52) for the eculizumab arm (P = 0.001).

Quality of Life in Neurological Disorders Fatigue Scale

When assessing the Neuro-QoL Fatigue scale in patients who completed 26 weeks without rescue therapy, the mean (SD) change from baseline to week 26 in Neuro-QoL Fatigue total score was greater in patients who received eculizumab (–18.2 [19.60]) than in patients who received placebo (–9.1 [14.58]). The worst-rank change from baseline to week 26,was lower in the eculizumab arm (LS mean 53.5; 95% CI, 44.68 to 62.28) compared to the placebo arm (LS mean 68.7; 95% CI, 59.92 to 77.51); the difference in LS means reached statistical significance (–15.2; 95%CI, –27.68 to –2.79; P = 0.0168).

The LS mean (SEM) change in Neuro-QoL Fatigue total score from baseline to week 26 using the ANCOVA sensitivity analysis was –15.3 (2.22) for the eculizumab arm and –8.3 (2.20) for the placebo arm (P = 0.0254).

European Quality of Life Health 5-Dimensions Questionnaire

For patients who completed 26 weeks without rescue therapy, the mean (SD) change from baseline to week 26 in EQ-5D index score was similar in patients who received eculizumab when compared to those who received placebo (P = 0.982) (Table 12). When assessing the worst-rank change from baseline, both groups ranked similar, with ranked scores LS means (95%CI) of 63.1 (54.99 to 71.18) in the eculizumab group versus 63.2 (55.19 to 71.24) in the placebo group.

Harms

Only those harms identified in the review protocol are reported below. See Table 14 for detailed harms data.

Adverse Events

The percentage of patients with adverse events was similar between treatment arms (85.5% versus 88.9%, eculizumab versus placebo, respectively; Table 14). In both treatment arms, most adverse events were of mild or moderate severity.

The most commonly reported adverse events (occurring in 10% ore more of patients in either treatment group) were headache, upper respiratory infection, nasopharyngitis, MG, nausea, and diarrhea.

Serious Adverse Events

A total of 18 (28.6%) patients in the placebo arm and nine (14.5%) in the eculizumab arm reported serious adverse events. The most common serious adverse event was MG (five [8.1%] with eculizumab; eight [12.7%] with placebo). Most serious adverse events occurred in only one patient on either group (Table 14).

Withdrawals Due to Adverse Events

Adverse events were the reason for discontinuation in four patients, all of whom were in the eculizumab arm. The events were bacteremia/endocarditis, diverticulitis/intestinal perforation, MG crisis, and prostate cancer.

Mortality

No patients died during the study. One patient, a 73-year-old, white woman in the eculizumab arm, was hospitalized on the day 112 of the study and discontinued study drug on day 126. She was transferred to the hospital ICU on the same day and remained there until her death 90 days later (February 20, 2016).

Notable Harms

Notable harms (those of special interest derived from the protocol of this review) are presented in Table 14. No meningococcal infections were reported during the study. One patient in the eculizumab group developed bacteremia. Infections or infestations occurred in three patients (4.8%) in the eculizumab group and in six patients (9.5%) in the placebo group. The number of patients with low hemoglobin levels at the end of the study was similar between groups.

Table 14: Summary of Harms — Safety Analysis Set (REGAIN)

	Eculizumab N = 62	Placebo N = 63
Patients with ≥ 1 adverse event		
n (%)	53 (85.5)	56 (88.9)
Most common events,[a] n (%)		
Headache	10 (16.1)	12 (19.0)
Upper respiratory tract infection	10 (16.1)	12 (19.0)
Nasopharyngitis	9 (14.5)	10 (15.9)
Myasthenia gravis	6 (9.7)	11 (17.5)
Nausea	8 (12.9)	9 (14.3)
Diarrhea	8 (12.9)	8 (12.7)

	Eculizumab N = 62	Placebo N = 63
Patients with ≥ 1 adverse event		
Back pain	5 (8.1)	6 (9.5)
Dizziness	5 (8.1)	5 (7.9)
Urinary tract infection	4 (6.5)	5 (7.9)
Vomiting	3 (4.8)	5 (7.9)
Contusion	5 (8.1)	2 (3.2)
Insomnia	2 (3.2)	5 (7.9)
Myalgia	5 (8.1)	2 (3.2)
Paresthesia	3 (4.8)	4 (6.3)
Peripheral edema	4 (6.5)	2 (3.2)
Pain in extremity	4 (6.5)	2 (3.2)
Pyrexia	4 (6.5)	2 (3.2)
Chills	1 (1.6)	4 (6.3)
Neck pain	3 (4.8)	2 (3.2)
Oral herpes	5 (8.1)	0 (0.0)
Pruritus	1 (1.6)	4 (6.3)
Abdominal pain	2 (3.2)	2 (3.2)
Arthralgia	1 (1.6)	3 (4.8)
Bronchitis	3 (4.8)	1 (1.6)
Cough	1 (1.6)	3 (4.8)
Epistaxis	3 (4.8)	1 (1.6)
Fall	2 (3.2)	2 (3.2)
Lymphocyte count decreased	1 (1.6)	3 (4.8)
Muscle spasms	3 (4.8)	1 (1.6)
Oropharyngeal pain	1 (1.6)	3 (4.8)
Pneumonia	3 (4.8)	1 (1.6)
Urticaria	1 (1.6)	3 (4.8)
Weight increased	2 (3.2)	2 (3.2)
Acne	1 (1.6)	2 (3.2)
Anemia	3 (4.8)	0 (0.0)
Patients with ≥ 1 serious adverse event		
n (%)	9 (14.5)	18 (28.6)
Patients who stopped treatment due to adverse events		
n (%)	4 (6.5)	0 (0.0)
Bacteremia/endocarditis	1 (1.61)	0 (0.0)
Diverticulitis/intestinal perforation	1 (1.61)	0 (0.0)
Myasthenia gravis crisis	1 (1.61)	0 (0.0)
Prostate cancer	1 (1.61)	0 (0.0)

	Eculizumab N = 62	Placebo N = 63
Patients with ≥ 1 adverse event		
Deaths		
n (%)	0 (0.0)	0 (0.0)
Notable harms, n of patients (%)		
Infusion reactions	0 (0.0)	2 (3.2)
Bacteremia	1 (1.6)	0 (0.0)
Meningococcal infections	0 (0.0)	0 (0.0)
Low hemoglobin at week 26	16 (28.6)	14 (23.3)

[a] Frequency > 1%.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Critical Appraisal

Internal Validity

The REGAIN study is the only RCT included in this review. The investigators used appropriate randomization methods and a proper concealment of the randomization process using a central randomization scheme under the sponsor's supervision by means of an interactive voice or web response system until the patients were enrolled and assigned to the interventions. Blinding was also adequate, with all patients, investigational personnel, and all sponsor's staff blinded to the patient treatment assignments and blinding maintained throughout the study. The double blind was maintained through the use of identical study drugs kits and labels and an identical placebo. This also provided an adequate blinding assessment of the outcomes by the investigators, clinicians, and patients. Only one patient (in the eculizumab group) was unblinded due to a MG crisis.

Although there were imbalances in the baseline characteristics of patients randomized in REGAIN related to ethnicity, region, MGFA class III, history of thymectomy, and previous chronic PLEX treatment, the differences were unlikely to be clinically important. The clinical experts consulted by CADTH agreed with this interpretation. However, the imbalances that were observed suggest the randomization process may not have been optimal. In the context of an RCT for a rare disease, given the relatively small sample size and number of categories within most of the aforementioned characteristics, imbalances between groups are expected.

Protocol deviations occurred in 62 (49.2%) patients overall (24 [38.1%] patients in the placebo arm and 38 [60.3%] patients in the eculizumab arm). These include both minor deviations from study procedures (e.g., safety reporting, informed consent) and major deviations, such as concomitant medications (three in placebo and six in eculizumab group) and eligibility criteria (one in the eculizumab group). The overall protocol deviations were high and were even higher in the eculizumab arm than in the placebo arm. Both signalled suboptimal trial conduct and therefore lead to concern about data quality.

Fifteen patients who had major protocol deviations were excluded from the PP set, including seven patients from the placebo arm and eight patients from the eculizumab arm. The most common reason for exclusion from the PP set was not having a stable dosage of IST therapy at the time of enrolment and/or having a change in IST status during the study. These deviations were similar between study groups (five patients from the placebo arm and seven patients from the eculizumab arm).

Multiplicity was controlled using a closed testing hierarchical procedure to control for an overall type I error rate. The hierarchy included many of the outcomes pre-specified in the protocol for this review.

Patients who discontinued treatment were accounted for in the analysis of the worst-rank change from baseline; however, the sample size used in this trial can be considered inadequate to allow for the informative use of the worst-rank analytical approach.[23] This can be noted in the differences found on the ANCOVA sensitivity analyses and in the pre-specified responder analyses that measured the proportion of patients with an improvement of at least three points in the MG-ADL total score and the proportion of patients with a reduction of at least five points in QMG total score. The trial failed to demonstrate a statistically significant difference between treatment groups in the primary end point, although there was a difference in the mean change from baseline to week 26 in MG-ADL total score, eculizumab versus placebo: –4.7 (SD 4.3) versus –2.8 (SD 3.1), respectively. The large SD relative to the mean in both groups indicates substantial variation in the data. The normal distribution assumption, required for the analysis of continuous data with mean and SD, may not have been met.

The worst-rank analysis approach was used following consultation with regulatory agencies. This type of analysis enabled patients who needed rescue medication to be included in the efficacy analysis by treating rescue medication use or discontinuation for any reason as a negative outcome. This approach is a conservative method of handling informatively missing data (i.e., data that are not missing at random). In REGAIN, these patients were assigned a rank that represents a "worst-rank score" relative to those who did not have an event that qualified for the worst-rank (e.g., receiving rescue therapy). Twelve patients in the placebo group and 10 patients in the eculizumab group received the worst ranks related to death, MG crisis, received rescue therapy, or discontinued the study. Sensitivity analyses based on the change from baseline in MG-ADL and repeated-measures methods demonstrated a statistically significant difference in favour of eculizumab for this outcome. Therefore, the primary outcome analysis was sensitive to the method of analysis and how administration of rescue therapy or study discontinuation were handled.

The results of the sensitivity analyses for the MG-ADL aligned with the results of the key secondary outcomes, including physician assessment of improvement (QMG total score), and responder analyses for MG-ADL and QMG total score, which showed statistically and clinically significant differences in favour of eculizumab.

The tools used for evaluating outcomes were appropriate and validated (Appendix 4), the processes to carry out outcome measurements were well-described, and the patients were assessed in a blinded fashion. There is low risk of bias due to selection of the reported results.

Subgroup analyses were adequately specified a priori and performed to examine the consistency of the treatment effect observed for the primary and secondary outcomes. The small sample size might be a factor precluding adequate subgroup analyses.

External Validity

The population enrolled in the REGAIN study is generally reflective of the population seen in clinical practice settings who would be expected to be prescribed eculizumab, according the expert panel consulted by CADTH. However, the panel noted some differences and a higher or more complete exposure to medications that could be considered different from what would happen in real-life practice (e.g., more patients in the placebo group had interruptions of the study drug infusion) and how patients were disposed throughout the

study. Patients in REGAIN represent those with an inadequate response to ISTs, with or without chronic PLEX or IVIG. The expert panel indicated that eculizumab would generally be reserved for this patient population (i.e., those who have severe MG, refractory to ISTs, including rituximab and chronic PLEX or IVIG).

Patients with thymoma and recent thymectomy were excluded from REGAIN. This may be rational in terms of designing a RCT of a drug intervention, but, in practice, patients with thymoma are treated with ISTs. The expert panel consulted by CADTH agreed that they would treat patients with thymoma and recent thymectomy with eculizumab; therefore, excluding them from the study reduces the generalizability and applicability of the results.

Eculizumab efficacy was measured mainly in a way and with the tools that efficacy would be measured in clinical practice settings, as stated by the expert panel members. The drug regimen used in REGAIN would be used in practice; dose intensification is unlikely to be used, but the panel noted that patients would be weaned off eculizumab if positive effects are seen and maintained during treatment. This is the approach taken with currently available therapies.

The duration of follow-up in REGAIN was deemed appropriate for seeing efficacy outcomes; the effect appeared to peak between week 12 and week 16, with little additional effect thereafter. However, REGAIN was too short for assessing long-term safety. Longer-term safety data are available from the extension study, ECU-MG-302, which is presented in the Other Relevant Evidence section of this review report.

Indirect Evidence

A supplemental literature search was conducted to address direct and indirect treatment comparisons (ITCs) between eculizumab and other interventions as main comparators used in clinical practice in patients with generalized MG.

One sponsor-submitted systematic literature review was included.[37] This was a systematic literature evaluation (scoping review) to inform the pharmacoeconomic model and to assess the feasibility of performing a full ITC (network meta-analysis [NMA]). Therefore, this study is addressed as supplementary evidence (Appendix 5).

Another systematic review and NMA was found through the literature search. This NMA aims to compare and rank all the immunotherapies, including ISTs or monoclonal antibodies, for MG.[38] However, this review did not provide complete information about patient characteristics for classification or specific information on outcomes; therefore, it was excluded.

Other Relevant Evidence

This section includes submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

Long-Term Extension Study (ECU-MG-302)

ECU-MG-302 was a phase III, open-label extension of REGAIN that enrolled 117 patients from 72 sites across 17 countries. The extension study took place between November 12, 2014, and January 15, 2019. The primary objective was to evaluate the long-term safety of

eculizumab in patients with rgMG. Secondary objectives were to evaluate the long-term efficacy of eculizumab as measured by the improvement or maintenance of the MG-ADL total score, QMG total score, and MGC total score, and to characterize the effect of eculizumab on quality-of-life measures.

Methods

ECU-MG-302 was composed of three phases: a blind induction phase (to preserve blinding in REGAIN), an open-label maintenance phase, and a safety follow-up phase. Randomization from REGAIN (61 patients had received blinded placebo and 56 had received blinded eculizumab) defined the treatment arms in ECU-MG-302.

Populations

Patients were eligible to enter the extension study within two weeks of completing the 26-week study REGAIN. Female patients of child-bearing potential had to have a negative pregnancy test, and all patients were required to practise an effective, reliable, and medically approved contraceptive regimen. Patients were required to be revaccinated against *Neisseria meningitidis* to provide active coverage.

Baseline patient characteristics are presented in Table 15.

Table 15: Summary of Baseline Characteristics — ECU-MG-302 Long-Term Extension Study

Variable	Placebo/Eculizumab (N = 61)	Eculizumab/Eculizumab (N = 56)	Total (N = 117)
Age at first dose in Study ECU-NMO-302 (years), mean (SD)	47.5 (17.85)	47.2 (15.52)	47.4 (16.70)
Female, n (%)	41 (67.2)	38 (67.9)	79 (67.5)
Race, n (%)			
Asian	16 (26.2)	3 (5.4)	19 (16.2)
Black or African-American	2 (3.3)	0	2 (1.7)
White	41 (67.2)	47 (83.9)	88 (75.2)
Multiple	0	1 (1.8)	1 (0.9)
Unknown	0	1 (1.8)	1 (0.9)
Other	2 (3.3)	4 (7.1)	6 (5.1)
Baseline IST use			
Patients with any MG drugs, n (%)	60 (98.4)	55 (98.2)	115 (98.3)
Corticosteroids	48 (78.7)	42 (75.0)	90 (76.9)
Azathioprine	20 (32.8)	19 (33.9)	39 (33.3)
Mycophenolate mofetil	16 (26.2)	15 (26.8)	31 (26.5)
Cyclosporine	8 (13.1)	6 (10.7)	14 (12.0)
Tacrolimus	6 (9.8)	5 (8.9)	11 (9.4)
Methotrexate	3 (4.9)	5 (8.9)	8 (6.8)
Cyclophosphamide	0	0	0

IST = immunosuppressive therapy; MG = myasthenia gravis.

Source: Clinical Study Report for ECU-MG-302.[39]

Interventions

In the blind induction phase of ECU-MG-302, patients who had received eculizumab in REGAIN were treated with eculizumab four vials/1,200 mg on day 1 and week 2 (visits 1 and 3), and placebo four vials/0 mg at weeks 1 and 3 (visits 2 and 4). Patients who had received placebo in REGAIN were treated with eculizumab (three vials/900 mg) plus placebo (one vial/0 mg) on day 1 and weeks 1 through 3 (visits 1 through 4).

In the open-label maintenance phase, all patients were treated with eculizumab four vials/1,200 mg every two weeks starting at visit 5 (week 4) until the end of the study.

Patients who had plasmapheresis (PLEX) as rescue therapy received supplemental eculizumab, two vials/600 mg, administered within one to two hours of the end of plasmapheresis (PLEX).

Patients were permitted to use, adjust, and discontinue ISTs, including corticosteroids and acetylcholinesterase inhibitors, throughout the study (Table 16).

Table 16: Summary of Changes in Immunosuppressant Therapy Status — ECU-MG-302 Long-Term Extension Study

Variable	Placebo/Eculizumab (N = 61)	Eculizumab/Eculizumab (N = 56)	Total (N = 117)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

IST = immunosuppressive therapy; MG = myasthenia gravis.

Source: Clinical Study Report for ECU-MG-302.[39]

Outcomes

The following primary and secondary efficacy end points were assessed in ECU-MG-302:

Primary end point:

- Change from baseline in the MG-ADL total score

Secondary end points:

- Change from baseline in QMG total score

- Proportion of patients with at least a three-point reduction in the MG-ADL total score from baseline and with no rescue therapy
- Proportion of patients with at least a five-point reduction in the QMG total score from baseline and with no rescue therapy
- Change from baseline in the MGC total score
- Change from baseline in Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15)

The safety outcomes assessed in ECU-MG-302 were adverse events, serious adverse events, and mortality.

Statistical Analysis

In ECU-MG-302, the primary efficacy end point (change from baseline in the MG-ADL total score) was assessed using repeated-measures models with effects for ECU-MG-302, baseline MG-ADL total score, and visit. Results for LS mean change from baseline, 95% CIs, and P values were presented. Secondary end points were assessed similarly to the primary end point. Missing data were not imputed for any of the end points.

ECU-MG-302 had an extension FAS and an extension safety set. The extension FAS consisted of all patients who received at least one dose of eculizumab in ECU-MG-302 and had at least one post-study assessment of drug infusion efficacy. The extension safety set consisted of patients who received at least one dose of eculizumab in ECU-MG-302.

Patient Disposition

A total of 117 patients were enrolled in ECU-MG-302 (Table 17). This represents 61 out of 63 (97%) and 56 out of 63 (89%) original patients randomized to the placebo and eculizumab groups from REGAIN. In the placebo/eculizumab arm, 27.9% of patients discontinued, compared to 23.3% in the eculizumab/eculizumab arm. The most common reason for discontinuation was “withdrawal by patient” and adverse events, which occurred more frequently in the placebo/eculizumab arm.

Table 17: Patient Disposition — ECU-MG-302 Long-Term Extension Study

	Placebo/Eculizumab N (%)	Eculizumab/Eculizumab N (%)	Total N (%)
Enrolled	61 (100.0)	56 (100.0)	117 (100.0)
Treated	61 (100.0)	56 (100.0)	117 (100.0)
Completed	44 (72.1)	43 (76.8)	87 (74.4)
Discontinued	17 (27.9)	13 (23.2)	30 (25.6)
Adverse event	5 (8.2)	2 (3.6)	7 (6.0)
Death	1 (1.6)	2 (3.6)	3 (2.6)
Physician decision	3 (4.9)	3 (5.4)	6 (5.1)
Withdrawal by patient	8 (13.1)	5 (8.9)	13 (11.1)
Other	0	1 (1.8)	1 (0.9)
Continued to receive eculizumab	40 (65.6)	34 (60.7)	74 (63.2)

Source: Clinical Study Report for ECU-MG-302.[39]

Exposure to Study Treatments

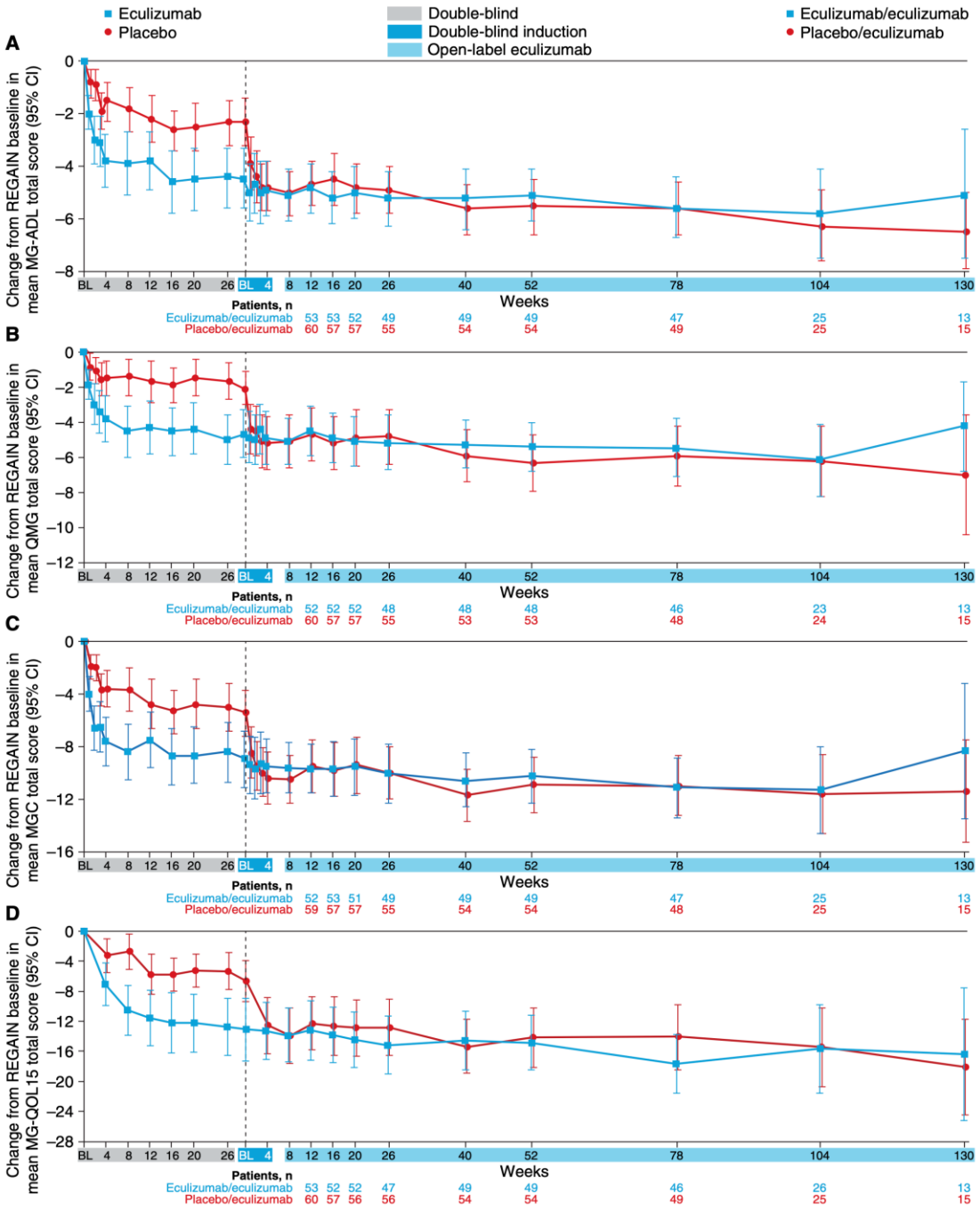
In ECU-MG-302, patients in the placebo/eculizumab arm had a mean study duration of 848 days, while patients in the eculizumab/eculizumab arm had a mean study duration of 894.6 days. The mean number of infusions per patient were 61.7 and 65.3 for the placebo/eculizumab arm and eculizumab/eculizumab arm, respectively. Adherence was similar between arms. Full compliance was achieved for 90.2% of patients in the placebo/eculizumab arm and 96.4% of patients in the eculizumab/eculizumab arm.

Efficacy

Efficacy outcomes are reported in Table 18. The primary efficacy end point, the change from ECU-MG-302 baseline to study end in the MG-ADL total score, was –2.7 (95% CI, –3.8 to –1.6) in the placebo/eculizumab arm and –0.0 (95% CI, –1.1 to 1.0) in the eculizumab/eculizumab arm. The proportion of patients in the placebo/eculizumab arm with at least a three-point reduction in MG-ADL total score from ECU-MG-302 baseline to study end was 36.1% (95% CI, 24.2 to 49.4). Results were not reported for the eculizumab/eculizumab arm.

The change from ECU-MG-302 baseline in the QMG total score to study end was –3.1 (95% CI, –4.7 to –1.6) in the placebo/eculizumab arm and –0.4 (95% CI, –1.6 to 0.9) in the eculizumab/eculizumab arm. The proportion of patients in the placebo/eculizumab arm with at least a five-point reduction in QMG total score from ECU-MG-302 baseline to study end was 31.1% (95% CI, 19.9 to 44.3).The change from ECU-MG-302 baseline to study end in the MGC total score was –6.4 (95% CI, –7.89 to –4.82; P < 0.0001) in the placebo/eculizumab arm and –0.2 (95% CI, –2.77 to 2.47; P = 0.9066) in the eculizumab/eculizumab arm. The change from ECU-MG-302 baseline to study end in the MG-QoL 15 total score was –7.0 (95% CI, –9.74 to –4.27; P < 0.0001) in the placebo/eculizumab arm and –0.2 (95% CI, –4.12 to 3.68; P = 0.9097) in the eculizumab/eculizumab arm. These effects estimates are presented in Figure 5.

Figure 5: Change From REGAIN Baseline to Week 130 in the Long-Term Extension Study



BL = baseline; CI = confidence interval; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite scale; MG-QoL15 = Myasthenia Gravis Quality of Life 15; QMG = Quantitative Myasthenia Gravis score.

Note: Change from REGAIN baseline to week 130 in the open-label extension study in MG-ADL (A), QMG (B), MGC (C), and MGQOL15 (D) total scores (mean [95% CI]) by treatment arm over time (FAS). Patient numbers were not the same for each assessment.

Source: Clinical Study Report for ECU-MG-302.[39]

A subset of patients with a recent history of IVIG use before study entry (received IVIG at least four times in one year, with at least one IVIG treatment cycle during the six months before the first REGAIN study dose) showed similar clinical improvements at week 52 of the extension study based on descriptive results for MG-ADL, QMG, MGC, and MG-QoL15. Statistical analyses were not performed (Table 19).

Table 18: Efficacy Outcomes — ECU-MG-302 Long-Term Extension Study

	ECU-MG-302	
	Placebo/Eculizumab (N = 61)	Eculizumab/Eculizumab (N = 56)
Activities of daily living		
MG-ADL total score		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Disease severity		
QMG total score		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
MGC total score		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	ECU-MG-302	
	Placebo/Eculizumab (N = 61)	Eculizumab/Eculizumab (N = 56)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Health-related quality of life		
MG-QoL 15 total score		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CI = confidence interval; NR = not reported; MG-ADL = Myasthenia Gravis Activities of Daily Living score; MGC = Myasthenia Gravis Composite score; MG-QoL 15 = Myasthenia Gravis Quality of Life 15-item score; QMG = Quantitative Myasthenia Gravis score; SD = standard deviation.

[a] 95% CI was obtained using simple Student t-test of the change from ECU-MG-301 baseline for each treatment group at each visit.

[b] 95% CI was obtained using simple Student t-test of the change from ECU-MG-302 baseline for each treatment group at each visit.

[c] P value from a restricted maximum likelihood (REML)–based repeated-measures analysis of change from baseline, testing whether the LS mean equals 0. The model included terms of visit and baseline value.

Source: Clinical Study Report for ECU-MG-302.[39]

Table 19: Subset of Patients Who Previously Used Chronic IVIG — Extension Study Data

	ECU-MG-302	
	Placebo/Eculizumab (N = 9)	Eculizumab/Eculizumab (N = 9)
Activities of daily living		
MG-ADL total score		
N	8	7
Change from baseline MG-ADL total score at OLE week 52, mean (95% CI)[a]	−5.9 (−9.5 to −2.3)	−4.7 (−7.2 to −2.2)
Disease severity		
QMG total score		
N	7	7
Change from baseline QMG total score at OLE week 52, mean (95% CI)[a]	−7.7 (−11.1 to −4.3)	−6.3 (−9.1 to −3.5)
MGC total score		
N	8	7
Change from baseline MGC total score at OLE week 52, mean (95% CI)[a]	−9.0 (−17.5 to −0.5)	−11.3 (−16.2 to −6.3)
Health-related quality of life		
MG-QoL15 total score		
N	8	7

	ECU-MG-302	
	Placebo/Eculizumab (N = 9)	Eculizumab/Eculizumab (N = 9)
Change from baseline MG-QoL 15 total score at OLE week 52, mean (95% CI)[a]	−16.5 (−27.8 to −5.2)	−14.7 (−23.3 to −6.1)

CI = confidence interval; MG-ADL = Myasthenia Gravis Activities of Daily Living score; MGC = Myasthenia Gravis Composite score; MG-QoL 15 = Myasthenia Gravis Quality of Life 15-item scale; OLE = open-label extension; QMG = Quantitative Myasthenia Gravis score.

Note: Subset refers to patients receiving IVIG before REGAIN at least four times in 1 year, with at least one IVIG treatment administered within 6 months before the first dose of REGAIN study drug.

[a] LOCF for one patient who discontinued before REGAIN week 26.

Source: Jacob et al. (2020).[40]

Harms

A summary of harms data is presented in Table 20. Adverse events occurred in almost all patients, [redacted]. The most common adverse events were headache, nasopharyngitis, diarrhea, and worsening of MG. [redacted]. There were three deaths in the extension trial, one in the placebo/eculizumab arm, and two in the eculizumab/eculizumab arm. In all deaths, the sponsor and investigator considered the event to be unrelated to eculizumab.

One patient in the eculizumab/eculizumab arm experienced an infection with meningococcal meningitis on January 23, 2018, despite having been vaccinated before the study (July 24, 2015), and revaccinated on November 17, 2016. The event was considered resolved on January 31, 2018, and the patient was discharged from the hospital.

Table 20: Summary of Harms — ECU-MG-302 Long-Term Extension Study

	ECU-MG-302		
	Placebo/Eculizumab (N = 61)	Eculizumab/Eculizumab (N = 56)	Total (N = 117)
Patients with ≥ 1 adverse event			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

	ECU-MG-302		
	Placebo/Eculizumab (N = 61)	Eculizumab/Eculizumab (N = 56)	Total (N = 117)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

NR = not reported.

[a] Frequency ≥ 10%.

[b] Frequency ≥ 2 patients.

Source: Clinical Study Report for ECU-MG-302.[39]

Critical Appraisal

ECU-MG-302 was limited by its open-label and noncomparative design. The population enrolled largely reflects those from REGAIN; all 61 patients from the placebo group who completed REGAIN were enrolled in the extension study, and all but one person from the original eculizumab group continued into the extension study. The blinded induction phase of ECU-MG-302 was useful in maintaining blinding status of REGAIN. Missing data were not imputed in the extension study. Efficacy analysis for the proportion of patients with at least a three-point reduction in MG-ADL total score and the analysis for proportion of patients with at least a three-point reduction in QMG total score were only available for the

placebo/eculizumab arm. Results were not reported for the eculizumab/eculizumab arm, as specified in the statistical analysis plan for ECU-MG-302. It is unclear why the eculizumab/eculizumab arm was not assessed. The absence of this data reduces the ability the interpret the results.

Patients were permitted to use, adjust, and discontinue ISTs, including corticosteroids and acetylcholinesterase inhibitors, throughout the extension study. [redacted]. The effectiveness of eculizumab over the extension period may be difficult to interpret, given the impact of IST use.

Summary of the Extension Study ECU-MG-302

ECU-MG-302 was a long-term extension study that assessed the safety and efficacy of eculizumab in 117 patients who had completed the 26-week REGAIN study. The effect as measured by MG-ADL, QMG, MGC, and MG-QoL 15 appeared to be maintained in the open-label extension phase in the eculizumab/eculizumab group from 26 weeks onward to 78 weeks. However, after 78 weeks to study end (at 130 weeks), more than half of the patients had dropped out of the study.

For those patients who were on the placebo/eculizumab group, there was a statistically significant improvement when the patients shifted from placebo to active treatment, as measured by all of the four outcome measures from 26 weeks to 78 weeks, and this trend continued. However, after 78 weeks to study end, more than half the patients dropped out of the study. The magnitude of effect for the placebo/eculizumab group was similar to that in the eculizumab group in the primary trial.

As in REGAIN, most patients were receiving concomitant treatment at the start of the extension study (77% were taking a corticosteroid and approximately 88% were taking one or more ISTs). Concomitant treatments could be modified, and a decrease of the daily dose of at least one IST was observed in more than 63% of patients, with the most common reason for change being improvement in MG symptoms. It is unknown whether the potential IST-sparing effect is maintained with longer exposure than in the extension study.

The frequency and types of adverse events appeared similar to those in the 26-week REGAIN study. Despite the more than four years of follow-up, several factors make it difficult to interpret the results and draw conclusions on the long-term safety of eculizumab for gMG from these data: the percentage of patients who prematurely discontinued, adjustments to background therapies, and the lack of a comparator group.

Other Evidence: Phase II Pilot Study (Howard et al. [2013])

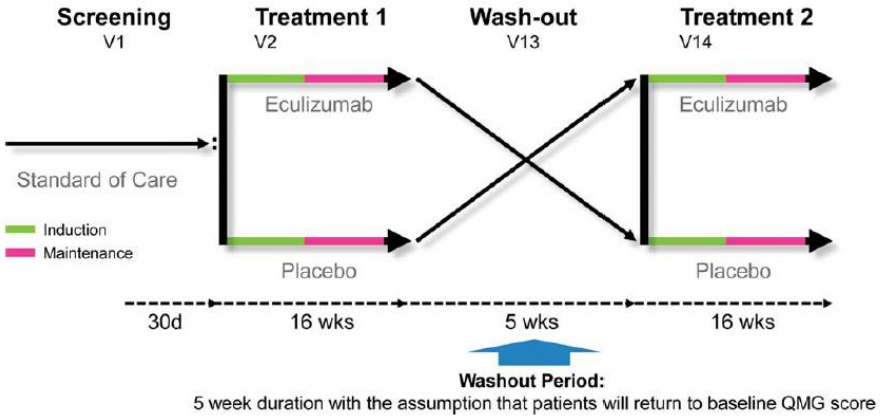
One phase II pilot study of eculizumab in patients with rgMG was identified in the literature.[36] Given the limited body of evidence for the clinical question of this review, this phase II study was described in brief, as it may provide further information on safety and efficacy outcomes.

Methods

The phase II pilot study was a randomized, double-blind, placebo-controlled, crossover trial involving 14 patients with severe rgMG. It was designed to study the efficacy and safety of treatment with eculizumab. Patients were recruited across 24 sites in the US, Canada, and the UK.

After a screening period of two to four weeks, patients were randomized in a 1:1 ratio to receive treatment with eculizumab or placebo for 16 weeks, followed by a five-week washout period, and then crossed over to receive the opposite treatment for an additional 16 weeks (Figure 6).

Figure 6: Pilot Study Design



QMG = Quantitative Myasthenia Gravis score; v = visit; wk = week.

Reprinted from Muscle Nerve, Vol 48 (1), Howard et al., A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis. Pages 76-84, Copyright 2013, with permission from Wiley.[36]

Population

Patients aged 18 to 80 years with a diagnosis of AChR-antibody–positive gMG with persistent, moderate-to-severe muscle weakness despite treatment with at least two immunosuppressive agents (including prednisone) for at least one year were eligible for inclusion in the pilot study. Patients were excluded if they had purely ocular muscle MG, severe weakness predominantly affecting oropharyngeal or respiratory muscles, or myasthenic crisis at the time of enrolment. Patients who had known disorders of complement, previous meningococcal disease, previous splenectomy, or history of thymoma were excluded.

Patients were required to be taking a constant dose of their treatment medications (if applicable) before study entry. All patients were required to be vaccinated against *Neisseria meningitidis* at least 14 days before receiving the first dose of study medication.

Interventions

Treatments with eculizumab and placebo were divided into an induction and maintenance phase.

- induction phase: 600 mg eculizumab or a matching placebo infused intravenously over approximately 35 minutes weekly for four weeks, followed by a fifth dose of 900 mg or matching placebo one week later
- maintenance phase: 900 mg of eculizumab or matching placebo infused intravenously over approximately 35 minutes every two weeks for an additional six doses (12 weeks)

Outcomes

The primary end points of the pilot study were the frequency of adverse events and the percentage of patients with a three-point reduction from baseline (responder rate) in QMG total score.

Secondary efficacy end points reported included changes from baseline in QMG total score and MG-ADL score.

Statistical Analysis

A sample size of 24 patients was needed to achieve 82% power to detect a difference of 65% to 20% responder rate between treatment regimens based on the primary efficacy end point (the percentage of patients with a three-point reduction from baseline in the QMG total score). The sample size was calculated using the exact McNemar test with a two-sided significance level of 0.05.

The pilot study included an intention-to-treat population, which consisted of all randomized patients who received any amount of the study drug in treatment period 1 and period 2.

Analysis was performed using the intention-to-treat population. The primary efficacy end point was analyzed using the McNemar test with the assumption of no carry-over and no period effect. The secondary end point — change from baseline in total QMG score — was assessed using repeated-measures analysis of all data in both treatment periods, and in period 1 alone.

Patient Disposition

The study included 14 patients, of which eight were women and six were men. At enrolment, seven patients were treated concomitantly with immunosuppression other than prednisone, seven were treated with prednisone, and 12 were treated with cholinesterase inhibitors. Eleven patients completed the study (78.5%). Three patients terminated the study early; two patients discontinued due to early termination of the trial by the sponsor, and one patient discontinued due to lack of efficacy (MG crisis requiring PLEX intervention) while on placebo during period 2.

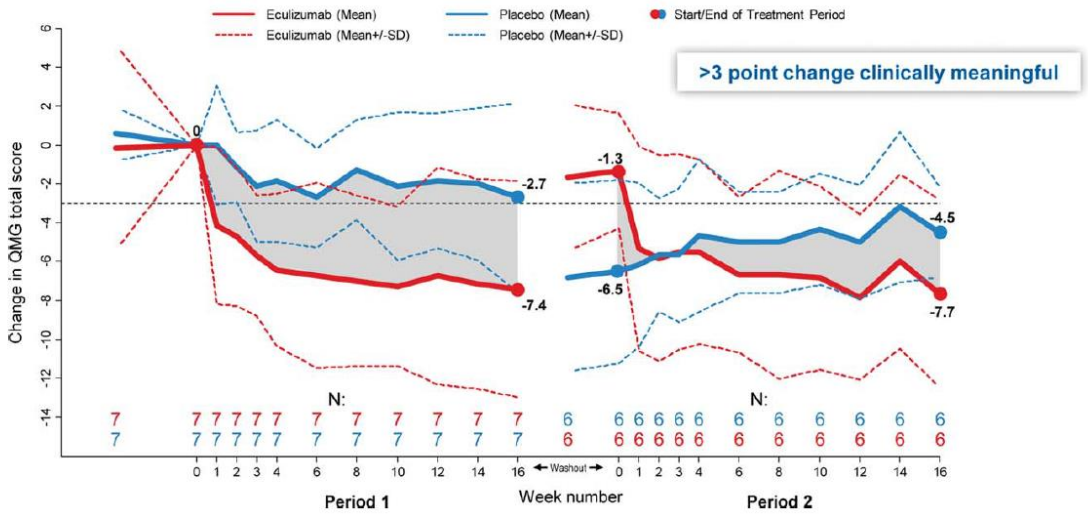
Efficacy

The primary efficacy end point, percentage of patients with a three-point reduction from baseline in the QMG total score, was achieved by 86% of eculizumab-treated patients compared with 57% of placebo-treated patients in period 1 (Figure 7). Patients did not return to baseline during the five-week washout period between treatment periods. Thus, results of period 2 were of less relevance. Using all patient data from both treatment periods 1 and 2, a repeated-measures mixed model demonstrated a difference (P = 0.0577) between eculizumab and placebo groups.

Based on data from both periods, the overall change in mean QMG total score was significantly different between eculizumab and placebo (P = 0.0144). The overall change in mean QMG total score from baseline was significantly different between eculizumab and placebo (P < 0.0001)

At the end of period 1, the difference in the MG-ADL score between eculizumab and placebo was –3.57 (95% CI, –6.97 to –0.17, P = 0.0410). The overall difference in the MG-ADL score based on both periods was –1.58 (95% CI, –4.08 to 0.91, P = 0.1873).

Figure 7: Total QMG Reduction by Treatment — Pilot Study



QMG = Quantitative Myasthenia Gravis score.

Harms

All patients treated with eculizumab had at least one adverse event, compared to 84.6% of patients treated with placebo. In both arms, most adverse events were mild or moderate in severity. Common adverse events were nausea, back pain, nasopharyngitis, and headache. One patient had two serious adverse events — MG exacerbation and MG crisis during the washout period of eculizumab and again during treatment with placebo.

Critical Appraisal

The efficacy analysis of the pilot study was limited by the insufficient length of the washout period (five weeks). A carry-over effect of the previous treatment was observed in both arms, as neither returned to baseline QMG after five weeks. The presence of a carry-over effect violated the assumptions of the McNemar test used in the assessment of the primary efficacy end point. Given the presence of carry-over effects, efficacy results related to period 2 or combined periods 1 and 2 are difficult to interpret. The dosage regimen specified in the pilot study differs from the current dosage regimen specified in the product monograph for eculizumab. This difference in dosage limits the ability to generalize findings of the pilot study to the clinical population that would be treated with the drug. Additionally, based on feedback received from clinical experts consulted for this review, patients with a history of thymoma would be treated in clinic with eculizumab. The exclusion of these patients in the pilot study is another factor that reduces the external validity of the study results.

Discussion

Summary of Available Evidence

The body of evidence covered in this review includes an individual study, the REGAIN trial, with an accompanying long-term, open-label extension study, ECU-MG-302. A phase II, pilot, crossover randomized trial of eculizumab was assessed and described as other relevant evidence.

The REGAIN study was a multinational, double-blind, placebo-controlled, randomized trial evaluating the safety and efficacy of eculizumab in patients with rgMG. Patients were required to be seropositive for AChR antibodies, have a MG-ADL score at baseline of 6 or higher, and a MGFA classification from II to IV. Patients included those who had received two or more ISTs, or at least one IST with IVIG or PLEX at least four times per year for 12 months, without achieving symptom control. The study excluded those patients with a history of thymoma or thymic neoplasms, thymectomy within 12 months before screening, or use of IVIG or PLEX within four weeks before randomization, or rituximab within six months before screening. Patients were randomized (1:1) to either intravenous eculizumab (N = 62) or placebo (N = 63) for 26 weeks, stratified by MGFA classification. During the study, patients could use existing MG therapies and rescue medications. The primary efficacy outcome was the change from baseline to week 26 in MG-ADL total score analyzed by worst-rank ANCOVA. Secondary efficacy end points included changes from baseline in mean QMG, MGC, and MG-QoL15 total scores over time and the proportion of patients achieving clinically meaningful responses to eculizumab, defined as improvements from baseline of at least three points in MG-ADL total score or at least five points in QMG total score.

Study ECU-MG-302 (N = 117) was an open-label extension of the REGAIN study to evaluate the longer-term safety and efficacy of eculizumab in patients who continued treatment or switched from placebo to eculizumab from REGAIN.

A third study, the pilot, phase II, randomized trial, had a crossover design to address frequency of adverse events and proportion of patients with a three-point reduction from baseline in the QMG score and MG-ADL score, including 14 patients with the same eligibility criteria as in the REGAIN study.

Interpretation of Results

Efficacy

For the primary outcome (change in the MG-ADL score), when using worst-rank analysis, the REGAIN study showed no statistically significant difference between eculizumab and placebo groups (LS mean rank-based treatment difference −11.7; 95% CI, −24.3 to 0.96; P = 0.0698). The investigators had decided to use worst-rank score ANCOVA following input from regulators who wanted the analysis to account for the potential influence of rescue medication on efficacy results. Thus, this analysis approach was a conservative one. In the primary analysis, 12 patients in the placebo group and 10 patients in the eculizumab group received the worst ranks: death (of which there were none), MG crisis, rescue therapy, or discontinuation of the study. Sensitivity analyses did demonstrate a statistically significant difference between groups on the MG-ADL; however, the treatment differences were less than two points, the difference that has been reported as clinically important. Therefore,

there is uncertainty as to the benefit of eculizumab compared with placebo for the change from baseline in MG-ADL.

Despite the inconsistent evidence related to change from baseline MG-ADL, other data from REGAIN suggest eculizumab may provide a clinically relevant effect for patients with rgMG. The proportion of patients with at least a three-point reduction in MG-ADL score was 59.7% (37 patients) in the eculizumab group versus 39.7% (25 patients) in the placebo arm, a difference in proportions of 20.0 percentage points (95% CI, 2.8 to 37.2 percentage points; P = 0.0229). The clinical important threshold has been suggested as two points; therefore, the proportion of patients achieving a three-point change is clinically important. On average, five patients need to be treated (number needed to treat) with eculizumab for 26 weeks for one patient to achieve an additional three-point or greater reduction in MG-ADL as compared to placebo.

Disease severity measured using the QMG was a key secondary outcome in REGAIN, for which the results were more robust than the primary analysis, given the more objective assessment criteria and clear separation of effects between groups. The difference between eculizumab and placebo was both statistically and clinically significant for the change from baseline (worst-rank-based treatment difference −16.0; 95% CI, −28.48 to –3.43; P = 0.0129) and the proportion of patients with at least a five-point reduction in QMG score (45.2% in the eculizumab group versus 19.0% in the placebo group; difference in proportions of 26.2 percentage points; 95% CI, 10.4 to 41.8 percentage points; P = 0.0018]). A two- to three-point change on the QMG has been reported as clinically meaningful. The clinical panel indicated that QMG is considered the gold standard outcome for interventional trials in gMG. Based on these results, plus the MG-ADL responder analysis, the data support a benefit of eculizumab versus placebo. Regulatory agencies likewise drew this conclusion to support approval of the gMG indication for eculizumab.

The comparison between eculizumab and placebo for the change in the MGC was not statistically significant, although — as for the MG-ADL — the sensitivity analyses did achieve a statistically significant result. Because the comparison for MGC was not significant, the pre-specified analysis hierarchy was stopped at this level. Thus, the subsequent comparison between groups on the disease-specific health-related quality of life measure, MG-QoL 15, was considered uninterpretable per the analysis plan despite achieving a P value less than 0.05. The between-group differences on the MGC and MG-QoL 15 would have been considered clinically significant if they could have been interpreted as statistically significant.

The small sample size led to some uncertainty, not only in the precision but also in the robustness of effect estimates in the primary outcome. On the other hand, the sensitivity analyses for MG-ADL and the consistently statistically significant differences on disease severity evaluated by the QMG score as well as in the MG-QoL15 scores confirmed the beneficial effect from eculizumab compared to placebo. In particular, the percentage of patients who had achieved a pre-specified response threshold of three points or greater in MG-ADL showed a statistically significant difference (20.0 percentage points; 95% CI, 2.8 to 37.2 percentage points). This measure would be more appropriate in assessing the treatment effect than the mean difference between treatment arms. The selected individual patient-level threshold is greater than the two-point threshold. The latter was recognized as the optimal cut-off point in terms of best sensitivity and specificity in indicating clinical important change. The study results presented consistently important differences by using

different thresholds, which can strengthen the certainty in the results on the beneficial effect from eculizumab as compared to placebo.

So, why was there inconsistency in demonstrating benefit across outcome measures? Two possible reasons are the following. Patients enrolled in REGAIN were those with rgMG who had had an inadequate response to ISTs and chronic PLEX or IVIG. Most patients received eculizumab as add-on to concomitant therapies for MG; demonstrating added effect in this population may be difficult. As well, the placebo response on the MG-ADL (and MGC) was higher than expected. The sample size calculations assumed a mean change from baseline on the MG-ADL of –1.5 points in the placebo group. The observed value in the trial at week 26 was –2.8 points. Similarly, as noted previously, the percentage of patients with at least a three-point reduction in MG-ADL score was almost 40% in the placebo group (versus 60% in the eculizumab group). Based on the worst-rank ANCOVA approach, patients who discontinued the study were considered as having a negative outcome. Three patients in the eculizumab group discontinued because they did not meet the pre-specified criteria for MG clinical deterioration and did not receive rescue therapy, but they met predefined protocol criteria for MG significant clinical improvement before discontinuation.

MG exacerbations were reported in six (10%) patients in the eculizumab group and 15 (24%) in the placebo group. Six (10%) patients in the eculizumab group and 12 (19%) in the placebo group required rescue therapy. However, these data were descriptive and, therefore, no conclusions could be drawn for the comparative effects of eculizumab on these outcomes.

The longer-term extension study indicates that the effects of eculizumab are generally maintained, although the aforementioned limitations of this study preclude making definitive conclusions regarding the long-term efficacy of eculizumab in rgMG.

Harms

Overall, data from the REGAIN study, the long-term extension study (ECU-MG-302), and the pilot phase II study (with the three studies providing a total of 139 patients observed for more than three years) indicate that the safety profile of eculizumab in gMG is similar to what has been reported for the other indications the drug is approved for and in the product monograph.

Patients in the eculizumab arm had a similar frequency of serious adverse events as those in the placebo arm. The most common general adverse events in the REGAIN study in both groups were headache and upper respiratory tract infection (16% for both events in the eculizumab group and 19% for both in the placebo group). No deaths or cases of meningococcal infection occurred during the study. In the long-term study, the safety profile of eculizumab was consistent with REGAIN; no cases of meningococcal infection were reported during the interim analysis period. The most common adverse events were headache and nasopharyngitis, which were experienced by 37.6% and 31.6% of patients, respectively. The most common serious adverse event was MG worsening, which occurred in 12.8% of patients. Three patients died during the long-term study, but their deaths were deemed unrelated to the study drug or MG.

Conclusions

The single reviewed RCT, REGAIN, suggested that eculizumab at the maintenance dose of 1,200 mg IV every two weeks improves activities of daily living (measured using the change from baseline in the MG-ADL score) versus placebo after 26 weeks of treatment. The treatment effect for this outcome, however, is uncertain because the results were sensitive to the statistical methods used for the analysis. Eculizumab did demonstrate benefit, as observed by a greater proportion of patients achieving improvement of at least three points in the MG-ADL score with the drug than with placebo. This was also seen in other disease-severity measures such as the QMG score. The effects of eculizumab on health-related quality of life and exacerbations of MG are uncertain. The sustainability of the treatment effect may be maintained beyond 26-week period, yet the longer-term data are not robust.

The safety profile from the current evidence appears similar to that reported in the product monograph for eculizumab. However, because of the relatively small sample size and limited long-term evaluation for rare and serious adverse events, there is uncertainty about the balance between the longer-term benefit and harms of eculizumab in the gMG patient population. The study excluded patients with history of thymoma or thymectomy, patients who were pregnant or breastfeeding, or patients with MGFA class V. The generalizability of the findings to those patients are therefore limited.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–) Embase (1974–) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	Apr 30, 2020
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY

Line #	Search Strategy
1	(Soliris* or eculizumab* or solirus or Elizaria or HSDB 8394 or H5G11* or H5G1 1* or 5G11* or 5G1 1* or A3ULP0F556).ti,ab,kf,ot,hw,rn,nm.
2	exp Myasthenia gravis/ or exp Myasthenic Syndromes, Congenital/
3	(myastheni* or goldflam* or MuSK MG or Eaton-Lambert or Lambert-Eaton).ti,ab,kf.
4	2 or 3
5	1 and 4

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
6	5 use medall
7	*eculizumab/
8	(Soliris* or eculizumab* or solirus or Elizaria or HSDB 8394 or H5G11* or H5G1 1* or 5G11* or 5G1 1*).ti,ab,kw,dq.
9	7 or 8
10	exp Myasthenia gravis/
11	(myastheni* or goldflam* or MuSK MG or Eaton-Lambert or Lambert-Eaton).ti,ab,kw,dq.
12	10 or 11
13	9 and 12
14	13 use oemezd
15	14 not (conference review or conference abstract).pt.
16	6 or 15
17	remove duplicates from 16

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated before the completion of stakeholder feedback period. Search terms: (Soliris* OR eculizumab* OR h5G1.1) AND (myasthenia gravis)	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Search dates:	April 24-27, 2020
Keywords:	Soliris* OR eculizumab* OR h5G1.1
Limits:	None
Updated:	Search updated before the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free).

Appendix 2: Excluded Studies

Table 21: Excluded Studies

Reference	Reason for Exclusion
Vissing J, O'Brien F, Wang JJ, Howard JF, Jr. Correlation between myasthenia gravis-activities of daily living (MG-ADL) and quantitative myasthenia gravis (QMG) assessments of anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis in the phase 3 regain study. Muscle Nerve. 2018;58(2):E21–E22.	Conference abstract
Wang L, Huan X, Xi JY, et al. Immunosuppressive and monoclonal antibody treatment for myasthenia gravis: a network meta-analysis. CNS Neurosci Ther. 2019;25(5):647–658.	Systematic review / NMA

Appendix 3: Detailed Outcome Data

Table 22: Sensitivity Analyses — REGAIN

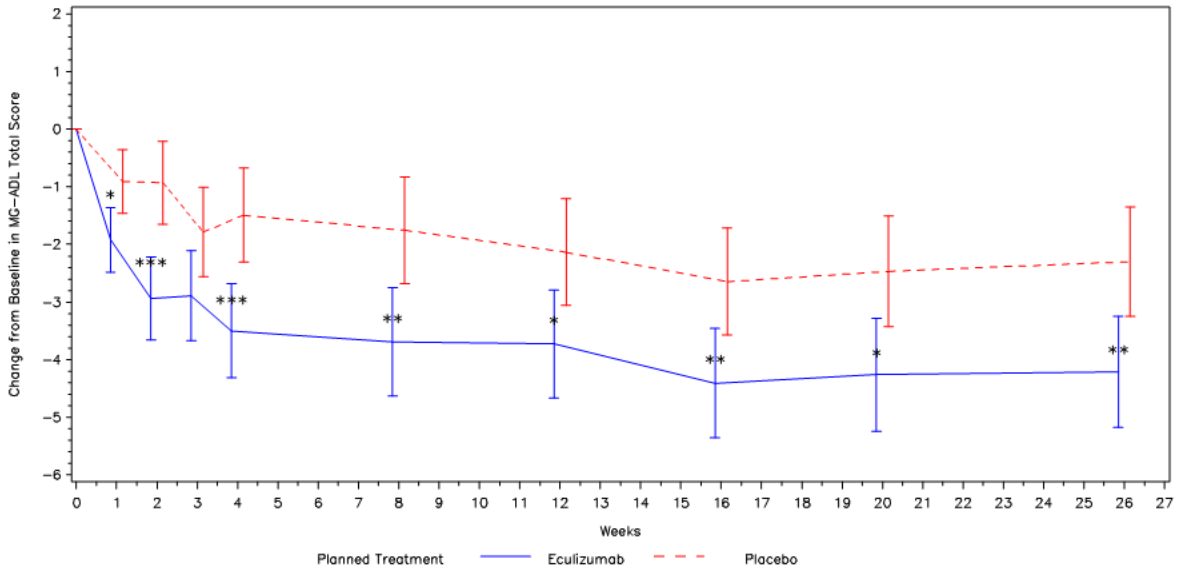
	REGAIN STUDY (ECU-MG-301)	
	Eculizumab N = 62	Placebo N = 63
Activities of daily living		
MG-ADL score, ANCOVA sensitivity analysis — FAS		
Baseline MG-ADL total score, mean (SD)	10.5 (3.06)	9.9 (2.58)
Week 26 MG-ADL total score (LOCF), mean (SD)	6.4 (4.76)	7.4 (3.50)
Change from baseline to week 26 in MG-ADL total score, mean (SD)	–4.1 (4.48)	–2.4 (3.32)
Change from baseline, LS mean (95% CI)[a]	–4.0 (–4.96 to –3.04)	–2.6 (–3.52 to –1.63)
Difference in LS means (95% CI)	–1.4 (–2.77 to –0.07)	
P value	0.0390	
Disease severity		
QMG score, ANCOVA sensitivity analysis — FAS		
Baseline QMG total score, mean (SD)	17.3 (5.10)	16.9 (5.56)
Week 26 QMG total score (LOCF), mean (SD)	13.1 (6.54)	15.3 (6.17)
Change from baseline to week 26 in QMG total score, mean (SD)	–4.2 (5.35)	–1.6 (4.21)
Change from baseline, LS mean (95% CI)[a]	–4.2 (–5.37 to –3.00)	–1.6 (–2.82 to –0.47)
Difference in LS means (95% CI)	–2.5 (–4.21 to –0.87)	
P value	0.0032	
MGC score, ANCOVA sensitivity analysis — FAS		
Baseline MGC total score, mean (SD)	20.4 (6.13)	18.9 (5.95)
Week 26 MGC total score (LOCF), mean (SD)	12.4 (9.00)	14.2 (7.79)
Change from baseline to week 26 in MGC total score, mean (SD)	–8.0 (8.70)	–4.7 (6.65)
Change from baseline, LS mean (95% CI)[a]	–7.8 (–9.70 to –5.93)	–5.0 (–6.90 to –3.17)
Difference in LS means (95% CI)	–2.8 (–5.43 to –0.12)	
P value	0.0406	
Quality of life		
MG-QoL15 score, ANCOVA sensitivity analysis — FAS		
Baseline MG-QoL15 total score, mean (SD)	33.6 (12.21)	30.7 (12.72)
Week 26 MG-QoL15 total score (LOCF), mean (SD)	22.2 (16.88)	25.0 (13.66)
Change from baseline to week 26 in MG-QoL15 total score, mean (SD)	–11.5 (14.09)	–5.7 (9.54)
Change from baseline, LS mean (95% CI)[a]	–11.3 (–14.24 to –8.28)	–6.0 (–8.99 to –3.08)
Difference in LS means (95% CI)	–5.2 (–9.43 to –1.03)	
P value	0.0152	

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living score; MG-QoL 15 = Myasthenia Gravis Quality of Life 15-item scale; QMG = Quantitative Myasthenia Gravis score; SD = standard deviation.

[a] LS means are from ANCOVA model.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Figure 8: Change from Baseline in MG-ADL Total Score (LS Mean and 95% CI) by Treatment Arm Over Time from Baseline to Week 26 Using a Repeated-Measures Model — Full Analysis Set



CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living score.

The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, and the MG-ADL total score at baseline. Missing MG-ADL total score values were not imputed.

* P < 0.05. All P values two-sided.

** P < 0.01.

*** P < 0.001.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Table 23: Summary of Mean Change from Baseline in MG-ADL Total Score at Week 26 by Treatment Group and Randomization Stratification Group — Full Analysis Set

		Eculizumab N = 62			Placebo N = 63		
	Statistic	Baseline	Week 26	Change From Baseline	Baseline	Week 26	Change From Baseline
MGFA class IIa or IIIa	N	27	27	27	32	32	32
	Mean (SD)	9.7 (2.73)	6.4 (4.53)	3.3 (4.06)	9.2 (2.03)	7.3 (3.56)	–2.0 (3.21)
MGFA class IVa	N	4	4	4	2	2	2
	Mean (SD)	12.5 (2.08)	6.8 (0.96)	–5.8 (2.99)	10.0 (1.41)	10.5 (0.71)	0.5 (0.71)
MGFA class IIb or IIIb	N	23	23	23	23	23	23
	Mean (SD)	10.0 (2.87)	4.8 (4.10)	–5.1 (4.42)	10.3 (2.80)	6.9 (3.19)	–3.3 (3.41)
MGFA class IVb	N	3	3	3	3	3	3
	Mean (SD)	14.7 (4.16)	7.3 (7.77)	–7.3 (6.66)	13.3 (4.51)	13.3 (3.79)	0.0 (2.00)

MGFA = Myasthenia Gravis Foundation of America; SD = standard deviation.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

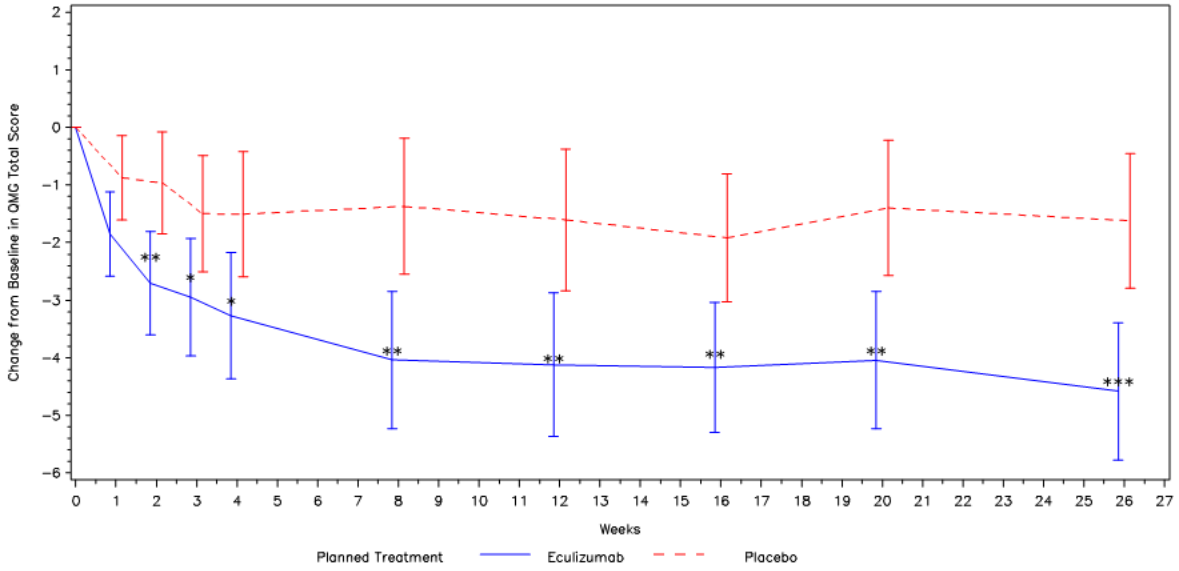
Table 24: Change from Baseline in Myasthenia Gravis Foundation of America Post-Intervention Status at Week 26 and Other Study Visits by Treatment Arm (CMH Test Analysis) – Full Analysis Set

	Eculizumab (N = 62)			Placebo (N = 63)			
Visit	Improved n/N (%)	Unchanged n/N (%)	Worse n/N (%)	Improved n/N (%)	Unchanged n/N (%)	Worse n/N (%)	P value
Week 4	32/60 (53.3)	27/60 (45.0)	1/60(1.7)	15/62 (24.2)	42/62 (67.7)	5/62 (8.1)	0.0006
Week 12	30/56 (53.6)	25/56 (44.6)	1/56 (1.8)	22/61 (36.1)	35/61 (57.4)	4/61 (6.6)	0.0361
Week 26	35/57 (61.4)	21/57 (36.8)	1/57 (1.8)	25/60 (41.7)	30/60 (50.0)	5/60 (8.3)	0.0178

CMH = Cochran–Mantel–Haenszel; MGFA = Myasthenia Gravis Foundation of America.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Figure 9: Change from Baseline to Week 26 in QMG Total Score (LS Mean and 95% CI) by Treatment Arm Using a Repeated-Measures Model — Full Analysis Set



CI = confidence interval; LS = least squares; QMG = Quantitative Myasthenia Gravis score.

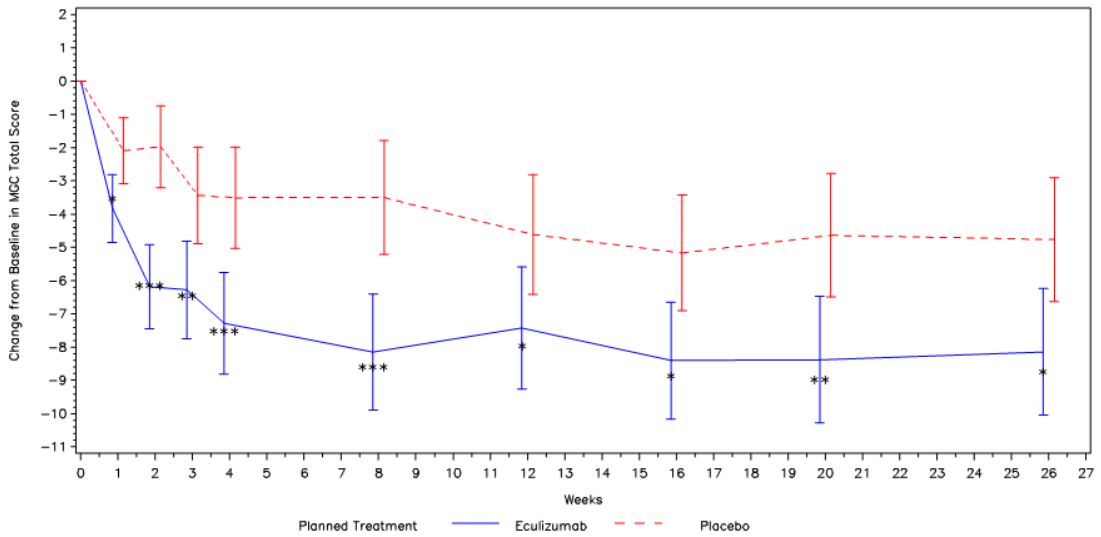
* P < 0.05. All P values two-sided.

** P < 0.01.

*** P < 0.001.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Figure 10: Change from Baseline to Week 26 in MGC Total Score (LS Mean and 95% CI) by Treatment Arm Using a Repeated-Measures Model — Full Analysis Set



CI = confidence interval; LS = least squares; MGC = Myasthenia Gravis Composite score.

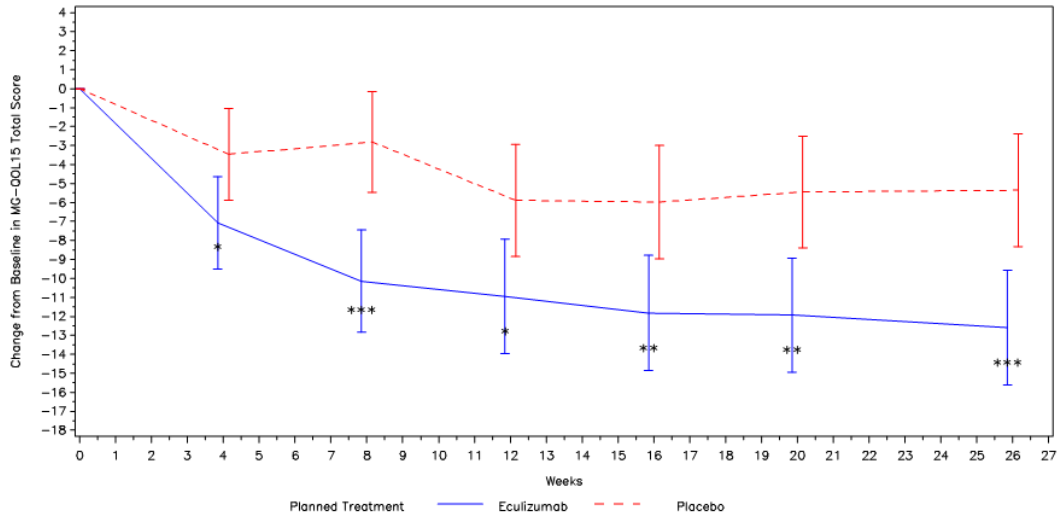
* P < 0.05. All P values two-sided.

** P < 0.01.

*** P < 0.001.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Figure 11: Change from Baseline to Week 26 in MG-QoL15 Total Score (LS Mean and 95% CI) by Treatment Arm Using a Repeated-Measures Model – Full Analysis Set



CI = confidence interval; LS = least squares; MG-QoL15 = Myasthenia Gravis Quality of Life 15-item scale.

* P < 0.05. All P values two-sided.

** P < 0.01.

*** P < 0.001.

Source: Clinical Study Report for ECU-MG-301 (REGAIN).[7]

Appendix 4: Additional Sponsor-Submitted Systematic Literature Review

Objectives

The aim of the sponsor-submitted systematic literature review (SLR) was to identify all relevant scientific evidence needed to inform the pharmacoeconomic model regarding relevant comparators of eculizumab for maintenance therapy of AChR-antibody–positive rgMG in Canada (Table 25). The objective of this review was to determine:

- whether any treatments other than eculizumab have available evidence supporting efficacy in the population of interest
- the quality of evidence supporting the comparators relative to the quality of evidence supporting eculizumab
- the feasibility of conducting an indirect comparison (i.e., through an ITC) of eculizumab with any comparators to provide information on the relative efficacy of the treatment options
- the relative efficacy of any comparators versus eculizumab in the population of interest.

The research question of the review was: What is the comparative efficacy of eculizumab versus alternative treatments for the maintenance treatment of AChR-antibody–positive rgMG?

Table 25: Study Selection Criteria and Methods for the Systematic Literature Search (Sponsor-Submitted)

	Sponsor-Submitted SLR
Population	Adult ≥ 18 years AChR-antibody–positive Refractory MG
Intervention	Eculizumab
Comparators	Rituximab Intravenous immunoglobulin Plasmapheresis Cyclophosphamide
Outcome	NA — the SLR assessed the outcomes included in REGAIN and compared feasibility of including these in a future ITC
Study design	Placebo- or active-controlled RCTs
Publication characteristics	No restrictions on language, country, or others; excluded animal studies, post hoc analyses, subgroup analyses, drugs not applicable
Exclusion criteria	Patients undergoing exacerbation, pediatric patients, MuSK antibody–positive specific, and nonrefractory specific patients
Databases searched	PubMed, Embase, and ClinicalTrials.gov
Selection process	No mention of articles screened independently by two or more researchers
Data extraction process	By one reviewer; extracted publication information, study characteristics (e.g., design, country)
Quality assessment	Used elements of NICE-STA guidance for RCTs

ITC = indirect treatment comparison; MG = myasthenia gravis; NA = not applicable; NICE-STA = National Institute for Health and Care Excellence Single Technology Appraisal; RCT = randomized controlled trial; SLR = systematic literature review.

Source: Sponsor-submitted SLR.[37]

Study Selection Methods

The study searched PubMed (completed March 2020) for the review of relevant comparators with the entry terms “myasthenia gravis AND (eculizumab OR eculizumab OR rituximab OR Rituxan) OR (IVIG OR intravenous immune globulin OR intravenous immunoglobulin OR PLEX OR plasmapheresis OR plasma exchange OR cyclophosphamide).” No limits on publication date, country, language, or other limits were applied in the PubMed search in order to ensure that the SLR was as broad as possible and would capture all possible research to which eculizumab could be compared. However, the Embase search was limited to articles with search term(s) in the abstract and the clinicaltrials.gov database to limits of “active, not recruiting” and “completed” to produce records with results. Articles were initially assessed and categorized according to relevance in meeting the eligibility criteria by title. The titles were screened individually, removing obviously irrelevant records such as animal studies, reviews, case reports, and patient populations out of scope. The number of records removed was recorded. After removing the obviously nonapplicable articles, the remaining records were assessed in more detail through a review of the text. Type of study, exacerbation/maintenance, antibody specificity, and patient refractory status were recorded. These articles were assessed in detail to determine the degree to which they met the eligibility criteria. At the end of the selection process, a list of included and excluded studies identified through the searches was provided.

Methods

No pooling of studies was attempted, and no specific efficacy analysis was performed. Rather, the study focused on detecting possible comparators for eculizumab and the appropriateness of comparing these in an NMA.

Data extraction and quality assessment were carried out by one reviewer. Quality checking was undertaken on a sample (25%) of records by a second reviewer. Any discrepancies were resolved by a third reviewer. The list of extracted items included:

- general publication information
- author, title, journal, publication date
- study characteristics
- trial design, study aim, country, time frame, inclusion/exclusion criteria, statistical methods, length of follow-up, number of patients randomized/treated, clinical outcomes
- drug name, dose, dosing regimen
- treatment of an exacerbation or maintenance therapy, antibody specificity, refractory status.

Appraisal of the relevant studies was conducted using the elements suggested in the National Institute for Health and Care Excellence Single Technology Appraisal guidance.

Results

The initial search contained a total of 1,857 articles. The search of the Clinicaltrials.gov database returned an additional 12 records. There were 141 duplicates, which were manually removed. Of the 1,728 unique records remaining, 1,543 were removed during initial title screening, leaving 185 for a detailed screening of the full-text records. Upon full-text screening, 173 studies were excluded because they assessed short-term therapies, the

wrong populations, the wrong intervention, or because results were not available. Twelve studies were included for assessment as follows.

Two studies of eculizumab were identified. Of the 10 remaining studies, seven were placebo-controlled, two were active-controlled (IVIG versus PLEX and Immunoadsorption versus IVIG), and one was a randomized active crossover study, as follows:

- one study of cyclophosphamide versus placebo
- two studies of IVIG versus PLEX
- one study of double-filtration plasmapheresis versus IVIG versus immunoadsorption
- two studies of IVIG versus placebo
- one study of rituximab versus placebo
- two studies of Immune Globulin (human), 10% Caprylate/Chromatography Purified (IGIV-C) versus placebo
- one study of mycophenolate mofetil versus placebo.

The population in the 10 reviewed studies appeared to be similar to the population included in the REGAIN and other eculizumab trials, in that they treated adults with moderate-to-severe rgMG not undergoing an exacerbation and required a positive titre for AChR antibodies. However, the trial populations differed in terms of duration of disease, previous treatment history, average patient age, end points studied, and duration of study. Two studies included patients with MuSK antibody titres, and it was impossible to extract information on the efficacy of the treatments in the subtype of patients with the AChR antibody. Moreover, there was a lack of clear and consistent definition of *refractory* across the studies.

These added to the uncertainty of making a valid ITC to eculizumab, due to the substantial heterogeneity among patient populations.

The outcomes used in the two eculizumab clinical were the change in MG-ADL (primary) or QMG (secondary). Of other included studies, eight of 10 reported these outcomes. There was significant variation in study duration. Specifically, four studies had a study duration between 14 and 42 days, and another four trials had a longer-term duration, similar to that in the eculizumab studies.

In general, risk of bias in the individual studies was deemed low to medium, with issues in the definition of outcomes and unclear reporting in four out of 12 studies.

Critical Appraisal

Overall, 12 studies met the criteria of being a placebo- or active-controlled RCT treating patients with maintenance therapy for AChR-antibody–positive rgMG. These trials differed in terms of new/late onset of disease, antibody status, previous treatment history, patient age, end points, and treatment/dosage duration. As the definition of *refractory* varied across the studies, refractory status could not be used to definitively determine whether the populations were similar enough to that in the two eculizumab trials.

The systematic review was performed with an adequate search strategy, screening, and data extraction. It falls short, however, in its completeness of the evaluation of the evidence (no actual comparison between drugs was made) because its main goal is addressing and exploring comparators. The authors state this from the outset.

To further determine whether an indirect comparison or NMA could be made between eculizumab and the comparators, the study end points of each individual study were also assessed. Of the 10 other gMG studies included, eight reported similar outcomes to the eculizumab trials (MG-ADL, QMG, and MGC). Of the eight studies with relevant outcomes reported, four reported these outcomes at longer-term follow-up time frames (i.e., 16, 52, 24, and 36 weeks from baseline). The four remaining studies assessed IVIG versus PLEX, and rituximab, IGIV-C, or MMF versus placebo. Some of these studies have not yet been published, and, therefore, the clinical and statistical methodology has not been described. As a result, risk of bias, and thus uncertainty, is inherent with these trials.

Conclusions

There was considerable amount of heterogeneity among the 12 identified studies regarding the population of interest, methodology, and dosage, as well as a lack of comparable outcomes and timing of outcome measurements. The conclusion of this SLR was that the available studies do not provide a basis of comparison to evaluate the efficacy of eculizumab (used for its Health Canada–approved indication) relative to any other active comparator through an indirect comparison or NMA.

Appendix 5: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- Myasthenia Gravis Activities of Daily Living scale (MG-ADL)
- Quantitative Myasthenia Gravis (QMG) score
- Myasthenia Gravis Composite (MGC) score
- Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15)
- Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS)
- Quality of Life in Neurological Disorders Fatigue Scale (Neuro-QoL Fatigue)
- European Quality of Life (EuroQol) Health 5-Dimensions (EQ-5D) questionnaire.

Table 26: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome Measure	REGAIN — ECU-MG-301
MG-ADL	Primary
QMG score	Secondary
MGC	Secondary
MG-QoL 15	Secondary
MGFA-PIS	Exploratory (tertiary)
Neuro-QoL Fatigue Scale	Exploratory (tertiary)
EQ-5D	Exploratory (tertiary)

MG-ADL = Myasthenia Gravis Activities of Daily Living scale; QMG = Quantitative Myasthenia Gravis score; MGC = Myasthenia Gravis Composite score; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MG-QoL 15 = Myasthenia Gravis Quality of Life 15-item scale; Neuro-QoL = Quality of Life in Neurological Disorders; EQ-5D = European Quality of Life Health 5-Dimensions questionnaire.

Findings

The validity, reliability, responsiveness, and MID of each outcome measure were summarized and evaluated. Interpretation of the reliability and validity metrics were based on the following criteria:

Inter-rater reliability, kappa statistics (level of agreement):[41]

- < 0 = poor agreement
- 0.00 to 0.21 = slight agreement
- 0.21 to 0.40 = fair agreement
- 0.41 to 0.60 = moderate agreement
- 0.61 to 0.8 = substantial
- 0.81 to 1.00 = almost perfect agreement.

Internal consistency (Cronbach's alpha) and test–retest reliability: ≥ 0.7 is considered acceptable.[42]

Validity; i.e., between-scale comparison (correlation coefficient, r):[43]

- ≤ 0.3 = weak
- 0.3 to ≤ 0.5 = moderate
- 0.5 = strong.

Table 27: Summary of Outcome Measures and Their Measurement Properties

Outcome Measure	Type	Conclusions About Measurement Properties	MID
MG-ADL	An 8-item patient-reported outcome measure assessing MG symptoms and functional activities related to activities of daily living and producing a total score ranging from 0 to 24, where higher scores indicate greater severity of symptoms. The MG-ADL is composed of items related to patients' assessment of functional disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb impairment (2 items).	**Validity** The MG-ADL highly correlated with the MGC (r = 0.85; P < 0.0001) and MG-QoL15 (r = 0.76; P < 0.0001).[24] Correlation of the MG-ADL score and physician impression of change between the visits was strong (r = 0.70; P < 0.0001).[24] **Reliability** Test–retest reliability coefficient of 93.7% among 20 patients, with lower bound of the 95% CI at 87.3%, tested twice within one week.[24] **Responsiveness** The MG-ADL was assessed at two visits, where the mean improvement in score in patients who improved, based on the gold standard, was 3.88 (SD 2.7).[24]	An MID for patients with MG was not identified in the literature. A 2-point improvement in MG-ADL score is a threshold that optimally (in terms of best sensitivity and specificity when referenced to MG-QoL15) indicates clinical improvement at the level of the individual for patients with MG.[24]
QMG score	A 13-item direct physician assessment scoring system that quantifies disease severity, based on impairments of body functions and structures. The total QMG score ranges from 0 to 39, where higher scores indicated greater disease severity. The QMG score is composed of the following items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item).	**Validity** Construct validity was assessed through correlations with the Manual Muscle Test (r = 0.69)[44] and the Myasthenia Muscle Score (r = 0.87).[45] **Reliability** Internal consistency assessed via Cronbach's alpha value was 0.74 for the QMG, demonstrating an acceptable threshold.[42,46] Test–retest reliability was studied in 209 stable patients assessed two weeks apart. The intraclass correlation coefficient for the total scores was 0.88 (95% CI, 0.85 to 0.91).[42,46]	An MID of 2.6 points in patients with MG was determined in the original QMG publication.[27] There is some evidence that the MID should be higher in patients with higher baseline QMG scores, where the MID with mild to moderate MG (QMG ≤ 16) was calculated to be 2 points, compared to patients with higher baseline values (QMG > 16) that had a higher MID of 3 points.[20] A MID of 3.5 has been used in previous MG trials.[20]

Outcome Measure	Type	Conclusions About Measurement Properties	MID
		Responsiveness The QMG has demonstrated responsiveness to change in various clinical trials (involving IVIG, cyclosporine), where patients showed statically significant improvement in the QMG after treatment compared to the placebo group.[20]	An MID of 3.5 has been used in previous trials for patients with MG.[20] The minimally detectable change is 4.3 points for the QMG score in patients with MG.[46]
MGC	The MGC is a 10-item instrument that measures the symptoms and signs of MG based on physician examination and patient history. Items relate to ptosis, double vision, eye closure, talking, chewing, swallowing, breathing, neck flexion, shoulder abduction, and hip flexion. Each item is scored on an ordinal scale with 4 possible categories and weighted. The total score ranges from 0 to 50, where higher scores indicating more severe impairments.	**Validity** The MGC score showed correlations with the MG-QoL15 total score (r = 0.68, 95% CI, 0.59 to 0.75), the MG-ADL total score (r = 0.85, 95% CI, 0.77 to 0.90), and the MMT total score (r = 0.80, 95% CI, 0.72 to 0.86).[28] **Reliability** Internal consistency assessed with Cronbach's alpha value was 0.66.[42,46] Based on tests conducted the same day by two neurologists, the test–retest reliability coefficient of the MGC was 98%.[28] In a study of 209 stable patients, assessed two weeks apart, the intraclass correlation coefficient for the total scores was 0.82 (95% CI, 0.77 to 0.85).[42,46] **Responsiveness** Responsiveness of the MGC was assessed in 151 patients using different gold standards of clinical change (e.g., physician impression of improvement, improvement in MG-QoL15 score).[28]	A 3-point improvement in the MGC represents a meaningful improvement to most patients with MG.[28]
MG-QoL 15	The MG-QoL15 is a 15-item questionnaire that allows clinicians to estimate a patient's quality of life relevant to MG. Items on the MG-QoL15 relate to physical, social, and psychological components and are scored from 0 (not at all) to 4 (quite a bit). The cumulative scores range from 0 to 60, with higher scores representing worse quality of life.	**Validity** The MG-QoL15 correlated with the MGC (r = 0.53, 95% CI, 0.41 to 0.65, P < 0.0001),[47] the physical and mental components of the SF-36, as well as with MG-specific measures (QMG, MG-ADL, and Manual Muscle Test).[20] The MG-QoL15 internal consistency was assessed, with Cronbach's alpha value of 0.89.	The MID has not been fully determined.[20]

Outcome Measure	Type	Conclusions About Measurement Properties	MID
		Reliability The test–retest reliability coefficient for the MG-QoL15 was 98.6%.[47]	
MGFA-PIS	The MGFA-PIS is designed to assess the clinical state of MG patients after they have received treatment. It provides the physician's global assessment of the patient's clinical status.	Not applicable	Not applicable
Neuro-QoL Fatigue Scale	The Neuro-QoL Fatigue Scale is a generic 19-item survey of fatigue. Items are scored from 1 (never) to 5 (sometimes). Total scores range from 19 to 95, where higher scores indicate greater fatigue and greater impact of MG on activities.	**Validity** Evidence assessing the validity of the Neuro-QoL-Fatigue in patients with MG was limited to evidence from REGAIN, the pivotal study assessed in this CDR. Based on data from 125 patients with rgMG, the correlations of the Neuro-QoL Fatigue with the MG-QoL15 were identified for patients treated with eculizumab (r = 0.74; 95% CI, 0.59 to 0.84; P = 0.0002) and placebo (r = 0.65; 95% CI, 0.47 to 0.84; P = 0.0002).[32] **Responsiveness** Neuro-QoL Fatigue was responsive, based on significant improvements after treatment with eculizumab, consistent with improvements in MG-ADL, QMG, and MG-QoL15.[32]	An MID for patients with MG was not identified in the literature.
EQ-5D	Generic preference-based HRQoL instrument, consisting of a VAS and a composite index score of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.	No studies assessing validity or reliability were identified for patients with MG.	The MID for patients with MG was not identified in the literature.

EQ-5D = European Quality of Life Health 5-Dimensions questionnaire; HRQoL = health-related quality of life; IVIG = intravenous immunoglobulin; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living score; MGC = Myasthenia Gravis Composite score; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; MG-QoL 15 = Myasthenia Gravis Quality of Life 15-item scale; MID = minimally important difference; MMT = Manual Muscle Test; Neuro-QoL = Quality of Life in Neurological Disorders; QMG = Quantitative Myasthenia Gravis score; SD = standard deviation; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

Myasthenia Gravis Activities of Daily Living Scale (MG-ADL)

The MG-ADL is an eight-item patient-reported outcome measure assessing MG symptoms and functional activities related to activities of daily living.[48] Each of the items is scored from 0 (normal) to 3 (most severe), providing a total MG-ADL score ranging from 0 to 24, where higher scores indicate greater severity of symptoms. The MG-ADL is composed of items related to patients' assessment of functional disability secondary to ocular (two items), bulbar (three items), respiratory (one item), and gross motor or limb impairment (two items). The MG-ADL can be completed in two to three minutes with no need for specialized equipment or training.

Figure 12: Myasthenia Gravis Activities of Daily Living Scale

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Total score _____

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Measurement Properties

Validity of the MG-ADL was assessed in a study of 87 patients with MG with a confirmed diagnosis based on clinical, serologic, and electrodiagnostic testing.[24] The MG-ADL assesses domains that are considered important to patients and clinicians.

The MG-ADL is strongly correlated with other measures, including the MGC ($r = 0.85$, $P < 0.0001$) and the MG-QoL15 ($r = 0.76$, $P < 0.0001$).[24] Correlation between the MG-ADL score and physician impression of change between the visits was strong ($r = 0.70$, $P < 0.0001$).[24]

Test–retest analysis in 20 patients who completed the two tests demonstrated a high reliability coefficient of 93.7%, with lower bound of the 95% CI at 87.3% for patients with MG tested twice within one week.[24]

The responsiveness of the MG-ADL was assessed between two visits, where the mean improvement in ADL score in patients who improved based on the gold standard (improvement in MG-QoL15 score plus improvement in physician impression of change score) was 3.88 (SD 2.7). The standardized mean change was 1.43.[24]

Minimally Important Difference

A two-point reduction in MG-ADL total score optimally indicates improvement for patients with MG based on a receiver operator characteristic curve approach, where a two-point reduction showed both the best sensitivity and specificity. This study was performed using patients who were treated based on physician discretion with no specifications related to

changing treatment/management.[24] The two-point reduction was derived from a clinical population with the following mean baseline scores: MG-ADL = 4.89, MGC = 8.89, and MG-QoL = 20.8. This threshold of a two-point difference is recognized as a definition of responder with clinical important improvement. No study is available in the literature with regard to MID in MG-ADL.

Other Considerations

The MG-ADL is designed to be based on patient recall and is often used in collaboration with other quantitative tools such as the QMG.

Quantitative Myasthenia Gravis

The QMG is a 13-item direct physician assessment scoring system that quantifies disease severity based on impairments of body functions and structures.[27] Each item is quantitatively assessed and scored from 0 to 3 (where 3 represents the most severe), providing a total QMG score ranging from 0 to 39. The QMG is composed of the following items: ocular (two items), facial (one item), bulbar (two items), gross motor (six items), axial (one item), and respiratory (one item). According to a 2000 publication by the Task Force of the Medical Scientific Advisory Board of the MGFA, the QMG score was recommended for use in all prospective MG clinical trials for evaluating treatment-related clinical change.[25]

Table 28: Quantitative Myasthenia Gravis Scale

Test Items Weakness	None	Mild	Moderate	Severe
Double vision on lateral gaze **right** or **left** (circle one)	61	11–60	1–10	spontaneous
Ptosis (upward gaze)	61	11–60	1–10	spontaneous
Facial muscles	normal lid	complete, weak, some resistance	complete, without resistance	incomplete
Swallowing 4 oz. water (½ cup)	normal	Minimal coughing or throat clearing	severe coughing/ choking or nasal regurgitation	cannot swallow (test not attempted)
Speech following counting aloud from 1 to 50 (onset of dysarthria)	none at #50	dysarthria at #30–49	dysarthria at #10–29	dysarthria at #9
Right arm outstretched (90° sitting)	240	90–239	10–89	0–9
Left arm outstretched (90° sitting)	240	90–239	10–89	0–9
Vital capacity (% predicted)	≥80%	65–79%	50–64%	<50%
Right hand grip (kg)				
male	≥45	15–44	5–14	0–4
female	≥30	10–29	5–9	0–4
Left hand grip (kg)				
male	≥35	15–34	5–14	0–4
female	≥25	10–24	5–9	0–4
Head lifted (45° supine)	120	30–119	1–29	0
Right leg outstretched (45° supine)	100	31–99	1–30	0
Left leg outstretched (45° supine)	100	31–99	1–30	0

[a]Total QMG score range 0–39.

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Measurement Properties

The QMG assesses relevant impairments of body functions and structures. Construct validity has been studied by demonstration of correlations with other measures used in the assessment of MG, including the Manual Muscle Test (r = 0.69[44]; r = 0.73[49]) and the Myasthenia Muscle Score (r = 0.87).[45]

test–retest reliability was studied in 209 stable patients assessed two weeks apart. The intraclass correlation coefficient for the total scores was 0.88 (95% CI, 0.85 to 0.91).[42,46] Internal consistency assessed through Cronbach's alpha value was 0.74 for the QMG, demonstrating an acceptable threshold.[42,46]

A longitudinal study of 53 patients with an average of 186 days between visits determined that the difference in the QMG score was significantly higher in those improved (based on the physician's impression of change), compared with those who were stable.[49]

The QMG has demonstrated responsiveness to change in various clinical trials (involving IVIG, cyclosporine), where patients showed statically significant improvement in the QMG after treatment compared to the placebo group.[20]

Minimally Important Difference

The original study by Barohn et al. (1998) that designed the version of the QMG in use today identified an MID of 2.6 points.[27] Some have suggested that the MID should be higher in patients with higher baseline QMG scores. Specifically, for a baseline of mild to moderate MG (QMG ≤ 16), the MID was calculated to be two points, compared to higher baseline values (QMG > 16), for which the MID was higher, at three points.[20] An MID of 3.5 has been used in previous MG trials.[20] A study performed in 2016 found the minimally detectable change to be 4.3 points for the QMG score in patients with MG.[46]

Limitations

The QMG is measured using a dynamometer and spirometer and can take up to 25 minutes to complete, which may make it more difficult to use than other measures.

Myasthenia Gravis Composite

The MGC is a 10-item instrument that measures the symptoms and signs of MG based on physician examination and patient history.[50] Items are related to ptosis, double vision, eye closure, talking, chewing, swallowing, breathing, neck flexion, shoulder abduction, and hip flexion. Each item is scored on an ordinal scale with four possible categories and weighted. The total score ranges from 0 to 50, with higher scores indicating more severe impairments. The MGC is composed of items originating from other scales (i.e., QMG, MMT, MG-ADL).

Measurement Properties

Weighting of the MGC items was established by 35 MG experts from across the world.[50] Based on an assessment of 175 patients with MG, the MGC score showed strong correlations with the MG-QoL15 total score (r = 0.68; 95% CI, 0.59 to 0.75), the MG-ADL total score (r = 0.85; 95% CI, 0.77 to 0.90), and the MG-MMT total score (r = 0.80; 95% CI, 0.72 to 0.86). Longitudinal testing of the MGC and other tools, involving 151 patients over an average span of 4.7 months, showed nearly identical correlations.[28] Internal consistency assessed with Cronbach's alpha value was 0.66.[42,46]

Based on testing performed on 38 patients on the same day by two neurologists, the test–retest reliability coefficient of the MGC was 98%, with a lower bound of the 95% CI of 97%.[28] In a study of 209 stable patients assessed two weeks apart, the intraclass correlation coefficient for the total scores was 0.82 (95% CI, 0.77 to 0.85).[42,46]

Responsiveness of the MGC was assessed in 151 patients using different gold standards of clinical change (e.g., physician impression of improvement, improvement in MG-QoL15 score).[28]

Minimally Important Difference

A three-point improvement in the MGC represents a meaningful improvement for most patients with MG.[28]

Myasthenia Gravis Quality of Life 15-Item Scale (MG-QoL15)

The MG-QoL15 is a 15-item questionnaire that allows clinicians to estimate a patient's quality of life relevant to MG.[31] Items on the MG-QoL15 relate to physical, social, and psychological components and are scored from 0 (not at all) to 4 (quite a bit). The cumulative scores range from 0 to 60, with higher scores representing worse quality of life. The MG-QoL15 was constructed based on the most relevant and responsive items from the 60-item version of the questionnaire, with the goal of having a quick, easy-to-use, and easy-to-interpret questionnaire.

Measurement Properties

The MG-QoL15 is strongly correlated with the MGC ($r = 0.53$; 95% CI, 0.41 to 0.65; $P < 0.0001$)[47] and is correlated with the physical ($r = –0.61$; 95% CI, –0.73 to –0.44; $P < 0.001$) and mental ($r = –0.45$; 95% CI, –0.61 to –0.25; $P < 0.001$) components of the Short Form (36) Health Survey (SF-36).[20] The MG-QoL15 is moderately correlated with MG-specific measures, including the QMG ($r = 0.55$ to 0.45), MG-ADL ($r = 0.70$ to 0.48) and MMT ($r = 0.44$ to 0.33).[20] The MG-QoL15 has good internal consistency (Cronbach's alpha = 0.89).[20] Test–retest reliability was assessed based on 38 patients assessed two to four days apart. The test–retest reliability coefficient for the MG-QoL15 was 98.6%, with a lower bound of the 95% CI of 97.5%.[47]

Minimally Important Difference

The MID has not been fully determined.[20]

Myasthenia Gravis Foundation of America Post-Intervention Status

The MGFA-PIS (Table 29) is designed to assess the clinical state of MG patients after they have received treatment for MG.[25] It provides the physician's global assessment of the patient's clinical status.

Table 29: Myasthenia Gravis Foundation of America Post-Intervention Status

Complete stable remission (CSR)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic remission (PR)	The same criteria as for CSR, except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal manifestations (MM)	The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least 1 year.
MM-1	The patient continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy.
MM-2	The patient has received only low-dose cholinesterase inhibitors (< 120 mg pyridostigmine/day) for at least 1 year.
MM-3	The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.
Change in status	
Improved (I)	A substantial decrease in pre-treatment clinical manifestations or a sustained substantial reduction in MG medications, as defined in the protocol. In prospective studies, this should be defined as a specific decrease in QMG score.
Unchanged (U)	No substantial change in pre-treatment clinical manifestations or reduction in MG medications, as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in QMG score.
Worse (W)	A substantial increase in pre-treatment clinical manifestations or a substantial increase in MG medications, as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG score.
Exacerbation (E)	Patients who have fulfilled criteria of CSR, PR, or MM but subsequently developed clinical findings greater than permitted by these criteria.
Died of MG (D of MG)	Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy. List the cause (see Morbidity and Mortality table).

CSR = complete stable remission; MG = myasthenia gravis; MM = minimal manifestations; PR = pharmacologic remission; QMG = Quantitative Myasthenia Gravis score.

Quality of Life in Neurological Disorders Fatigue Scale (Neuro-QoL Fatigue)

The Neuro-QoL-Fatigue is a generic 19-item survey of fatigue. Items are scored from 1 (never) to 5 (sometimes).[7] Total scores range from 19 to 95, where higher scores indicate greater fatigue and greater impact on activities. The Neuro-QoL-Fatigue is a subscale of Neuro-QoL.

Measurement Properties

The validity of the Neuro-QoL-Fatigue in patients with MG was limited to the pivotal study assessed in this review. Based on data from 125 patients with rgMG, the Neuro-QoL Fatigue was strongly correlated with the MG-QoL15 for patients treated with eculizumab (r = 0.74; 95% CI, 0.59 to 0.84; P = 0.0002) and placebo (r = 0.65; 95% CI, 0.47 to 0.84; P = 0.0002).[32] Strong to weak correlations of the Neuro-QoL Fatigue with the MG-ADL and

QMG were also reported in this study. Data from the same study showed that the Neuro-QoL Fatigue was responsive, based on significant improvements in scores after patients were treated with eculizumab. Improvements in the Neuro-QoL Fatigue were consistent with improvements in MG-ADL, QMG, and MG-QoL15.

Minimally Important Difference

An MID for patients with MG was not identified in the literature. For patients with multiple sclerosis, cut-off points have been established with < 45 meaning no problem, 45 to 55 indicating mild problems, 55 to 65 meaning moderate problems, and > 65 indicating severe problems.[33]

European Quality of Life Health 5-Dimensions Questionnaire (EQ-5D)

The European Quality of Life Health 5-Dimensions questionnaire (EQ-5D) is a generic, standardized patient self-administered instrument that provides a simple, descriptive profile and a single index value for health status. The EQ-5D comprises five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of three levels (some, moderate, extreme problems), generating a total of 243 theoretically possible health states. The set of responses provided by each patient represents a health state that can be converted into a single index value, where 0.0 represents death and 1.0 represents perfect health. Assessments were also made using the EQ-5D visual analogue scale (EQ-5D VAS), which captures the self-rating of current health status using a visual “thermometer” with the end points of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom.

Measurement Properties

No studies assessing validity or reliability of the EQ-5D-3L were identified for patients with MG. However, validity and reliability of the EQ-5D-3L has been established in various other disease areas.[51]

The EQ-5D includes domains such as walking (mobility) and mood (anxiety/depression) that patients considered important to their quality of life, yet other critical domains, such as fatigue and cognition, are not included in EQ-5D.

Minimally Important Difference

The MID for patients with MG was not identified in the literature. Reported minimal clinically important differences for this scale in the general population have ranged from 0.033 to 0.074.[35]

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