REPORT AT A GLANCE: **MYASTHENIA GRAVIS**

OCTOBER 2021

KEY FINDINGS

	eculizumab (Soliris®, Alexion Pharmaceuticals, Inc.)	efgartigimod (argenx)
Evidence Rating	B+; moderate certainty that eculizumab delivers a small net benefit over conventional therapy alone, with the possibility of a substantial net benefit	C++; comparable to conventional therapy alone, with the possibility of delivering a substantial net benefit in adults with gMG positive for anti-AChR antibodies.
Estimated Annual Price	$653,100	Placeholder price: $418,400
Annual Health-Benefit Price Benchmark	$13,200-$19,400	$18,300-$28,400
Change from Annual Price Required to Reach Threshold Price	97%-98%	N/A: discounts not presented due to placeholder price

"Myasthenia gravis is a serious lifelong disease with life-threatening manifestations, and conventional therapy with high-dose corticosteroids remains inadequate for most patients. While our review of available evidence suggests that both eculizumab and efgartigimod appear to significantly improve function and quality of life for these patients, there are uncertainties about longer-term outcomes for efgartigimod and how it will be dosed in real-world settings. Efgartigimod's price is not yet known, but our analysis suggests that the current list price for eculizumab is far higher than the usual thresholds for cost-effectiveness. Further, it's important to monitor these treatments' effectiveness in minority populations to develop a complete picture of their overall efficacy."

– ICER's Vice President of Research, Foluso Agboola, MBBS, MPH

THEMES AND RECOMMENDATIONS

- All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with gMG are introduced in a way that will help reduce health inequities.
- Payers should use the FDA label as the guide to coverage policy and engage clinical experts and diverse patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time.
- Payers should use step therapy based on clinical trial eligibility and/or authoritative evidence-based clinical specialty guidelines as they become available. Given the limited current evidence base for efgartigimod, payers should not require therapy with efgartigimod prior to coverage of eculizumab. However, as additional clinical evidence accumulates, it may be reasonable to require step therapy based on price.
- Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the

Summary

setting of these new interventions for gMG, there remains substantial uncertainty regarding their longer-term safety and effectiveness. Manufacturer pricing should reflect these considerations in more moderate launch pricing.

- Clinical specialty societies should continue to bear witness to the impact of high prices for novel therapies on patients.
- Patient organizations have a vital role to play by complementing existing clinical research with patient focused surveys collecting data on the impact of gMG on the diversity of patient experiences and the impact on caregivers.
- Researchers should collect data on the larger societal impact of novel therapeutics used to treat patients with gMG, not just the immediate impacts on patients.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

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 and the annual incidence is approximately 2.2 per 100,000. The characteristic finding of MG is muscle weakness that worsens with repeated use ("fatigable weakness").

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. Currently, about 20,000 patients with generalized MG are intolerant or have an inadequate response to conventional treatment options.

In this Report, ICER reviewed 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, and an FDA decision on efgartigimod is expected on December 17, 2021.

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 1), 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). In the open label extension through 130 weeks of follow up, the benefits were maintained, and may have increased compared with 26 weeks. 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.

Clinical Analyses

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 1). 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 1. 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	-1.8	-1.7	-1.0	-1.2

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

Note: Numbers are digitized estimates. Efgartigimod ADAPT trial results for AChR-positive patients only

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 above information on short-term benefits, but uncertainties about dosing, long-term benefits, and long-term safety, we concluded that there is moderate certainty of a comparable, small, or substantial net health benefit of efgartigimod added to conventional

Clinical Analyses

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.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

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-antibodies. The analyses were conducted over a two-year time horizon, taking a health system perspective. Based on an annual cost of $653,100, the incremental cost per QALY and incremental cost per evLYG for eculizumab were estimated to be $5,210,000. For efgartigimod, using a placeholder price of $418,400, the incremental cost per QALY and incremental cost per evLYG were estimated to be $2,076,000. From the cost-effectiveness base case, we estimated the health benefit price benchmark (HBPB) for each intervention. The HBPB range for eculizumab was estimated to be $13,200 to $19,400 (97%-98% discount from the Federal Supply Schedule [FSS] price). For efgartigimod, the HBPB range was estimated to be $18,300 to $28,400 (discounts not presented due to placeholder price).

The model was sensitive to several inputs, including the QMG improvement 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 $3.8 million per QALY gained for eculizumab and $1.7 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.

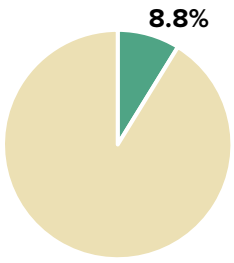
Economic Analyses

POTENTIAL BUDGET IMPACT

The percentage of the eligible population that can be treated with efgartigimod without passing the updated potential budget impact threshold is 8.8% at placeholder price ($418,000* 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 ($28,400 per year), $100,000/QALY ($18,300 per year), and $50,000/QALY ($8,200 per year).

We did not calculate the budget impact of eculizumab because it received FDA approval in October 2017.

** This is an unvalidated placeholder price that is 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. Interpret findings for this placeholder plotted point with caution.*



Percent of eligible patients with myasthenia gravis that could be treated in a given year before crossing the ICER potential budget impact threshold

Public Meeting Deliberations

VOTING RESULTS

For adults with gMG, defined by MGFA clinical classes of II to IV for whom conventional immunosuppressive therapies have not been effective or have not been tolerated, and who are anti-AChR antibody positive:

- All panelists found that the evidence is adequate to demonstrate a net health benefit of eculizumab added to convential therapy when compared to conventional therapy alone.
- A majority of panelists found that the evidence is adequate to demonstrate a net health benefit of efgartigimod added to conventional therapy over convential therapy alone.
- All panelists found the evidence is not adequate to distinguish a net health benefit of eculizumab from that of efgartigimod.
- All panelists found the evidence is not adequate to distinguish the net health benefit of IVIG from that of eculizumab and efgartigimod.
- A majority of panelists found the evidence is not adequate to distinguish the net health benefit of rituximab from that of eculizumab and efgartigimod.

Public Meeting Deliberations

For adults with gMG, defined by MGFA clinical classes of II to IV for whom conventional immunosuppressive therapies have not been effective or have not been tolerated, and who are anti-AChR antibody negative:

- All panelists found that the evidence is not adequate to demonstrate a net health benefit of efgartigimod added to conventional therapy compared to conventional therapy alone.

During their deliberations, panel members also weighed the therapies' other potential benefits, disadvantages, and contextual considerations. For both treatments, voting highlighted the following as particularly important for payers and other policymakers to note:

- The acuity of need for treatment based on the severity of myasthenia gravis;
- The magnitude of the lifetime impact on individual patients of myasthenia gravis;
- Patients' ability to achieve major life goals related to education, work, or family life; and
- Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life.

The independent appraisal committee voted on the long-term value for money of eculizumab and efgartigimod. They focused on adults with gMG, defined by MGFA clinical classes of II to IV for whom conventional immunosuppressive therapies have not been effective or have not been tolerated, and who are anti-AChR antibody positive:

- A majority of panelists found that eculizumab represents "low" long-term value for money. ICER's recommended health-benefit price benchmark (HBPB) range for eculizumab is $13,200-$19,400, pricing levels that would require a 97-98% discount off the treatment's wholesale acquisition cost (WAC) of $653,100.
- All panelists found that efgartigimod represents "low" long-term value for money at the assumed price of $418,400. ICER's recommended health-benefit price benchmark (HBPB) range for efgartigimod is $18,300-$28,400. The price of efgartigimod is not yet known.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

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