# Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis: Effectiveness and Value

**Draft Evidence Report**

**July 22, 2021**

**Prepared for**

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**DATE OF PUBLICATION:** July 22, 2021

**How to cite this document:** Tice JA, Nikitin D, Campbell J, Moradi A, Rind DM, Pearson SD, Agboola F. Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, July 22, 2021. https://icer.org/assessment/myasthenia-gravis/#timeline

Jeffrey A. Tice served as the lead author for the Report. Dmitriy Nikitin led the systematic review in collaboration with Avery McKenna. Daniel R. Touchette was responsible for the development of the cost-effectiveness model. Jon Campbell provided oversight of the cost-effectiveness analyses and developed the budget impact model in collaboration with Ashton Moradi. Foluso Agboola, David M. Rind, and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would like to thank Maggie O'Grady and Monica Frederick for their contributions to this Report.

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The funding for this Report comes from government grants and non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 19% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. There are no life science companies relevant to this review who participate in this program. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

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*In the development of this Report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and Report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this Report, nor should it be assumed that they support any part of it. The Report should be viewed as attributable solely to the ICER team and its affiliated researchers.*

*For a complete list of stakeholders from whom we requested input, please visit:* https://icer.org/wp-content/uploads/2021/04/ICER_Myasthenia-Gravis_Stakeholder_List_041221.pdf

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# Table of Contents



**Supplemental Materials**

## List of Acronyms and Abbreviations Used in this Report

| | |
|---|---|
| **AChR** | Acetylcholine receptor |
| **AE** | Adverse event |
| **AHRQ** | Agency for Healthcare Research and Quality |
| **CADTH** | Canadian Agency for Drugs and Technologies in Health |
| **CSR** | Complete stable remission |
| **GDP** | Gross domestic product |
| **gMG** | Generalized myasthenia gravis |
| **IVIG** | Intravenous immunoglobulin |
| **LRP4** | Lipoprotein receptor-related protein 4 |
| **MG** | Myasthenia gravis |
| **MG-ADL** | Myasthenia gravis activities of daily living |
| **MGC** | Myasthenia gravis composite |
| **MGFA** | Myasthenia Gravis Foundation of America |
| **MGFA-PIS** | MGFA Post-Intervention Status |
| **MG-QOL** | Myasthenia gravis quality of life |
| **MM** | Minimal manifestation |
| **MMF** | Mycophenolate mofetil |
| **MuSK** | Muscle specific kinase |
| **NMA** | Network meta-analysis |
| **PLEX** | Plasma exchange |
| **PR** | Pharmacologic remission |
| **QMG** | Quantitative myasthenia gravis score |
| **RCT** | Randomized controlled trial |
| **RTX** | Rituximab |
| **SAE** | Serious adverse event |
| **USPSTF** | US Preventative Services Task Force |

# Executive Summary

Myasthenia Gravis (MG) is an autoimmune disease that affects the neuromuscular junction. The prevalence in the United States is estimated to be between 14 and 20 per 100,000 people[1,2] and the annual incidence is approximately 2.2 per 100,000.[3] The characteristic finding of MG is muscle weakness that worsens with repeated use ("fatigable weakness").[4]

With progressive disease, treatment typically includes high-dose corticosteroids combined with or followed by "steroid-sparing" immunosuppressive drugs (most commonly azathioprine and mycophenolate mofetil [MMF]). The goal of therapy is to maintain the patient with minimal manifestations (MM) of disease (no symptoms or functional limitations from MG despite minimal weakness on examination) or better.[5] Currently, about 20,000 patients with generalized MG are intolerant or have an inadequate response to conventional treatment options.[6]

In this Report, ICER reviews eculizumab, a monoclonal antibody, and efgartigimod, an immunoglobulin fragment that targets the neonatal Fc receptor. Eculizumab received US Food and Drug Administration (FDA) approval in October 2017 for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-AChR antibody positive,[7] and an FDA decision on efgartigimod is expected on December 17, 2021.[8]

We identified one Phase III trial each for eculizumab (REGAIN) and efgartigimod (ADAPT) but found insufficient data to compare these drugs to maintenance intravenous immunoglobulin IVIG and rituximab (RTX). In the Phase III REGAIN trial, patients with anti-AChR antibody positive, treatment-resistant gMG who received eculizumab had significantly better improvement in the myasthenia gravis activities of daily living (MG-ADL) and quantitative myasthenia gravis (QMG) scores than those on placebo at four weeks and eight weeks (Table ES1), and the improvements were sustained at 26 weeks. In addition, at week 26, the proportion of patients with minimal symptom expression (MG-ADL score of 0 or 1) was much greater in the eculizumab group (21.4% vs. 1.7%, p=0.0007).[9] In the open label extension through 130 weeks of follow up, the benefits were maintained, and may have increased compared with 26 weeks.[10] There were no excess adverse events (AEs) in the trials, although more patients in the eculizumab group stopped treatment due to AEs, and it carries a black box warning for meningococcal infections.

The Phase III ADAPT trial was conducted in gMG patients with or without anti-AChR-antibody; however, the primary outcome was in the subgroup of anti-AChR antibody positive patients. The proportion of patients with clinically meaningful improvement (≥2-point MG-ADL improvement sustained for ≥4 weeks) was much greater in the efgartigimod group compared to the placebo group. Anti-AChR antibody positive gMG patients who received efgartigimod did significantly better on MG-ADL and QMG than those who received placebo (Table ES1). However, the improvements were greater at four weeks than at eight weeks, reflecting the unusual dosing schedule in the trial.

Patients received their second treatment cycle only when they no longer had a clinically meaningful improvement on the MG-ADL. Thus, many patients were back near baseline at eight weeks. The anti-AChR antibody negative patients randomized to efgartigimod were only slightly more likely to respond based on the MG-ADL (68% vs. 63% in placebo group, p=NR). AEs did not appear to be more common with efgartigimod, but there are long term concerns about infections with lowering of IgG levels.

**Table ES1. Pivotal Trial Results**

| Intervention (Trial) | Arms | Δ MG-ADL | | Δ QMG | |
|---|---|---|---|---|---|
| | | 4 weeks | 8 weeks | 4 weeks | 8 weeks |
| **REGAIN** | Eculizumab | -3.5 | -3.7 | -3.3 | -4.0 |
| | Placebo | -1.5 | -1.8 | -1.5 | -1.4 |
| **ADAPT** | Efgartigimod | -4.6 | -2.2 | -6.2 | -2.9 |
| | Placebo | -1.7 | -1.7 | -1.0 | -1.2 |

MG-ADL: Myasthenia Gravis Activities of Daily Living score, QMG: Quantitative Myasthenia Gravis score

One important area of uncertainty is that it is not clear if or when to stop either of the drugs in patients who are responding to them. For efgartigimod, the primary uncertainty is the appropriate dosing regimen. In the ADAPT trial, subsequent cycles were started once patients lost clinical benefits. It seems likely that in routine practice, patients and clinicians will not want to wait until the benefits have receded before starting another round of therapy. Also, despite their use in clinical practice, there is a lack of comparative efficacy data for both rituximab and IVIG used as maintenance therapy for gMG.

Taking into consideration the above information on the benefits and AEs of eculizumab, we believe there is moderate certainty of a small or substantial net health benefit with high certainty of at least a small benefit for eculizumab added to conventional therapy (B+) in adults with gMG positive for anti-AChR antibodies "refractory" to conventional therapy. For efgartigimod, given the uncertainties about dosing and consistent long-term benefits of therapy, we concluded that there is moderate certainty of a comparable, small, or substantial net health benefit of efgartigimod added to conventional therapy with high certainty of at least comparable net health benefit (C++) in adults with gMG positive for anti-AChR antibodies. While there is evidence for efgartigimod in adults with gMG negative for anti-AChR antibodies, it is sparse and of uncertain clinical and statistical significance. Thus, we concluded that the evidence was insufficient (I) to distinguish the net health benefit of efgartigimod added to conventional therapy from conventional therapy alone in patients who test negative for anti-AChR antibodies. In addition, the evidence is insufficient (I) to distinguish the net health benefits of rituximab and IVIG from placebo, eculizumab, and efgartigimod.

In economic modeling, we evaluated the cost-effectiveness of (1) eculizumab plus conventional therapy versus conventional therapy alone in patients with refractory anti-AChR antibody positive gMG as defined in the REGAIN trial and (2) efgartigimod plus conventional therapy versus

conventional therapy alone in the patients with gMG including those with or without anti-AChR-antibody. The analyses were conducted over a two-year time horizon, taking a health system perspective. Based on an annual cost of $470,200, the incremental cost/QALY and incremental cost/evLYG for eculizumab were estimated to be $3,746,000. For efgartigimod, using a placeholder price of $286,100, the incremental cost/QALY and incremental cost/evLYG were estimated to be $1,426,000.

The model was sensitive to several inputs, including the utility values assigned to improved and unimproved MG and the proportion of patients achieving at least a 3-point reduction in the QMG for efgartigimod or its comparator, or eculizumab and its comparator. However, despite the large impact of changing these inputs on the results, the incremental cost-effectiveness ratio was never less than $2.5 million per QALY gained for eculizumab and $1.14 million per QALY gained for efgartigimod. In addition, the results of the probabilistic sensitivity analysis and scenario analyses had similar cost/QALY estimates.

There are other potential benefits and important contextual considerations not fully captured in the economic model. For example, MG is a serious, lifelong disease with life-threatening manifestations, and most patients do not achieve treatment goals with conventional therapy. Additionally, there is potential to improve childbearing and career opportunities for women who are often diagnosed early in their lives. This is particularly relevant for Black women who typically present at younger ages and may have a more severe disease course than other patient groups.

In conclusion, both eculizumab and efgartigimod significantly improve function and quality of life for patients with gMG. However, at the current price for eculizumab the estimated cost-effectiveness is well above typical thresholds; the cost-effectiveness of efgartigimod will depend on its actual price.

# 1. Background

Myasthenia Gravis (MG) is an autoimmune disease that affects the neuromuscular junction. The prevalence in the United States is estimated to be between 14 and 20 per 100,000 people[1,2] and the annual incidence is approximately 2.2 per 100,000.[3]

The characteristic finding of MG is muscle weakness that worsens with repeated use ("fatigable weakness").[4] MG symptoms often begin with ptosis (drooping eyelids) and diplopia (double vision) that worsens with activity and by the end of the day.[11] Ocular weakness may progress to affect the muscles controlling speech, swallowing, or body function ("generalized MG").[11] Weakness of respiratory muscles can result in life-threatening respiratory failure requiring intubation.[11] The majority of patients (~80%) progress to some form of generalized disease, typically within the first two years of symptom onset.[3,11]

The majority of patients with MG have autoantibodies that bind to the acetylcholine receptor (AChR).[4] First-line symptomatic treatment is pyridostigmine, which inhibits the breakdown of acetylcholine by acetylcholinesterase.[12] With progressive disease, disease-modifying therapy typically includes high-dose corticosteroids, frequently in combination with or followed by "steroid sparing" immunosuppressive drugs (most commonly azathioprine and mycophenolate mofetil (MMF)) in order to reduce the corticosteroid dose while maximizing patients' quality of life. The goal of therapy is to maintain the patient with minimal manifestations (MM) of disease (no symptoms or functional limitations from MG despite minimal weakness on examination) or better (sustained remission of symptoms and full functional capacity) with minimal side effects.[5] Currently, about 20,000 patients with generalized MG are intolerant or have inadequate response to conventional treatment options.[6] The average annual cost per patient for MG-specific care paid by a private health plan was $15,675 in 2009.[13] The largest costs were home health services and intravenous immunoglobulin (IVIG) infusions.

New therapies are becoming available for patients with MG (Table 1.1). Eculizumab is a monoclonal antibody that inhibits the cleavage of C5, thus reducing the formation and deposition of terminal complement complex C5b-9 at the neuromuscular junction.[14] It received US Food and Drug Administration (FDA) approval in October 2017 for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-AChR antibody positive.[7] Efgartigimod is an immunoglobulin fragment that targets the neonatal Fc receptor and reduces IgG antibody levels by about 50% after a single infusion and 75% after repeated infusions.[15] An FDA decision on efgartigimod is expected on December 17, 2021.[8]

**Table 1.1. Interventions of Interest**

| Intervention Generic Name (Brand Name) | Mechanism of Action | Delivery Route | Recommended Dose |
|---|---|---|---|
| **Eculizumab (Soliris®)** | Monoclonal antibody inhibiting C5 cleavage reducing complement deposition at the neuromuscular junction | Intravenous infusion | 900 mg weekly x 4 weeks, then 1200 mg week 5, then 1200 mg every two weeks |
| **Efgartigimod** | Immunoglobulin G1 Fc fragment antibody to the neonatal Fc receptor leading to decreased IgG levels | Intravenous infusion | 10 mg/kg weekly for 4 weeks, followed by dosing based on patient symptoms* |

*Dosage at which investigational agent was evaluated in clinical trials.

# 2. Patient and Caregiver Perspectives

This Report was developed with input from diverse stakeholders, including patient advocacy organizations, clinicians, researchers, and manufacturers of the agents of focus in this review.

Patients with MG often experience a long and frustrating path to diagnosis and appropriate treatment. This reflects the paucity of experience physicians have in caring for patients with MG because the disease is rare. The disease is often referred to as a "snowflake disease" because of its heterogeneity, making the diagnosis even more difficult. As a result, patients are misdiagnosed and see many specialists before they receive the diagnosis of MG. Patients also experience significant side effects from current therapies, such as corticosteroids and non-steroidal immunosuppressive agents. The side effects can contribute as much to patient disability as the disease itself. Some patient advocates feel that the manufacturers of drugs for MG downplay the impact of these side effects on patients' lives. In addition, patients experience significant barriers accessing some therapies. They particularly highlighted the challenges in accessing IVIG as maintenance therapy. Based on public comments that both IVIG and rituximab are widely used to treat patients with MG for whom other conventional immunosuppressive therapies have failed or not been tolerated, we have summarized the evidence base for both drugs as maintenance therapy. Patients also highlighted the importance of the caregiver role and the impact of MG on the lives of caregivers.

Stakeholders highlighted that eculizumab is very expensive. Some stakeholders noted that this has created a barrier to access for patients who might benefit from this treatment. Other stakeholders noted that while the pivotal trial of eculizumab studied patients with refractory disease, the drug is sometimes used in patients who have not received an adequate trial of less expensive conventional immunosuppressive therapy.

We also heard how important it was to consider the impact of MG on delayed childbearing potential in women, particularly Black women. In response, we added lost or delayed childbearing to the list of outcomes that matter to patients. In addition, we paid attention to race/ethnicity differences. For example, Black patients are diagnosed with MG at significantly younger ages than white patients.

# 3. Comparative Clinical Effectiveness

## 3.1. Methods Overview

Please see Supplement Section D for details of the literature search, quality assessment, and quantitative summary methods.

### Scope of Review

This review compares the outcomes of adding eculizumab or efgartigimod to standard therapy with the outcomes of standard therapy alone in adults with gMG for whom conventional immunosuppressive therapies have not been effective or have not been tolerated. We also sought to compare the interventions to each other and to two off label interventions: rituximab and maintenance IVIG. We searched for evidence on patient-important outcomes, including symptom improvement (using Myasthenia Gravis Activities of Daily Living [MG-ADL], Quantitative Myasthenia Gravis score [QMG]), remission, minimal symptom expression, and quality of life. We also looked for data on subpopulations of interest, including those who are positive for anti-muscle-specific kinase (MuSK) antibodies and those who test negative for all known MG-associated antibodies ("seronegative MG"). The full scope of the review, including the complete outcomes list, can be found in Supplement Section D.

### Evidence Base

A total of 11 references on eculizumab and efgartigimod met our inclusion criteria. Of these, we identified one Phase III randomized controlled trial (RCT) of eculizumab (REGAIN, Table 3.1)[16] with many additional reports[9,10,17-21] and one small (n=14) Phase II RCT of eculizumab.[22] For efgartigimod, we identified one Phase III RCT (ADAPT, Table 3.1[23] and one small (n=24) Phase II RCT.[24] A summary of the pivotal trials of eculizumab (REGAIN) and efgartigimod (ADAPT) is presented below. Additional details are available in Supplement Section D.

In the pivotal trial of eculizumab (REGAIN), 125 patients with gMG that is anti-AChR antibody-positive and “refractory” to conventional therapy were randomized 1:1 to intravenous eculizumab or intravenous placebo for 26 weeks. There are a number of different definitions of "refractory." In the REGAIN study, "refractory" was defined as having failed two or more immunosuppressive therapies or at least one immunosuppressive therapy with either IVIG or PLEX given at least four times annually for at least one year without symptom control.

In the pivotal trial of efgartigimod (ADAPT), 167 patients with gMG were randomized 1:1 to intravenous efgartigimod or intravenous placebo for 26 weeks. The ADAPT trial enrolled patients with or without anti-AChR antibody; however, the primary outcome was in the subgroup of patients

who are antibody positive (n=129). We also obtained academic-in-confidence data from the manufacturer on the subgroup of patients in the ADAPT trial who were anti-AChR antibody-positive and "refractory" to conventional therapy, using the same definition of “refractory” that was used in the REGAIN trial.

In both the ADAPT and REGAIN trials, patients continued background conventional therapy throughout the trial periods. The outcomes assessed in each trial are presented in Table 3.1.

The clinical evidence is summarized separately below for each drug because the pivotal trials for the two drugs differed in the populations studied. However, despite differences in inclusion and exclusion criteria (Supplement Table D2.2), the baseline characteristics of the anti-AChR antibody-positive patients in the pivotal trials of eculizumab and efgartigimod were similar (Table 3.2), and even more similar for the patients "refractory" to conventional treatment using the definition of refractory used in the REGAIN trial.

We did not identify any published results in comparable patient populations on rituximab and IVIG. However, we identified one unpublished trial of rituximab (BeatMG)[25] and two unpublished trials of IVIG in ClinicalTrials.gov that met our inclusion criteria.[26,27] Due to key differences across trials in patient characteristics and trial design, we did not compare the interventions to rituximab or IVIG. Detailed descriptions of these trials can be found in Supplement Table D2.2.

**Table 3.1. Overview of Pivotal Randomized Trials**

| Drug | Trials | N | Outcomes |
|---|---|---|---|
| **Eculizumab** | REGAIN | 125 | Primary: Change from baseline in MG-ADL at 26 weeks<br>Secondary: QMG, MG-QoL15, MGC |
| **Efgartigimod** | ADAPT | 129* | Primary: Proportion of anti-AChR Ab+ patients with at least a 2-point reduction in MG-ADL for at least 4 consecutive weeks in the first treatment cycle (8 weeks)<br>Secondary: QMG, MG-QoL15r, MGC |

MG-ADL: Myasthenia Gravis Activities of Daily Living score, MGC: Myasthenia gravis composite scale, MG-QOL15r: Revised 15-item myasthenia gravis quality of life, QMG: Quantitative Myasthenia Gravis score
*Includes only adults with gMG positive for anti-AChR antibodies

**Table 3.2. Baseline Characteristics of Anti-AChR Antibody Positive Participants in the Pivotal Randomized Trials**

| | REGAIN Trial | | ADAPT Trial | |
|---|---|---|---|---|
| | **Eculizumab** | **Placebo** | **Efgartigimod** | **Placebo** |
| **N** | 62 | 63 | 65 | 64 |
| **Age, years** | 47.5 | 46.9 | 44.7 | 49.2 |
| **Sex- Female, %** | 66 | 65 | 71 | 63 |
| **Duration MG, years** | 9.9 | 9.2 | 9.7 | 8.9 |
| **MG-ADL, mean** | 10.5 | 9.9 | 9.0 | 8.6 |
| **QMG, mean** | 17.3 | 16.9 | 16.0 | 15.2 |
| **MGC, mean** | 20.4 | 18.9 | 18.6 | 18.1 |
| **MGFA Class, %** | | | | |
| **II** | 29 | 46.8 | 43.1 | 39.1 |
| **III** | 58.7 | 46.0 | 53.8 | 56.3 |
| **IV** | 11.3 | 7.9 | 3.1 | 4.7 |
| **Prior non-steroidal immunosuppressive therapy, %** | 100 | 100 | 72.3 | 67.2 |

MG: myasthenia gravis, MG-ADL: Myasthenia Gravis Activities of Daily Living score, MGFA: Myasthenia Gravis Foundation of America, N: total number, QMG: Quantitative Myasthenia Gravis score

# 3.2. Results

## Clinical Benefits

The Phase III trials of eculizumab (REGAIN) and efgartigimod (ADAPT) assessed four commonly used outcome measures (MG-ADL, QMG, MG-QOL15 or MG QOL15r, MGC) at multiple timepoints (Supplement Table A1 for details of the measures, Supplement Tables D2.6 to D2.14 for detailed results). We did not identify any data on remission, lost or delayed childbearing, mental health (anxiety, depression), corticosteroid side effects, and immunosuppressive side effects and burden on any of the interventions.

### *Eculizumab*

In the Phase III REGAIN trial, patients with anti-AChR antibody positive, "refractory" gMG who received eculizumab did not significantly differ from placebo on the primary outcome as measured by the worst-rank ANCOVA (least-squares mean rank 56.6 [SEM 4.5]) vs. 68.3 [4.5]; rank- difference −11.7 [95% CI −24.3 to 0.96], p=0.698).[16] The worst-rank analysis assigned the lowest rank to all patients who dropped out regardless of the reason for discontinuation. Of note, four discontinuations (2 in placebo arm and 2 in eculizumab arm) met the criteria for clinical worsening, while the remaining three discontinuations (all in eculizumab arm due to adverse events) were reported to have clinical improvements. However, in repeated-measures analysis that assessed

changes in MG-ADL from baseline, patients on eculizumab had significantly better improvement in MG-ADL score than those on placebo at 4 weeks and 8 weeks (Table 3.3), and the improvement was sustained at 26 weeks (-4.2 vs. -2.3; p=0.0058). Similar patterns of improvement that favored eculizumab compared to placebo were seen for the changes in QMG (Table 3.3), MG-QOL-15, and MGC (Supplement Table D2.7). For example, at week 4, the eculizumab group had a greater reduction in the 60-point MG-QOL15 scale (-7.2 vs. -3.6 points, p=0.0395). At week 26, the proportion of patients with minimal symptom expression (MG-ADL score of 0 or 1) was much greater in the eculizumab group (21.4% vs. 1.7%, p=0.0007).[9] In the open label extension through 130 weeks of follow-up, the benefits were maintained and may have increased compared with 26 weeks.[10]

**Table 3.3. Pivotal Trial Results. Adults with gMG positive for anti-AChR antibodies**

| Intervention (Trial) | Arms | Δ MG-ADL | | Δ QMG | |
|---|---|---|---|---|---|
| | | 4 weeks | 8 weeks | 4 weeks | 8 weeks |
| **REGAIN** | Eculizumab | -3.5 | -3.7 | -3.3 | -4.0 |
| | Placebo | -1.5 | -1.8 | -1.5 | -1.4 |
| **ADAPT** | Efgartigimod | -4.6 | -2.2 | -6.2 | -2.9 |
| | Placebo | -1.7 | -1.7 | -1.0 | -1.2 |

MG-ADL: Myasthenia Gravis Activities of Daily Living score, QMG: Quantitative Myasthenia Gravis score

### *Efgartigimod*

In the Phase III ADAPT trial, patients with anti-AChR antibody positive gMG who received efgartigimod did significantly better than those who received placebo on the primary outcome (significant improvement in MG-ADL during the first treatment cycle (MG-ADL responder), 68% vs. 30%, p<0.0001).[23] In addition, at week. 4, the efgartigimod group had a greater reduction in the 30-point MG-QOL15r scale (-7.3 vs. -2.3 points, p<0.05). Note that this quality of life scale is a revised version of the scale used in the REGAIN trial. The improvements in the efgartigimod group compared to the placebo group were better at 4 weeks than at 8 weeks (Table 3.3 above), reflecting the unusual dosing schedule in the trial. Patients received their second treatment cycle when they no longer had a clinically meaningful improvement on the MG-ADL. Thus, many patients were back near baseline at 8 weeks.

The subgroup analyses for patients in the ADAPT trial who were anti-AChR antibody negative did not report p-values or confidence intervals. Patients randomized to efgartigimod were only slightly more likely to respond based on the MG-ADL (68% vs. 63%, p=NR). There were trends towards greater benefits on other measures as well in exploratory analyses (Supplement Table D2.6-D2.9).

***Rituximab***

In the unpublished BeatMG Phase II study, rituximab did not significantly differ from placebo on the primary outcome of achieving at least a 75% reduction in daily prednisone dose after two cycles of rituximab separated by six months (60% vs. 55.6%, p=NR). Changes in QMG and MGC were nominally greater in the rituximab group (Supplement Table D2.7). As noted above, the patient population in the BeatMG trial was very different from the REGAIN and ADAPT study populations.

***IVIG***

In the unpublished trials of IVIG for maintenance therapy, IVIG failed to reduce prednisone dosing more than placebo in the first study[26] but appeared to lead to a greater reduction in the QMG in the second study (-4.6 vs. -2.7, p=NR, Supplement Table D2.7).[27]

**Network Meta-analyses Comparing Eculizumab, Efgartigimod, and Placebo at four weeks in anti-AChR antibody Positive Patients Refractory to Conventional Therapy Using the Definition of "Refractory" from the REGAIN Trial**

Using academic-in-confidence data provided by the manufacturer, we compared efgartigimod to eculizumab in patients who were anti-AChR antibody-positive and "refractory" to conventional therapy, as defined by the REGAIN trial. The NMA evaluated improvement in MG-ADL and QMG at four weeks (Tables 3.4 and 3.5 below). Baseline characteristics of the subgroup of patients in the ADAPT trial who were anti-AChR antibody-positive and "refractory" to conventional therapy (academic-in-confidence) were similar to the REGAIN trial. NMA results showed that both eculizumab and efgartigimod significantly improved MG-ADL and QMG compared with placebo at four weeks. However, efgartigimod had significantly greater improvements compared with eculizumab. For instance, the mean improvement in MG-ADL was 1.0 points greater for efgartigimod than that for eculizumab (CrI: 0.8 to 1.2). At eight weeks, the results for efgartigimod had returned to near baseline due to the dosing schedule and were lower than those for eculizumab (data in confidence).

**Table 3.4. NMA Results of Change in MG-ADL Score at Week Four from Baseline (Fixed Effect Model): Mean Difference (95% Credible Interval)**

| **Efgartigimod** | | |
|---|---|---|
| 1.0 (0.8 to 1.2) | **Eculizumab** | |
| 3.0 (2.8 to 3.2) | 2.0 (1.9 to 2.1) | **Placebo** |

**Table 3.5. NMA Results of Change in QMG Score at Week Four from Baseline (Fixed Effect Model): Mean Difference (95% Credible Interval)**

| Efgartigimod | | |
|---|---|---|
| 3.5 (3.1 to 3.9) | **Eculizumab** | |
| 5.3 (5 to 5.6) | 1.8 (1.6 to 2.0) | **Placebo** |

## Harms

### *Eculizumab*

In the REGAIN trial, Serious adverse events (SAEs) were less common in the patients randomized to eculizumab than those randomized to placebo (Supplement Tables D2.12-D2.14). There was one MG crisis in a patient in the eculizumab group who died from the crisis 90 days after the last eculizumab dose. Otherwise, the most common AEs (headache, upper respiratory tract infections, nausea, etc.) were similar or more common in the placebo group. However, there were more discontinuations because of AEs in the eculizumab group (6% vs. 0%). Eculizumab carries a black box warning for meningococcal infection, and patients are required to be vaccinated at least two weeks prior to the first dose of the drug. There were no cases of deaths associated with meningococcal infection in the REGAIN trial.

### *Efgartigimod*

In the ADAPT trial, infections were more common in the efgartigimod group compared to the placebo group (46% vs. 37%). SAEs were less common in the patients randomized to efgartigimod than those randomized to placebo (Supplement Tables D2.12-D2.14). Similarly, the most common AEs (headache, upper respiratory infections, nausea, etc.) were similar or more common in the placebo group. However, the risk for discontinuations due to AEs was similar in both groups (4% vs. 4%).

### *Rituximab*

In the BeatMG trial, SAEs were slightly lower in the rituximab group compared with placebo (36.0% vs. 51.9%, p=NR). Treatment related discontinuations were not reported. Progressive multifocal leukoencephalopathy (PML) is a known, rare SAEs in patients treated with rituximab. The occurrence of PML was not measured in the BeatMG trial.

### *IVIG*

In the two Phase II studies of IVIG, SAEs were higher in the IVIG group compared with placebo in one study (16.7% vs. 12.5%) and lower in the other (13.3% vs. 20.0%). In addition, treatment related discontinuations were slightly higher in the IVIG group compared with placebo in both trials (6.7% vs. 6.3%; 20.0% vs. 13.3%).

## Subgroup Analyses and Heterogeneity

There are many subgroups of interest for which we had no data or very limited data. No results were presented by race/ethnicity nor were data broken out by patients positive for the MuSK or lipoprotein receptor-related protein 4 (LRP4) antibodies. Eculizumab was studied only in treatment-resistant anti-AChR antibody positive patients with no data in patients who are not treatment resistant but who may benefit from early treatment with eculizumab. Finally, efgartigimod was studied in both anti-AChR antibody positive and negative patients, but the majority of patients (Supplement Table D2.3) were antibody positive, and their primary endpoint was in antibody positive patients.

## Uncertainty and Controversies

Both eculizumab and efgartigimod share many uncertainties. First, it is not clear if or when to stop either of the drugs once initiated other than for patients not responding after some period of time. Additionally, their target population is uncertain. For instance, eculizumab was studied only in refractory patients using a specific definition of refractory, but the FDA label does not specify limiting use to refractory patients. Efgartigimod's pivotal trial included anti-AChR antibody positive and negative patients, but the primary outcome was in antibody positive patients. Should it be used to treat antibody negative patients? In general, there are insufficient data to assess their effectiveness in other important subgroups such as patients who are positive for the anti-MUSK antibody for efgartigimod (eculizumab will not work due to mechanism of action), LRP4 antibody positive patients, non-white populations, and those with disabling ocular disease. Finally, there are limited data on long-term safety, given that these drugs may be used for many years.

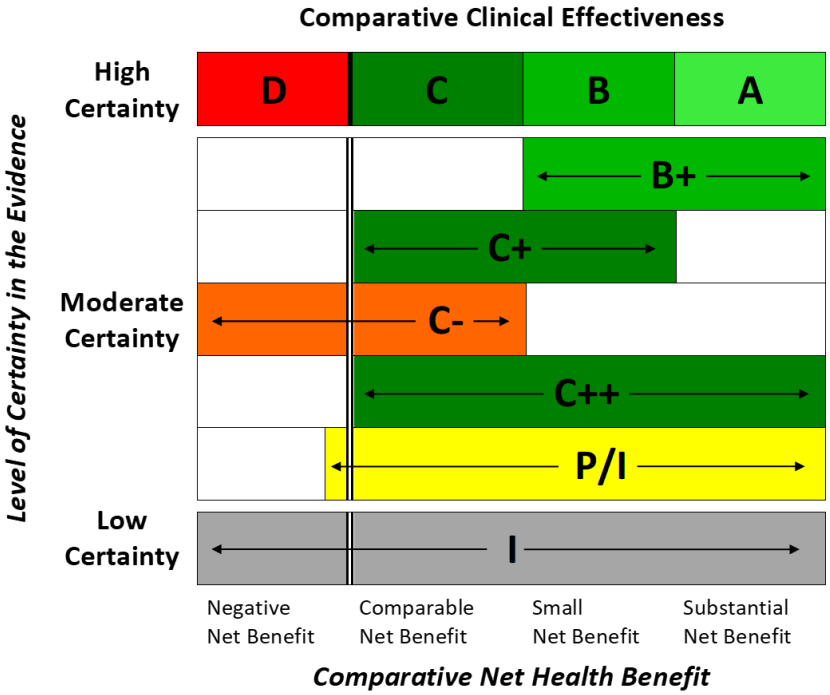
For efgartigimod, the primary uncertainty is the appropriate dosing regimen. In the ADAPT trial, subsequent cycles were started once patients lost clinical benefits. It seems likely that in routine practice, patients and clinicians will not want to wait until the benefits have receded before starting another round of therapy. At this time, there is also considerable uncertainty about the long-term benefits of therapy.

Despite their use in clinical practice, there is a lack of comparative efficacy data for both rituximab and IVIG used as maintenance therapy for gMG.

## 3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided in Supplement Section D.

**Figure 3.1. ICER Evidence Rating Matrix**




***A = "Superior" -*** *High certainty of a substantial (moderate-large) net health benefit*
***B = "Incremental" -*** *High certainty of a small net health benefit*
***C = "Comparable"-*** *High certainty of a comparable net health benefit*
***D= "Negative"-*** *High certainty of an inferior net health benefit*
***B+= "Incremental or Better" –*** *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
***C+ = "Comparable or Incremental" -*** *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
***C- = "Comparable or Inferior" –*** *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
***C++ = "Comparable or Better" -*** *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
***P/I = "Promising but Inconclusive"*** *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
***I = "Insufficient" –*** *Any situation in which the level of certainty in the evidence is low*

## Adults with gMG Positive for Anti-AChR Antibodies

Eculizumab did not meet its primary endpoint in the Phase III REGAIN trial, which was studied in adults with gMG positive for anti-AChR antibodies refractory to conventional therapy. However, there were consistent, clinically important improvements in the MG-ADL and QMG scores at four weeks that were maintained through 26 weeks in the trial and through 130 weeks in long-term follow-up. There were no excess AEs, although more patients in the eculizumab group stopped treatment due to AEs, one died following an MG crisis, and it carries a black box warning for meningococcal infections. Overall, we have moderate certainty of a small or substantial net health

benefit with high certainty of at least a small benefit for eculizumab added to conventional therapy compared with conventional therapy alone (B+) in adults with gMG positive for anti-AChR antibodies refractory to conventional therapy.

In the subgroup of the ADAPT trial, with these patient characteristics (i.e., gMG positive for anti-AChR antibodies 'refractory' to conventional therapy using the REGAIN trial definition of refractory) and the broader population of patients with gMG positive for anti-AChR antibodies, efgartigimod treated patients had a greater response to therapy than those in the placebo group. In the NMA, efgartigimod had a greater improvement in MG-ADL and QMG scores than eculizumab. However, the benefits decreased significantly at eight weeks. AEs did not appear to be more common with efgartigimod, but there are long term concerns about infections with lowering of IgG levels. Given the uncertainties about dosing and consistent long-term benefits of therapy, we concluded that there is moderate certainty of a comparable, small, or substantial net health benefit of efgartigimod added to conventional therapy with high certainty of at least comparable net health benefit (C++). Given the same uncertainties about dosing and long-term benefits and the indirect comparisons, we concluded that the evidence was insufficient (I) to distinguish the net health benefits of efgartigimod from eculizumab.

The evidence is insufficient (I) to distinguish the net health benefits of rituximab and IVIG from placebo, eculizumab, and efgartigimod.

## Adults with gMG Negative for Anti-AChR Antibodies

Eculizumab is not approved for treatment in patients who test negative for anti-AChR antibodies and has not been studied in RCTs in this population.

While there is evidence for efgartigimod in this population, it is sparse and of uncertain clinical and statistical significance. Thus, we concluded that the evidence was insufficient to distinguish the net health benefits of efgartigimod added to conventional therapy from conventional therapy alone in this population.

**Table 3.6. Evidence Ratings**

| Treatment | Comparator | Evidence Rating |
|---|---|---|
| ***Adults with gMG positive for anti-AChR antibodies*** | | |
| **Eculizumab** | Placebo | B+ |
| **Efgartigimod** | Placebo | C++ |
| **Eculizumab** | Efgartigimod | I |
| **Eculizumab/Efgartigimod** | Rituximab | I |
| **Eculizumab/Efgartigimod** | IVIG | I |
| ***Adults with gMG negative for anti-AChR antibodies*** | | |
| **Eculizumab** | Placebo | I |

AChR: acetylcholine receptor, IVIG: intravenous immunoglobulin, QMG: quantitative myasthenia gravis score

# 4. Long-Term Cost Effectiveness

## 4.1. Methods Overview

The primary aim of this analysis was to estimate the cost effectiveness of eculizumab and, separately, efgartigimod, each added to conventional therapy versus conventional therapy alone. The base-case analysis evaluated eculizumab plus conventional therapy versus conventional therapy alone in patients with "refractory" anti-AChR antibody positive gMG, as defined in the REGAIN trial. We also evaluated efgartigimod plus conventional therapy versus conventional therapy alone in the broader population of patients with gMG, where the broader population includes patients with or without anti-AChR antibodies. Although we rated the evidence for efgartigimod as insufficient in anti-AChR negative antibody gMG, the base case for efgartigimod focused on the broader gMG population, in alignment with the studied population in the ADAPT trial.

To provide further context around the cost effectiveness of eculizumab and efgartigimod, we conducted several scenario analyses that are described in Supplement Section E1. Productivity changes and other indirect costs and effects were not available due to an absence of evidence on the impact of treatments on productivity, caregiver burden, and other costs and outcomes considered important from a societal perspective. Therefore, all analyses take the health care system perspective and although a modified societal perspective was explored, the absence of evidence does not differentiate the draft findings between the modified societal perspective and that of the health care system perspective (Supplement Table E1). The time horizon chosen for this analysis was two years. This horizon is shorter than the ICER reference case of a lifetime due to the following reasons: 1. In discussion with clinical experts, we heard that MG was heterogeneous but not considered progressive; 2. The interventions or their comparators, within our scope, do not have evidence supporting differences in mortality; 3. The interventions of interest have evidence supporting an onset of action within one model cycle (i.e., 28 days) and a stable maximal effect within two model cycles and; 4. The cost-effectiveness findings are thought to stabilize within a two-year time period.

The following base-case analyses were conducted:

- Compared eculizumab plus conventional therapy to conventional therapy in patients with "refractory" anti-AChR antibody positive gMG, four-state model (Figure 4.1)
- Compared efgartigimod plus conventional therapy to conventional therapy in patients with gMG, four-state model (Figure 4.1)

The base-case analysis comparing eculizumab plus conventional therapy to conventional therapy alone in patients with "refractory" anti-AChR antibody positive gMG used a four-state Markov model, shown in Figure 4.1, and response definitions, shown in Table 4.1, with a four-week cycle length and two-year time horizon. Simulated patients entered the model through the Markov state, "Unimproved MG on initial treatment," and received eculizumab plus conventional therapy or conventional therapy alone. The QMG was chosen as the primary outcome measure for two reasons: experts suggested that there were significant floor and ceiling effects with the MG-ADL that were less problematic with the QMG; and the QMG was reported in studies evaluating the cost effectiveness of all therapies included in this review, while the MG-ADL was not reported in the included studies evaluating IVIG and rituximab. Patients with a minimum three-point improvement in QMG remained on the initial treatment (i.e., eculizumab or efgartigimod) and transitioned to the "Improved MG on initial treatment" Markov state. Those patients with less than a three-point improvement in QMG by week eight (two model cycles) discontinued the initial treatment and transitioned to the "Unimproved MG off-treatment" state. All living patients remained in the "Improved MG on initial treatment" or "Unimproved MG off-treatment" for all future cycles. Patients entered the "Death" state from any model state and in any cycle. In addition, simulated patients could experience MG-related hospitalizations and emergency room visits in any living state of the model. The probability of hospitalizations and emergency room visits were higher for patients in the "Unimproved MG off-treatment" Markov state. Costs, utilities, and effectiveness outcomes for each state were summed for each cycle.

The base-case analysis comparing efgartigimod versus conventional therapy in all patients used the same four-state Markov model structure, shown in the model schematic Figure 4.1, and response definitions shown in Table 4.1. Simulated patients with gMG (with or without anti-AChR antibody) enter the model through the Markov state, "Unimproved MG on the initial line of treatment," and received either efgartigimod plus conventional therapy or conventional therapy alone. Response, defined as the proportion of patients with a minimum three-point improvement in QMG, was evaluated at four weeks for efgartigimod. Otherwise, patients moved through the model as described for the eculizumab analysis.

To provide further context around the cost effectiveness of eculizumab and efgartigimod, several scenario analyses were conducted. Scenario analyses explored the costs and utility of eculizumab and efgartigimod as first-line treatments in addition to conventional therapy, followed by IVIG or rituximab in those who receive insufficient benefit from eculizumab or efgartigimod (treatment "pathway" scenarios). Treatment "pathway" scenarios were conducted to evaluate the degree to which costs and benefits of treatment were altered by the inclusion of a secondary treatment where the primary treatment had failed. These pathway scenarios were considered exploratory and an incremental cost-effectiveness was not calculated, due to evidence gaps and differences across study populations included in clinical trials. Additional analyses evaluated IVIG therapy and,

separately, rituximab, each in addition to conventional therapy compared with conventional therapy alone in the populations in which each of those treatments were studied in clinical trials.

All scenario analysis treatment strategies and comparisons that were conducted are described below:

1. A modified societal perspective was explored, but due to an absence of evidence, did not differentiate from the health care system base-case perspective.

2. Efgartigimod plus conventional therapy versus conventional therapy alone, assessed in patients with "refractory" anti-AChR antibody positive gMG, as defined by the REGAIN trial (data was obtained as academic-in-confidence from the manufacturer).

3. Eculizumab plus conventional therapy versus efgartigimod plus conventional therapy, assessed in patients with "refractory" anti-AChR antibody positive gMG, as defined by the REGAIN trial.

4. IVIG or rituximab plus conventional therapy versus conventional therapy, represented by the placebo control group from the corresponding clinical trial, in patients with gMG.

5. Efgartigimod plus conventional therapy, dosed with four weeks between treatment courses (i.e., four weeks with efgartigimod, four weeks without efgartigimod), versus conventional therapy alone, assessed in all patients enrolled in the ADAPT trial.

Finally, eculizumab or efgartigimod, followed by IVIG or rituximab as second-line treatment in patients with gMG (efgartigimod only) or "refractory" anti-AChR antibody positive gMG (eculizumab or efgartigimod), using effectiveness estimates from a population mix from these respective clinical trials. This analysis was exploratory and therefore not included in the numbered scenario list.

Additional information about the methods used to evaluate the cost effectiveness of treatments for MG, including models and methods for scenario analyses, are located in Supplement Section E1.

**Figure 4.1. Model Schematic: Four-State Model Depicting Treatment for Myasthenia Gravis**

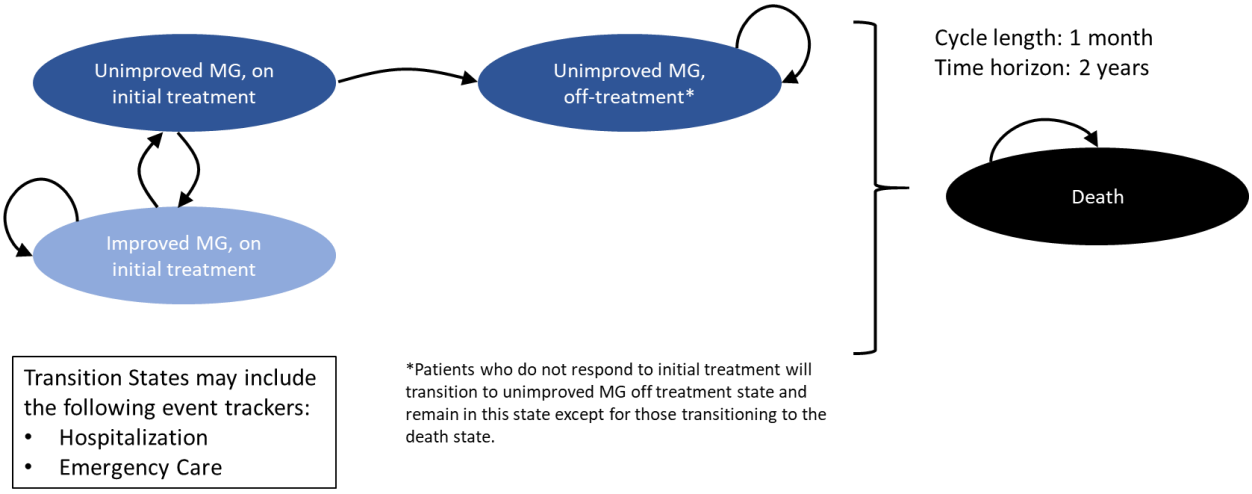



**Table 4.1. Treatment Response Definitions Used in the Base-Case Model**

| Markov State | Definition | Calculation from Clinical Trials |
|---|---|---|
| Unimproved MG on (initial) treatment | All patients are in this state in the first cycle. For subsequent cycles, patients transition to either "Improved MG on treatment" or "Unimproved MG off treatment," depending on whether a three-point or greater improvement in QMG score was achieved. | All patients start in this state in the first cycle. Transition out of this state depends on the proportion of patients with a less than or greater than a three-point improvement in QMG from baseline at four and eight weeks (at four weeks only for efgartigimod). |
| Improved MG on (initial) treatment | A three-point or greater improvement in QMG while on initial treatment. | Proportion of patients with a three-point or greater improvement in QMG from baseline at four and eight weeks (at four weeks only for efgartigimod). |
| Unimproved MG, off-treatment | A less than three-point improvement in QMG from baseline, with initial treatment discontinued. | Proportion of patients with a less than three-point improvement in QMG from baseline at eight weeks (at four weeks for efgartigimod). |

QMG: quantitative myasthenia gravis score

## 4.2. Key Model Assumptions and Inputs

In order to estimate the cost effectiveness of eculizumab and efgartigimod, several assumptions were needed. These assumptions were based on clinical expert opinion, a review of the available evidence, and/or the investigators' experience with developing similar models. The key model assumptions and rationale for each assumption are listed in Table 4.2. Additional model assumptions are described in Supplement Section E2.

**Table 4.2. Key Model Assumptions**

| Assumption | Rationale |
|---|---|
| Efgartigimod will be continually dosed at weekly intervals. | Efgartigimod is not yet approved by the FDA. Therefore, the recommended dosing frequency has not yet been determined, requiring an assumption. This assumption will be updated as more information about the likely approved dosing frequency becomes available. The dosing frequency will be tested in scenario analyses to determine its impact on cost effectiveness. |
| Patients who do not respond to treatment will have that treatment discontinued. | Ineffective therapies would typically not be continued in a real-world setting. Clinical trials were short term and did not include sufficient information on treatment discontinuation to determine whether discontinuation was due to insufficient treatment effect. Furthermore, clinical trials are often designed to retain patients with insufficient response and may not reflect real-world medication use. |
| Differences in cost or utility are proportional to differences in the QMG, regardless of the baseline QMG score. The relationships between cost or utility and QMG are linear. | There were very limited data available on the differences in costs and utilities for patients with differing health statuses. This assumption allows differential costs and utility be applied to the "Unimproved MG" and "Improved MG" Markov states. |
| There are no differences in mortality among living model states. | A thorough review of the literature did not identify differences in mortality among patients with differing health status, as measured by MG-ADL or QMG. The impact of treatment on mortality was not evaluated in clinical trials. |

FDA: Food and Drug Administration, MG-ADL: myasthenia gravis activities of daily living, QMG: quantitative myasthenia gravis score

The key model inputs are shown in Table 4.3. For both base-case analyses, the proportion of patients achieving a minimum three-point improvement in QMG was derived from clinical trials by bootstrapping mean change in QMG at four and eight weeks for eculizumab and four weeks for efgartigimod using the mean, standard deviation, and assuming a normal distribution.[16,23,28] The bootstrapping method also allowed for changes in QMG score to be estimated for individuals. From these, the proportion of patients with a minimum three-point improvement and the mean change in QMG for each of the "Improved MG" or "Unimproved MG" Markov states were estimated.

The probabilities of hospitalization and emergency department visits were obtained from a study evaluating patient health status and health care resource use for patients who were labeled as having ever-refractory or non-refractory MG.[29]

The probability of AEs was estimated from clinical trials evaluating eculizumab or efgartigimod in patients with MG.[16,23] AEs were included in the model only if they occurred at a probability of at least 5% or would be expected to result in a substantial cost to treat, or decrease in utility, and were significantly higher than placebo. As a result, only the cost of meningococcal vaccine was included for all patients receiving eculizumab. There were no AEs included in patients receiving efgartigimod.

Mortality for patients from any Markov state was estimated using age- and gender-adjusted estimates for the general population sourced from the USA Human Mortality Database.[30] As evidence suggesting that mortality is different among patients with differing severity of MG is lacking, and treatments have not been evaluated for their impact on mortality, treatments in the model were assumed to not have an impact on mortality.

Health state utilities were derived from a deidentified data source provided by Dr. Barnett.[31,32] In the dataset, the QMG and EuroQoL EQ5D-5L states were reported for a cohort of 257 patients with gMG. Utility was determined using the EQ5D-5L health states and the US-based societal value set developed by Pickard et al.[33] The association between QMG and EQ5D-5L was estimated using a univariate linear regression model, including 252 patients with complete QMG scores. The model estimated that patients with a QMG score of "0" had a starting utility of 0.97 and that each 1-point increase in QMG score was associated with a 0.03 decrease in utility.

Pricing for eculizumab was derived using FSS prices and is shown in Table 4.3.[34] Pricing for efgartigimod was not yet known at the time of this draft report. However, a public statement from argenx suggested that pricing for efgartigimod would be between the prices of IVIG and eculizumab.[35] We, therefore, used a price that was the midpoint of these two treatments for the model. Treatment administration costs were included in the model and are presented in Supplement Table E2.4.

Non-drug health care costs were derived from published literature. The cost of patients experiencing MG-related hospitalizations was derived from Omorodion et al.[36] The cost for an MG-related emergency visit was not available through a literature search or other public sources. Therefore, the mean cost for an emergency department visit in the US, obtained from the Healthcare Cost and Utilization Project, was used.[37]

All costs were adjusted for inflation to 2021 US dollars as per ICER's Reference Case. Additional key model inputs, supporting the sensitivity and scenario analyses, are presented in Section E2 of the Supplement.

**Table 4.3. Key Model Inputs**

| Parameter | Input | Source |
|---|---|---|
| Proportion of patients achieving 3 point or more reduction in QMG with **eculizumab** plus CT at 4 weeks (i.e., transition probability from unimproved to improved state) | 0.53 | Bootstrapped value derived from Howard 2017[16] |
| Proportion of patients achieving 3 point or more reduction in QMG with **eculizumab** plus CT at 8 weeks (i.e., transition probability from unimproved to improved state) | 0.58 | Bootstrapped value derived from Howard 2017[16] |
| Proportion of patients achieving 3 point or more reduction in QMG with **CT** (eculizumab comparator) at 4 weeks (i.e., transition probability from unimproved to improved state) | 0.37 | Bootstrapped value derived from Howard 2017[16] |
| Proportion of patients achieving 3 point or more reduction in QMG with **efgartigimod** plus CT at 4 weeks (i.e., transition probability from unimproved to improved state) | 0.73 | Bootstrapped value derived from Howard 2021[23] |
| Proportion of patients achieving 3 point or more reduction in QMG with **CT** (efgartigimod comparator) at 4 weeks (i.e., transition probability from unimproved to improved state) | 0.38 | Bootstrapped value derived from Howard 2021[23] |
| Mean change in QMG among responders to **eculizumab** plus CT | -6.95 | Bootstrapped value derived from Howard 2017[16] |
| Mean change in QMG among responders to **CT** (eculizumab comparator) | -6.53 | Bootstrapped value derived from Howard 2017[16] |
| Mean change in QMG among responders to **efgartigimod** plus CT | -8.94 | Bootstrapped value derived from Howard 2021[23] |
| Mean change in QMG among responders to **CT** (efgartigimod comparator) | -6.94 | Bootstrapped value derived from Howard 2021[23] |
| Hospitalizations per cycle among those with unimproved MG | 0.04 | Harris 2020[29] |
| Hospitalizations per cycle among those with improved MG | 0.02 | Harris 2020[29] |
| Emergency visits per cycle among those with unimproved MG | 0.04 | Harris 2020[29] |
| Emergency visits per cycle among those with improved MG | 0.03 | Harris 2020[29] |
| Utility at baseline | 0.47 | Barnett 2021[31,32] |
| Increase in utility for each 1 point reduction in QMG score | 0.03 | Barnett 2021[31,32] |
| Eculizumab cost for first cycle (induction) | $52,100 | Federal Supply Schedule 2021[34] |
| Eculizumab cost per cycle for subsequent cycles | $34,700 | Federal Supply Schedule 2021[34] |
| Cost of vaccination for meningococcal infection (all patients receiving eculizumab) | $77 | Federal Supply Schedule 2021[34] |
| Efgartigimod cost per cycle (Placeholder Price)* | $21,900 | The Motley Fool 2020, assumption[35] |
| Cost per hospitalization | $109,609 | Omorodion 2017[36] |
| Cost per emergency visit | $563 | Healthcare Cost and Utilization Project 2021[37] |

CT: conventional therapy, MG: myasthenia gravis, QMG: quantitative myasthenia gravis score

*Placeholder price: midpoint between annual cost of eculizumab and IVIG

## 4.3. Results

### Base-Case Results

The total discounted lifetime costs, QALYs, and time in an improved state over the two-year time horizon are shown for eculizumab and its comparator and for efgartigimod and its comparator in Tables 4.4 and 4.5, respectively. The mean undiscounted QMG score was 12.11 for eculizumab and 9.82 for efgartigimod. Undiscounted base-case results are presented in Supplement Section E3. As previously noted, all base-case results take the health care system perspective.

**Table 4.4. Results for the Base-Case for Eculizumab plus Conventional Therapy Compared to Conventional Therapy Alone, in Patients with Refractory anti-AChR-Antibody Positive gMG**

| Treatment | Drug Cost | Total Cost | QALYs | Life Years | evLYG | Time in Improved State (years) |
|---|---|---|---|---|---|---|
| **Eculizumab plus CT** | $547,700 | $642,400 | 1.14 | 1.93 | 1.14 | 1.13 |
| **CT alone** | $0 | $95,500 | 0.99 | 1.93 | 0.99 | 0.71 |

CT: conventional therapy, evLYG: equal value of life years gained, QALY: quality-adjusted life year

**Table 4.5. Results for the Base-Case for Efgartigimod plus Conventional Therapy Compared to Conventional Therapy Alone, in All Patients**

| Treatment | Drug Cost | Total Cost | QALYs | Life Years | evLYG | Time in Improved State (years) |
|---|---|---|---|---|---|---|
| **Efgartigimod plus CT*** | $428,500 | $504,500 | 1.28 | 1.93 | 1.28 | 1.41 |
| **CT alone** | $0 | $94,800 | 0.99 | 1.93 | 0.99 | 0.74 |

CT: conventional therapy, evLYG: equal value of life years gained, QALY: quality-adjusted life year
*Efgartigimod evaluated using a placeholder price

Incremental cost/QALY over the two-year time horizon are shown in Table 4.6 for eculizumab plus conventional therapy versus conventional therapy alone and for efgartigimod plus conventional therapy versus conventional therapy alone.

**Table 4.6. Incremental Cost-Effectiveness Ratios for the Base Case**

| Treatment | Comparator | Cost per QALY Gained (same as Cost per evLYG) | Cost per Life Year Gained* |
|---|---|---|---|
| **Eculizumab plus CT** | CT alone | $3,746,000 | n/a |
| **Efgartigimod plus CT**** | CT alone | $1,426,000 | n/a |

CT: conventional therapy, evLYG: equal value of life years gained, QALY: quality-adjusted life year

*There were no differences in survival. Cost per life-year gained could not be calculated whereas cost per evLYG is equal to the cost per QALY gained

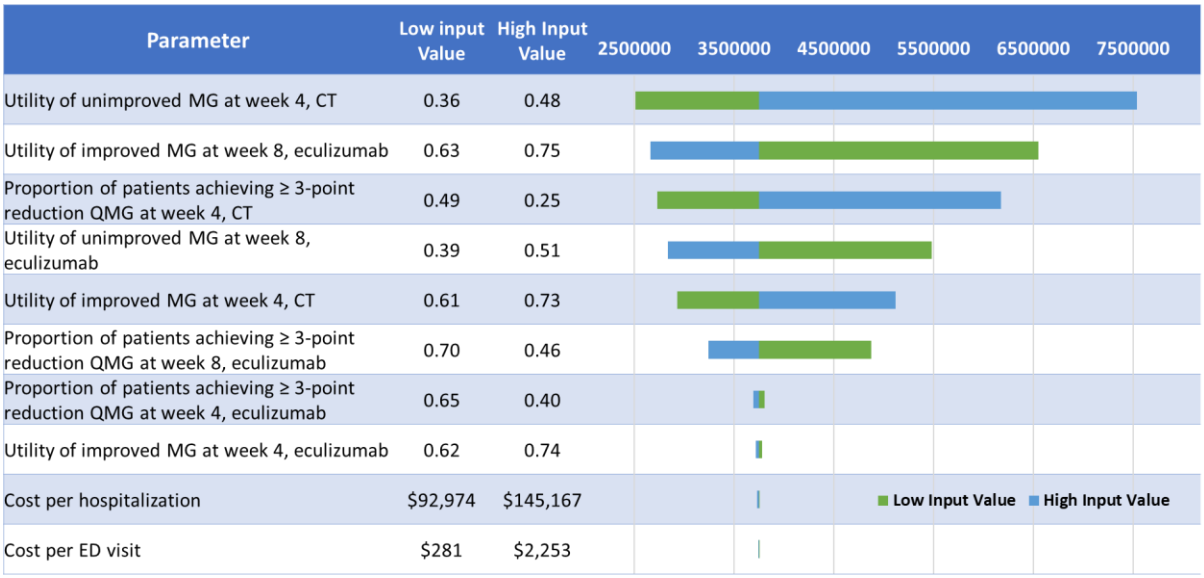
**Efgartigimod evaluated using a placeholder price

## Sensitivity Analyses

The model was sensitive to several inputs, including the utility values assigned to improved and unimproved MG and proportion of patients achieving at least a three-point reduction in the QMG for efgartigimod or its comparator, or for eculizumab and its comparator. Despite the large impact of changing these inputs on the results, the incremental cost-effectiveness ratio was never less than $2.5 million per QALY gained for eculizumab and $1.14 million per QALY gained for efgartigimod, when using the placeholder price for efgartigimod. One-way sensitivity analysis results are shown in Figures 4.2 and 4.3.

The probabilistic sensitivity analysis shows the overall variability in the models comparing efgartigimod or its comparator and eculizumab and its comparator. Results of the sensitivity analyses showed that neither therapy was considered preferred compared with conventional therapy in any of the Monte Carlo runs using willingness-to-pay thresholds of up to $200,000 per QALY gained (Table 4.7). The full cost-effectiveness acceptability curves are shown in the Supplement Section E4.

**Figure 4.2. One-Way Sensitivity Tornado Diagram Varying Model Inputs for Eculizumab plus Conventional Therapy versus Conventional Therapy**




CT: conventional therapy, MG: myasthenia gravis, QMG: quantitative myasthenia gravis score

**Figure 4.3. One-Way Sensitivity Tornado Diagram Varying Model Inputs for Efgartigimod plus Conventional Therapy versus Conventional Therapy**


CT: conventional therapy, MG: myasthenia gravis, QMG: quantitative myasthenia gravis score

**Table 4.7. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Eculizumab plus Conventional Therapy versus Conventional Therapy and Efgartigimod plus Conventional Therapy versus Conventional Therapy**

| | Cost Effective at $50,000 per QALY | Cost Effective at $100,000 per QALY | Cost Effective at $150,000 per QALY | Cost Effective at $200,000 per QALY |
|---|---|---|---|---|
| **Eculizumab plus CT** | 0% | 0% | 0% | 0% |
| **Efgartigimod plus CT*** | 0% | 0% | 0% | 0% |

CT = Conventional therapy, QALY: quality-adjusted life year

*Efgartigimod evaluated using a placeholder price

## Scenario Analyses

The incremental cost-effectiveness ratios for each of the scenario analyses by treatment and comparator are shown in Table 4.8. Due to an absence of evidence, the modified societal perspective did not yield results different from that of the health care system perspective (i.e., base-case results).

**Table 4.8. Incremental Cost-Effectiveness Ratios for the Scenario Analyses**

| Treatment | Comparator | Cost per QALY Gained |
|---|---|---|
| Efgartigimod plus CT (Scenario 1) | CT alone | $1,355,600* |
| Efgartigimod plus CT (Scenario 2) | Eculizumab | Eculizumab is dominated (i.e., efgartigimod is more effective and lower cost) |
| IVIG plus CT (Scenario 3a) | CT alone | $1,076,800 |
| Rituximab (Scenario 3b) | CT alone | $221,300 |
| Efgartigimod plus CT, dosed every 8 weeks (Scenario 4) | CT alone | $1,068,300* |

CT = Conventional therapy, IVIG: Intravenous immunoglobulin, QALY: quality-adjusted life year

*Efgartigimod evaluated using a placeholder price

## Threshold Analyses

The annualized prices required to achieve thresholds of $50,000 to $200,000 per QALY gained are shown in Table 4.9.

**Table 4.9. QALY-Based Threshold Analysis Results**

| | Annual List Price (FSS) | Annual Net Price (FSS) | Annual Price to Achieve $50,000 per QALY | Annual Price to Achieve $100,000 per QALY | Annual Price to Achieve $150,000 per QALY | Annual Price to Achieve $200,000 per QALY |
|---|---|---|---|---|---|---|
| **Eculizumab plus CT** | $653,100 | $470,200 | $6,900 | $13,200 | $19,500 | $25,700 |
| **Efgartigimod plus CT** | n/a | $286,100* | $8,200 | $18,300 | $28,400 | $38,500 |

CT = Conventional therapy, QALY: quality-adjusted life year

*Efgartigimod evaluated using a placeholder price

## Model Validation

Model validation steps are described in the Supplement, Section E7.

## Uncertainty and Controversies

Eculizumab has only been evaluated in a single Phase III RCT of 125 patients with "refractory" generalized anti-AChR antibody positive MG.[16] Efgartigimod has been evaluated in a single Phase III RCT of 167 patients with gMG.[23] Similarly, the results of small clinical trials of IVIG and rituximab as chronic treatments have only recently become available and are still unpublished. The small study sample sizes resulted in greater uncertainty in the true effectiveness of treatments evaluated and prevented subgroup analysis of patients with specific antibodies. Furthermore, studies primarily reported change from baseline QMG and MG-ADL as the primary outcome. Since Markov models require estimates of the proportion of patients benefitting from a treatment at specific times and the impact of that treatment in those patients, we had to bootstrap the needed model inputs. The bootstrapped results may not precisely replicate the study's results due to assumptions needed to conduct the bootstrapping, such as the assumption that the change in QMG from baseline was normally distributed.

Differences in the timing of assessments in clinical trials also limited the ability to compare treatments to each other. For example, eculizumab and efgartigimod outcomes were evaluated at 4 weeks, while IVIG and rituximab were evaluated at 24 and 52 weeks, respectively. Therefore, it was necessary to make assumptions about when the onset of each treatment occurred and when the peak effect was reached, using evidence from other studies.

Another uncertainty encountered was that there were no published studies evaluating associations between MG-ADL or QMG and utility. However, we were able to identify unpublished data that could be used to estimate this association.

There were very limited studies evaluating the association between QMG or MG-ADL and the costs of MG treatment. We identified a single study that assessed differences in hospitalizations and emergency care visits in patients who were classified as ever-refractory or non-refractory. While we were able to identify the cost of hospitalization, we were not able to identify a study quantifying the cost of an emergency care visit in patients with gMG. Additionally, we were unable to identify studies quantifying the impact of treatment on productivity, caregiver burden, or other societal costs or benefits. It is likely that there are additional differences in the direct and indirect cost of care for MG patients with differing health status that might be impacted by effective treatment.

The impact of treatment with eculizumab or efgartigimod on steroid use has not been sufficiently evaluated. Therefore, a potential steroid-sparing effect of these agents was not assumed in the model.

## 4.4 Summary and Comment

The cost effectiveness of eculizumab, at its current price, is well beyond typical thresholds. A substantial discount would be needed to meet commonly used cost-effectiveness thresholds. The cost effectiveness of IVIG and rituximab were also well above commonly used cost-effectiveness thresholds, although rituximab was substantially more cost effective than eculizumab or IVIG. The cost-effectiveness of efgartigimod will depend on its price.

Sensitivity analyses identified that the uncertainty in utility and treatment effectiveness estimates had a large impact on estimated incremental cost effectiveness. However, at the current (for eculizumab) and placeholder (for efgartigimod) prices, the treatments remained well above common cost-effectiveness thresholds across a range of analyses.

# 5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this Report, the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the interventions in this review.

**Table 5.1. Contextual Considerations**

| Contextual Consideration | Relevant Information |
|---|---|
| Acuity of need for treatment of individual patients based on the severity of the condition being treated | MG is a serious illness with potentially large effects on quality of life, and 60% to 80% of patients with gMG do not achieve treatment goals with conventional therapy. |
| Magnitude of the lifetime impact on individual patients of the condition being treated | MG is a lifelong disease with periodic exacerbations that impacts vision, mobility, speech, swallowing, and breathing. |
| Other (as relevant) | |

**Table 5.2. Potential Other Benefits or Disadvantages**

| Potential Other Benefit or Disadvantage | Relevant Information |
|---|---|
| Patients' ability to achieve major life goals related to education, work, or family life | MG affects particularly women in their early working lives leading to reduced working hours, slow career progression, and early retirement. It also impacts women during childbearing years and may lead to delayed childbearing due, in part, to the toxicities of the treatments. |
| Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life | Caregivers may be needed to help with travel, feeding, and communication. |
| Patients' ability to manage and sustain treatment given the complexity of regimen | Not applicable |
| Society's goal of reducing health inequities | MG tends to present at younger ages in women and later ages in men. It also presents significantly earlier for Black Americans, and they may have a more severe disease course. |
| Other (as relevant) | |

# 6. Health Benefit Price Benchmarks

ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We, therefore, caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmarks that will be presented in the next version of this Report.

# 7. Potential Budget Impact

## 7.1. Overview of Key Assumptions

ICER used results from the cost-effectiveness model to estimate the potential total budgetary impact of efgartigimod in the treatment of patients with MG and MGFA clinical classification II-IV disease. We used an estimate of WAC, an estimate of net price, and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) in our estimates of efgartigimod's potential budget impact. Consistent with the cost-effectiveness analysis, efgartigimod was assigned a placeholder net price equal to the average between IVIG and eculizumab annual net prices. Placeholder prices will be updated in future versions of the Report should actual pricing information become available.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at select prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2021-2022, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $734 million per year for new drugs.

ICER's methods for estimating potential budget impact are described in detail in the Report Supplement Section F. For this analysis, we calculated the budget impact of efgartigimod added to conventional therapy (i.e., thymectomy when appropriate, acetylcholinesterase inhibitor, corticosteroids and/or non-steroidal immunosuppressive therapy) given its displacement of eculizumab (assumed 2.27% market share by patient volume) and conventional therapy (97.73% market share by patient volume) and by assigning an additional 9,374 new individuals to efgartigimod treatment per year for five years (46,870 individuals in total over five years).

## 7.2. Results

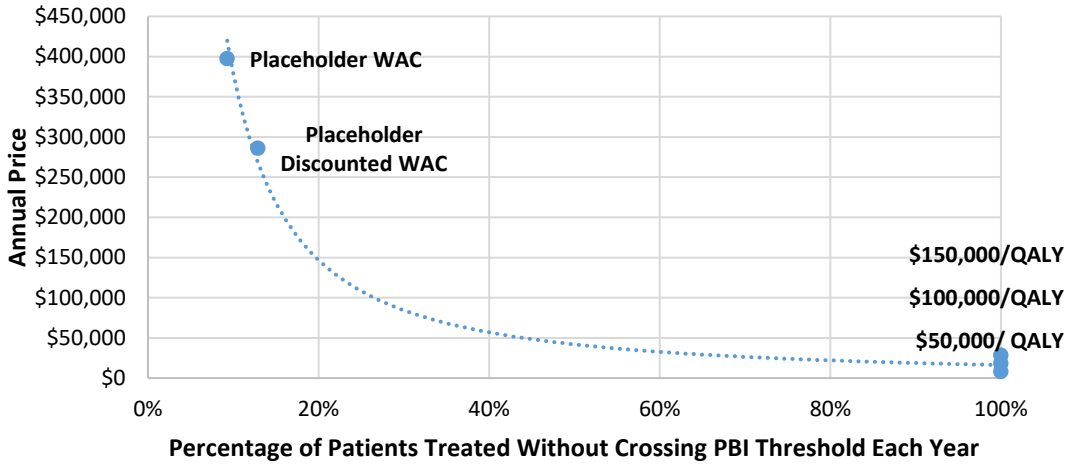
Report Supplement Section F displays the average annual per patient budget impact findings across the five unit prices (placeholder WAC, placeholder discounted WAC, and the prices that achieve three different cost-effectiveness thresholds) for efgartigimod. Further, Report Supplement Section F details the cumulative per-patient budget impact estimates for efgartigimod.

Figures 7.1 illustrates the potential budget impact of efgartigimod treatment for the eligible population based on the respective five unit prices (placeholder WAC, placeholder discounted WAC, and the prices that achieve three different cost-effectiveness thresholds) as a function of the percent of the eligible population that can be treated without crossing the potential budget impact threshold.

In accordance with Figure 7.1, the percentage of the eligible population that can be treated with efgartigimod without passing the updated potential budget impact threshold is 9.3% at placeholder WAC price ($397,000* per year) and 12.9% at discounted placeholder WAC price ($286,000* per year). In contrast, 100% of the eligible population could be treated at health benefit price benchmarks aligned with each of the incremental cost-effectiveness ratios of $150,000/QALY, $100,000/QALY, and $50,000/QALY.

* These are unvalidated placeholder prices that are assumed to be the midpoint between calculated IVIG price and calculated eculizumab price; this methodology is partially sourced from argenx Q2 and Q3 earnings calls.[38,35] Interpret findings for these two placeholder plotted points with caution.

**Figure 7.1. Budgetary Impact of Efgartigimod**



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# Supplemental Materials

# A. Background: Supplemental Information

## A1. Definitions

**The Myasthenia Gravis Foundation of America (MGFA) Clinical Classification**[39]: The MGFA clinical classification was established to create a uniform approach to classifying MG disease severity for research and the clinical management of patients. Patients are classified by the following disease severity and localization of symptoms:

> ***Class I***: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
> ***Class II:*** Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
>
> - IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
> - IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
>
> ***Class III:*** Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
>
> - IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
> - IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
>
> ***Class IV****:* Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
>
> - IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
> - IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
>
> ***Class V:*** Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

**Generalized Myasthenia Gravis**: Generalized MG is a subset of the disease that progresses beyond initial manifestation of weakness in the ocular muscles (ocular MG) to other regions of the body.[40] Patients with ocular MG typically develop generalized MG within the first two years of disease; early diagnosis and immunosuppressive treatment may delay progression of ocular MG to gMG.[11,41]

**Refractory Myasthenia Gravis**[42]: The 2016 MGFA international consensus guidance for MG defines refractory MG as no improvement or worsening of symptoms after an adequate trial of corticosteroids and two or more immunosuppressive agents.[12] There are other definitions for refractory MG which include a patient's inability to reduce immunosuppressive therapy, the need for ongoing rescue therapy (intravenous immunoglobulin G (IVIg) or plasma exchange [PE]), or the inability to tolerate the side-effects of conventional treatment.[43] Approximately 10 to 20 percent of patients with MG are considered refractory; they have a greater burden of illness and experience greater rates of myasthenic crises and hospitalization.[42]

**Minimal Manifestations (MM)**[39]: A subset of the MGFA Post-intervention Status used to assess the clinical state of a patient after treatment for MG. A patient with MM has no symptoms of functional limitations from MG but has some weakness on examination of some muscles.

**Anti-Acetylcholine Receptor Antibody (AChR-Ab+)-associated Myasthenia Gravis**: Patients with anti-AChR-Ab+-associated MG have antibodies against the AChR in the neuromuscular junction.[4] This disrupts neuromuscular transmission in the body and leads to muscle weakness and fatigability.[4] Anti-AChR antibodies are highly specific for MG disease and are used as part of the diagnostic evaluation.[44] Approximately 80% of generalized MG patients have AChR autoantibodies.[45] They are less common (50-75%) in ocular MG patients.[44] Other less common autoantibodies associated with MG include those against the MuSK and LRP4 receptors.[45]

**Myasthenia Gravis–specific Activities of Daily Living scale (MG-ADL)**: The MG-ADL scale is an eight-item instrument consisting of patient reported outcomes assessing two ocular, three bulbar, one respiratory, and two limb symptoms of MG.[46] A two-point improvement in the MG-ADL scale is considered clinically significant.[47] The MG-ADL is an increasingly common primary endpoint used in MG-related clinicals trials.[48]

**Quantitative Myasthenia Gravis Score (QMG):** The QMG is a 13-item instrument that assesses disease severity via physical examination of ocular (two items), facial (one item), bulbar (two items), gross motor (six items), axial (one item), and respiratory (one item) function.[46] In patients with mild to moderate MG (baseline QMG ≤16), a 2-point change in score is considered clinically significant; for patients with severe MG (baseline QMG ≥16) a three-point change in score is considered clinically significant.[49] The QMG evaluation requires use of two medical instruments (spirometers, dynamometer) and can take up to 25 minutes to perform, making it better suited for research settings versus routine clinical assessments.[49]

**Myasthenia Gravis Quality of Life 15 scale (MG-QOL15):** The MG-QOL15 scale is a patient-reported 15-item instrument derived from the 60-item Myasthenia Gravis Quality of Life Scale. It assesses MG health-related quality of life via the following criteria: mobility (nine items), symptoms (three items), and emotional well-being (three items).[50] The MG-QOL15 scale provides added context to

the MG patient experience beyond symptom expression and is sensitive to the fluctuations in MG symptoms that may not be apparent on physical examination.

**Myasthenia Gravis Quality of Life scale revised (MG-QOL15r)**: The revised MG-QOL15 scale is a patient-reported 15-item instrument that assesses MG health-related quality of life via the following criteria: mobility (nine items), symptoms (three items), and emotional well-being (three items).[49] The MG-QOL15r scale provides added context to the MG patient experience beyond symptom expression and is sensitive to the fluctuations in MG symptoms that may not be apparent on physical examination.[51]

**Myasthenia Gravis Composite (MGC) scale**: The MGC scale is a 10-item instrument that derives patient reported outcomes from MG-ADL and physical examination outcomes from the QMGS and Manual Muscle Test.[49] It include three ocular, three bulbar, one respiratory, one neck, and two limb items and is weighted to highlight the increased relevance of bulbar and respiratory symptoms.[49] A three-point improvement in total MGC score represents both a clinical improvement and a meaningful improvement to patients.[52]

**Table A1. Summary of the Key Outcome Measures in Myasthenia Gravis**

| | MG-ADL | QMG | MGC | MG-QOL15r |
|---|---|---|---|---|
| **Items** | 8 | 13 | 10 | 15 |
| **Score Range** | 0-24 | 0-39 | 0-50 | 0-30 |
| **Interpretation** | Higher indicates worse functioning and greater disability | Higher indicates worse functioning and greater disability | Higher indicates worse functioning and greater disability | Higher indicates a worse quality of life and more severe disease |
| **Minimum Clinically Important Difference** | 2 points | 2 points for mild-moderate<br><br>3 points for severe disease | 3 points | Depends on disease severity |
| **Key Features** | 100% patient reported | Objective, no patient reported symptoms: spirometer, dynamometer | 4/10 patient reported; 6/10 clinician assessed. | 100% patient reported |

MG-ADL: Myasthenia gravis activities of daily living, MGC: Myasthenia gravis composite scale, MG-QOL15r: Revised 15-item myasthenia gravis quality of life, QMG: Quantitative Myasthenia Gravis score

## A2. Potential Cost-Saving Measures in Myasthenia Gravis

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/wp-content/uploads/2021/03/ICER_2020_2023_VAF_013120-4-2.pdf). These services are not ones that would be directly affected by eculizumab or efgartigimod (e.g., use of azathioprine), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of myasthenia gravis beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient. We have reviewed the Choosing Wisely recommendations of the Neurology professional societies and none of them seem to apply.

We have received two recommendations from clinical experts:

- Stop serial monitoring of anti-AChR antibodies as there is little correlation with disease severity or response to therapy.
- Decrease lab monitoring for side effects of immunosuppressive agents
- Reduce frequent swallow evals or Pulmonary tests in the absence of clinical symptoms

# B. Patient Perspectives: Supplemental Information

## B1. Methods

During ICER's scoping, open input, and public comment periods, we received public comment submissions from eight stakeholders (two patient advocacy groups, two manufacturers, two clinicians, and one individual) and participated in conversations with 15 key informants (two patient advocacy groups, eight clinical experts, one industry analyst, one manufacturer, two researchers, and one individual). The feedback received from written input and scoping conversations helped us to discuss the impact on patients described in Chapter 2 of the Report.

# C. Clinical Guidelines

## Myasthenia Gravis Foundation of America (MGFA)

A task force of 15 international experts was appointed by the MGFA to develop consensus guidance on the diagnosis and treatment of MG.[12] An updated version of the consensus guidance was published in 2021 to incorporate new evidence, including new recommendations for the use of eculizumab and rituximab.[5]

Goals of Therapy:

MMs or remission with no more than grade 1 AEs from medications used for treatment.

Symptomatic and Immunosuppressive Treatment of MG

1. Pyridostigmine should be first-line treatment with dose adjustments based on symptom severity. If treatment goals are not met, then corticosteroids or immunosuppressive therapies should be considered.
2. Nonsteroidal immunosuppressive agents should be used with corticosteroids in patients to minimize the steroid dose to reduce steroid side effects. If corticosteroids are contraindicated or refused, a nonsteroidal immunosuppressive agent should be used alone.
3. Nonsteroidal immunosuppressive agents for MG include azathioprine, cyclosporine, MMF, methotrexate, and tacrolimus.
    a. There is limited evidence on the comparative effectiveness of the above agents.
    b. Azathioprine is supported by expert consensus and randomized control trial (RCT) evidence as a first-line agent.
    c. Cyclosporine has potential SAEs and drug interactions.
    d. MMF and tacrolimus are widely used despite limited RCT evidence.
4. Patients with refractory MG may be treated with:
    a. Immunosuppressive agents as described above.
    b. Maintenance IVIG and chronic plasma exchange (PLEX)
    c. Cyclophosphamide
    d. Eculizumab for severe, refractory, AChR-Ab+ generalized MG.
        i. Until more evidence is available, eculizumab should be used after failure with other immunotherapies.
    e. Rituximab is an option for refractory AChR-Ab+ MG after failure/medication intolerance of other immunosuppressive agents, but evidence of efficacy is uncertain.
5. After Treatment Goal is met:

a. Corticosteroid dose should be gradually tapered. Long-term low dose usage of corticosteroids may be necessary to maintain treatment goal.
b. Once the treatment goal is achieved and maintained for 6 months to 2 years, nonsteroidal immunosuppressive agents should be tapered to the minimal effective amount. Rapid tapering is associated with the risk of relapse, particularly for symptomatic patients. Therefore, dose adjustments should be limited to every 3-6 months.

## Canadian Agency for Drugs and Technologies in Health[46,53]

In their 2020 review of eculizumab, 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.

Goals of Therapy:

1. Achieving remission, defined as the reduction of MG disease to mild or moderate symptoms, and maintaining this state for as long as possible.
2. Improvement in QoL and daily activities.

In refractory MG patients, goals of treatment also include:

1. Reducing the quantity and severity of relapses
2. Shortening the duration of hospital visits
3. Using the lowest possible medication dosage
4. Minimizing adverse effects, particularly from corticosteroids and other long term-use therapies

Role of Eculizumab in Refractory MG Patients

Eculizumab was deemed useful for patients with refractory MG as an adjunct to other therapies or as a last line of treatment.

The CADTH Drug Expert Committee recommended that eculizumab be reimbursed for treatment of refractory generalized MG after satisfaction of a 6-point initiation criteria[53]:

1. The patient has refractory gMG defined as not achieving symptom control after:

    - an adequate trial of two or more immunosuppressive therapies (ISTs), either in combination or as monotherapy in the previous 12 months, OR
    - an adequate trial of at least one IST and chronic plasmapheresis or PLEX or IVIG at least four times (every three months) in the previous 12 months.

2. The patient has all of the following:

    - AChR-Ab+ status
    - Baseline MG-ADL score of ≥ 6
    - MGFA class II to IV disease

3. The patient does not have a thymoma or is within 12 months of thymectomy.
4. Eculizumab should not be initiated during a gMG exacerbation or crisis.
5. MG-ADL and QMG score must be measured and provided by the physician at baseline.
6. Maximum duration of initial authorization is six months.

# D. Comparative Clinical Effectiveness: Supplemental Information

## D1. Detailed Methods

### Population, Intervention, Comparators, Outcomes, Timing, and Settings Framework (PICOTS)

### Population

The population of focus for the review was adults with gMG, defined by Myasthenia Gravis Foundation of America (MGFA) clinical classes of II to IV for whom conventional immunosuppressive therapies have not been effective or have not been tolerated.[39]

We evaluated the evidence on the following subpopulations:

- Patients with anti-AChR antibodies
- Patients with anti- AChR antibodies who are refractory to treatment

Due to lack of data, we were unable to evaluate patients with MuSK, LRP4, or triple seronegative autoantibodies.

### Interventions

The two interventions of interest for this review are:

- Eculizumab (Soliris®, Alexion Pharmaceuticals, Inc.)
- Efgartigimod (argenx)

Both were added to conventional therapy (thymectomy when appropriate, acetylcholinesterase inhibitor, corticosteroids and/or non-steroidal immunosuppressive therapy) for maintenance therapy in patients with generalized MG.

### Comparators

We compared the agents to each other and to the following:

- Conventional therapy
- Maintenance IVIG therapy (GAMUNEX®-C, Grifols Therapeutics LLC)
- Rituximab (Rituxan®, Roche Holding AG, Biogen, Inc.)

## Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Remission
    - Minimal symptom expression
    - Measures of treatment response (e.g., Myasthenia Gravis Activities of Daily Living [MG-ADL], Quantitative MG score [QMG], etc.)
    - Quality of life (MG Quality of Life, 15, revised [MG-QoL15]; EQ-5D; etc.)
    - Fatigue (Neurology Quality of Life, etc.)
    - MG-related hospitalizations
    - Myasthenic crisis
    - Return to work
    - Lost or delayed childbearing
    - Mental health (anxiety, depression)
    - Corticosteroid side effects (weight gain, acne, diabetes, osteoporosis, cataracts, glaucoma, infections, psychological, etc.)
    - Immunosuppressive side effects and burden (hepatitis, cytopenia, teratogenicity, infusion reactions, etc.)
    - Corticosteroid dose ≤ 5mg prednisone equivalents
    - AEs including:
        - Treatment-related AEs
        - SAEs
        - AEs leading to drug discontinuation
        - Infections including meningococcal disease
        - Malignancies
        - Death
- Other Outcomes
    - MGFA Post-Intervention Status (MGFA-PIS)
        - Complete Stable Remission (CSR)
        - Pharmacologic Remission (PR)
        - Minimal Manifestations (MM)

## Timing

Evidence on intervention effectiveness and harms was derived from studies of at least four weeks duration.

## Setting

All relevant settings were considered, with a focus on patients treated in outpatient settings in the United States.

**Table D1. PRISMA 2009 Checklist**

| | | Checklist Items |
|---|---|---|
| **TITLE** | | |
| **Title** | 1 | Identify the report as a systematic review, meta-analysis, or both. |
| **ABSTRACT** | | |
| **Structured summary** | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. |
| **INTRODUCTION** | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of what is already known. |
| **Objectives** | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). |
| **METHODS** | | |
| **Protocol and registration** | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. |
| **Eligibility criteria** | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. |
| **Information sources** | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. |
| **Search** | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. |
| **Study selection** | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). |
| **Data collection process** | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. |
| **Data items** | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. |
| **Risk of bias in individual studies** | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or |

| | | |
|---|---|---|
| | | outcome level), and how this information is to be used in any data synthesis. |
| **Summary measures** | 13 | State the principal summary measures (e.g., risk ratio, difference in means). |
| **Synthesis of results** | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. |
| **Risk of bias across studies** | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). |
| **Additional analyses** | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. |
| **RESULTS** | | |
| **Study selection** | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |
| **Study characteristics** | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. |
| **Risk of bias within studies** | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). |
| **Results of individual studies** | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |
| **Synthesis of results** | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. |
| **Risk of bias across studies** | 22 | Present results of any assessment of risk of bias across studies (see Item 15). |
| **Additional analysis** | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). |
| **DISCUSSION** | | |
| **Summary of evidence** | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). |
| **Limitations** | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). |
| **Conclusions** | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. |
| **FUNDING** | | |
| **Funding** | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. |

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

## Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for MG followed established best research methods.[54,55,56] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[57] The PRISMA guidelines include a checklist of 27 items, which are described further in Table D1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data.

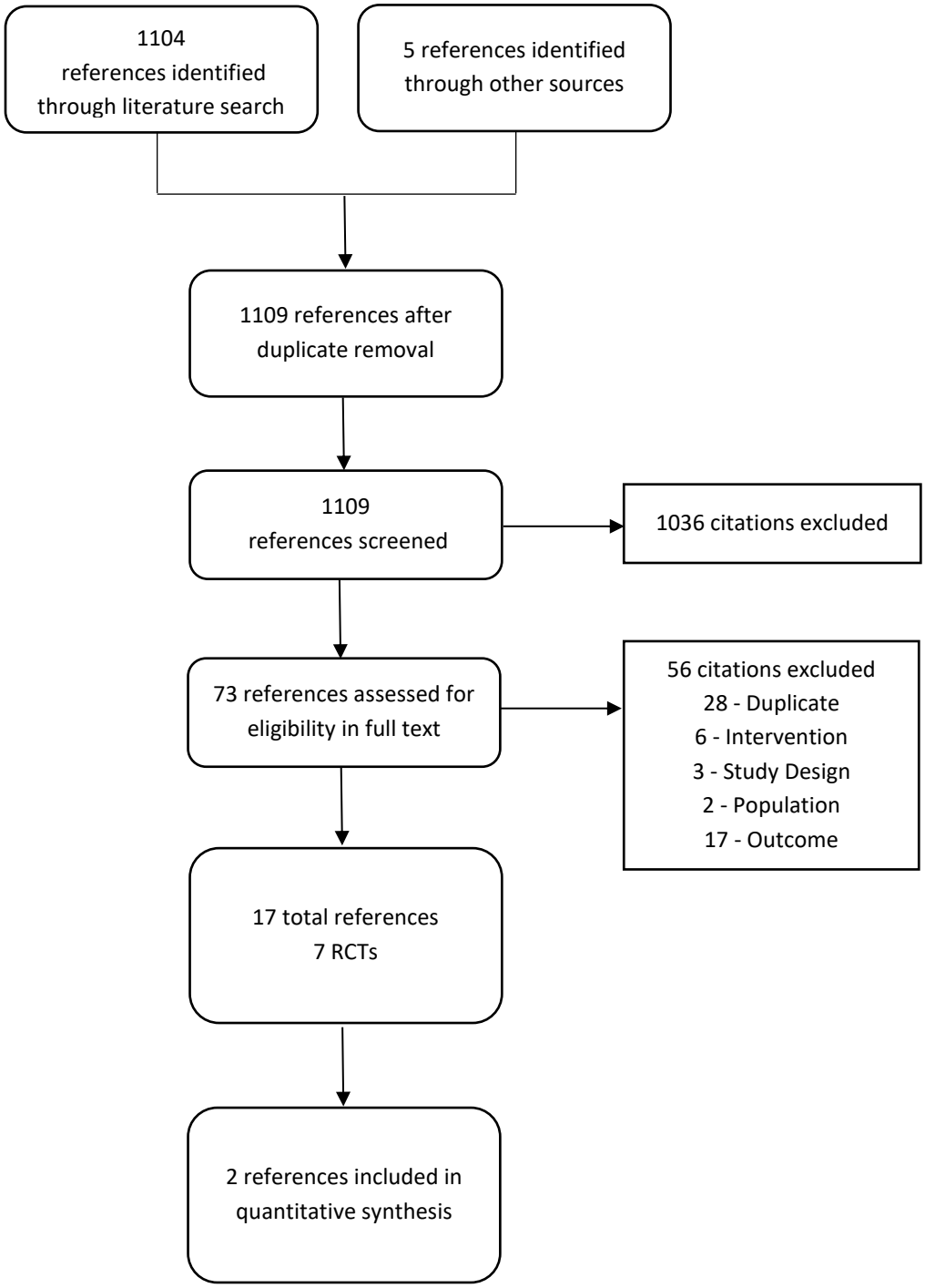
**Table D2. Search Strategy of Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present**

| | |
|---|---|
| 1 | myasthenia gravis/ |
| 2 | (myasthenia gravis OR generalized myasthenia gravis OR myasthen$).ti,ab |
| 3 | 1 OR 2 |
| 4 | (efgartigimod OR ARGX-113 OR ARGX113 OR ARGX 113).ti,ab |
| 5 | (eculizumab OR soliris OR 5G11 OR h5G11).ti,ab |
| 6 | Immunoglobulin, intravenous/ OR ('intravenous immunoglobulin' OR 'IV immunoglobulin' OR 'IVIG').ti,ab |
| 7 | (rituximab OR Rituxan OR IDECC2B8 OR IDEC C2B8).ti,ab OR (mabthera OR Rituxan hycela OR RG105 OR RG 105).ti,ab |
| 8 | 4 OR 5 OR 6 OR 7 |
| 9 | 3 AND 8 |
| 10 | (addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt. |
| 11 | 9 NOT 10 |
| 12 | (animals not (humans and animals)).sh. |
| 13 | 11 NOT 12 |
| 14 | Limit 13 to English language |

**Table D3. Search Strategy of EMBASE SEARCH**

| | |
|---|---|
| #1 | 'myasthenia gravis'/exp |
| #2 | ('myasthenia gravis' OR 'generalized myasthenia gravis' OR 'myasthen$'):ti,ab |
| #3 | #1 OR #2 |
| #4 | ('efgartigimod' OR 'ARGX-133' OR 'ARGX113' OR 'ARGX 113'):ti,ab |
| #5 | ('eculizumab' OR 'soliris' OR '5G11' OR 'h5G11'):ti,ab |
| #6 | (intravenous immunoglobulin OR IV immunoglobulin OR IVIG):ti,ab |
| #7 | ('rituximab' OR 'Rituxan' OR 'IDECC2B8' OR 'IDEC C2B8'):ti,ab OR ('mabthera' OR 'Rituxan hycela' OR 'rituximab and hyaluronidase' OR 'RG105' OR 'RG 105'):ti,ab |
| #8 | #4 OR #5 OR #6 OR #7 |
| #9 | #3 AND #8 |
| #10 | 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it |
| #11 | #9 NOT #10 |
| #12 | ('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp |
| #13 | #11 NOT #12 |
| #14 | #13 AND [English]/lim |
| #15 | ##14 AND [medline]/lim |
| #16 | #14 NOT #15 |

**Figure D1. PRISMA flow Chart Showing Results of Literature Search for MG Treatments**



## Study Selection

We performed screening at both the abstract and full-text levels. Two investigators independently screened all abstracts identified through electronic searches using DistillerSR (Evidence Partners, Ottawa, Canada) according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. We retrieved the citations that were accepted during abstract-level screening for full-text appraisal. Two investigators reviewed full papers and provided justification for the exclusion of each excluded study.

## Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted trials. We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[58] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review .

***Good:*** *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

***Fair:*** *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

***Poor:*** *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

## Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Figure 3.1).[59,60]

## Assessment of Bias

We performed an assessment of publication bias for eculizumab, efgartigimod, rituximab, and maintenance IVIG using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. We found two instances of potential publication bias: the results of the rituximab BeatMG Phase II trial (NCT02110706) and the IVIG Phase II trial (NCT02473952).

## Data Synthesis and Statistical Analyses

Data on key outcomes were summarized in evidence tables (see Section D2 below) and synthesized quantitatively and qualitatively in the body of the review. We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessment for each outcome of interest. Based on data availability, we created networks to compare change from baseline in MG-ADL and QMG scores at 4 weeks in two trials of eculizumab and efgartigimod. We used a subpopulation from the ADAPT trial that met the eculizumab REGAIN trial inclusion criteria of anti-AChR antibody positive, refractory MGFA Class II-IV generalized MG patients. This data was provided in confidence by the manufacturer. The network-meta-analyses (NMAs) were conducted using a Bayesian framework with fixed effects on the treatment parameters using the IndiRect NMA platform (CRG-EVERSANA, 2020TM). The outcomes were continuous and were analyzed using a generalized linear model and identity link. League tables were presented for the treatment effects (mean difference of each drug versus each other and placebo, along with 95% credible intervals (95% CrI). Due to inconsistent or limited data reporting, other outcomes are either described narratively or presented in tables.

# D2. Evidence Tables

**Table D2.1. Study Quality Metrics**

| Study | Comp. Groups | Non-Differential Follow-Up | Patient/Investigator Blinding (Double-Blind) | Clear Def. of Intervention | Clear Def. of Outcomes | Selective Outcome Reporting | Valid Measure-ments | ITT Analysis | Approach to Missing Data | USPSTF Rating |
|---|---|---|---|---|---|---|---|---|---|---|
| **Efgartigimod** | | | | | | | | | | |
| **Phase III ADAPT**[23] | Yes | Yes | Yes | Yes | Yes | No | Yes | mITT | NR | Good |
| **Phase II**[24] | Yes | Yes | Yes | Yes | Yes | No | Yes | mITT | MMRM | Good |
| **Eculizumab** | | | | | | | | | | |
| **REGAIN**[16] | Yes | Yes | Yes | Yes | Yes | No | Yes | mITT | LOCF | Good |
| **REGAIN OLE**[17] | No | No | No | Yes | Yes | No | Yes | mITT | LOCF | NA |
| **Phase II**[22] | Yes | Yes | Yes | Yes | Yes | No | Yes | mITT | NR | Good |
| **Rituximab** | | | | | | | | | | |
| **Phase II: BeatMG**[61] | Yes | Yes | Yes | Yes | Yes | No | Yes | ITT | MI, LOCF | Good |
| **Maintenance IVIG** | | | | | | | | | | |
| **Phase II NCT 02473952**[27] | No | No | Yes | Yes | Yes | No | Yes | mITT | LOCF | Poor |
| **Phase II NCT02473965**[26] | Yes | Yes | Yes | Yes | Yes | No | Yes | mITT | LOCF | Good |

ITT: intention-to-treat, LOCF: last observation carried forward, MI: Multiple imputation approach, mITT: modified intention-to-treat, MMRM: mixed-model repeated-measures analysis, NA: Not Applicable, not RCT or comparative cohort study, NR: not reported, USPSTF: United States Preventive Services Task Force

**Table D2.2. Study Design**

| Trial Name Ref & NCT # | N | Design | Population | Primary Outcome(s) | Arms & Dosing Regimen | Inclusion / Exclusion Criteria |
|---|---|---|---|---|---|---|
| ***Efgartigimod*** | | | | | | |
| **Phase III ADAPT**<br><br>**Howard 2021[62]**<br><br>**NCT03669588** | 167 | Phase III, DB, PC, MC RCT | Patients with diagnosis of MG with generalized muscle weakness (AChR+/-) | **[Time frame: week 8]**<br><br>Efficacy of efgartigimod as assessment by the percentage of MG-ADL responders in the AChR+ population | 1. Efgartigimod (IV)<br>2. Placebo<br><br>Dosing: 4 weekly IV infusions (10 mg/kg) in cycle 1. followed by individualized treatment cycles (up to 3 cycles in 26 weeks) with time between cycles determined by duration of clinically meaningful improvement | ***Inclusion***<br>• Patients ≥ 18 years<br>• MGFA class I or MG crisis at screening (MGFA class V)<br>• History of thymoma or other neoplasms of the thymus<br>• History of thymectomy within 12 months prior to screening<br>• Use of rituximab within 6 months of screening<br>• Use of IVIg within 4 weeks of randomization<br>***Exclusion***<br>• MGFA class I and V patients<br>• Patients with worsening muscle weakness secondary to concurrent infections or medications<br>• Patients with known seropositivity or who test positive for an active viral infection at screening with HBV, HCV, or HIV<br>• Received rituximab or eculizumab in the 6 months before screening, undergone thymectomy within 3 months, had IVIG or plasma exchange within 1 month of screening |
| **Phase II**<br><br>**Howard 2019[24]**<br><br>**NCT02965573** | 24 | Phase II DB, PC RCT | Patients with diagnosis of MG with generalized muscle weakness | **[Time Frame: day 78]**<br><br>Number of patients with TEAEs and TE-SAEs | 1. Efgartigimod (IV) (10 mg/kg)<br>2. Placebo<br><br>Patients received ARGX-113 at a dose of 10 mg/kg in 4 intravenous (IV) infusions, administered 1 | ***Inclusion***<br>• Patients ≥ 18 years<br>• Diagnosis of autoimmune MG with generalized muscle weakness meeting clinical criteria for diagnosis of MG as defined by MGFA classification class II, III, IVa and not in need of a respirator<br>• Positive serologic test for anti-AChR antibodies<br>• Total score of ≥5 on MG-ADL at screening and baseline with more than 50% attributed to non-ocular items<br>• Required to be on stable dose of MG treatment |

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| | | | | | week apart, in addition to SoC. Patients received matching placebo in 4 IV infusions, administered 1 week apart, in addition to SoC. | prior to randomization (e.g. AZA, other NSAIDs, steroids, and/or cholinesterase inhibitors)<br>***Exclusion***<br>• MGFA class I, IVb and V.<br>• Active or recent serious infection within 8 weeks prior to screening<br>• History of HIV, HBV, and HCV or mycobacterium tuberculosis<br>• Clinically significant laboratory abnormalities at screening (e.g. AST and ALT > 2x ULN, clinically significant proteinuria, hemoglobin ≤9 g/L, et.c)<br>• Use of rituximab, belimumab, eculizumab or any monoclonal antibody within 6 months prior to first dosing<br>• BMI ≥35 kg/m2 |
| ***Eculizumab*** | | | | | | |
| **Phase III REGAIN**<br><br>**Howard 2017**[16]<br><br>**NCT01997229** | 125 | DB, PC, MC RCT | AcHR+ positive patients with refractory generalized MG | **[Time frame: week 26]**<br>Change in MG-ADL total score from baseline | 1. Eculizumab 900 mg IV weekly for 4 weeks during induction and 1200 mg IV every 2 weeks during weeks 4-26 of maintenance<br>2. Placebo | ***Inclusion***<br>• Patients ≥ 18 with MG diagnosis<br>• AChR+ at screening and at least one of the following: history of abnormal neuromuscular transmission test or repetitive nerve stimulation, history of positive anticholinesterase test, or has demonstrated improvement in MG signs on oral cholinesterase inhibitors<br>• MGFA clinical classification class II to IV at screening<br>• MG-ADL total score ≥6 at screening and randomization<br>• Failed treatment with at least 2 immunosuppressive agents or failed treatment with at least one immunosuppressive agent and require chronic plasma exchange or IVIg<br>***Exclusion***<br>• MGFA class I or MG crisis at screening (MGFA class V)<br>• History of thymoma or other neoplasms of the thymus<br>• History of thymectomy within 12 months prior to |

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| | | | | | | screening<br>• Use of rituximab within 6 months of screening<br>• Use of IVIg within 4 weeks of randomization |
| **REGAIN OLE**<br><br>**Muppidi 2019[17]**<br><br>**NCT02301624** | 117 | OL Extension of REGAIN trial | AcHR+ positive patients with refractory generalized MG | **[Time frame week 208]**<br>Participants with TEAEs | **Blinded induction phase [4 weeks]**<br>1. ECU in REGAIN: ECU 1,200 mg on day 1 and week 2 and placebo at weeks 1 and 3<br>2. PBO in REGAIN: ECU 900 mg and placebo on day 1 and at weeks 1, 2, and 3.<br><br>**OLE**<br>1. ECU 1,200 every 2 weeks up to week 208 | ***Inclusion***<br>• Patients who completed study ECU-MG-301 (REGAIN)<br>***Exclusion***<br>• Patients who withdrew from REGAIN as a result of an AE due to study drug<br>• Unresolved meningococcal infection<br>• Hypersensitivity to murine proteins or to one of the excipients of eculizumab |
| **Phase II**<br><br>**Howard 2013[22]**<br><br>**NCT00727194** | 14 | DB, PC, Cross-over, MC, RCT | Patients with refractory generalized MG | **[Time frame: week 16]**<br>Percentage of patients with a 3-point reduction in the QMG total score from baseline | 1. Eculizumab: 600 mg IV weekly for 4 doses followed by 900 mg IV every 2 weeks for 7 doses<br><br>2. Placebo: IV weekly for 4 doses then every 2 weeks for 7 doses | ***Inclusion***<br>• Patients ≥ 18 years<br>Generalized MG with MGFA clinical classification class II, III, IVa<br>• QMG total score ≥12 with minimum score of 2 in 4 or more tests in the QMG<br>• Have failed at least two immunosuppressants after one year of treatment<br>• AChR+ at screening and one of the following: history of abnormal neuromuscular transmission test or repetitive nerve stimulation, history of positive anticholinesterase test, or has demonstrated improvement in MG signs on oral cholinesterase inhibitors<br>***Exclusion***<br>• History of thymoma or other neoplasms of the thymus |

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| | | | | | | • History of thymectomy within 12 months of screening<br>• Current or chronic use of plasmapheresis/plasma exchange<br>• IVIG treatment within 8 weeks prior to screening<br>• Use of etanercept or rituximab within 2 or 6 months of screening, respectively<br>• MGFA class I, IVb, V |
| ***Rituximab*** | | | | | | |
| **Phase II BeatMG**<br><br>**Nowak 2019 [Abstract]** [61]<br><br>**NCT02110706** | 52 | Phase II, DB, PC, RCT | generalized MG, AChR+, class II-IV | **[Time frame: week 48]**<br>Percent of subjects that achieve a ≥ 75% reduction in mean daily prednisone dose in the 4 weeks prior to week 52 and have clinical improvement or no significant worsening of symptoms (≤ 2 point increase in MGC score) as compared to 4-week period prior to randomization and initiation of treatment. | 1. Treatment group received two cycles of rituximab (375mg/m2 iv), separated by 6 months. Each cycle defined as one infusion per week for four consecutive weeks.<br><br>2. Placebo group received infusion containing only vehicle components of rituximab solution. Infusion was done in 2 cycles, separated by 6 months. Each cycle defined as one infusion per week for four consecutive weeks | ***Inclusion***<br>• Subjects 21 to 90 generalized MG, class II to IV at screening, AChR+<br>• Subject on stable standard immunosuppressive regimen: a. Prednisone only b. Prednisone plus another immunosuppressive therapy (IST).<br>***Exclusion***<br>• No history of thymoma, tumor, infection, or interstitial lung disease on chest CT, MRI, or chest x-ray.<br>• Thymectomy in the previous six months. Subjects who have been medicated with immunosuppressive drugs not listed in inclusion #5 within the last 8 weeks (56 days) prior to the baseline visit<br>• medicated with an immunosuppressive agent such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus or methotrexate, that is withdrawn within 8 weeks (56 days) of the Baseline Visit.<br>• Subjects who have received IVIg or PLEX treatment within the last 4 weeks (28 days) prior to the baseline visit.<br>• Unstable dose or a stable dose of > 480 mg/day of pyridostigmine in 2 weeks prior to screening visit.<br>• Previous treatment with rituximab<br>• Subjects that do not record daily prednisone doses for at least 28 days before the Baseline Visit, or |

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| | | | | | | subjects whose prednisone dose varies by ≥6mg/day on average.<br>Prednisone dose of more than 100 mg/day (or 200 mg over a two day period |
| **Brauner 2020[63]** | 98 | Retrospective cohort study | Refractory and new-onset gMG, AChR+ | **[Time frame: New-onset MG= 44 months average, treatment refractory= 40mo]**<br><br>1. Time to remission<br>2. Use of rescue therapies/additional immuno.<br>3. Time spent in remission | 1. Treatment with Rituximab (most often 500mg every 6 months)<br>2. Conventional immuno. | ***Inclusion***<br>• patients residing in Stockholm County who received 1 or more dose of rituximab before December 31, 2018.<br>***Exclusion***<br>• Presence of anti-MuSK+ antibodies,<br>• less than 12months' observation time,<br>• a maximum (QMG) score of less than 4 during the year preceding treatment start,<br>• less than 2 recorded follow-up visits,<br>• initiation or follow-up of rituximab treatment outside of Stockholm County,<br>• concurrent neurologic diseases interfering with the assessments, and immunosuppressive therapy for other indications during the observation period. |
| ***Maintenance IVIG*** | | | | | | |
| **Phase II**<br><br>**Griffin 2017 [Abstract][64]**<br><br>**NCT02473952** | 62 | Phase II, DB, PC, RCT | Generalized MG, AChR+, class II-Iva | **[Time frame: week 24]**<br><br>Mean change in QMG score from baseline. An average 3-point improvement in QMG score indicates clinically meaningful improvement. | 1. IGIV-C, initial loading dose of 2g/kg at baseline (week 0, visit 1) followed by 1g/kg maintenance doses every third week through Week 21 (visit 8)<br><br>2. Placebo infusion at same intervals as treatment arm | ***Inclusion***<br>• AChR+ Confirmed diagnosis of generalized myasthenia gravis (MG). MGFA Class II, III, or IVa inclusive at Screening. QMG >= 10 at Screening. Note: Subjects who only have a history of ocular MG may not enroll.<br>• **Receiving standard of care MG treatment at a stable dose** (including cholinesterase inhibitors, prednisone, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus)<br>***Exclusion***<br>• Have received cyclophosphamide or any other immunosuppressive agent apart from the ones allowed per inclusion criteria within the past 6 months<br>• Any change in MG treatment regimen between Screening (Week -3, Visit 0) and Baseline (Week 0, |

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| | | | | | | Visit 1)<br>• Greater than two point change in QMG score, increased or decreased, between Screening (Week -3, Visit 0) and Baseline (Week 0, Visit 1)<br>• Any episode of myasthenic crisis in the one month prior to Screening<br>• Thymectomy within the preceding 6 months<br>• Rituximab, belimumab, eculizumab or any monoclonal antibody used for immunomodulation within the past 12 months<br>• Have received immune globulin (Ig) treatment given by intravenous (IV), subcutaneous, or intramuscular route within the last 3 months<br>• Current known hyper viscosity or hypercoagulable state<br>• Documented diagnosis of thrombotic complications to polyclonal intravenous immunoglobulin (IVIG) therapy in the past<br>• PLEX performed within the last 3 months |
| **Phase II**<br><br>**Griffin 2017 [Abstract][65]**<br><br>**NCT02473965** | 60 | Phase II, DB, PC, RCT | Generalized MG, AChR+, class II-V | **[Time frame: Week 39]**<br><br>Percent of Subjects Achieving a 50% or Greater Reduction in CS Dose (Prednisone or Equivalent) From Baseline to Week 39 | 1. IGIV-C, Run-Phase: 1 loading dose of 2 g/kg IGIV-C and 2 maintenance doses of 1 g/kg IGIV-C<br><br>Corticosteroid Tapering/IGIV-C Maintenance Phase: 1 g/kg IGIV-C every 3 weeks for up to 36 weeks<br><br>2. Placebo | ***Inclusion***<br>• AChR+<br>• Confirmed diagnosis of generalized MG historically meeting the clinical criteria for diagnosis of MG defined by the Myasthenia Gravis Foundation of America (MGFA) classification of Class II, III, IV, or V historically<br>• At Screening, subjects may have symptoms controlled by CS or were MGFA Class II-IVa inclusive (Class IVb and Class V excluded). Subjects who only have a history of ocular MG may not enroll.<br>• On systemic CS for a minimum period of at least 3 months and on a stable CS dose of >=15 mg/day and <=60 mg/day (prednisone equivalent) for the month prior to Screening.<br>• Had a tapering CS dose that the study investigator considered to be appropriate.<br>• At least 1 previous completed attempt to taper CS |

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| | | | | | | in order to minimize CS dose (lowest feasible dose based on observed MG signs and symptoms)<br>***Exclusion***<br>• Any dose change in concomitant immunosuppressant therapy, other than CS, in the prior 6 months<br>• Any change in CS dose or acetylcholinesterase inhibitor (e.g., pyridostigmine) dose in the 1 month prior to Screening<br>• A 3-point change in Quantitative Myasthenia Gravis score, increased or decreased, between the Screening/Week -3 (Visit 0) and Baseline (Week 0 [Visit 1])<br>• Any episode of myasthenic crisis (MC) in the 1 month prior to Screening, or (at any time in the past) MC or hospitalization for MG exacerbation associated with a previous CS taper attempt<br>• Thymectomy within the preceding 6 months prior to Screening<br>• Rituximab, belimumab, eculizumab or any monoclonal antibody used for immunomodulation within the past 12 months prior to Screening<br>• Have received immune globulin treatment given by IV, subcutaneous, or intramuscular route within the last 3 months prior to Screening<br>• Received plasma exchange performed within the last 3 months prior to Screening |

AChR+/-: acetylcholine receptor positive/negative, AE: adverse events, AZA: azathioprine, CS: corticosteroids, DB: double blind, ECU: eculizumab, gMG: generalized myasthenia gravis, HBV: hepatitis B, HCV: hepatitis C, HIV: human immunodeficiency viruses, IGIV-C: immune globulin intravenous -c, Immuno.: Immunosuppressants, IV: intravenous, IVIG: intravenous immunoglobulin, Kg/m2: kilogram per meter squared, MC: multicenter, MG: myasthenia gravis, MG-ADL: myasthenia gravis- activities of daily living, MGFA: myasthenia gravis foundation of America, Mg/kg: milligram per kilogram, MRI: magnetic resonance imaging, N: total number, NSAIDs: non-steroidal anti-inflammatory drugs, OL: open label, PBO: placebo, PC: placebo controlled, PLEX: plasma exchange, QMG: quantitative myasthenia gravis , RCT: randomized controlled trial, SoC: standard of care, TEAE: treatment emergent adverse event

**Table D2.3. Key Baseline Characteristics I**

| Study Name / Trial Identifier | Population + Arms | | N | Age at Baseline, mean (SD) | Sex, n (%) | | Scores at Baseline, mean (SD) | | | | MGFA Class at screening, n (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Female | Male | MG-ADL | QMG | MGC | MG-QOL15* | Class II | Class III | Class IV |
| **Efgartigimod** | | | | | | | | | | | | | |
| **Phase III ADAPT[21,66]** | **AChR Ab+** | **EFGART** | 65 | 44.7 (15.0) | 46 (70.8) | 19 (29.2) | 9.0 (2.5) | 16.0 (5.1) | 18.6 (6.1) | 15.7 (6.3) | 28 (43.0) | 35 (54.0) | 2 (3.0) |
| | | **PBO** | 64 | 49.2 (15.5) | 40 (62.5) | 24 (37.5) | 8.6 (2.1) | 15.2 (4.4) | 18.1 (5.2) | 16.6 (5.5) | 25 (39.0) | 36 (56.0) | 3 (5.0) |
| | **AChR Ab+ Refract.** | **EFGART** | | | | | | | NR | | | | |
| | | **PBO** | | | | | | | NR | | | | |
| | **Overall** | **EFGART** | 84 | 45.9 (14.4) | 63 (75.0) | 21 (25.0) | 9.2 (2.6) | 16.2 (5.0) | 18.8 (6.1) | 16.1 (6.4) | 34 (40.0) | 47 (56.0) | 3 (4.0) |
| | | **PBO** | 83 | 48.2 (15.0) | 55 (66.3) | 28 (33.7) | 8.8 (2.3) | 15.5 (4.6) | 18.3 (5.5) | 16.8 (5.7) | 31 (37.0) | 49 (59.0) | 3 (4.0) |
| | | **Total** | 167 | | 118 (70.7) | 49 (29.3) | | | NR | | 65 (39.0) | 96 (57.5) | 6 (3.6) |
| **Phase II Howard 2019[24]** | **Overall (AChR Ab+)** | **EFGART** | 12 | 55.3 (13.6) | 7 (58.3) | 5 (41.7) | 8.0 (3.0) | 14.5 (6.3) | 16.7 (8.7) | 19.7 (5.7) | 6 (50.0) | 6 (50.0) | 0 (0) |
| | | **PBO** | 12 | 43.5 (19.3) | 8 (66.7) | 4 (33.3) | 8.0 (2.2) | 11.8 (5.4) | 14.5 (4.5) | 14.5 (6.1) | 7 (58.4) | 4 (33.3) | 1 (8.3) |
| | | **Total** | 24 | 49.4 (17.4) | 15 (62.5) | 9 (37.5) | 8.0 (2.6) | 13.2 (5.9) | 15.6 (6.9) | 17.1 (6.4) | 13 (54.2) | 10 (41.7) | 1 (4.2) |
| **Eculizumab** | | | | | | | | | | | | | |
| **REGAIN Phase III[16]** | **Overall (Refract. AchR Ab+)** | **ECU** | 62 | 47.5 (15.7) | 41 (66.1) | 21 (33.9) | 10.5 (3.1) | 17.3 (5.1) | 20.4 (6.1) | 33.6 (12.2) | 18 (29.0) | 37 (59.7) | 7 (11.3) |
| | | **PBO** | 63 | 46.9 (18.0) | 41 (65.1) | 22 (34.9) | 9.9 (2.6) | 16.9 (5.6) | 18.9 (6.0) | 30.7 (12.7) | 29 (46.0) | 29 (46.0) | 5 (7.9) |
| | | **Total** | 125 | 47.2 (16.8) | 82 (65.6) | 43 (34.4) | 10.2 (2.8) | 17.1 (5.3) | 19.6 (6.1) | 32.1 (12.5) | 47 (37.6) | 66 (52.8) | 12 (9.6) |

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| **REGAIN OLE[17]** | **Overall (Refract. AchR Ab+)** | **ECU/ECU** | 56 | 47.2 (15.5) | 38 (67.9) | 18 (32.1) | 10.3 (3.0) | NR | NR | 32.5 (12.0) | NR | NR | NR |
| | | **PBO/ECU** | 61 | 47.5 (17.9) | 41 (67.2) | 20 (32.8) | 9.9 (2.6) | NR | NR | 30.8 (12.9) | NR | NR | NR |
| | | **Total** | 117 | 47.4 (16.7) | 79 (67.5) | 38 (32.5) | 10.1 (2.8) | NR | NR | 31.6 (12.5) | NR | NR | NR |
| **Phase II Howard 2013[22]** | **Overall (Refract.)** | **Total** | 14 | Median (range): 48 (30-72) | 8 (57.0) | 6 (43.0) | NR | Median: 18 (12-36) | NR | NR | 4 (28) | 8 (57) | 2 (14) |
| **Nowak 2020[19]** | **Overall (Refract. AchR Ab+)** | **PRED** | 90 | 48.3 (16.5) | 56 (62.2) | 34 (37.8) | NR | NR | NR | NR | 83 (92.2) | | 7 (7.8) |
| | | **AZA** | 39 | 46.7 (16.9) | 25 (64.1) | 14 (35.9) | NR | NR | NR | NR | 34 (87.2) | | 5 (12.8) |
| | | **MMF** | 30 | 49.4 (17.5) | 21 (70) | 9 (30.0) | NR | NR | NR | NR | 28 (93.3) | | 2 (6.7) |
| | | **All Patients** | 117 | 47.4 (16.7) | 79 (67.5) | 38 (32.5) | NR | NR | NR | NR | 105 (89.7) | | 12 (10.2) |
| **Rituximab** | | | | | | | | | | | | | |
| **Phase II BeatMG[61]** | **Overall (AChR Ab+)** | **RTX** | 25 | 53.2 (17.5) | 11 (44) | 14 (56) | 5.8 (3.6) | 11.0 (5.1) | 11.1 (6.1) | 22.7 (14.1) | 15 (60) | 9 (36) | 1 (4) |
| | | **PBO** | 27 | 56.8 (17.0) | 12 (44.4) | 15 (55.6) | 4.0 (3.4) | 9.2 (3.9) | 8.5 (4.0) | 17.7 (10.6) | 16 (59.3) | 9 (33.3) | 1 (3.7) |
| **Brauner 2020[63]** | **Treated with RTX** | **New-Onset MG** | 24 | 58 (20) | 10 (42) | 14 (58) | NR | 8 (4) | NR | NR | NR | NR | NR |
| | | **Refractory MG** | 34 | 63 (16) | 14 (41) | 20 (59) | NR | 7 (5) | NR | NR | NR | NR | NR |
| | **Control** | **New-Onset MG** | 26 | 68 (11) | 3 (12) | 23 (88) | NR | 8 (5) | NR | NR | NR | NR | NR |

| Maintenance IVIG | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase II NCT02473952[27]** | **Overall (AChR Ab+)** | **IGIV-C** | 30 | 54.6 (17.1) | 14 (46.7) | 16 (53.3) | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 32 | 48.0 (13.7) | 19 (59.4) | 13 (40.6) | NR | NR | NR | NR | NR | NR | NR |
| | | **Total** | 62 | 51.2 (15.6) | 33 (53.2) | 29 (46.8) | NR | NR | NR | NR | NR | NR | NR |
| **Phase II NCT02473965[26]** | **Overall (AChR Ab+)** | **IGIV-C** | 30 | 47.6 (17.0) | 16 (53.3) | 14 (46.7) | NR | 12.1 (6.98) | NR | NR | NR | NR | NR |
| | | **PBO** | 30 | 48.5 (14.5) | 18 (60.0) | 12 (40.0) | NR | 11.2 (6.48) | NR | NR | NR | NR | NR |
| | | **Total** | 60 | 48.1 (15.7) | 34 (56.7) | 26 (43.3) | NR | 11.6 (6.7) | NR | NR | NR | NR | NR |

%: percent, AChR Ab+: acetylcholine receptor antibody positive, AIC: academic in confidence, Efgart: efgartigimod, MG-ADL: myasthenia gravis -activities of daily living, MGC: myasthenia gravis composite, MG_QOL15: myasthenia gravis quality of life 15 scale, QMG: quantitative myasthenia gravis, MGFA: myasthenia gravis foundation of america, n: number, N: total number, NR: not reported, PBO: placebo, Refract.: refractory, RTX: rituximab, SD: standard deviation

* Eculizumab trials use MG-QoL non-revised (scale 0-60) and Efgartigimod trials use MG-QoL revised (scale 0-30)

**Table D2.4. Key Baseline Characteristics II**

| Study Name / Trial Identifier | Population + Arms | | N | Race, n (%) | | | | Anti-AChR+, n(%) | MG Duration, years mean (SD) | Previous thym. | Mean time from thym., years (SD) | BMI (kg/m$^2$) mean (SD) | History of MG exacerbations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | White | Black | Asian | Other | | | | | | |
| **Efgartigimod** | | | | | | | | | | | | | |
| **Phase III ADAPT**[21,66] | **AChR Ab+** | **EFGART** | 65 | 54 (83.0) | 1 (2.0) | 7 (11.0) | 3 (5.0) | 129 (100) | 9.7 (8.3) | 45 (69.0) | NR | | NR |
| | | **PBO** | 64 | 56 (88.0) | 3 (5.0) | 4 (6.0) | 1 (2.0) | | 8.9 (8.2) | 30 (47.0) | NR | | NR |
| | **AChR Ab+ Refract.** | **EFGART** | | NR | NR | NR | NR | | | | NR | | NR |
| | | **PBO** | | NR | NR | NR | NR | | | | NR | | NR |
| | **Overall** | **EFGART** | 84 | 69 (82.0) | 3 (4.0) | 9 (11.0) | 3 (4.0) | 65 (77.0) | 10.1 (9.0) | 59 (70.0) | NR | | NR |
| | | **PBO** | 83 | 72 (87.0) | 3 (4.0) | 7 (8.0) | 1 (1.0) | 64 (77.0) | 8.8 (7.6) | 36 (43.0) | NR | | NR |
| | | **Total** | 167 | 141 (84.4) | 6 (3.6) | 16 (9.6) | 4 (2.4) | 129 (77.0) | | 95 (57.0) | NR | | NR |
| **Phase II Howard 2019**[24] | **Overall (AChR Ab+)** | **EFGART** | 12 | 11 (91.7) | 0 (0) | 1 (8.3) | 0 (0) | 12 (100) | 8.2 (9.0) | 5 (41.7) | 11.6 (12.6) | NR | NR |
| | | **PBO** | 12 | 11 (91.7) | 1 (8.3) | 0 (0) | 0 (0) | 12 (100) | 13.3 (11.2) | 7 (58.4) | 9.8 (8.1) | NR | NR |
| | | **Total** | 24 | 22 (91.7) | 1 (4.2) | 1 (4.2) | 0 (0) | 24 (100) | 10.8 (10.3) | 12 (50.0) | 10.0 (9.7) | NR | NR |
| **Eculizumab** | | | | | | | | | | | | | |
| **REGAIN Phase III**[16] | **Overall (Refract. AchR Ab+)** | **ECU** | 62 | 53 (85) | 0 (0) | 3 (5) | 6 (10) | 62 (100) | 9.9 (8.1) | 37 (60) | 11 (8.51) | 31.4 (9.0) | 46 (74.0) |
| | | **PBO** | 63 | 42 (67) | 3 (5) | 16 (25) | 2 (3) | 63 (100) | 9.2 (8.4) | 31 (49) | 11.3 (9.67) | 30.5 (8.4) | 52 (83.0) |
| | | **Total** | 125 | 95 (76) | 3 (2) | 19 (15) | 8 (6) | 125 (100) | 9.6 (8.2) | 68 (54) | 11.1 (8.99) | 30.9 (8.7) | 98 (78.0) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **REGAIN OLE[17]** | **Overall (Refract. AchR Ab+)** | **ECU/ECU** | 56 | 47 (83.9) | 0 (0) | 3 (5.4) | 4 (7.1) | 56 (100) | 10.7 (7.9) | NR | NR | NR | NR |
| | | **PBO/ECU** | 61 | 41 (67.2) | 2 (3.3) | 16 (26.2) | 2 (3.3) | 61 (100) | 9.8 (8.5) | NR | NR | NR | NR |
| | | **Total** | 117 | 88 (75.2) | 2 (1.7) | 19 (16.2) | 6 (5.1) | 117 (100) | 10.2 (8.2) | NR | NR | NR | NR |
| **Phase II Howard 2013[22]** | **Overall (Refract.)** | **Total** | 14 | NR | NR | NR | NR | 14 (100) | Median (range): 7.0 (1.5-30.1) | 6 (42.9) | NR | NR | 12 (85.7) |
| **Nowak 2020 [19]** | **Overall (Refract. AchR Ab+)** | **PRED** | 90 | 67 (74.4) | 0 (0) | 18 (20) | 4 (4.4) | 90 (100) | 9.9 (8.1) | NR | NR | NR | NR |
| | | **AZA** | 39 | 34 (87.2) | 0 (0) | 2 (5.1) | 2 (5.1) | 39 (100) | 9.7 (8.2) | NR | NR | NR | NR |
| | | **MMF** | 30 | 26 (86.7) | 1 (3.3) | 1 (3.3) | 2 (6.7) | 30 (100) | 10.3 (8.6) | NR | NR | NR | NR |
| | | **All Patients** | 117 | 88 (75.2) | 2 (1.7) | 19 (16.2) | 6 (5.1) | 117 (100) | 10.2 (8.2) | NR | NR | NR | NR |
| **Rituximab** | | | | | | | | | | | | | |
| **Phase II BeatMG[61]** | **Overall (AChR Ab+)** | **RTX** | 25 | 20 (80) | 2 (8) | 0 (0) | NR | 25 (100) | NR | 8 (32) | NR | NR | NR |
| | | **PBO** | 27 | 15 (55.6) | 9 (33) | 1 (3.7) | NR | 27 (100) | NR | 4 (14.8) | NR | NR | NR |
| **Brauner 2020[63]** | **Treated with RTX** | **New-Onset MG** | 24 | NR | NR | NR | NR | 20 (83) | NR | 9 (38) | NR | NR | NR |
| | | **Refractory MG** | 34 | NR | NR | NR | NR | 28 (82) | NR | 16 (47) | NR | NR | NR |
| | **Control** | **New-Onset MG** | 26 | NR | NR | NR | NR | 24 (92) | NR | 11 (42) | NR | NR | NR |

| Maintenance IVIG | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase II NCT02473952[27]** | **Overall (AChR Ab+)** | **IGIV-C** | 30 | 29 (96.7) | 1 (3.3) | 0 (0) | 0 (0) | 30 (100) | NR | NR | NR | NR | NR |
| | | **PBO** | 32 | 30 (93.8) | 0 (0) | 1 (3.1) | 1 (3.1) | 32 (100) | NR | NR | NR | NR | NR |
| | | **Total** | 62 | 59 (95.2) | 1 (1.6) | 1 (1.6) | 1 (1.6) | 62 (100) | NR | NR | NR | NR | NR |
| **Phase II NCT02473965[26]** | **Overall (AChR Ab+)** | **IGIV-C** | 30 | 27 (90.0) | 0 (0.0) | 3 (10.0) | 0 (0) | 30 (100) | NR | NR | NR | NR | NR |
| | | **PBO** | 30 | 27 (90.0) | 1 (3.3) | 2 (6.7) | 0 (0) | 30 (100) | NR | NR | NR | NR | NR |
| | | **Total** | 60 | 54 (90.0) | 1 (1.7) | 5 (8.3) | 0 (0) | 60 (100) | NR | NR | NR | NR | NR |

%: percent, AChR Ab+: acetylcholine receptor antibody positive, AIC: academic in confidence, AZA: azathioprine, Efgart: efgartigimod, IGIV-C: immune globulin intravenous -c, kg/m2: kilogram per meter squared, MG: myasthenia gravis, MMF: mycophenolate mofetil, n: number, N: total number, NR: not reported, PBO: placebo, Pred: prednisone, Refract.: refractory, RTX: rituximab, SD: standard deviation

**Table D2.5. Key Baseline Characteristics III**

| Study Name / Trial Identifier | Population + Arms | | N | Previous long-term IVIG therapy, n (%) | Prior plasma exchange use, n (%) | MG Therapies at Baseline (Standard of Care), n (%) | | | | | Prior IST use, n(%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | NSIST | Cholin. Inhibitors | Any Steroids | None | Other | ≥2 ISTs | ≥3 ISTs | ≥4 ISTs |
| **Efgartigimod** | | | | | | | | | | | | | |
| **Phase III ADAPT[21,66]** | **AChR Ab+** | **EFGART** | 65 | | | 40 (62.0) | | 46 (71.0) | 13 (20.0) | NR | NR | NR | NR |
| | | **PBO** | 64 | | | 37 (58.0) | | 51 (80.0) | 6 (9.0) | NR | NR | NR | NR |
| | **AChR Ab+ Refract.** | **EFGART** | | | | | | | NR | NR | NR | NR | NR |
| | | **PBO** | | | | | | | NR | NR | NR | NR | NR |
| | **Overall** | **EFGART** | 84 | | | 51 (61.0) | | 60 (71.0) | 16 (19.0) | NR | NR | NR | NR |
| | | **PBO** | 83 | | | 51 (61.0) | | 67 (81.0) | 7 (8.0) | NR | NR | NR | NR |
| | | **Total** | 167 | | | | | | 23 (14.0) | NR | NR | NR | NR |
| **Phase II Howard 2019[24]** | **Overall (AChR Ab+)** | **EFGART** | 12 | NR | NR | 9 (75.0) | 12 (100.0) | 8 (66.7) | NR | NR | NR | NR | NR |
| | | **PBO** | 12 | NR | NR | 3 (25.0) | 10 (83.3) | 5 (41.7) | NR | NR | NR | NR | NR |
| | | **Total** | 24 | NR | NR | 12 (50.0) | 22 (91.7) | 13 (54.2) | NR | NR | NR | NR | NR |
| **Eculizumab** | | | | | | | | | | | | | |
| **REGAIN Phase III[16]** | **Overall (Refract. AchR Ab+)** | **ECU** | 62 | 18 (29.0) | 4 (6.0) | 56 (90.3) | NR | 47 (76.0) | NR | 2 (3.0) | 61 (98.0) | 31 (50.0) | NR |
| | | **PBO** | 63 | 17 (27.0) | 10 (16.0) | 56 (88.9) | NR | 51 (81.0) | NR | 0 (0) | 62 (98.0) | 34 (54.0) | NR |
| | | **Total** | 125 | 35 (28.0) | 14 (11.0) | 112 (89.6) | NR | 98 (78.0) | NR | 2 (2.0) | 123 (98.0) | 65 (52.0) | NR |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **REGAIN OLE Muppidi 2019[17]** | **Overall (Refract. AchR Ab+)** | **ECU/ECU** | 56 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO/ECU** | 61 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **Total** | 117 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Phase II Howard 2013[22]** | **Overall (Refract.)** | **Total** | 14 | NR | NR | 7 (50) | 12 (85.7) | 7 (50) | 1 (7.1) | NR | NR | NR | NR |
| **Nowak 2020[19]** | **Overall (Refract. AchR Ab+)** | **PRED** | 90 | 70 (77.8) | 39 (43.3) | NR | NR | NR | NR | NR | 42 (46.7) | 27 (30.0) | 20 (22.2) |
| | | **AZA** | 39 | 29 (74.4) | 17 (43.6) | NR | NR | NR | NR | NR | 32 (82.1) | 5 (12.8) | 2 (5.1) |
| | | **MMF** | 30 | 24 (80.0) | 17 (56.7) | NR | NR | NR | NR | NR | 9 (30.0) | 14 (46.7) | 6 (20.0) |
| | | **All Patients** | 117 | 92 (78.6) | 57 (48.7) | NR | NR | NR | NR | NR | 52 (44.4) | 39 (33.3) | 24 (20.5) |
| **Rituximab** | | | | | | | | | | | | | |
| **Phase II BeatMG[61]** | **Overall (AChR Ab+)** | **RTX** | 25 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 27 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Brauner 2020[63]** | **Treated with RTX** | **New-Onset MG** | 24 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **Refract. MG** | 34 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | **Control** | **New-Onset MG** | 26 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Maintenance IVIG** | | | | | | | | | | | | | |
| **Phase II NCT02473952[27]** | **Overall (AChR Ab+)** | **IGIV-C** | 30 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 32 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **Total** | 62 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Phase II NCT02473965[26]** | **Overall (AChR Ab+)** | **IGIV-C** | 30 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 30 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **Total** | 60 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |

%: percent, AChR Ab+: acetylcholine receptor antibody positive, AIC: academic in confidence, AZA: azathioprine, Cholin.: cholinesterase, Efgart: efgartigimod, IGIV-C: immune globulin intravenous -c, IST: immunosuppressant therapy, IVIG: intravenous immunoglobulin, kg/m2: kilogram per meter squared, MG: myasthenia gravis, MMF: mycophenolate mofetil, n: number, N: total number, NR: not reported, PBO: placebo, Pred: prednisone, Refract.: refractory, RTX: rituximab, SD: standard deviation

**Table D2.6. Key Efficacy Outcomes I**

| Study Name / Trial Identifier | Arms | | Base-line N | Change from baseline in MG-ADL | | | | Change from baseline in QMG | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | mean (95% CI) | SE | p-value | n | mean (95% CI) | SE | p-value |
| **Efgartigimod** | | | | | | | | | | | |
| **Phase III ADAPT[21,66]** | **AChR Ab+** | **Week 4** | | | | | | | | | |
| | | **Efgart** | 65 | 63 | *-4.6 (NR)* | *0.4* | <0.05 | 62 | *-6.2 (NR)* | *0.7* | <0.05 |
| | | **Placebo** | 64 | 60 | *-1.7 (NR)* | *0.3* | – | 58 | *-1.0 (NR)* | *0.4* | – |
| | | **Week 8 (Cycle 1)** | | | | | | | | | |
| | | **Efgart** | 65 | 63 | *-2.2 (NR)* | *0.4* | NS | 62 | *-2.9 (NR)* | *0.5* | <0.05 |
| | | **Placebo** | 64 | 59 | *-1.7 (NR)* | *0.4* | – | 55 | *-1.2 (NR)* | *0.3* | – |
| | | **Cycle 2** | | | | | | | | | |
| | | NR | | | | | | | | | |
| | **AChR Ab+ Refractory** | **Week 4** | | | | | | | | | |
| | | **Efgart** | [redacted] | | | | NR | [redacted] | | | NR |
| | | **Placebo** | | | | | NR | | | | NR |
| | **AChR Ab-** | **Week 8 (Cycle 1)** | | | | | | | | | |
| | | NR | | | | | | | | | |
| | **Overall** | **Week 8 (Cycle 1)** | | | | | | | | | |
| | | NR | | | | | | | | | |
| | | **Cycle 2** | | | | | | | | | |
| | | NR | | | | | | | | | |
| **Phase II Howard 2019[24]** | **Overall (AChR Ab+)** | **Week 11 (Day 80)** | | | | | | | | | |
| | | **Efgart** | 12 | NR | *-3.5 (NR)* | 1.1 | NS | NR | *-4.8 (NR)* | 2.4 | NS |
| | | **Placebo** | 12 | NR | *-1.8 (NR)* | 1.2 | NS | NR | *-2.1 (NR)* | 1.5 | NS |

| Eculizumab | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **REGAIN Phase III[16]** | **Overall (Refractory AchR Ab+)** | **Week 4** | | | | | | | | | |
| | | **ECU** | 62 | 62 | *-3.5 (-4.3 to -2.7)* | *0.4* | 0.0008 | 62 | *-3.3 (-4.4 to -2.2)* | *0.6* | 0.0256 |
| | | **Placebo** | 63 | 63 | *-1.5 (-2.3 to -0.7)* | *0.4* | – | 63 | *-1.5 (-2.6 to -0.4)* | *0.6* | – |
| | | **Week 8** | | | | | | | | | |
| | | **ECU** | 62 | 62 | *-3.7 (-4.6 to -2.7)* | *0.5* | 0.0046 | 62 | *-4 (-5.2 to -2.8)* | *0.6* | 0.0021 |
| | | **Placebo** | 63 | 63 | *-1.8 (-2.7 to -0.8)* | *0.5* | – | 63 | *-1.4 (-2.5 to -0.3)* | *0.6* | – |
| | | **Week 26** | | | | | | | | | |
| | | **ECU** | 62 | NR | *-4.2 (-5.2 to -3.3)* | *0.5* | 0.0058 | NR | *-4.6 (-5.8 to -3.4)* | *0.61* | 0.0006 |
| | | **Placebo** | 63 | NR | *-2.3 (-3.2 to -1.4)* | *0.5* | – | NR | *-1.6 (-2.8 to -0.5)* | *0.59* | – |
| **REGAIN OLE Muppidi 2019 [17]** | **Overall (Refractory AchR Ab+)** | **Week 4** | | | | | | | | | |
| | | **ECU/ECU** | 56 | 56 | *-0.3 (-0.8 to -0.3)* | *0.1* | ≤ 0.0001 | 56 | *-0.1 (-0.8 to 0.7)* | *0.38* | ≤ 0.0001 |
| | | **PBO/ECU** | 60 | 60 | *-2.5 (-3.2 to -1.7)* | *0.4* | - | 60 | *-3.0 (-4.1 to -2.0)* | *0.54* | – |
| | | **Week 8** | | | | | | | | | |
| | | **ECU/ECU** | 56 | 53 | *-.5 (-1.0 to 0)* | *0.3* | ≤ 0.0001 | 52 | *-0.3 (-1 to 0.5)* | *0.38* | ≤ 0.0001 |
| | | **PBO/ECU** | 60 | 60 | *-2.7 (-3.4 to -1.9)* | *0.4* | – | 60 | *-2.9 (-4 to -1.8)* | *0.56* | - |
| | | **Week 26** | | | | | | | | | |
| | | **ECU/ECU** | 56 | 49 | *-.5 (-1.0 to .1)* | *0.3* | ≤ 0.0001 | 48 | *-0.1 (-.09 to .07)* | *0.41* | ≤ 0.0001 |
| | | **PBO/ECU** | 60 | 55 | *-2.5 (-3.3 to -1.8)* | *0.4* | – | 55 | *-2.8 (-3.8 to -1.6)* | *0.56* | - |
| | | **Week 52** | | | | | | | | | |
| | | **ECU/ECU** | 56 | 49 | *-.3 (-.9 to .3)* | *0.2* | ≤ 0.0001 | 48 | *-0.4 (-1.2 to 0.3)* | *0.38* | ≤ 0.0001 |
| | | **PBO/ECU** | 60 | 54 | *-2.9 (-3.7 to -2.2)* | *0.4* | – | 53 | *-3.9 (-4.9 to -2.7)* | *0.56* | - |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase II Howard 2013[22]** | **Overall (Refractory)** | **Week 16 (Period 1)** | | | | | | | | | |
| | | **ECU** | 7 | NR | NR | NR | NR | 7 | *-7.4* | *SD: 5.7* | NR |
| | | **PBO** | 7 | NR | NR | NR | NR | 7 | *-2.7* | *SD: 4.8* | – |
| | | **Week 16 (Period 2)** | | | | | | | | | |
| | | **ECU** | 6 | NR | NR | NR | NR | 6 | *-7.7* | *SD: 4.8* | NR |
| | | **PBO** | 6 | NR | NR | NR | NR | 6 | *-4.5* | *SD: 2.5* | – |
| **Nowak 2020[19]** | **Start of OLE to Last Assessment** | | | | | | | | | | |
| | **Total** | | 117 | 117 | -3.6 (SD: 4.1) | 0.38 | NR | 117 | -4.1 (SD: 5.8) | 0.54 | NR |
| | **PRED** | **Patients who decreased and/or stopped** | 45 | 45 | -4.7 (SD: 3.9) | 0.58 | NR | 45 | -5.6 (SD: 5.2) | 0.78 | NR |
| | | **Patients with no change** | 36 | 36 | -2.3 (SD: 4.1) | 0.68 | NR | 36 | -1.5 (SD: 5) | 0.83 | NR |
| | | **Patients who increased and/or started** | 10 | 10 | -0.7 (SD: 4.2) | 1.33 | NR | 10 | 0.2 (SD: 4.9) | 1.55 | NR |
| | **AZA** | **Patients who decreased and/or stopped** | 16 | 16 | -3.4 (SD: 4.0) | 1 | NR | 16 | -3.8 (SD: 6.8) | 1.7 | NR |
| | | **Patients with no change** | 20 | 20 | -4.7 (SD: 3.8) | 0.85 | NR | 20 | -5.1 (SD: 5.3) | 1.19 | NR |
| | | **Patients who increased and/or started** | 3 | 3 | 0.3 (SD: 2.3) | 1.33 | NR | 3 | -2.7 (SD: 4.9) | 2.83 | NR |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **MMF** | **Patients who decreased and/or stopped** | 13 | 13 | -5.1 (SD: 3.6) | 1 | NR | 13 | -4.9 (SD: 3.5) | 0.97 | NR |
| | | **Patients with no change** | 14 | 14 | -2.5 (SD: 3.4) | 0.91 | NR | 14 | -1.6 (SD: 4.0) | 1.07 | NR |
| | | **Patients who increased and/or started** | 7 | 7 | -5.3 (SD: 3.6) | 1.36 | NR | 7 | -7.9 (SD: 5.2) | 1.97 | NR |
| **Rituximab** | | | | | | | | | | | |
| **Phase II BeatMG[61]** | **Week 52** | | | | | | | | | | |
| | **RTX** | | 25 | NR | NR | NR | NR | 25 | -3.95 | 1.1 | 0.39 |
| | **PBO** | | 27 | NR | NR | NR | NR | 27 | -1.7 | 0.8 | – |
| **Maintenance IVIG** | | | | | | | | | | | |
| **Phase II NCT02473952[27]** | **Week 24** | | | | | | | | | | |
| | **IGIV-C** | | 30 | NR | NR | NR | NR | 30 | -4.6 (SD: 5.11) | 0.9 | NR |
| | **PBO** | | 32 | NR | NR | NR | NR | 32 | -2.7 (SD: 6.23) | 1.1 | NR |
| **Phase II NCT02473965[26]** | **Week 39** | | | | | | | | | | |
| | NR | | | | | | | | | | |

95% CI: 95% confidence interval, AChR Ab+: acetylcholine receptor antibody positive, AIC: academic in confidence, Aza: azathioprine, Efgart.: efgartigimod, ECU: eculizumab, IGIV-C: immune globulin intravenous -c, MG-ADL: myasthenia gravis - activities of daily living, MMF: mycophenolate mofetil, n: number, N: total number, NR: not reported, NS: not significant, OLE: open-label extension, PBO: placebo, Pred: prednisone, QMG: quantitative myasthenia gravis, SE: standard error, SD: standard deviation, RTX: rituximab

Note: Italicized numbers are digitized estimates

**Table D2.7. Key Efficacy Outcomes II**

| Study Name / Trial Identifier | Arms | | Baseline N | Change from baseline in MGC | | | | Change from baseline in MG-QoL15r | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | mean (95% CI) | SE | p-value | n | mean (95% CI) | SE | p-value |
| **Efgartigimod** | | | | | | | | | | | |
| **Phase III ADAPT[21,66]** | **AChR Ab+** | **Week 4** | | | | | | | | | |
| | | **Efgart** | 65 | 63 | *-9.4 (NR)* | *0.9* | <0.05 | 63 | *-7.3 (NR)* | *0.8* | <0.05 |
| | | **Placebo** | 64 | 60 | *-3.4 (NR)* | *0.7* | – | 60 | *-2.3 (NR)* | *0.5* | – |
| | | **Week 8 (Cycle 1)** | | | | | | | | | |
| | | **Efgart** | 65 | 63 | *-3.8 (NR)* | *0.8* | NS | 63 | *-4.6 (NR)* | *0.8* | <0.05 |
| | | **Placebo** | 64 | 59 | *-3.2 (NR)* | *0.6* | – | 59 | *-2.3 (NR)* | *0.6* | – |
| | | **Cycle 2** | | | | | | | | | |
| | | **Efgart** | NR | | | | | | | | |
| | **AChR Ab+ Refractory** | **Week 4** | | | | | | | | | |
| | | **Efgart** | [redacted] | | | | NR | [redacted] | | | NR |
| | | **Placebo** | | | | | NR | | | | NR |
| | **AChR Ab-** | **Week 8 (Cycle 1)** | | | | | | | | | |
| | | NR | | | | | | | | | |
| | **Overall** | **Week 8 (Cycle 1)** | | | | | | | | | |
| | | NR | | | | | | | | | |
| | | **Cycle 2** | | | | | | | | | |
| | | NR | | | | | | | | | |
| **Phase II Howard 2019[24]** | **Overall (AChR Ab+)** | **Week 11 (Day 80)** | | | | | | | | | |
| | | **Efgart** | 12 | NR | *-7.1 (NR)* | 2.8 | NS | NR | *-2.7 (NR)* | 1.7 | NS |
| | | **Placebo** | 12 | NR | *-3.7 (NR)* | 2 | NS | NR | *-1.5 (NR)* | 1 | NS |

| Eculizumab | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **REGAIN Phase III[16]** | **Overall (Refractory AchR Ab+)** | **Week 4** | | | | | | | | | |
| | | **ECU** | 62 | 62 | *-7.2 (-8.8 to -5.8)* | *0.8* | 0.0007 | 62 | *-7.2 (-9.5 to -4.7)* | *1.2* | 0.0395 |
| | | **Placebo** | 63 | 63 | *-3.5 (-5 to -2)* | *0.8* | - | 63 | *-3.6 (-5.9 to -1.1)* | *1.2* | - |
| | | **Week 8** | | | | | | | | | |
| | | **ECU** | 62 | 62 | *-8.1 (-9.8 to -6.4)* | *0.9* | 0.0003 | 62 | *-10.2 (-12.8 to -10.2)* | *0.7* | 0.0002 |
| | | **Placebo** | 63 | 63 | *-3.5 (-5.2 to -1.8)* | *0.9* | – | 63 | *-2.8 ( -5.4 to -0.3)* | *1.3* | - |
| | | **Week 26** | | | | | | | | | |
| | | **ECU** | 62 | NR | *-8.1 (-10 to -6.2)* | *0.97* | 0.0134 | NR | *-12.6 (-15.7 to -9.6)* | *1.56* | 0.001 |
| | | **Placebo** | 63 | NR | *-4.8 (-6.6 to -2.9)* | *0.94* | – | NR | *-5.4 (-8.4 to -2.5)* | *1.51* | - |
| **REGAIN OLE Muppidi 2019[17]** | **Overall (Refractory AchR Ab+)** | **Week 4** | | | | | | | | | |
| | | **ECU/ECU** | 56 | 56 | *-0.3 (-1.4 to 0.7)* | *0.54* | ≤ 0.0001 | 56 | *-0.1 (-2.1 to 1.8)* | *0.99* | ≤ 0.0001 |
| | | **PBO/ECU** | 60 | 60 | *-4.7 (-6.1 to -3.3)* | *0.71* | - | 60 | *-5.3 (-8.0 to -2.8)* | *1.33* | - |
| | | **Week 8** | | | | | | | | | |
| | | **ECU/ECU** | 56 | 52 | *-.5 (-1.5 to 0.5)* | *0.51* | ≤ 0.0001 | 53 | *-0.9 (-3.0 to 0.9)* | *0.99* | ≤ 0.0001 |
| | | **PBO/ECU** | 60 | 59 | *-4.8 (-6.2 to -3.4)* | *0.71* | – | 60 | *-6.8 (-9.4 to -4.2)* | *1.33* | - |
| | | **Week 26** | | | | | | | | | |
| | | **ECU/ECU** | 56 | 49 | *-0.9 (-1.9 to 0.1)* | *0.51* | ≤ 0.0001 | 47 | *-0.8 (-2.9 to 1.2)* | *1.05* | ≤ 0.0001 |
| | | **PBO/ECU** | 60 | 55 | *-4.7 (-6.0 to -3.2)* | *0.71* | – | 56 | *--5.7 (-8.3 to -3.1)* | *1.33* | – |
| | | **Week 52** | | | | | | | | | |
| | | **ECU/ECU** | 56 | 49 | -1.0 (-1.9 to 0.2) | 0.54 | ≤ 0.0001 | 49 | *-0.6 (-2.6 to 1.4)* | *1.02* | ≤ 0.0001 |
| | | **PBO/ECU** | 60 | 54 | -5.2 (-6.5 to -3.7) | 0.71 | – | 54 | *-6.2 (-8.9 to -3.6)* | *1.35* | – |
| **Phase II Howard 2013[22]** | **Overall (Refractory)** | **Week 16 (Period 1)** | | | | | | | | | |
| | | NR | | | | | | | | | |
| | | **Week 16 (Period 2)** | | | | | | | | | |
| | | NR | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Nowak 2020[19]** | **Total** | **Start of OLE to Last Assessment** | | | | | | | | |
| | | NR | | | | | | | | |
| **Rituximab** | | | | | | | | | | |
| **Phase II BeatMG[61]** | **Week 52** | | | | | | | | | |
| | **RTX** | 25 | 25 | -5.7 (NR) | 1.5 | 0.93 | NR | NR | NR | NR |
| | **PBO** | 27 | 27 | -4 (NR) | 0.8 | – | NR | NR | NR | NR |
| **Maintenance IVIG** | | | | | | | | | | |
| **Phase II NCT02473952[27]** | **Week 24** | | | | | | | | | |
| | NR | | | | | | | | | |
| **Phase II NCT02473965[26]** | **Week 39** | | | | | | | | | |
| | NR | | | | | | | | | |

95% CI: 95% confidence interval, AChR Ab+: acetylcholine receptor antibody positive, AIC: academic in confidence, Efgart.: efgartigimod, ECU: eculizumab, IGIV-C: immune globulin intravenous -c, MGC: ,myasthenia gravis composite, MG-QoL15/r: myasthenia gravis - quality of life / revised, n: number, N: total number, NR: not reported, NS: not significant, OLE: open-label extension, PBO: placebo, QMG: quantitative myasthenia gravis, SE: standard error, RTX: rituximab

Note: Italicized numbers are digitized estimates

* Eculizumab trials use MG-QoL non-revised (scale 0-60) and Efgartigimod trials use MG-QoL revised (scale 0-30)

**Table D2.8. Key Efficacy Outcomes III**

| Study Name / Trial Identifier | Arms | | Baseline N | MG-ADL Responders* | | QMG Responders† | |
|---|---|---|---|---|---|---|---|
| | | | | n (%) | p-Value | n (%) | p-Value |
| **Efgartigimod** | | | | | | | |
| **Phase III ADAPT[21,66]** | **AChR Ab+** | **Week 4** | | | | | |
| | | NA | | | | | |
| | | **Week 8 (Cycle 1)** | | | | | |
| | | **Efgart** | 65 | 44 (68.0) | < 0.0001 | 41 (63.0) | < 0.0001 |
| | | **Placebo** | 64 | 19 (30.0) | – | 9 (14.0) | – |
| | | **Cycle 2** | | | | | |
| | | **Efgart** | 51 | 36 (70.6)ǂ | NR | NR | NR |
| | | **Placebo** | NR | NR | NR | NR | NR |
| | **AChR Ab+ Refractory** | **Week 4** | | | | | |
| | | **Efgart** | [redacted] | NR | NR | NR | NR |
| | | **Placebo** | [redacted] | NR | NR | NR | NR |
| | **AChR Ab-** | **Week 8 (Cycle 1)** | | | | | |
| | | **Efgart** | 19 | 13 (68.0) | NR | 10 (53.0) | NR |
| | | **Placebo** | 19 | 12 (63.0) | – | 7 (37.0) | – |
| | **Overall** | **Week 8 (Cycle 1)** | | | | | |
| | | **Efgart** | 84 | 57 (68.0) | < 0.0001 | NR | NR |
| | | **Placebo** | 83 | 31 (37.0) | – | NR | NR |
| | | **Cycle 2** | | | | | |
| | | **Efgart** | 51 | 36 (71.0) | NR | NR | NR |
| | | **Placebo** | 43 | 11 (26.0) | NR | NR | NR |
| **Phase II Howard 2019[24]** | **Overall (AChR Ab+)** | **Week 11 (Day 80)** | | | | | |
| | | NR | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Eculizumab** | | | | | | | |
| **REGAIN Phase III[16]** | **Overall (Refractory AchR Ab+)** | **Week 4** | | | | | |
| | | NR | | | | | |
| | | **Week 8** | | | | | |
| | | NR | | | | | |
| | | **Week 26** | | | | | |
| | | NR | | | | | |
| **REGAIN OLE Muppidi 2019[17]** | **Overall (Refractory AchR Ab+)** | **Week 4** | | | | | |
| | | NR | | | | | |
| | | **Week 8** | | | | | |
| | | NR | | | | | |
| | | **Week 26** | | | | | |
| | | NR | | | | | |
| | | **Week 52** | | | | | |
| | | NR | | | | | |
| **Phase II Howard 2013[22]** | **Overall (Refractory)** | **Week 16 (Period 1)** | | | | | |
| | | **ECU** | 7 | 6 (85.7) | NR | 6 (86) | NR |
| | | **PBO** | 7 | 4 (57.1) | NR | 4 (57) | NR |
| | | **Week 16 (Period 2)** | | | | | |
| | | **ECU** | 6 | NR | NR | 5 (83) | NR |
| | | **PBO** | 6 | NR | NR | NR | NR |
| **Nowak 2020[19]** | **Start of OLE to Last Assessment** | | | | | | |
| | NR | | | | | | |
| **Rituximab** | | | | | | | |
| **Phase II BeatMG[61]** | **Week 52** | | | | | | |
| | NR | | | | | | |
| **IVIG** | | | | | | | |
| **Phase II NCT02473952[27]** | **Week 24** | | | | | | |
| | NR | | | | | | |

| Phase II NCT02473965[26] | Week 39 |
|---|---|
| | NR |

AChR Ab+: acetylcholine receptor antibody positive, Efgart.: efgartigimod, ECU: eculizumab, IVIG: intravenous immunoglobulin, MG-ADL: myasthenia gravis - activities of daily living, QMG: quantitative myasthenia gravis, n: number, N: total number, NA: not applicable, NR: not reported, NS: not significant, OLE: open-label extension, PBO: placebo, QMG: quantitative myasthenia gravis, SE: standard error, RTX: rituximab

* Efgartigimod trials defined MG-ADL Responders as having ≥2 point improvement (reduction) in total MG-ADL score

† Efgartigimod trials defined QMG Responders as having ≥ 3 point improvement (reduction) in total QMG Score

ǂ Includes both responders and non-responders from cycle 1

**Table D2.9. Key Secondary Efficacy Outcomes I**

| Study Name / Trial Identifier | Arms | | Base-line N | Minimal Symptom Expression | | Early Onset MG-ADL Responder (within 2 weeks) | | Cumulative number of patients with a response n(%) | | Duration of MG-ADL Response in MG-ADL responders, weeks n (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | % | p-Value | n (%) | p-Value | MG-ADL Early Response | QMG Early Response | 4 to < 6 | 6 to <8 | 8 to ≤ 12 | 12+ | Median |
| **Efgartigimod** | | | | | | | | | | | | | | |
| **Phase III ADAPT[21]** | **AChR Ab+** | **Week 8 (Cycle 1)** | | | | | | | | | | | | |
| | | **Efgart** | 65 | 40 | < 0.0001 | 37 (57.0) | NR | NR | NR | 5 (11.4) | 14 (31.8) | 10 (22.7) | 15 (34.1) | NR |
| | | **PBO** | 64 | 11.1 | – | 16 (25.0) | – | NR | NR | NR | NR | NR | NR | NR |
| | | **Cycle 2** | | | | | | | | | | | | |
| | | **Efgart** | 51 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 43 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **AChR Ab-** | **Week 8 (Cycle 1)** | | | | | | | | | | | | |
| | | **Efgart** | 19 | 32 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 19 | 16 | – | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | **Overall** | **Week 8 (Cycle 1)** | | | | | | | | | | | | |
| | | **Efgart** | 84 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 83 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Phase II Howard 2019[24] [67]** | **Overall (AChR Ab+)** | **Week 11 (Day 80)** | | | | | | | | | | | | |
| | | **Efgart** | 12 | 42 | NR | NR | NR | NR | NR | **≥6 weeks:** Efgart: 9 (75) Placebo: 3 (25) Diff: 50.34%; 95%CI: 15.93 - 84.74; p=0.0391 **8 Weeks after last dose:** Efgart: 6 (50.0) | | | | |
| | | **PBO** | 12 | 8 | NR | NR | NR | NR | NR | | | | | |
| **Eculizumab** | | | | | | | | | | | | | | |
| **REGAIN Phase III[9,16]** | **Overall (Refract. AchR Ab+)** | **Week 4** | | | | | | | | | | | | |
| | | **ECU** | 62 | *12.3* | <0.01 | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 63 | 0 | – | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **Week 26** | | | | | | | | | | | | |
| | | **ECU** | 62 | 21.4 | 0.0007 | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 63 | 1.7 | – | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **REGAIN OLE Muppidi 2019[9,17]** | **Overall (Refract. AchR Ab+)** | **Week 4** | | | | | | | | | | | | |
| | | **ECU/ ECU** | 55 | *16.4* | NS | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO/ ECU** | 61 | *21.3* | – | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **Week 26** | | | | | | | | | | | | |
| | | **ECU/ ECU** | 49 | *24.1* | NS | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO/ ECU** | 55 | *23.5* | – | NR | NR | NR | NR | NR | NR | NR | NR | NR |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Week 52** | | | | | | | | | | | | |
| | | **ECU/ECU** | 49 | *22.4* | NS | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO/ECU** | 54 | *23.9* | – | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **Week 130** | | | | | | | | | | | | |
| | | **ECU/ECU** | 35 | 22.9 | 0.7861 | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO/ECU** | 36 | 27.8 | – | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Phase II Howard 2013[22]** | **Overall (Refract.)** | **Week 16 (Period 1)** | | | | | | | | | | | | |
| | | **ECU** | 7 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 7 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **Week 16 (Period 2)** | | | | | | | | | | | | |
| | | **ECU** | 6 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | | **PBO** | 6 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Howard 2021[21]** | **Overall (Refract. AchR Ab+)** | **Week 4** | | | | | | | | | | | | |
| | | **ECU** | 98 | NR | NR | NR | NR | 56 (57.1) | 46 (46.9) | NR | NR | NR | NR | NR |
| | | **Week 8** | | | | | | | | | | | | |
| | | **ECU** | 98 | NR | NR | NR | NR | 63 (64.3) | 52 (53.1) | NR | NR | NR | NR | NR |
| | | **Week 26** | | | | | | | | | | | | |
| | | **ECU** | 98 | NR | NR | NR | NR | 72 (73.5) | 61 (62.2) | NR | NR | NR | NR | NR |
| **Rituximab** | | | | | | | | | | | | | | |
| **Brauner 2020[63]** | **gMG** | NR | | | | | | | | | | | | |

| Maintenance IVIG | | |
|---|---|---|
| **Phase II NCT02473952[27]** | **Overall (AChR Ab+)** | NR |
| **Phase II NCT02473965[26]** | **Overall (AChR Ab+)** | NR |

%: percent, AChR Ab+: acetylcholine receptor antibody positive, Efgart.: efgartigimod, ECU: eculizumab, gMG: generalized myasthenia gravis, IVIG: intravenous immunoglobulin, MG-ADL: myasthenia gravis - activities of daily living, QMG: quantitative myasthenia gravis, n: number, N: total number, NR: not reported, PBO: placebo, Refract.: refractory

**Table D2.10. Key Secondary Efficacy Outcomes II**

| Study Name / Trial Identifier | Arms | | Baseline N | Prespecified worst-rank ANCOVA score | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | MG-ADL | Difference (95% CI) | QMG | Difference (95% CI) | MGC | Difference (95% CI) | MG-QOL15 | Difference (95% CI) |
| **Efgartigimod** | | | | | | | | | | | |
| **Phase III ADAPT[21]** | **Overall** | NR | | | | | | | | | |
| **Phase II Howard 2019[24]** | **Overall** | NR | | | | | | | | | |
| **Eculizumab** | | | | | | | | | | | |
| **REGAIN Phase III[16]** | **Overall (Refractory AchR Ab+)** | **Week 26** | | | | | | | | | |
| | | **ECU** | 62 | 56.6 (4.5) | -11.7 (-24.3, 0.96) | 54.7 (4.5) | -16.0 (-28.5, -3.4) | 57.3 (4.5) | -10.5 (-23.1, 2.1) | 55.5 (4.6) | -14.3 (-27.0, -1.6) |
| | | **Placebo** | 63 | 68.3 (4.5) | - | 70.7 (4.5) | - | 67.7 (4.5) | - | 69.7 (4.5) | - |
| **REGAIN OLE Muppidi 2019[17]** | **Overall (Refractory AchR Ab+)** | **NR** | | | | | | | | | |
| **Phase II Howard 2013[22]** | **Overall (Refractory)** | **NR** | | | | | | | | | |
| **Howard 2021** | **Overall (Refractory AchR Ab+)** | **NR** | | | | | | | | | |
| **Rituximab** | | | | | | | | | | | |
| **Brauner 2020[63]** | **gMG** | **NR** | | | | | | | | | |
| **Maintenance IVIG** | | | | | | | | | | | |
| **Phase II NCT02473952[27]** | **Overall (AChR Ab+)** | **NR** | | | | | | | | | |
| **Phase II NCT02473965[26]** | **Overall (AChR Ab+)** | **NR** | | | | | | | | | |

95% CI: 95% confidence interval, AChR Ab+: acetylcholine receptor antibody positive, ANCOVA: analysis of covariance, ECU: eculizumab, gMG: generalized myasthenia gravis, IVIG: intravenous immunoglobulin, MG-ADL: myasthenia gravis - activities of daily living, MGC: ,myasthenia gravis composite, MG-QoL15/r: myasthenia gravis - quality of life / revised, N: total number, NR: not reported, QMG: quantitative myasthenia gravis

**Table D2.11. Key Secondary Efficacy Outcomes III**

| Study Name / Trial Identifier | Arms | | Baseline N | MGFA Post-Intervention Status (PIS) | | | | Mean change from baseline Neuro-QOL Fatigue total score | | | Proportion of Patients in Remission | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Improved, n (%) | Patients achieving MM, n(%) | Unchanged n (%) | Worse, n (%) | n | mean (95% CI) | p-value | No. at risk | % |
| **Efgartigimod** | | | | | | | | | | | | |
| **Phase III ADAPT[21]** | **AChR Ab+** | | NR | | | | | | | | | |
| **Phase II Howard 2019[24]** | **Overall (AChR Ab+)** | | NR | | | | | | | | | |
| **Eculizumab** | | | | | | | | | | | | |
| **REGAIN Phase III[10,16,18]** | **Overall (Refractory AchR Ab+)** | **Week 4** | | | | | | | | | | |
| | | **ECU** | 62 | 30 (54.5) | 10 (18.2) | 25 (45.5) | 0 (0) | NR | NR | NR | NR | NR |
| | | **Placebo** | 63 | 15 (24.6) | 5 (8.2) | 41 (67.2) | 5 (8.2) | NR | NR | NR | NR | NR |
| | | **Week 26** | | | | | | | | | | |
| | | **ECU** | 62 | 34 (60.7) | 14 (25.0) | 21 (37.5) | 1 (1.8) | 56 | -16.3 (-20.8 to -11.8) | 0.0081 | NR | NR |
| | | **Placebo** | 63 | 25 (41.7) | 8 (13.3) | 30 (50) | 5 (8.3) | 60 | -7.7 (-12.1 to -3.3) | - | NR | NR |
| **REGAIN OLE Muppidi 2019[10,17,18]** | **Overall (Refractory AchR Ab+)** | **Week 4** | | | | | | | | | | |
| | | **ECU/ECU** | NR | NR | NR | NR | NR | 52 | -17.8 (-22.5 to -13.0) | NR | NR | NR |
| | | **PBO/ECU** | NR | NR | NR | NR | NR | 60 | -17.4(-22.0 to -12.9) | - | NR | NR |
| | | **Week 26** | | | | | | | | | | |
| | | **ECU/ECU** | 56 | 36 (75.0) | 22 (45.8) | 12 (25.0) | 0 (0) | NR | NR | NR | NR | NR |
| | | **PBO/ECU** | 60 | 40 (71.4) | 27 (48.2) | 15 (26.8) | 1 (1.8) | NR | NR | NR | NR | NR |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Week 52** | | | | | | | | | | |
| | | **ECU/ECU** | 56 | 41 (85.4) | 22 (45.8) | 6 (12.5) | 1 (2.1) | 48 | -17.5 (-22.5 to -12.5) | NR | NR | NR |
| | | **PBO/ECU** | 60 | 44 (81.5) | 31 (57.4) | 10 (18.5) | 0 (0) | 54 | -15.7 (-20.5 to -10.9) | - | NR | NR |
| | | **Week 130** | | | | | | | | | | |
| | | **ECU/ECU** | 35 | 28 (80.0) | 18 (51.4) | 5 (14.3) | 2 (5.7) | NR | NR | NR | NR | NR |
| | | **PBO/ECU** | 36 | 33 (94.3) | 22 (62.9) | 2 (5.7) | 0 (0) | NR | NR | NR | NR | NR |
| **Phase II Howard 2013[22]** | **Overall (Refractory)** | NR | | | | | | | | | | |
| **Howard 2021** | **Overall (Refractory AchR Ab+)** | NR | | | | | | | | | | |
| **Rituximab** | | | | | | | | | | | | |
| **Brauner 2020[63]** | | **Month 20** | | | | | | | | | | |
| | **RTX Treatment** | **New-onset gMG** | 24 | NR | NR | NR | NR | NR | NR | NR | 3 | *88.8* |
| | | **Refractory gMG** | 34 | NR | NR | NR | NR | NR | NR | NR | 11 | *60.7* |
| | **New-onset Disease** | **RTX** | 24 | NR | NR | NR | NR | NR | NR | NR | *NA* | *89* |
| | | **Control** | 26 | NR | NR | NR | NR | NR | NR | NR | *NA* | *66* |
| | | **Month 40** | | | | | | | | | | |
| | **RTX Treatment** | **New-onset gMG** | NR | NR | NR | NR | NR | NR | NR | NR | 0 | *NA* |
| | | **Refractory gMG** | NR | NR | NR | NR | NR | NR | NR | NR | 3 | *78.9* |
| | **New-onset Disease** | **RTX** | NR | NR | NR | NR | NR | NR | NR | NR | *NA* | *NA* |
| | | **Control** | NR | NR | NR | NR | NR | NR | NR | NR | *NA* | *73* |
| **Maintenance IVIG** | | | | | | | | | | | | |
| **Phase II NCT02473952[27]** | **Overall (AChR Ab+)** | NR | | | | | | | | | | |
| **Phase II NCT02473965[26]** | **Overall (AChR Ab+)** | NR | | | | | | | | | | |

%: percent, 95%CI: 95% confidence interval, AChR Ab+: acetylcholine receptor antibody positive, ECU: eculizumab, gMG: generalized myasthenia gravis, IVIG: intravenous immunoglobulin, MGFA: myasthenia gravis foundation of america, MM: minimal manifestations, n: number, No.: number, NA: not applicable, Neuro-QoL: neurological quality of life scale, NR: not reported, PIS: post intervention status, RTX; rituximab

**Table D2.12. Safety Outcomes I**

| Study Name / Trial Identifier | Arms | Time point | N | AE* | SAE† | Treatment-related AE | Discont. Treatment due to AEs | Death | Infection AE | ≥ 1 Infusion-related reaction event | Hospital Admis. | MG Exacerbation | MG Crisis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n (%) | | | | | | | | | |
| **Efgartigimod** | | | | | | | | | | | | | |
| **Phase III ADAPT[21]** | **EFGART** | Week 26 | 84 | 65 (77.0) | 4 (5.0) | [redacted] | 3 (4.0) | 0 (0) | 39 (46.0) | 3 (4.0) | NR | NR | NR |
| | **PBO** | | 83 | 70 (84.0) | 7 (8.0) | | 3 (4.0) | 0 (0) | 31 (37.0) | 8 (10.0) | NR | NR | NR |
| **Phase II Howard 2019[24]** | **EFGART** | Day 78 | 12 | 10 (83.3) | 0 (0) | NR | 0 (0) | 0 (0) | NR | NR | NR | NR | NR |
| | **PBO** | | 12 | 10 (83.3) | 0 (0) | NR | 0 (0) | 0 (0) | NR | NR | NR | NR | NR |
| | **Total** | | 24 | 20 (83.3) | 0 (0) | NR | 0 (0) | 0 (0) | NR | NR | NR | NR | NR |
| **Eculizumab** | | | | | | | | | | | | | |
| **REGAIN[16]** | **ECU** | Week 26 | 62 | NR | 9 (15) | NR | 4 (6) | 0 (0) | NR | NR | 9 (15) | 6 (10) | 1 (1.6) |
| | **PBO** | | 63 | NR | 18 (29) | NR | 0 (0) | 0 (0) | NR | NR | 18 (29) | 15 (24) | 0 (0) |
| | **Total** | | 125 | NR | 27 (22) | NR | 4 (3) | 0 (0) | NR | NR | 27 (22) | 21 (17) | 1 (0.1) |
| **REGAIN OLE Muppidi 2019[17]** | **Total** | Week 208 | 117 | 113 (96.6) | 52 (44.4) | NR | 6 (5.1) | 3 (2.6) | 22 (18.8) | NR | NR | 29 (24.8) | 3 (2.6) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase II Howard 2013[22]** | **ECU** | Week 37 (Includes Washout Period) | 13 | 13 (100) | 1 (7.7) | 7 (53.8) | NR | 0 (0) | NR | NR | NR | NR | NR |
| | **PBO** | | 13 | 11 (84.6) | 1 (7.7) | 6 (46.2) | NR | 0 (0) | NR | NR | NR | NR | NR |
| **Nowak 2020[19]** | **PRED** | End of OLE | 90 | 87 (96.7) | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | **AZA** | | 39 | 38 (97.4) | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | **MMF** | | 30 | 29 (96.7) | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | **Total** | | 117 | 114 (97.4) | NR | NR | 7 (6.0) | 3 (2.6) | NR | NR | NR | NR | NR |
| **Rituximab** | | | | | | | | | | | | | |
| **Phase II BeatMG[61]** | **RTX** | Week 52 | 25 | 25 (100) | 9 (36.0) | 19 (76.0) | 2 (8.0) | 0 (0) | NR | NR | NR | NR | NR |
| | **PBO** | | 27 | 26 (96.3) | 14 (51.9) | 22 (81.5) | 3 (11.1) | 0 (0) | NR | NR | NR | NR | NR |
| **Brauner 2020[63]** | **RTX** | First 24 months | 24 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | **Control** | | 26 | NR | NR | NR | 12 (46.0) | NR | NR | NR | NR | NR | NR |
| **Maintenance IVIG** | | | | | | | | | | | | | |
| **Phase II NCT02473952[27]** | **IGIV-C** | Week 24 | 30 | 22 (73.3) | 5 (16.7) | NR | 2 (6.7) | 1 (3.3) | NR | NR | NR | NR | NR |
| | **PBO** | | 32 | 21 (65.6) | 4 (12.5) | NR | 2 (6.3) | 0 (0) | NR | NR | NR | NR | NR |
| **Phase II NCT02473965[26]** | **IGIV-C** | Week 39 | 30 | 21 (70.0) | 4 (13.3) | NR | 6 (20.0) | 1 (3.33) | NR | NR | NR | NR | NR |
| | **PBO** | | 30 | 24 (80.0) | 6 (20.0) | NR | 4 (13.3) | 2 (6.7) | NR | NR | NR | NR | NR |

%: percent, AE: adverse event, Admis.: Admission, AZA: azathioprine, Discont.: discontinuation, Efgart.: efgartigimod, ECU: eculizumab, IGIV-C: immune globulin intravenous -c, IVIG: intravenous immunoglobulin, MMF: mycophenolate mofetil, n: number, N: total number, NR: not reported, PBO: placebo, Pred.: prednisone, RTX; rituximab, SAE: serious adverse event

* AE: includes AEs indicated as AE, any AE, or treatment-emergent AE

† SAE: includes SAEs indicated as SAE, any SAE, or treatment-emergent SAE

**Table D2.13. Safety Outcomes II**

| Study Name / Trial Identifier | Arms | Time-point | N | Commonly reported AEs | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Head-ache | Nasopharyngitis | Nausea | Diarr-hea | Upper Resp. Tract Infection | UTI | Arthralgia | Fatigue | HZ | Cough |
| | | | | n (%) | | | | | | | | | |
| **Efgartigimod** | | | | | | | | | | | | | |
| **Phase III ADAPT[21]** | **EFGART** | Week 26 | 84 | 24 (29.0) | 10 (12.0) | 7 (8.0) | 6 (7.0) | 9 (11.0) | 8 (10.0) | NR | NR | NR | NR |
| | **PBO** | | 83 | 23 (28.0) | 15 (18.0) | 9 (11.0) | 9 (11.0) | 4 (5.0) | 4 (5.0) | NR | NR | NR | NR |
| **Phase II Howard 2019[24]** | **EFGART** | Day 78 | 12 | 4 (33.3) | 1 (8.3) | 1 (8.3) | 1 (8.3) | 0 (0) | NR | 0 (0) | NR | 1 (8.3) | NR |
| | **PBO** | | 12 | 3 (25.0) | 0 (0) | 1 (8.3) | 1 (8.3) | 1 (8.3) | NR | 2 (16.7) | NR | 0 (0) | NR |
| | **Total** | | 24 | 7 (29.2) | 1 (8.3) | 2 (8.3) | 2 (8.3) | 1 (8.3) | NR | 2 (8.3) | NR | 1 (4.2) | NR |
| **Eculizumab** | | | | | | | | | | | | | |
| **REGAIN[16]** | **ECU** | Week 26 | 62 | 10 (16) | 9 (15) | 8 (13) | 8 (13) | 10 (16) | 0 | NR | NR | NR | NR |
| | **PBO** | | 63 | 12 (19) | 10 (16) | 9 (14) | 8 (13) | 12 (19) | 1 (2)* | NR | NR | NR | NR |
| | **Total** | | 125 | 22 (18) | 19 (15) | 17 (14) | 16 (13) | 22 (18) | 1 (1)* | NR | NR | NR | NR |
| **REGAIN OLE Muppidi 2019[17]** | **Total** | Week 208 | 117 | 44 (37.6) | 37 (31.6) | 21 (17.9) | 27 (23.1) | 27 (23.1) | 17 (14.5) | 22 (18.8) | 17 (14.5) | NR | 17 (14.5) |
| **Phase II Howard 2013[22]** | **ECU** | Week 37 (Includes Washout Period) | 13 | 3 (23.1) | 3 (23.1) | 4 (30.8) | NR | NR | NR | NR | NR | NR | NR |
| | **PBO** | | 13 | 3 (23.1) | 2 (15.4) | 2 (15.4) | NR | NR | NR | NR | NR | NR | NR |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Nowak 2020[19]** | **PRED** | End of OLE | 90 | 34 (37.8) | 34 (37.8) | 16 (17.8) | 17 (18.9) | 21 (23.3) | 9 (10.0) | 18 (20) | NR | NR | 13 (4.4) |
| | **AZA** | | 39 | 17 (43.6) | 8 (20.5) | 9 (23.1) | 14 (35.9) | 15 (38.5) | 4 (10.3) | 10 (25.6) | NR | NR | 8 (20.5) |
| | **MMF** | | 30 | 9 (30) | 9 (30) | 6 (20.0) | 7 (23.3) | 6 (20.0) | 6 (20.0) | 5 (16.7) | NR | NR | 5 (16.7) |
| | **Total** | | 117 | 47 (40.2) | 42 (35.9) | 22 (18.8) | 29 (24.8) | 28 (23.9) | 19 (16.2) | 23 (19.7) | NR | NR | 22 (18.8) |
| **Rituximab** | | | | | | | | | | | | | |
| **Phase II BeatMG[61]** | **RTX** | Week 52 | 25 | 8 (32) | NR | 2 (8) | 3 (12) | 9 (36) | 2 (8) | 6 (24) | 3 (12) | NR | 0 |
| | **PBO** | | 27 | 7 (25.9) | NR | 6 (22.2) | 2 (7.4) | 5 (18.5) | 3 (11.1) | 10 (37) | 8 (29.6) | NR | 3 (11.1) |
| **Brauner 2020[63]** | **RTX** | First 24 months | 24 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| | **Control** | | 26 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| **Maintenance IVIG** | | | | | | | | | | | | | |
| **Phase II NCT02473952[27]** | **IGIV-C** | Week 24 | 30 | 9 (30.0) | 3 (10.0) | 3 (10.0) | 3 (10.0) | 0 (0) | NR | 2 (6.7) | 2 (6.7) | NR | 3 (10.0) |
| | **PBO** | | 32 | 4 (12.5) | 4 (12.5) | 1 (3.1) | 2 (6.3) | 3 (9.4) | NR | 0 (0) | 0 (0) | NR | 0 (0) |
| **Phase II NCT02473965[26]** | **IGIV-C** | Week 39 | 30 | 10 (33.3) | 2 (6.7) | 5 (16.7) | 1 (3.3) | 6 (20.0) | 1 (3.3) | 4 (13.3) | 2 (6.7) | NR | 3 (10.0) |
| | **PBO** | | 30 | 3 (10.0) | 5 (16.7) | 1 (3.3) | 3 (10) | 3 (10.0) | 3 (10.0) | 6 (20.0) | 2 (6.7) | NR | 2 (6.7) |

%: percent, AZA: azathioprine, Efgart.: efgartigimod, ECU: eculizumab, HZ: herpes zoster, IGIV-C: immune globulin intravenous -c, IVIG: intravenous immunoglobulin, MMF: mycophenolate mofetil, n: number, N: total number, NR: not reported, PBO: placebo, Pred.: prednisone, RTX; rituximab, UTI: urinary tract infection

* Classified as serious bacterial urinary tract infection

**Table D2.14. Safety Outcomes III**

| Study Name / Trial Identifier | Arms | Timepoint | N | Rescue therapy used during treatment period | | | |
|---|---|---|---|---|---|---|---|
| | | | | High-dose Corticosteroids | Plasmapheresis or plasma exchange | IVIG | Other |
| | | | | n (%) | | | |
| **Efgartigimod** | | | | | | | |
| **Phase III ADAPT[21]** | **EFGART** | Week 26 | 84 | NR | NR | NR | NR |
| | **PBO** | | 83 | NR | NR | NR | NR |
| **Phase II Howard 2019[24]** | **EFGART** | Day 78 | 12 | NR | NR | NR | NR |
| | **PBO** | | 12 | NR | NR | NR | NR |
| | **Total** | | 24 | NR | NR | NR | NR |
| **Eculizumab** | | | | | | | |
| **REGAIN[16]** | **ECU** | Week 26 | 62 | 0 | 3 (5) | 4 (6) | 1 (2) |
| | **PBO** | | 63 | 5 (8) | 4 (6) | 6 (10) | 2 (3) |
| | **Total** | | 125 | 5 (4) | 7 (6) | 10 (8) | 3 (2) |
| **REGAIN OLE Muppidi 2019[17]** | **Total** | Week 208 | 117 | NR | NR | NR | NR |
| **Phase II Howard 2013[22]** | **ECU** | Week 37 (Includes Washout Period) | 13 | NR | NR | NR | NR |
| | **PBO** | | 13 | NR | NR | NR | NR |
| **Nowak 2020[19]** | **PRED** | End of OLE | 90 | NR | NR | NR | NR |
| | **AZA** | | 39 | NR | NR | NR | NR |
| | **MMF** | | 30 | NR | NR | NR | NR |
| | **Total** | | 117 | NR | NR | NR | NR |
| **Rituximab** | | | | | | | |
| **Phase II BeatMG[61]** | **RTX** | Week 52 | 25 | NR | NR | NR | NR |
| | **PBO** | | 27 | NR | NR | NR | NR |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Brauner 2020[63]** | **RTX** | First 24 months | 24 | *0.4 (1.5)* | | | |
| | **Control** | | 26 | *1.3 (2.9)* | | | |
| **Maintenance IVIG** | | | | | | | |
| **Phase II NCT02473952[27]** | **IGIV-C** | Week 24 | 30 | NR | NR | NR | NR |
| | **PBO** | | 32 | NR | NR | NR | NR |
| **Phase II NCT02473965[26]** | **IGIV-C** | Week 39 | 30 | NR | NR | NR | NR |
| | **PBO** | | 30 | NR | NR | NR | NR |

%: percent, AZA: azathioprine, Efgart.: efgartigimod, ECU: eculizumab, IGIV-C: immune globulin intravenous -c, IVIG: intravenous immunoglobulin, MMF: mycophenolate mofetil, n: number, N: total number, NR: not reported, PBO: placebo, Pred.: prednisone, RTX; rituximab

# D3. Ongoing Studies

**Table D3.1. Ongoing Studies**

| Title / Trial Sponsor | Study Design | Treatment Arms | Patient Population | Primary Outcomes | Estimated Completion Date |
|---|---|---|---|---|---|
| **Efgartigimod** | | | | | |
| **ADAPT+**<br>NCT03770403<br>Sponsor: argenx | Long-Term, Single-Arm, Open-Label, Multicenter Phase 3 follow-on trial | 1. Efgartigimod (IV) | Patients who have completed at least 1 cycle of treatment and at least 1 year of trial ARGX-113<br>(N=151) | **[Time Frame: Up to 3 years]** Safety and Tolerability as measured by the incidence of treatment emergent (serious) adverse events in the AChR-positive population | June 2023 |
| **Phase III AdaptSC**<br>NCT04735432<br>Sponsor: argenx | Phase III OL, Parallel-Group, Randomized Trial | 1. Efgartigimod SC<br>2. Efgartigimod IV | Patients with a diagnosis of generalized MG<br><br>(N=76) | **[Time Frame: Up to 3 years]** Percent change from baseline in total Immunoglobulin (IgG) levels at day 29 | October 2021 |
| **Phase III AdaptSC+**<br>NCT04818671<br>Sponsor: argenx | Phase III Long-Term, Single-Arm, Open-Label, Multicenter Trial | 1. Efgartigimod SC | Patients with a diagnosis of generalized MG<br><br>(N=201) | **[Time Frame: Up to 2 years]** Incidence and severity of AEs, SAEs, and AEs of special interest | April 2023 |
| NCT04833894<br>Sponsor: argenx | Open-labeled uncontrolled trial to evaluated pharmacokinetics, pharmacodynamics, and safety | 1. Efgartigimod IV | Pediatric patients 2-18 with generalized MG<br><br>(N=12) | **[Time Frame: Up to 26 weeks]** Efgartigimod concentrations for clearance and volume of Distribution, total Immunoglobulin G, AchR-Ab. | March 2023 |
| **Eculizumab** | | | | | |
| **Phase III Pediatric**<br>NCT03759366<br>Sponsor: Alexion | OL Single-Arm Multicenter | 1. Eculizumab IV (300, 600, 900, 1200 mg based on weight) | Patients aged 6-18 with refractory generalized MG<br>(N=12) | **[Time Frame: week 26 (primary evaluation) and week 208 (ext. period)]** | July 2025 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Change in the QMG total score over time regardless of rescue treatment | |
| **Rituximab** | | | | | |
| **Phase III**<br>NCT02950155<br>Sponsor: Fredrik Piehl, Karolinska Institute | Phase III, Double-Blind, Placebo-Controlled, Multicenter RCT | 1. Rituximab – single infusion of 500mg<br>2. Placebo (sodium chloride solution) | Patients with oculobulbar, bulbar, or generalized MG<br><br>(N=47) | **[Time Frame: Week 16]**<br>Percentage of patients with a QMG score ≤ 4 and daily prednisolone dose of ≤ 10mg | June 2021 |
| **Maintenance IVIG** | | | | | |
| **Phase II**<br>NCT04728425<br>Sponsor: University Health Network, Toronto | Phase II RCT | 1. IVIG + SCIG<br>2. SCIG alone | Patients with moderate to severe myasthenia gravis class II-IV (QMG >10 or gMG impairment index score >11<br><br>(N=30) | **[Time Frame: 6 months]**<br>Myasthenia Gravis Impairment Index Efficacy Outcome | June 2022 |

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

# D4. Previous Systematic Reviews and Technology Assessments

We identified two health technology assessments conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) on eculizumab and rituximab and one network meta-analysis (NMA) that included eculizumab. All reports are briefly summarized below.

## CADTH Clinical Review Report of Eculizumab (2020)[46]

CADTH investigators performed a systematic review of the benefits and harms of eculizumab for the treatment of adults with refractory AChR-Ab+ generalized MG. The review found one RCT: the Phase III REGAIN trial.[16] This review found that a maintenance dose of 1,200mg IV twice weekly of eculizumab led to improvement in activities of daily living; this treatment effect was deemed uncertain due to the statistical methods used in the analysis. Similarly, CADTH investigators cited relatively small sample sizes and limited follow-up of rare and serious AEs as limitation of the drug's long-term benefits and harms.

CADTH investigators received and critically appraised a sponsor-submitted (Alexion) SLR whose objective was to identify relevant scientific evidence of comparators to eculizumab for maintenance therapy of AChR-Ab+ refractory MG. The SLR included the following comparators: rituximab, IVIG, PLEX, and cyclophosphamide. Twelve relevant studies were included in the assessment. There was an inconsistent definition of refractory MG among the studies. Likewise, there was heterogeneity among the studies' population, methodology, dosage, outcomes, and timing of outcomes which limits the feasibility of estimating the relative efficacy of eculizumab versus comparators via indirect comparison/NMA.

## CADTH Health Technology Review of Rituximab (2018 and 2021)[68,69]

CADTH has conducted a review of rituximab for the treatment of MG in 2018, with an update in 2021.[67] An evaluation of non-randomized studies suggests that rituximab may be associated with improvements in clinical status, quality of life, and use of concomitant medications. The evidence base for the use of rituximab was deemed to be low-quality due to the lack of randomization/ control groups, small sample sizes, and lack of explicit exclusion criteria. This report did not identify the BeatMG Rituximab Phase II RCT trial in its review of the scientific literature. Side effects of rituximab use were found to be common but not serious. No studies were found that evaluated the cost-effectiveness of rituximab.

## Wang, L. et al. (2019). "Immunosuppressive and monoclonal antibody treatment for myasthenia gravis: A network meta-analysis"[70]

Investigators conducted a NMA to compare and rank seven immunotherapies for the treatment of MG. The immunotherapies included cyclosporine A, eculizumab, tacrolimus, belimumab,

methotrexate, azathioprine, and MMF. This study did not include efgartigimod, rituximab, or maintenance IVIG. The total patient population was 808 MG patients across 14 RCTs with a median sample size of 39 patients. The primary outcome of the NMA was the reduction of QMG score; secondary outcomes included glucocorticoid reduction and hazard ratios from the counts of AEs. Both eculizumab and cyclosporine A reached statistical significance versus placebo in the primary outcome when controlling for intervention periods. Eculizumab was ranked as most tolerable therapy and causing the least counts of AEs. Investigators concluded that eculizumab represented the most effective and tolerable therapeutic alternative to be recommended for refractory MG.

# E. Long-Term Cost-Effectiveness: Supplemental Information

## E1. Detailed Methods

We developed a de novo decision analytic semi-Markov model with time-dependent transitions for this evaluation, informed by key clinical trials and prior relevant economic models. Costs and outcomes were discounted at 3% per year. The model focused on an intention-to-treat analysis with two different cohorts of patients: those with refractory AChR-antibody positive generalized MG (gMG) (defined by MGFA clinical class II to IV) and those with gMG for whom conventional immunosuppressive therapies are insufficiently effective. The model cycle length was one month, based on the rapid effect of eculizumab and efgartigimod from clinical trials and the desire to evaluate differing retreatment frequencies with efgartigimod in scenario analyses.

The base-case analysis compared eculizumab plus conventional therapy to conventional therapy alone in patients with refractory AChR-antibody positive gMG and efgartigimod plus conventional therapy to conventional therapy alone in the broader population of patients with gMG evaluated in the clinical trial of efgartigimod. A detailed description of the model structures used in the base-case analyses is provided in Section 4.1 of this report.

Scenario analyses were conducted to evaluate a comparison of efgartigimod plus conventional therapy to conventional therapy alone in patients with refractory AChR-antibody positive gMG, using a subpopulation of patients from the trial evaluating efgartigimod that met the inclusion criteria for the clinical trial evaluating eculizumab and results from the NMA described in Section 3 of this report. In addition, a direct comparison of efgartigimod and eculizumab was made and the incremental cost-effectiveness estimated. These analyses utilized the same model described in Section 4.1 of this report.

Scenario analyses were also conducted to evaluate IVIG plus conventional therapy, or separately, rituximab plus conventional therapy in patients with gMG using a 4-state Markov model. No modifications were made to the model to evaluate these therapies, with the exception that the clinical response for rituximab occurred in the fourth model cycle instead of the first to better reflect the delay observed in clinical response to rituximab.[16]

The same model and methods were used to evaluate the impact of an 8-week redosing cycle for efgartigimod on incremental cost-effectiveness, with the exception that some simulated patients were allowed to lose the effect of efgartigimod in the 4-week period that they were not receiving the treatment. The proportion of patients moving to the unimproved Markov state was derived

from data collected 8 weeks after the first dose. All patients returned to the improved Markov state upon being re-dosed with efgartigimod.

For the scenario evaluating eculizumab or efgartigimod (separately), followed by IVIG or rituximab as second line treatment in patients with gMG (efgartigimod) or refractory AChR-antibody positive gMG (eculizumab), a modified model was used to include these second line treatments, and is shown in Figure E1. For this analysis, a 6-state Markov model was used. Simulated patients entered the model through the Markov state, "Unimproved MG on initial line of treatment," and received either eculizumab or efgartigimod. Patients with at least a 3-point improvement in QMG transitioned to the "Improved MG on initial line of treatment" Markov state and remained in that state, if alive, for the duration of the time horizon. Those who did not receive a 3-point improvement in QMG transitioned to the "Unimproved MG on secondary treatment" state and received treatment with either 1) IVIG or 2) rituximab (evaluated in separate models). Depending on whether these treatments were effective, patients transitioned to either the "Improved MG on secondary treatment" Markov state (if treatment was effective) or to the "Unimproved MG, treatment discontinued" state (if treatment is insufficiently effective) and remained in those states for the remainder of the time horizon, if alive. Simulated patients could enter the "Death" state in any cycle of the model. Simulated patients could experience "MG-related hospitalizations" and "MG-related emergency room visits" in any living state of the model, with the probability of experiencing these events in any cycle being higher for patients in any "Unimproved MG" state.

**Figure E1. Model Schematic: Six-State Model Depicting Treatment for Myasthenia Gravis with Initial Treatment, Followed by Secondary Treatment for Patients Deriving Insufficient Benefit from Initial Treatment**

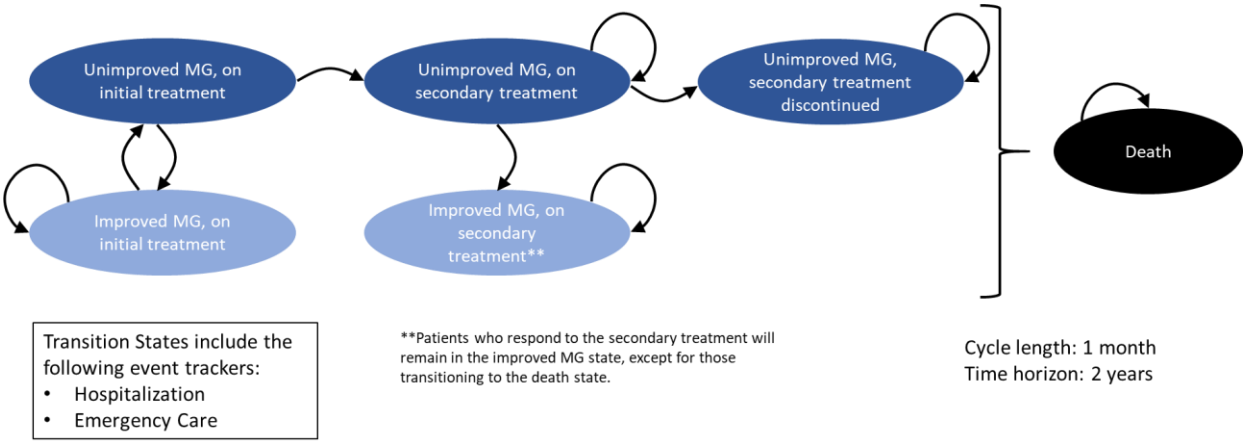


**Table E1.1. Impact Inventory**

| Sector | Type of Impact (Add additional domains, as relevant) | Included in This Analysis from […] Perspective? | | Notes on Sources (if quantified), Likely Magnitude & Impact (if not) |
|---|---|---|---|---|
| | | Health Care Sector | Societal | |
| **Formal Health Care Sector** | | | | |
| **Health Outcomes** | Longevity effects | X | Not Available | |
| | Health-related quality of life effects | X | Not Available | |
| | AEs | X | Not Available | |
| **Medical Costs** | Paid by third-party payers | X | Not Available | |
| | Paid by patients out-of-pocket | ☐ | Not Available | |
| | Future related medical costs | X | Not Available | |
| | Future unrelated medical costs | ☐ | Not Available | |
| **Informal Health Care Sector** | | | | |
| **Health-Related Costs** | Patient time costs | NA | Not Available | |
| | Unpaid caregiver-time costs | NA | Not Available | |
| | Transportation costs | NA | Not Available | |
| **Non-Health Care Sector** | | | | |
| **Productivity** | Labor market earnings lost | NA | Not Available | |
| | Cost of unpaid lost productivity due to illness | NA | Not Available | |
| | Cost of uncompensated household production | NA | Not Available | |
| **Consumption** | Future consumption unrelated to health | NA | ☐ | |
| **Social services** | Cost of social services as part of intervention | NA | ☐ | |
| **Legal/Criminal Justice** | Number of crimes related to intervention | NA | ☐ | |
| | Cost of crimes related to intervention | NA | ☐ | |
| **Education** | Impact of intervention on educational achievement of population | NA | ☐ | |
| **Housing** | Cost of home improvements, remediation | NA | ☐ | |
| **Environment** | Production of toxic waste pollution by intervention | NA | ☐ | |
| **Other** | Other impacts (if relevant) | NA | ☐ | |

NA: not applicable

Adapted from Sanders et al[71]

## Target Population

The populations of interest for this economic evaluation was the prevalent cohort of individuals in the United States with gMG, defined as MGFA clinical classification II to IV. Base-case analyses focused on patients with either refractory AChR-antibody positive gMG, when evaluating eculizumab, and a broader population of patients with gMG, including both refractory and non-refractory patients, for patients receiving efgartigimod. The baseline population characteristics and sources for patients with refractory AChR-antibody positive gMG and broader gMG are shown in Table E1.2. Since data stratified by gender and age was available only for the study evaluating efgartigimod, this study's data was used exclusively in the model when estimating patient mortality.

**Table E1.2. Base-Case Model Cohort Characteristics**

| | **Eculizumab (n=62), Refractory AChR-antibody positive gMG** | **Efgartigimod (n=84), All enrolled patients** |
|---|---|---|
| **Mean Age (SD), Years** | 47.15 (15.7) | 45.9 (14.4) |
| **Female, %** | 66.0 | 75.0 |
| **MGFA class, %** | | |
| **Class II** | 29.0 | 40.5 |
| **Class III** | 59.7 | 56.0 |
| **Class IV** | 11.3 | 3.6 |
| **AChR-Ab Status, %** | | |
| **Positive** | 100 | 77.4 |
| **Negative** | 0 | 22.6 |
| **MuSK-Ab Status** | N/A | N/A |
| **Positive** | | |
| **Negative** | | |
| **Source** | Howard 2017[16] | argenx 2021, Howard 2021[28,62] |

N/A: not available

*AchR-Ab positive subgroup from ADAPT trial

### Treatment Strategies

Treatment strategies included in the base-case were eculizumab plus conventional therapy compared with conventional therapy alone, represented by the placebo control group from the corresponding clinical trial, and eculizumab plus conventional therapy compared with conventional therapy alone, represented by the placebo control group from the corresponding clinical trial.

Additional treatment strategies were considered in scenario analyses, described in the Methods Overview Section of the main report.

## E2. Model Assumptions and Inputs

The key model inputs for base-case analyses are provided in Section 4.2 of this report. For scenario analyses, the effectiveness of IVIG and rituximab were estimated from long-term clinical trials evaluating these drugs plus conventional therapy compared with conventional therapy alone.[25,72] All additional model assumptions, definitions, and inputs used are shown in Tables E2.1 and E2.2.

## Model Inputs

### *Clinical Inputs*

**Table E2.1. Additional Model Assumptions**

| Assumption | Rationale |
|---|---|
| Efgartigimod administration will cost the same as that of eculizumab (Base Case) | Pricing is not available for efgartigimod administration as it is not yet approved by the FDA. Pricing for administering efgartigimod is likely to be similar to that of eculizumab. |
| IVIG's effect in the first cycle is the same as observed at 24 weeks | The effectiveness of IVIG at 4 weeks has not been reported. Since IVIG is nearly immediately effective, we assumed that the effectiveness at 4 weeks was similar to what was reported in the clinical trial.[72] |
| Rituximab's effect is observed in the 4$^{th}$ cycle after the first treatment (Scenario Analysis 3) | Evidence suggests that there is a delay in the onset of action of rituximab, with peak effectiveness observed at approximately month 4.5.[5] As the monthly impact of rituximab on QMG scores is not known, we have assumed that onset and peak action all occur in the 4$^{th}$ model cycle after rituximab administration. |
| Patients not responding to secondary treatment options will have that treatment discontinued and will remain in an unimproved MG state (Scenario Analysis 4) | We have chosen to evaluate only one additional treatment after eculizumab or efgartigimod. This assumption will affect a relatively small proportion of simulated patients (i.e., those in whom therapy with eculizumab or efgartigimod and IVIG or rituximab is ineffective) and is expected to have minimal impact on incremental cost effectiveness. |
| Patients who respond to treatment will remain in an improved MG state (All Models) | There is insufficient evidence available to determine what proportion of patients in whom therapy is initially effective eventually derive insufficient benefit from the same therapy. Multiple clinical trials have demonstrated similar response rates once peak treatment effectiveness is obtained. |

**Table E2.2. Additional Model Inputs**

| Parameter | Input | Source |
|---|---|---|
| Proportion of patients achieving 3 point or more reduction in QMG with efgartigimod plus CT in patients with refractory AChR-antibody positive gMG (Scenario Analyses 1 and 2) | 0.75 | Bootstrapped value derived from Howard 2021 and meta-analysis results[21] |
| Proportion of patients achieving 3 point or more reduction in QMG with IVIG (Scenario Analysis 3) | 0.62 | Bootstrapped value derived from NCT02473952[72] |
| Proportion of patients achieving 3 point or more reduction in QMG with CT (IVIG comparator) | 0.48 | Bootstrapped value derived from NCT02473952[72] |
| Proportion of patients achieving 3 point or more reduction in QMG with rituximab plus CT | 0.56 | Bootstrapped value derived from NCT02110706[25] |
| Proportion of patients achieving 3 point or more reduction in QMG with rituximab (efgartigimod comparator) | 0.36 | Bootstrapped value derived from NCT02110706[25] |
| Mean change in QMG among responders to efgartigimod plus CT in patients with refractory AChR-antibody positive gMG (Scenario Analyses 1 and 2) | -9.16 | Bootstrapped value derived from Howard 2021 and meta-analysis results[21] |
| Mean change in QMG among responders to IVIG (Scenario Analysis 3) | -7.82 | Bootstrapped value derived from NCT02473952[72] |
| Mean change in QMG among responders to CT (IVIG comparator) | -7.99 | Bootstrapped value derived from NCT02473952[72] |
| Mean change in QMG among responders to rituximab (Scenario Analysis 3) | -7.83 | Bootstrapped value derived from NCT02110706[25] |
| Mean change in QMG among responders to CT (rituximab comparator) | -5.88 | Bootstrapped value derived from NCT02110706[25] |
| IVIG cost for induction dose | $11,100** | Federal Supply Schedule 2021[34] |
| IVIG cost for maintenance dose | $5,600** | Federal Supply Schedule 2021[34] |
| Rituximab cost per 4-week regimen | $14,400*** | Federal Supply Schedule 2021[34] |
| Eculizumab administration, each | $230 | https://hcpcs.codes/j-codes/J1300/[73] |
| Efgartigimod administration, each | $230 | Assumed |
| IVIG administration, each | $74 | CMS.gov physician fee schedule lookup[74] |
| Rituximab administration | $58 | https://hcpcs.codes/j-codes/J9312/[73] |

CT = conventional therapy; *Midpoint between annual cost of eculizumab and IVIG; **Note that IVIG was dosed at 3-week intervals. Therefore per cycle costs were adjusted to account for additional doses in each 4-week cycle; ***Rituximab is dosed once weekly for 4 weeks, administered twice per year.

*Clinical Probabilities/Response to Treatment*

Clinical probabilities for the base-case are described in the Key Model Assumptions and Inputs Section of the report. As with the base-case, clinical probabilities for the scenario analyses were estimated from clinical trial data. The proportion of patients achieving a minimum 3-point improvement in QMG was derived from clinical trials by bootstrapping mean change in QMG at appropriate time points using the mean, standard deviation, and assuming a normal distribution. The bootstrapping method also allowed for changes in QMG score to be estimated for individuals. The primary clinical trial evaluating IVIG assessed outcomes at 24 weeks.[72] Due to the rapid action

of IVIG, we assumed that a similar response would be observed within 4 weeks as was observed at 24 weeks. The primary clinical trial evaluating rituximab assessed outcomes at 52 weeks. In addition, rituximab has a delayed onset of action, with peak effect occurring at 4.5 weeks in single dose clinical trials.[25] We therefore assumed that rituximab's onset of action would occur and peak in the model cycle representing weeks 16-20.

*Mortality*

Mortality was included in the model as described in the Key Model Assumptions and Inputs of this report. As evidence suggesting that mortality is different among patients with differing severity of MG is lacking and treatments have not been evaluated for their impact on mortality, treatments in the model were assumed to not have an impact on mortality.

*Utilities*

Health state utilities were derived from a deidentified data source provided by Dr. Barnett.[31,32] Health state utilities were derived from baseline QMG scores and changes to baseline QMG scores reported in clinical trials. Changes to baseline QMG scores were used to estimate state-specific QMG scores and corresponding utility in those in improved and unimproved Markov states, using a bootstrapping methodology described in the Key Model Assumptions and Inputs Section of the report.

*Adverse Events*

AEs were considered for inclusion in the model only if they occurred at a probability of at least 5% or would be expected to result in a substantial increased cost to treat or decrease in utility, and were significantly higher than placebo, or if the AE would be expected to result in a substantial increased cost to treat or decrease in utility. Due to the potential risk of meningitis (specifically, Neisseria meningitidis serogroups A, C, Y, and W-135), a meningococcal vaccine is required prior to receiving eculizumab. The cost of this vaccine was included for patients receiving eculizumab. The only other AEs that occurred with a statistically higher frequency in treatment than in placebo included headache with IVIG (33% vs. 10% with placebo) and first infusion reaction with rituximab (27% vs. 19% with placebo). However, costs of treatment of and disutility associated with these conditions was determined to be minimal and would not measurably impact these treatments' cost-effectiveness.

***Economic Inputs***

*Drug Acquisition Costs*

Drug acquisition costs were estimated using the Federal Supply Schedule, available through the Veterans Administration Drug Pricing Database.[34] Since efgartigimod is not yet approved, a

placeholder price was generated using the midpoint of the annual costs of IVIG and eculizumab.[35] Drug acquisition costs are shown in Table E2.3.

**Table E2.3. Drug Cost Inputs**

| Interventions | Administration | Unit | FSS per Unit * | Net Price per Unit | Annual Drug Cost** |
|---|---|---|---|---|---|
| **Eculizumab** | 900 mg weekly for 4 weeks, then 1200 mg maintenance every 2 weeks | 10mg/mL, 30 mL vial | $6,031 | $4,343 | $470,200 |
| **Efgartigimod** | Weekly IV infusions (10 mg/kg) | n/a | n/a | n/a | $286,100*** |
| **IVIG (for a 90 kg person)** | 180 g loading dose; 90 g maintenance every 3 weeks | 5g/vial | $428 | $308 | $102,000 |
| **Rituximab and biosimilars (for a person with BSA=1.9)** | 713 mg weekly for 4 consecutive weeks; re-dose every 6 months | 10mg/mL, 10 mL vial | $702‡ | $505‡ | $28,809 |

*FSS as of June 29, 2021

**The annual drug cost includes induction and maintenance doses. A discount of 28% was assumed for the net price calculation.

***The midpoint between the annual cost of IVIG and eculizumab was used to estimate the cost of efgartigimod

‡Mean cost for Rituxan and biosimilars.

*Administration and Monitoring Costs*

The costs for administering eculizumab, efgartigimod, IVIG, and rituximab were included in the model. Administration costs were obtained from CMS.gov.[74] Where these codes were not available, they were obtained from HCPCS.codes.[73] Administration costs used in the model are shown in Table E2.4.

**Table E2.4. Dose, Frequency of Administration, and Annual Monitoring and Administration Utilization**

| Intervention | Route | Frequency of Administration | Administration Cost per Dose | Administration Cost per Year |
|---|---|---|---|---|
| **Eculizumab** | IV | Induction weekly for 4 weeks, then every 2 weeks | $230 | $6470 |
| **Efgartigimod** | IV | Weekly infusions | $230 | $12,017 |
| **IVIG** | IV | Every 3 weeks | $74 | $1280 |
| **Rituximab and biosimilars** | IV | Weekly for 4 consecutive weeks, every 6 months | $94 | $753 |

*Health Care Utilization Costs*

The costs of hospitalizations and emergency visits were included in the model. These costs were described in the Key Model Inputs Table 4.3 in the report.

*Productivity Costs and Caregiver Burden*

The systematic review that we conducted identified no suitable studies that could provide inputs for productivity costs or caregiver burden. A modified societal perspective considering productivity and caregiver costs was not conducted.

## E3. Results

The total discounted lifetime costs, QALYs, and mean QMG score over the two-year time horizon are shown for all scenario analyses interventions and comparators in Table E3.1. Undiscounted base-case results are presented in Table E3.2. Incremental cost-effectiveness ratios for all scenarios are shown in the main report, in the section titled Scenario Analyses.

**Table E3.1. Discounted Results for All Scenario Analyses**

| Treatment | Drug Cost | Total Cost | QALYs | Life Years | evLYGs |
|---|---|---|---|---|---|
| **Efgartigimod plus CT (Scenarios 1 and 2)** | $419,700 | $516,800 | 1.30 | 1.93 | 1.30 |
| **IVIG plus CT (Scenario 3a)** | $123,600 | $210,700 | 1.17 | 1.93 | 1.17 |
| **CT (Scenario 3a)** | $0 | $90,700 | 1.06 | 1.93 | 1.06 |
| **Rituximab (Scenario 3b)** | $34,800 | $125,700 | 1.10 | 1.93 | 1.10 |
| **CT (Scenario 3b)** | $0 | $97,500 | 0.98 | 1.93 | 0.98 |
| **Efgartigimod plus CT, dosed every 8 weeks (Scenario 4)** | $206,700 | $300,500 | 1.18 | 1.93 | 1.18 |
| **Eculizumab/IVIG (Scenario 5)** | $600,800 | $685,700 | 1.24 | 1.93 | 1.24 |
| **Eculizumab/Rituximab (Scenario 5)** | $567,900 | $655,000 | 1.21 | 1.93 | 1.21 |
| **Efgartigimod/IVIG (Scenario 5)** | $439,600 | $531,600 | 1.35 | 1.93 | 1.35 |
| **Efgartigimod/Rituximab (Scenario 5)** | $416,400 | $509,100 | 1.33 | 1.93 | 1.33 |

CT: conventional therapy, evLYG: equal value of life years gained, IVIG: intravenous immunoglobulin, QALY: quality-adjusted life year

**Table E3.2. Undiscounted Results for All Base-Case and Scenario Analyses**

| Treatment | Drug Cost | Total Cost | QALYs | Life Years | evLYGs | Mean QMG |
|---|---|---|---|---|---|---|
| **Eculizumab plus CT** | $562,200 | $659,600 | 1.17 | 1.99 | 1.17 | 12.45 |
| **CT alone** | $0 | $98,200 | 1.02 | 1.99 | 1.02 | 14.89 |
| **Efgartigimod plus CT** | $418,400 | $518,700 | 1.31 | 1.99 | 1.31 | 10.10 |
| **CT alone** | $0 | $97,500 | 1.02 | 1.99 | 1.02 | 14.89 |
| **Efgartigimod plus CT (Scenarios 1 and 2)** | $431,500 | $531,400 | 1.34 | 1.99 | 1.34 | 9.71 |
| **IVIG plus CT (Scenario 3a)** | $126,900 | $216,400 | 1.20 | 1.99 | 1.20 | 11.86 |
| **CT (Scenario 3a)** | $0 | $93,300 | 1.09 | 1.99 | 1.09 | 13.71 |
| **Rituximab (Scenario 3b)** | $35,700 | $129,100 | 1.14 | 1.99 | 1.14 | 12.95 |
| **CT (Scenario 3b)** | $0 | $100,300 | 1.01 | 1.99 | 1.01 | 15.08 |
| **Efgartigimod plus CT, dosed every 8 weeks (Scenario 4)** | $212,200 | $308,600 | 1.22 | 1.99 | 1.22 | 11.68 |
| **Eculizumab/IVIG (Scenario 5)** | $616,800 | $704,000 | 1.28 | 1.99 | 1.28 | 10.70 |
| **Eculizumab/Rituximab (Scenario 5)** | $582,900 | $672,300 | 1.24 | 1.99 | 1.24 | 11.25 |
| **Efgartigimod/IVIG (Scenario 5)** | $452,000 | $546,500 | 1.39 | 1.99 | 1.39 | 8.83 |
| **Efgartigimod/Rituximab (Scenario 5)** | $428,100 | $523,400 | 1.37 | 1.99 | 1.37 | 9.18 |

CT: conventional therapy, evLYG: equal value of life years gained, IVIG: intravenous immunoglobulin, QALY: quality-adjusted life year, QMG: quantitative myasthenia gravis score

## E4. Sensitivity Analyses

Results of the sensitivity analyses are presented in the main report section titled Sensitivity Analyses. The full cost-effectiveness acceptability curves for eculizumab and efgartigimod are shown in Figures E2 and E3.

**Figure E2. Cost-Effectiveness Acceptability Curve for Eculizumab vs. Placebo**

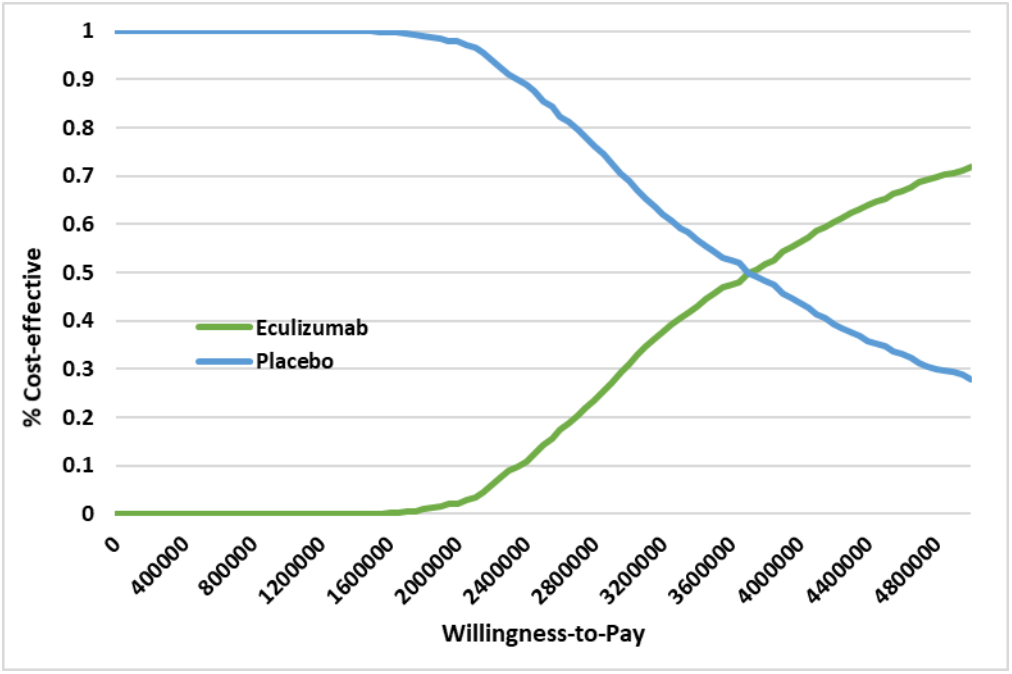
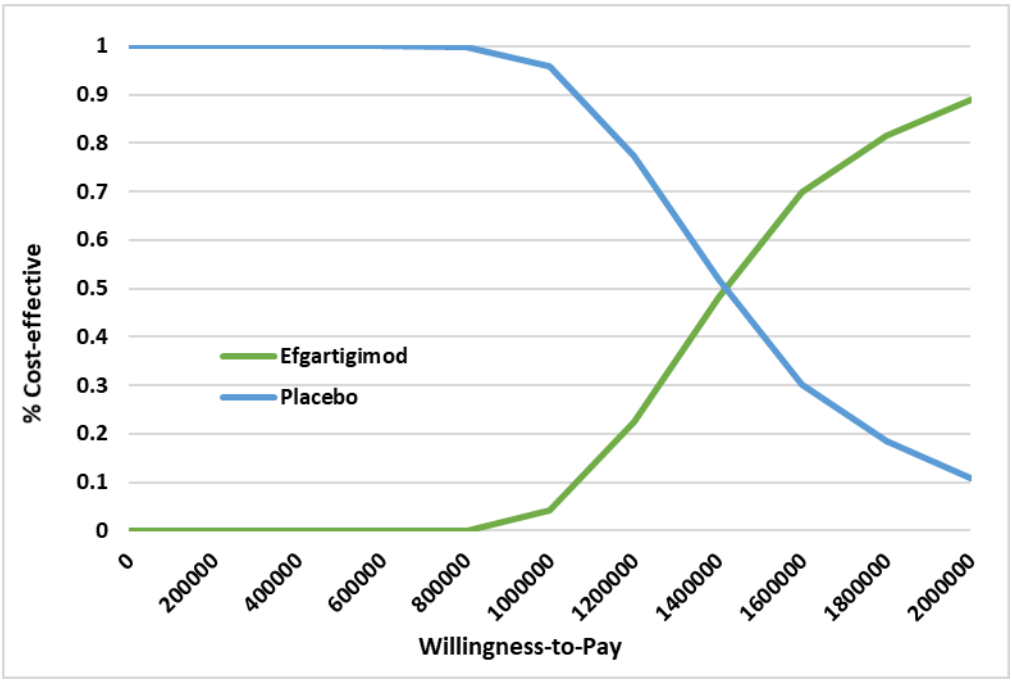



**Figure E3. Cost-Effectiveness Acceptability Curve for Efgartigimod vs. Placebo (based on placeholder pricing)**



## E5. Scenario Analyses

Scenario analyses were presented in the Section E3 results of this Supplement.

## E6. Heterogeneity and Subgroups

There are a number of factors that may affect treatment response in patients with MG. The presence of certain antibodies, such as MuSK, may predict a poorer outcome. Additionally, gender, race, age of onset, history of smoking, and concomitant autoimmune disease may be predictive of disease course, severity, and impact patient reported outcomes.[75-77] As a result, treatment efficacy may vary in clinical trials, depending on the demographics of the enrolled population. Unfortunately, little is known about the impact of these potential prognostic factors on treatment effectiveness. However, each of the clinical trials evaluated in this review included relatively small numbers of participants, with a large variation in patient age, antibody status, and prior treatment. This variability and lack of analysis of comparable subgroups, complicated the comparison of trial results.

## E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

### Prior Economic Models

In order to develop a comprehensive model and identify potential model inputs, we reviewed all identified published models for assessing treatments for MG. Chicaiza-Becerra evaluated the cost-effectiveness of open or thoracoscopic thymectomy compared to medical treatment in managing MG without thymomas from the Columbian health system perspective.[78] The Markov model included four states, not complete remission, complete remission, myasthenic crises, and death. The model evaluated a cohort of 22-year-old patients with a time-horizon of 55 years and used a one-year cycle length. There were several assumptions stated, including that myasthenic crisis occurred only in patients who were not in complete remission and that patients could not return to "without complete remission" after remission was achieved. The included thymectomy AEs were

surgical wound infection, mediastinitis, mediastinal hematoma and presence of pericardial exudate. The authors noted that a major limitation of the analysis was there was that the effectiveness estimates for the treatments were obtained from case series and not randomized, comparative trials. Additionally, data used to populate the model's transition probabilities were from small trials. Economic inputs were derived from the Columbian official tariff rates manual. This study provided important considerations to the conceptualization of our Markov model.

Heatwole evaluated the costs of IVIG and PLEX for patients with MG crisis using a simple decision tree model.[79] The decision tree evaluated the hospitalization costs of these treatments and their complications. As this model was evaluating short-term treatments and not long-term chronic treatment, the modeling methods did not apply well for assessing the cost-effectiveness of the treatments being evaluated in this report.

A review by CADTH described an unpublished cost-effectiveness model submitted by Alexion Pharma Canada Corporation evaluating the cost-effectiveness of eculizumab plus standard of care compared to standard of care alone.[80] Although the Markov model structure, inputs, and sources were not shown, a description of the model states was provided. Model states included an initial refractory gMG health state, health states defined by change in MG-ADL after 6 months of treatment, short-term exacerbation or myasthenic crisis states, and death. The cycle length was 6 months and time horizon was 52.5 years. Most model probabilities were derived from the REGAIN study.[16] Utility was estimated from MG-ADL using a post-hoc analysis of the REGAIN trial data. Drug costs were obtained from Canadian price lists. Administration costs were either covered by the sponsor or, in the case of home-based administration, were estimated using average hourly nursing wages. The resulting incremental cost-effectiveness ratio was $1.2 million (CAD) per QALY gained. Sensitivity analyses and a number of scenario analyses were conducted. Critical appraisal by CADTH identified important key limitations, including 1) not having rituximab as a comparator; 2) inclusion of a progressive MG course of illness over time, which is inconsistent with evidence; 3) higher than expected mortality in patients experiencing myasthenic crisis; 4) a disproportionate disutility for patients experiencing myasthenic crisis; and 5) discontinuation of eculizumab was not consistent with clinical practice. Upon reanalysis, addressing as many of the criticisms as were possible with the model design, the incremental cost-effectiveness of eculizumab was estimated at $1.5 million (CAD) per QALY gained. This report provided important considerations for the development of the model in this report.

# F. Potential Budget Impact: Supplemental Information

## F1. Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To this end, we used inputs for the projected average US population size from 2021-2025 (339,640,651 individuals) and MG prevalence in the setting of MGFA clinical classification II-IV (20,000 MG cases per 100,000 US individuals, 69% of which with classification II-IV disease), yielding 46,870 gMG patients.[81,82] Based on methods reported within a CADTH Common Drug Review report of eculizumab in gMG, we assumed that 100% of these gMG patients would be diagnosed.[80] We went on to assume that 100% of patients would be eligible for treatment with efgartigimod. For the purposes of this analysis, 20% of these 46,870 patients initiated new efgartigimod treatment in each of the five years, resulting in 9,374 additional patients treated each year.

Comparators in the budget impact model included eculizumab and conventional therapy. Conventional therapy consisted of thymectomy when appropriate, acetylcholinesterase inhibitor, corticosteroids and/or non-steroidal immunosuppressive therapy. Starting market share for eculizumab in the model was based off of analyst projections for eculizumab revenue and total MG pharmaceutical spend through 2025.[83-85] These analyses suggested an initial modeled market share of 2.27% by patient volume for eculizumab, with the remaining 97.73% of initial market share by patient volume attributed to conventional therapies. In the efgartigimod scenario, efgartigimod added to conventional therapy market uptake was drawn proportionally from eculizumab and conventional therapies.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[86,87] The intent of our revised approach to budgetary impact is to document

the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent five-year period for which data were available, and the contribution of spending on retail and facility-based drugs to total health care spending over the most recent five-year period for which data were available.

For 2021-2022, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $734 million per year for new drugs.

## F2. Results

Table F1 illustrates the per-patient budget impact results in more detail, for efgartigimod placeholder WAC ($397,000* per year), discounted placeholder WAC ($286,000* per year), and the benchmark prices to reach $150,000, $100,000, and $50,000 per QALY ($28,400, $18,300, and $8,200, per year, respectively) added to conventional therapy compared to eculizumab therapy and conventional therapy:

**Table F1. Average Annual Per-Patient Budget Impact Calculations Over a Five-year Time Horizon**

| | Average Annual Per-Patient Budget Impact for Each Calculated Price Point | | | | |
|---|---|---|---|---|---|
| | **WAC*** | **Discounted WAC*** | **$150,000/QALY** | **$100,000/QALY** | **$50,000/QALY** |
| **Efgartigimod and CT vs. eculizumab and CT** | $282,000 | $203,400 | $21,800 | $14,500 | $7,240 |

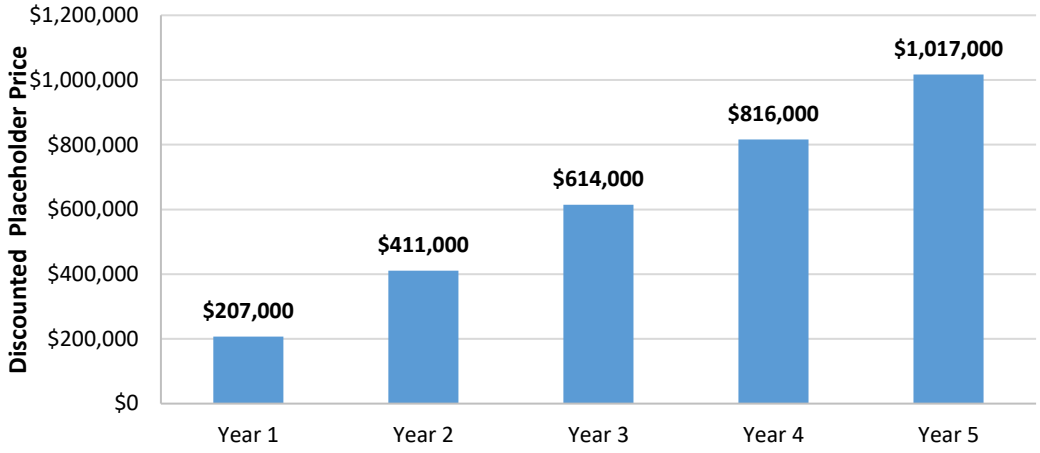
CT: conventional therapy, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*These are unvalidated placeholder prices that are assumed to lie at the midpoint between calculated IVIG price and calculated eculizumab price; this methodology is partially sourced from argenx Q2 and Q3 earnings calls.[35,38]

Figure F1 illustrates the cumulative per-patient budget impact calculations for efgartigimod added to conventional therapy compared to eculizumab and conventional therapy based on the net price used within the cost-effectiveness analysis. We suggest caution in interpreting the potential budget impact of efgartigimod due to the placeholder annual net price assumed. We observed the general

trend of slightly decreasing year over year per treated patient potential budget impacts due to treatment discontinuation over time.

**Figure F1. Cumulative Net Budget Impact Per Patient Treated with Efgartigimod for Five Years at Discounted WAC Price of $286,000 per Year***




* Placeholder price was assumed. Interpret findings with caution.