

Re: ICER's Assessment of Treatments for Generalized Myasthenia Gravis – Draft Evidence Report

Dear Dr. Pearson,

Alexion appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report for the assessment of the clinical effectiveness and economic value of eculizumab and efgartigimod for the treatment of generalized myasthenia gravis (gMG).

Alexion has been committed to serving patients and families affected by rare diseases and devastating conditions for more than 25 years through the discovery, development and commercialization of life-changing medicines. We continue to deepen our understanding of rare diseases, which began with our pioneering work in complement biology. The 2017 approval of eculizumab for patients with gMG who are anti-acetylcholine receptor antibody-positive (AChR+) represents the first FDA-approved treatment for this devastating disease in approximately 60 years.

MG is a chronic autoimmune neuromuscular disease that is debilitating to patients, significantly impacting their ability to perform activities of daily living. It has an erratic disease course that results in symptoms which fluctuate over time and can worsen within any given day. MG exacerbations are unpredictable, which can cause patients to live in constant fear and miss out on day-to-day activities. These fluctuating symptoms can have a huge emotional, social and physical impact on patients' lives that cannot easily be quantified. Patients often undergo a long journey to diagnosis, and prior to the approval of eculizumab, the only therapies available to them once they finally received an accurate diagnosis were limited to immunosuppressants and supportive care, both of which primarily address acute symptoms. A subset of patients found that they did not respond to or could not tolerate these medicines at all.

Alexion is pleased that ICER has acknowledged the clinical benefits of eculizumab in patients with AChR+ gMG compared to conventional therapy, with a better clinical rating (B+) compared to other interventions that were included in the report. The ICER report clearly recognizes the consistent and clinically important improvements in myasthenia gravis activities of daily living (MG-ADL) and quantitative myasthenia gravis (QMG) scores with eculizumab that were maintained through the 26-week Phase 3 study and the 130-week open-label extension. In addition to these trial data, there is evidence from real-world data that further strengthens the significant clinical benefit profile of eculizumab.

However, Alexion believes that conventional approaches for assessing cost-effectiveness of treatments should not be applied for rare diseases. Rare diseases should have their own HTA methodology, with a dedicated approach for considering evidence, QALY weighting, costs and epidemiology that would also allow for more focus on patient experience.

- ***Traditional approaches to cost-effectiveness analysis models are inappropriate for rare disease.*** Conventional cost-effectiveness analysis (CEA) models, such as the one used by ICER, do not account for disease severity, valuing all quality adjusted life years (QALY) increment improvements the same¹. Estimating QALYs gained is difficult for rare diseases and the underlying utility scores often do not accurately or adequately capture all aspects of patient benefit and caregiver experience. Given the diverse, heterogeneous, multi-faceted and unpredictable nature of gMG, there are no data on patient-reported MG-related health utilities by disease severity and different symptom type that adequately quantify the impact of the disease on patients' lives. Using traditional simplified assumptions due to limited understanding and quantification of disease impact for rare conditions penalizes interventions for rare patients and does not promote scientific advancements. The approach implemented in this gMG assessment takes a utilitarian measurement of health care costs and impacts from a direct payer. It does not consider any value from the societal need to bring the best therapeutic option to the rare disease

patients, nor the support environment. Factors such as pain, limitations in daily living and anxieties of living with an unpredictable disease are clearly costs to the patients, their families and society. A critical question is how to value improvements in the patient's condition and societal suffering in a comprehensive and holistic way that brings hope for the development of future treatments for those with rare conditions. This is particularly important, given the majority of rare diseases do not have an approved treatment.

- ***Full burden of rare disease on patients, their families, and society overall are not accounted for.*** Building on the previous point, CEA approaches do not account for the chronic nature of rare diseases and undervalue the ability of new treatments to offset the significant burden of rare disease on patients, their families and society at large. The National Economic Burden of Rare Disease Study published earlier this year by the EveryLife Foundation found that more than half the economic burden related to living with a rare disease is indirect and due to non-medical costs, including loss of productivity for patients, caregivers and employers, as well as home modifications and transportation expenditures². However, none of these costs are adequately captured in CEA models, meaning that more than half of the financial burden of the disease is unaccounted for when assessing a medicine's cost effectiveness. This is a particularly critical gap in MG, since the disease most often affects people of working age and significantly limits activities of daily life, including employment, where they may have to modify their work, reduce their working hours or are even forced to retire early.
- ***All rare diseases assessed to date have resulted in negative ICER assessment³.*** Conventional CEA approaches, including the one utilized by ICER, focus on monetizing clinical outcomes, as reported in clinical trials, and comparing the value of those monetized outcomes against the cost of using the treatment. Rare diseases tend to be highly heterogeneous with diverse patient symptomatology, which makes measuring and adequately capturing the full treatment impact challenging and means that population-based predictions are less meaningful when using mean values. As a result, ICER's assessments have yielded negative recommendations for all the rare disease therapies they have previously assessed, despite the significant clinical benefits demonstrated in robust Phase 3 trials and long-term data with positive health benefits³ – a fact that further reveals and reinforces the inadequacies of the CEA framework for rare diseases. For gMG, ICER found that none of the therapies it investigated, namely eculizumab, efgartigimod, rituximab and IVIG, were cost-effective at ICER's defined threshold of \$200,000 per QALY, which is a far lower threshold than is recommended for rare diseases. Alexion does not believe this cost-effectiveness finding is reflective of the overall value these treatments provide to patients with gMG.

We share ICER's commitment to the affordability of prescription medicines. However, without taking a comprehensive patient-centered value assessment, ICER's negative recommendations may lead to very real consequences for patients and their families in the form of restricted and delayed access to transformational therapies³, particularly for rare diseases, which is not in the best interest of patients, nor is it supportive of the future innovation needed to continue driving forward the development of new treatments for rare diseases and devastating conditions.

Alexion provides the following recommendations to improve the transparency and reporting of the evidence without which the conclusions can be misleading:

1. Adjust model assumptions to reflect chronic nature of gMG & include full spectrum of disease consequences over the long-term

It has been well established by the clinical community that gMG is a chronic disease⁴. gMG patients experience exacerbations and crises throughout their lifetimes and this is not adequately captured in the

current ICER model⁵. The current model lacks the sophistication needed to effectively account for the chronic nature of the disease, is biased towards short-acting treatments, and undervalues treatments such as eculizumab that have long-term sustained benefits, which may also have implications for directing future research and development.

Alexion recommends that ICER adjusts model assumptions in the base case to more accurately reflect the fact that gMG is a chronic disease and the value that treatments like eculizumab, which have long-term treatment benefits, bring to patients' lives.

2. Include a full societal perspective analysis

ICER states that a scenario analysis assessing a modified societal perspective was explored, but that no differences were found between the modified societal perspective and the health care system perspective due to insufficient evidence. Alexion would like to emphasize that a lack of published evidence regarding societal impacts does not mean they do not exist and should not be taken as endorsement of the hypothesis that they make no difference as stated in the report. Since gMG affects people of working age, it is important to account for these impacts. We also believe that it is important to reflect in a quantitative way the societal burden and impact of gMG disease on people with diverse racial and ethnic backgrounds, including women of color and their families.

Alexion recommends that ICER consider novel ways to incorporate societal burden into its model framework to adequately quantify the true economic burden of the disease.

3. Align assumptions related to treatment schedule & benefit with clinical practice and explicitly describe the impact of said assumptions

Questions and uncertainties exist regarding treatment patterns and the potential discrepancy between response to treatment and treatment schedule in clinical trials versus in the real-world and the assumptions adopted by ICER in the assessment. ICER's model is largely based upon treatment response rates over a shorter time frame of 4 weeks, conflicting with physician practices. Physicians generally assess patients' responses at a timeframe beyond 4 weeks due to the established chronic nature of the disease.

Alexion recommends that assumptions in the model assessing treatment response and benefit should reflect real-world clinical practice as much as possible, and that all assumptions be explained clearly and transparently, including their implications on the conclusions, to minimize the possibility of misinterpretation.

4. Provide more transparency on the network meta-analyses (NMA) comparing eculizumab and efgartigimod

ICER has concluded that there is insufficient evidence, defined as "any situation in which the level of certainty in the evidence is low," to compare eculizumab and efgartigimod. Yet, ICER conducts and reports outcomes for a NMA indirectly comparing the two therapies providing very limited information in the report on how the two trials were adjusted for their differences in patient characteristics, treatment schedule and endpoints.

Given the lack of appropriate evidence to conduct an indirect treatment comparison of the two therapies, the cost-effectiveness results comparing eculizumab versus efgartigimod in Table 4.8 is misleading. Additionally, there appears to be a calculation error in the confidence intervals in Table 3.4 of the Draft Evidence Report, unless ICER used an additional undisclosed trial to estimate pooled 4-week results.

Alexion recommends that ICER explicitly describe the methodology for NMA and potential sources of patient heterogeneity in its evidence report and note how they impacted and limited NMA findings as well as highlight the uncertainties of the results of head-to-head comparison. Alexion also asks that ICER review and correct any calculation errors or otherwise provide clarity and transparency into the underlying calculations.

5. Transparently report the utility values used in the base-case model and scenario analyses

In its Draft Evidence Report, ICER acknowledges that direct links between trial endpoints and EQ-5D are unavailable. However, since the Markov model framework that ICER created requires a utility for each state, ICER implemented several assumptions, including bootstrapping QMG differences and estimating linear models with only a single independent variable, to derive EQ-5D values. This approach suggests that ICER attempted to fit available data into a predetermined modeling framework instead of choosing the best modeling framework for the data.

Alexion recommends that ICER establish the following multi-pronged approach to ensure maximum methodological transparency: 1) Document the uncertainty in its utility estimates, 2) Explicitly label the utility values used for each state in each scenario, 3) Justify the high and low bounds used in the deterministic sensitivity analysis, and 4) Document how the probabilistic sensitivity analysis samples were generated (i.e., fitted distributions, bootstrapping, etc.).

6. Update report to accurately reflect eculizumab safety data

Alexion recognizes that ICER gathered and analyzed data from a large variety of sources and that transcriptional errors and uncertainties can occur when reviewing such evidence. Alexion appreciates that ICER summarized existing long-term data and real-world evidence; however, Alexion would like to bring to ICER's attention the following inaccuracy found in the Draft Evidence Report:

On page 19 in the "Harms" section for eculizumab, ICER notes, "There was one MG crisis in a patient in the eculizumab group who died from the crisis 90 days after the last eculizumab dose." This text does not make clear that the death occurred after the patient discontinued from the study.

Alexion requests that ICER clarify that **no deaths occurred during the study** as clearly stated in Howard et al. 2017⁶.

In summary, Alexion believes that values-based assessment should reflect value for patients, health systems and society, and should also account for future innovation. In addition, reviews should be transparent and patient-centric, making appropriate allowances for small populations with high unmet need. Rare disease treatments should have their own HTA methodology that treats them separately from non-rare diseases. Dedicated methods would allow for more focus on the patient experience, which should be paramount in driving decision making. Rare disease value assessments need to look at striking the balance between supporting access for people living with rare diseases and sustaining the ability for rare disease companies to bring innovative therapies to these people in the future.

At Alexion, we remain committed to advancing our goals of developing transformative medicines and providing optimal access to these medicines for rare diseases, including in gMG. At present, we remain concerned that ICER's approach inhibits rather than supports our goal of bringing transformative medicines to the rare disease community and urge consideration of the issues and recommendations noted above.

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6. Howard JF, Jr., Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *The Lancet Neurology*. 2017;16(12):976-986.

August 18, 2021

RE: argenx Response to ICER's Draft Evidence Report Assessing Treatments for Myasthenia Gravis

argenx US Inc. ("argenx") appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER's) draft evidence report for the assessment of treatments for myasthenia gravis (MG).

Efgartigimod's comparative clinical effectiveness rating should be changed from C++ to B+.

ICER gave efgartigimod (EFG) a C++ rating due to the uncertainties about dosing and long-term benefits. ICER considered that dosing in the ADAPT trial would not reflect routine practice because clinicians might not want to wait until the benefits have receded, as in the ADAPT trial, before initiating subsequent treatment cycles. The ADAPT trial considered an individualized dosing approach for EFG according to clinical evaluation. Specifically, each EFG treatment cycle was composed of a treatment period with 4 infusions at weekly intervals, followed by at least a 5-week period with no infusions. The timing between each cycle was individualized based on the duration of the patient's clinically meaningful response. Patients could not be re-treated until they returned to within 2 points of their baseline score on the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale. We agree that neither clinicians nor patients will want to allow the treatment benefits to return so near to baseline; however, physicians are expected to follow an individualized dosing schedule. Patients will receive subsequent treatment cycles according to clinical evaluation tailored to maximize their individual outcomes. This individualized dosing schedule is intuitive to clinicians, similar to how intravenous immunoglobulin (IVIg) is dosed in patients with MG, and is expected to be included in the EFG label. The use of treatment cycles, as in the ADAPT study, was based on a recommendations by patients consulted on the trial design for EFG. Additionally, in real-world practice, the individualized dosing schedule is expected to allow patients and clinicians to maximize the treatment effect without unnecessary drug doses.

The long-term treatment benefit is another area of uncertainty highlighted by ICER. In the draft evidence report, ICER primarily relied on the published ADAPT trial data to inform its clinical effectiveness rating. Additional data from the ADAPT extension study (ADAPT+) have recently become available and provide strong evidence of the long-term benefit of EFG (confidential data provided to ICER). All patients enrolled in the ADAPT study were eligible to roll over to the ADAPT+ trial to receive open-label treatment with EFG following an individualized dosing schedule for up to 3 years. At the time of the latest data cut, 79.1% of patients who received ≥ 1 dose of EFG in ADAPT+ remained in this study (median follow-up of >1 year), and patients continued to experience similar MG-ADL and Quantitative Myasthenia Gravis (QMG) scale improvements in all subsequent treatment cycles. The majority of patients enrolled in the ADAPT+ study continued on EFG for >1 year, indicating a lasting benefit from treatment with EFG.

At the time, ADAPT was the largest study (N=167) of a broad population of MG patients in a global phase 3 study. We believe that the ADAPT and ADAPT+ studies provide a high level of certainty to inform the clinical benefit of EFG. Taken together, the rating for EFG's comparative clinical effectiveness should be improved to B+ based on the evidence above.

ICER should revise the way the economic results are presented to fully characterize the individualized dosing of efgartigimod.

The base-case assumption that patients on EFG will have continual dosing at weekly intervals is not supported by the ADAPT trial data and fails to take into account the individualized dosing approach of EFG. See above for a detailed description of how patients in the ADAPT trial were dosed and what is expected in terms of real-world practice. In the current cost-effectiveness model, ICER included 13 treatment cycles within 1 year for patients who responded to the initial EFG treatment cycle; however, patients from the ADAPT and ADAPT+ trials

received an average of 4.7 treatment cycles in the first year of treatment. Additionally, 27% of patients were able to sustain response with ≤ 3 cycles of EFG treatment for 1 year. Ignoring the treatment cycle dosing approach ignores a value-based approach to treatment that will significantly decrease the average yearly costs of treating patients with EFG. ICER has acknowledged in the draft evidence report that the dosing frequency is one of the greatest uncertainties for EFG’s value. Regardless, ICER chose to primarily represent the economic value of EFG based on one extreme hypothetical dosing scenario in the base-case analysis. We do not believe the current presentation accurately reflects EFG’s individualized dosing schedule and could be misleading. We have the following suggestions to further improve the clarity of the report presentation:

- 1) ICER considered that EFG would be dosed with 4 weeks between treatment courses in a scenario analyses. This scenario is more aligned with EFG’s individualized dosing schedule in the ADAPT trial and how it will be used in real-world practice. Therefore, we suggest that ICER present findings from this scenario as a co-base-case analysis.
- 2) To reflect EFG’s individual dosing based on clinical evaluation, we suggest ICER add a scenario to estimate the value of EFG among the subgroup of patients who are able to sustain the response with ≤ 3 cycles of EFG treatment within 1 year. Our own evaluation using ICER’s cost-effectiveness model indicated that the economic value improved substantially in this scenario. The incremental cost-effectiveness ratio was less than \$250,000/QALY when all patients were assumed to receive 3 cycles of EFG annually. The incremental cost-effectiveness ratio further decreased to less than \$100,000/QALY when all patients were assumed to receive 1 cycle of EFG annually. This scenario is meaningful to represent the full spectrum of economic value associated with EFG treatment.
- 3) ICER should include language when presenting the cost-effectiveness results to highlight that these findings are contingent upon hypothetical assumptions of EFG’s dosing schedule. The economic value could vary substantially if a different assumption was considered.

ICER should update the cost-effectiveness model with more accurate data on response rate and utility based on observed data from the ADAPT trial.

ICER relied on assumptions to derive the response rate values and utility inputs for the model. The response rates based on QMG score were derived from clinical trials by bootstrapping the mean change in QMG at certain time points using the mean and standard deviation and assuming a normal distribution. ICER acknowledges that the bootstrapping methodology may not precisely replicate study results. Furthermore, the utility inputs were estimated based on an unpublished algorithm by Pickard et al using QMG scores. ICER should update the model using observed data directly from the ADAPT trial to reduce uncertainties within the model or provide a scenario analysis that includes the observed response rate and utility to clarify the impact of this assumption. The incremental cost-effectiveness ratio would decrease by 15% (25% for the scenario with 4 weeks between EFG treatment courses) if more accurate response and utility estimates were used.

The response rate as defined by 3-point reduction in QMG score at Week 4 based on the ADAPT trial is 73% for EFG and 32% for conventional treatment. These values are slightly different from the current estimated values using the bootstrapping approach. The observed Week 4 utility values estimated using the EQ-5D-5L instrument are provided below. These data provide more accurate estimates than the utility estimates produced by ICER. Specifically, ICER’s current approach considered that the utility improvement would only be dependent on the QMG score and would be independent of the treatment. However, our internal analysis has identified a statistically significantly positive effect from EFG treatment on the utility value for each QMG score (i.e., patients receiving EFG had higher utility value versus those receiving conventional treatment for the same QMG score). Therefore, ICER’s current utility approach underestimated the benefit associated with EFG treatment and should be revised.

	EFG plus conventional treatment	Conventional treatment alone
Improved MG	0.85	0.68
Unimproved MG	0.76	0.63

The base-case cost-effectiveness results were estimated based on several strong assumptions; ICER should expand the list of scenarios explored to fully account for the uncertainties.

- In addition to the dosing assumption, ICER’s economic modeling included the following assumptions:
- ICER assumed patients who do not respond to EFG during the first cycle will have the treatment discontinued

immediately and will remain in an unimproved MG state. In the ADAPT trial, an additional 12% of patients become responders (≥ 2 -point MG-ADL improvement sustained for ≥ 4 weeks per the ADAPT trial definition) after receiving the second cycle. Incorporating the benefit of these additional responders may have a big impact on the cost-effectiveness results.

- For IVIg, ICER assumed that the treatment effect in the first cycle would be the same as that observed at Week 24. Because of this assumption, ICER considered a substantially shorter duration of treatment for the nonresponders than what has been considered in the clinical trial. Specifically, all nonresponders to IVIg were assumed to only receive treatment for 4 weeks in the model, whereas in the clinical trial where IVIg's efficacy was derived, all subjects receive maintenance dosing of 1 g/kg every 3 weeks until Week 36. Because of this assumption considering equal clinical benefit with substantially less treatment utilization than the data, the economic value of IVIg was artificially inflated. Considering a scenario where IVIg's treatment effect was achieved on Week 24 (as consistent with the clinical trial data) will have a significant impact on the cost-effectiveness results.
- Finally, in the existing scenario analyses, ICER compared EFG with eculizumab at the same treatment line. In real-world practice, a novel therapy such as EFG that is more effective and $\geq 35\%$ less costly than eculizumab (as set by ICER) is likely to be preferred in payer policies. ICER should consider a scenario that compares EFG followed by eculizumab vs eculizumab alone to provide insights to payers.

Despite these substantial uncertainties, sensitivity analyses only varied utility values, QMG response at Week 4 and Week 8, and costs of hospitalizations/emergency department visits. The number of scenario analyses is also limited and is not sufficient to fully characterize the uncertainties associated with these assumptions. We suggest ICER expand the list of scenarios to explore the 4 additional scenarios suggested to better characterize the uncertainty and more objectively represent the value for the assessed interventions and comparators. In addition, ICER should include relevant language to highlight the considerable uncertainty associated with these assumptions to guide the interpretation of results.

The target population for efgartigimod is overestimated in the current budget impact analysis from the draft evidence report and should be updated.

In the draft evidence report, ICER considered all patients with MGFA clinical classification of II to IV for the target population for EFG in the potential budget impact. In clinical practice, EFG is anticipated to be used in patients inadequately treated by conventional treatments. Most patients with MG do not achieve a full pharmacologic remission with current treatment options and require additional therapies (Gilhus 2016a). Instead of assuming that 100% of the 46,870 gMG patients with MGFA clinical classification II to IV will be eligible for treatment with EFG, ICER should use the percentage of patients who require additional MG treatments. In an internal analysis, argenx found that of gMG patients, 42.1% will require additional MG treatments. Thus, 19,741 patients would be eligible for treatment with EFG. If 20% of these patients initiated new EFG treatment in each of the 5 years, this would result in 3,948 additional patients treated each year.

For voting questions 4 and 5, ICER should separate efgartigimod from eculizumab when evaluating the net health benefit versus IVIg and rituximab.

In voting questions 4 and 5, ICER asks if the evidence is adequate to distinguish the net health benefit of IVIg and rituximab (RTX), respectively, from that of eculizumab and EFG. EFG is fundamentally different from eculizumab in many dimensions and should not be grouped together in the same question. The 2 treatments have different mechanisms of action and dosing strategies. Additionally, the pivotal trial for each treatment, which provide the key evidence for clinical effectiveness, focused on different populations and had divergent study designs. With regard to clinical effectiveness, ICER noted in the draft evidence report that EFG has significantly greater improvements in MG-ADL and QMG scores compared with eculizumab. Furthermore, the safety profile is also very different; eculizumab is associated with increased risk for meningococcal infections, while EFG does not have such risk.

By combining EFG and eculizumab in the same voting question, ICER is implying that the 2 treatments are similar and interchangeable in their net health benefit. There is no evidence to support this, and this could be misleading to the audience. Although ICER included a note that additional votes would be cast for EFG and eculizumab if the response to voting question 3 is "yes," argenx believes that the votes should be separated,

regardless of the response to voting question 3. Even if current evidence might not be adequate to distinguish the net health benefit of eculizumab from EFG, the 2 treatments are still fundamentally different and should not be grouped together. Therefore, ICER should have 4 separate voting questions comparing IVIg and RTX to EFG and to eculizumab.

ICER should note that rituximab is only recommended as an off-label treatment option for patients with muscle-specific tyrosine kinase (MuSK)-positive MG, representing less than 10% of patients with MG.

ICER has included RTX as a comparator in scenario analyses in a broad MG patient population. As ICER acknowledged in the draft evidence report, RTX is not specifically indicated for MG, and there is a lack of rigorously designed randomized controlled trials to inform its clinical benefit in MG. The majority of evidence supporting the use of RTX in MG has considerable limitations and comes from retrospective observational studies. The BeatMG trial is the only randomized controlled trial of RTX in MG. The trial included only 52 participants, and RTX failed to demonstrate a significant difference from placebo on the primary outcome (75% reduction in daily prednisone dose after 2 cycles separated by 6 months; 60% vs 55.6%; $P=NR$). Additionally, RTX is associated with rare, but serious, safety concerns, such as prolonged hypogammaglobulinemia and progressive multifocal leukoencephalopathy (PML), requiring continuous monitoring of B-cell counts. RTX includes a black box warning for PML, and although the estimated incidence ranges from 1.39 to 1.87 per 10,000 RTX-exposed patients, PML can be fatal (D'Alo 2020). Prolonged hypogammaglobulinemia following RTX is also rare but can leave patients at risk for developing serious infections; reports note that the rate of serious infections following RTX may be as high as 5.2 per 100 patient-years (Barmettler 2018).

Consensus guidelines recommend RTX as an off-label, early therapeutic option for patients with MuSK-positive MG with an unsatisfactory response to initial immunotherapy due to observational efficacy data in that patient population. The efficacy of RTX in refractory AChR-positive MG patients is uncertain (Narayanaswami 2021). Patients with MuSK-positive MG make up between 1% and 10% of total MG patients (Gilhus 2016b).

ICER's report did not include language to provide relevant background on RTX and could mislead audiences regarding its positioning and clinical use in MG. Given the uncertain clinical efficacy of RTX and small MG patient population, the scenario analysis conducted in ICER's report is not representative of clinical practice. Using RTX as a comparator in a broad MG patient population when it is an off-label therapy that failed its primary endpoint and is only recommended in a small MuSK-positive patient population is not appropriate.

ICER should include statements to provide relevant context to guide the interpretation of the results for RTX. These statements should be reflected in the clinical effectiveness section when presenting the clinical effectiveness of RTX, and in the cost-effectiveness section when presenting the scenario analysis findings. A footnote should be included anywhere that data are presented on RTX explaining the significant limitations.

There are significant assumptions made in modeling IVIg, and additional data should be taken into account to more accurately reflect the value of IVIg.

IVIg is an off-label option used in some instances in MG. Consensus guidelines recommend IVIg as a maintenance therapeutic option for patients with refractory MG or those in whom immunosuppressive therapies are contraindicated (Sanders 2016). Two trials in acute settings demonstrated modest but statistically significant improvement (Zinman 2007, Barth 2011). These findings are in an acute treatment setting and should not be extrapolated to long-term, chronic IVIg administration. In another randomized controlled trial, IVIg failed to meet its primary endpoint of producing a $\geq 50\%$ reduction in corticosteroid dose (NCT02473965). This study with a failed primary endpoint was used by ICER to assign the clinical rating and economic rating of IVIg. Overall, there are limited data available to demonstrate a robust, long-term efficacy benefit of maintenance IVIg in MG. These uncertain clinical trial results have not been able to establish an effect that leads to an FDA label for the treatment of MG.

IVIg is associated with a significant adverse effects and patient burden due to frequency and duration of the administration. In the failed trial of IVIg, 70% in the IVIg group experienced an adverse event (AE) and 13.33% experienced a serious AE. Common AEs included headache (33.3%), upper respiratory tract infection (20.0%), nausea (16.7%), and arthralgia (13.3%) (NCT02473965). In a review of AEs from IVIg therapy across therapeutic areas, flu-like symptoms may occur in up to 87.5% of patients, and dermatological adverse effects may occur in

around 6% of patients (Guo 2018). More than half of patients develop headaches after IVIg, which are often severe and long-lasting (Guo 2018). Other adverse effects such as arrhythmia, hypotension, and transfusion-related acute lung injury are rare but may also occur following administration. Furthermore, delayed adverse effects such as thrombotic events, neurological disorders, renal impairment, hematologic disorders, electrolyte disturbance, and transfusion-related infection affect <1% of patients but can be severe and even lethal (Guo 2018). Each IVIg infusion session lasts several hours and may lead to adverse effects from the infusion that can disrupt quality of life. Given the long infusion duration, high rates of AEs, and frequent infusion schedule, IVIg can be a burdensome therapy (Jones 2018). ICER should consider adding data related to the adverse effects associated with IVIg administration, as well as include a footnote whenever they present IVIg data, that states this treatment is not indicated for MG and there is insufficient clinical evidence supporting its benefit.

The disease burden is not fully reflected in ICER's cost-effectiveness model and should be acknowledged in the draft evidence report.

Due to the rare nature of MG, there is insufficient evidence available to fully characterize the burden of the disease. Consequently, disease burden is underestimated in the cost-effectiveness analysis in ICER's draft evidence report, which considerably affects the value assessment of EFG. For example, up to 20% of patients with MG experience a potentially life-threatening myasthenic crisis, with respiratory failure requiring mechanical ventilation (Grob 2008, Wendell 2011) and extended hospital admissions. In a retrospective claims analysis of healthcare resource utilization and costs in patients with MG, the estimated annual costs to payers doubled in the year leading up to a crisis in comparison to the year prior. In patients who experienced a myasthenic crisis, costs increased by roughly sevenfold, from \$23,698 all-cause costs per year in the 12 to 24 months pre-crisis to \$181,790 all-cause costs in the 12 months following a crisis (Phillips 2021). These costs associated with myasthenic crisis are not fully accounted for in ICER's model.

Additionally, MG has considerable societal burden, as many patients are not able to work or must miss work due to MG exacerbation and treatment. A registry study analyzing work absenteeism/presenteeism in gMG patients showed that in 275 nonrefractory gMG patients over a 6-month timeframe, 27.6% missed 1 to 3 days of work, 23.3% missed 4 to 7 days, 28.7% missed 8 days to 4 weeks, and 20.4% missed ≥ 1 month (Harris 2019). The impact of gMG on productivity and the ability to work was not reflected by ICER in its scenario analysis considering the societal perspective due to a lack of available data.

ICER's current model does not adequately capture the value of treatments for rare diseases.

ICER's value assessment framework has been used in a variety of different therapeutic areas; however, a recent review indicates ICER found 0 out of 12 treatments for rare diseases to be cost-effective in reviews conducted from 2015 to 2020 (Kirschenbaum 2020). In the case of MG, ICER's methodology focuses solely on the number of quality-adjusted life-years that a therapy adds, and outcomes that are important to patients such as fatigue and muscle weakness are not adequately reflected in the cost-effectiveness calculation. ICER has used an alternative framework in ultra-rare disease with <10,000 individuals; this framework should be adapted to all rare diseases affecting <200,000 individuals in the United States.

We have a few additional comments and corrections that are listed in the Appendix. argenx appreciates the opportunity to provide comments for this assessment and believes that consideration should be given to the points we have made to ensure a scientifically sound assessment.

Sincerely,
Glenn A. Phillips, Ph.D.
Senior Director, Health Economics & Outcomes Research
argenx US Inc

References

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Appendix: Additional Comments and Corrections.

Based on our detailed review, we identified the following clarifications or inaccuracies in the Draft Evidence Report that we would like for ICER to address as they incorporate changes to the Revised Evidence Report:

1. On **page ES2, Table ES1**:
 - a. ICER should add a footnote to efgartigimod in the table to note that these results are among AChR-positive patients only.
 - b. The draft evidence report indicates that the Δ MG-ADL score at 4 weeks for the placebo group in ADAPT is -1.7 but the value should be -1.8.
2. On **page 7, Table 3.3**, the draft evidence report indicates that the Δ MG-ADL score at 4 weeks for the placebo group in ADAPT is -1.7 but the value should be -1.8.
3. On **page 15**, the draft evidence report describes 5 scenario analyses; however, the numbering for these scenario analyses is not consistent throughout the report (see Table 1 below). ICER should clarify the numbering and definition for each scenario analysis and ensure consistency throughout the report.
 - a. The numbering for scenario analyses is different on **page 23** where the incremental cost-effectiveness ratios for the scenario analyses are presented in **Table 4.8**.
 - b. In the supplemental appendix on page **E10/E11**, the numbering for the scenario analyses is similar to what is presented on **page 23**; however, there is an additional scenario 5 that is not labeled the same way on **page 15**.

Table 1. Scenario Analyses

Scenario	Pg. 15	Pg. 23	Pg. E10/E11
Modified societal perspective	1	N/A	N/A
Efgartigimod plus conventional therapy versus conventional therapy alone, assessed in patients with “refractory” anti-AChR antibody positive gMG, as defined by the REGAIN trial	2	1	1
Ecilizumab plus conventional therapy versus efgartigimod plus conventional therapy, assessed in patients with “refractory” anti-AChR antibody positive gMG, as defined by the REGAIN trial	3	2	2
IVIG or rituximab plus conventional therapy versus conventional therapy, represented by the placebo control group from the corresponding clinical trial, in patients with gMG	4	3a (IVIG), 3b (rituximab)	3a (IVIG), 3b (rituximab)
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.	5	4	4
Ecilizumab/IVIG, Ecilizumab/Rituximab, Efgartigimod/IVIG, Efgartigimod/Rituximab	N/A	N/A	5

4. On **page 32**, there is a line break error for reference #62.
5. On **page D21**, the standard deviation for percentages of patients with a previous thymectomy in the phase 3 ADAPT trial who are AChR Ab+ should be 69.2% instead of 69.0% for the efgartigimod group and 46.9% instead of 47.0% for the placebo group.
6. On **page D24** in **Table D2.5**, it is unclear where the column “None” is derived from – does this refer to patients with no MG therapies at baseline? This category should be revised to “No steroid or NSIST”

rather than “None” as in the source publication.

7. On **page D26** in **Table D2.6**, the draft evidence report indicates that the Δ MG-ADL score at 4 weeks for the placebo group in ADAPT is -1.7 but the value should be -1.8.
8. On **page D30** in **table D2.7**, the draft evidence report indicates that the Δ MGC score at 4 weeks for the efgartigimod group in ADAPT is -9.4 but the value should be -9.3.
9. On **page D30** in **Table D2.7**, the draft evidence report indicates that the standard error for the Δ MGC score at 4 weeks for the efgartigimod group in ADAPT is 0.9 but the value should be 0.99.
10. On **page D30** in **Table D2.7**, the draft evidence report indicates that the Δ MG-QoL15r score at 8 weeks for the placebo group in ADAPT is -2.3 but the value should be -2.2.
11. On **page D30** in **table D2.7** the draft evidence report indicates that the standard error for the Δ MG-QoL15r score at 8 weeks for the placebo group in ADAPT is 0.6 but the value should be 0.54.
12. On **page D33** in **Table D2.8**, week 8 should be removed as a label next to cycle 1, as these results are based on observations from the entire cycle, but do not apply to any specific week; therefore, the label should just read “Cycle 1.”
 - a. This applies to all responder-related outcomes; they were derived from observations during the entire cycle and are not related to a single timepoint.
13. On **page D33** in **Table D2.8**, the footnotes for MG-ADL responders and QMG responders read:
 - * 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

These footnotes are incorrect, as MG-ADL response was defined as a change in MG-ADL score of ≥ 2 points for at least 4 consecutive timepoints and QMG response was defined as a change in QMG score of ≥ 3 points over at least 4 consecutive time points; the footnotes should be updated to reflect these definitions.
14. On **page D33** in **Table D2.8**, the draft evidence report indicates that the MG-ADL responder *P*-value in Cycle 2 for the efgartigimod group is “NR” but the value should be “ <0.0001 .”
15. On **page D33** in **Table D2.8**, the draft evidence report indicates that the MG-ADL responder value in Cycle 2 for the placebo group is “NR” but the value should be “11 (25.6).”
16. On **page D43** in **Table D2.12**, the draft evidence report reports the safety outcomes; however, these outcomes are for the overall ITT patient population including both the AChR+ and AChR- patient populations; ICER should include a comment stating that the results include the overall ITT patient population, consisting of both AChR+ and AChR- patients.
17. On **page D43** in **Table D2.12**, the draft evidence report indicates that the discontinuation of treatment due to AE values in the phase 3 ADAPT study for the efgartigimod group is “3 (4.0)” but the value should be “3 (3.6).”
18. On **page D43** in **Table D2.12**, the draft evidence report indicates that the discontinuation of treatment due to AE values in the phase 3 ADAPT study for the placebo group is “3 (4.0)” but the value should be “3 (3.6).”



The Black Women's Health Imperative (BWHI) is pleased to comment on ICER's Draft Evidence Report assessing efgartigimod and eculizumab for the treatment of myasthenia gravis (MG). BWHI was founded in 1989 and remains the only national organization dedicated to improving the health and wellness of this nation's 21 million Black women and girls. We share ICER's stated concern that the potential benefits of emerging MG treatment options are not fully captured in ICER's economic model and appreciate its acknowledgment that the model's shortcomings are particularly pronounced within the context of the lived experience of Black women who typically manifest MG earlier and have more severe disease (Draft Evidence Report, ES3). We continue to believe that collaborative efforts between BWHI and ICER can play an important role in refining value frameworks to account for and proactively address the impact that centuries of systemic racism continue to exert on the health, lives, and economic productivity of Black women and other people of color in the US. Our comments are intended to help ICER ensure that its final assessment in MG continues progress tangibly toward that goal and, at a minimum, does not have the unintended effect of widening care gaps and disparate outcomes for Black women and girls diagnosed with generalized MG.

The rarity and heterogeneity of treatment-refractory MG patients significantly reduces ICER's ability to capture and quantify true disease burden and treatment impact within a QALY-driven model and analysis. The QALY metric grafts significant methodological shortfalls on analyses of costs and benefits associated with rare disease treatments, including (1) inability to address the heterogeneity in treatment options, disease burden, and impact on quality of life (QoL) and productivity; (2) limitations in very young or very old populations; and (3) failure to consider caregiver burden despite potentially profound caregiver burden in chronic, disabling rare diseases (Schlander, 2016). Moreover, QALY-driven economic models inherently rely on robust data that may not be available (or deemed sufficient) to account for age-at-onset, race, and access to care in MG and other rare disease states with heterogeneous populations experiencing disparate disease burdens. BWHI is concerned that these shortfalls can drive inequitable benchmarks that may be unattainable for treatments addressing subpopulations (e.g., refractory generalized MG) within a very rare condition.

In countries with single-payer health systems that rely on technology assessments to determine whether treatments meet rigid willingness-to-pay criteria, patients face denied or delayed access to new treatment options and lower associated survival (Schlander, 2016). BWHI has significant concerns that ICER's MG review will ultimately under-value the potentially profound difference these new therapies could make for the young Black women and girls who are disproportionately impacted by MG and live within severely narrowed margins for economic survival and adequate health outcomes due to systemic racism. Any resultant delays or denials in access would fall on younger patients who rely on private payers and Medicaid, whereas the predominately white male older-onset patients within Medicare fee for service would have coverage for these new treatments according to the FDA-approved label, without onerous prior authorization and step therapy requirements. We urge ICER to continue to work toward aligning health economics with true treatment value through use of methods such as multiple criteria decision analysis (MCDA).

ICER's cost-effectiveness analysis has inherent deficiencies due to its reliance on bootstrapping methodologies to derive clinical effectiveness data from clinical trials designed for a different purpose - to demonstrate safety and efficacy within the context of an investigational treatment. The clinical effectiveness data used by ICER have many limitations in terms of sample size and non-

representativeness and use of non-statistically significant results. The efgartigimod clinical trial data, for example, utilized dosing schedules that ICER [likely correctly] dismissed as unlikely to reflect real-world use, and declined to incorporate into its model. BWHI understands that ICER must rely solely on clinical trial data for efgartigimod and substitute assumptions for real-world evidence to extrapolate/interpolate clinical effectiveness. BWHI urges ICER to ensure that its model similarly incorporates and reflects the real-world use and associated outcomes for eculizumab, including reductions in steroid and immunosuppressant dose/use, reduction in myasthenic crises and exacerbations, and longer-term improvement in MG symptoms (Katyal 2021; Muppidi 2021).

To the extent that ICER is committed to reliance on a semi-Markov model, BWHI urges it to include additional health states that more accurately reflect MG disease course, and to incorporate subpopulation analyses that reduce the shortcomings of this approach in heterogenous populations.

MG is a chronic disease that is associated with day-to-day symptoms such as fatigue, muscle weakness, visual deficits, slurred speech, etc., that may not be captured within ICER's improved/unimproved states. MG is also characterized by episodic and potentially life-threatening symptom exacerbations and myasthenic crises. These "states" occur with greater frequency in ever-refractory patients and can have a profound impact on both patient outcomes and associated healthcare costs, and should be included within ICER's model.

- Although ICER's model assumes that neither treatment has an impact on morbidity or mortality, the increased mortality associated with myasthenic crises and frequent symptom exacerbations warrant their inclusion in the model;
- For the young, predominantly female population, reduction in previously frequent exacerbations and/or crises could be as important, if not more important than QMG or any other metric utilized to gauge efficacy within the clinical trial context; and
- Failure to capture these outcomes as health states within the model is likely to impact the validity and accuracy of ICER's model in predicting the incremental costs and benefits of newer, FDA-approved MG treatments.

BWHI further urges ICER to ensure that its model and analysis take into account age and sex-specific subpopulations, and to focus scenario analyses on young women with ever-refractory MG. As we noted in comment to ICER's Modelling Analysis Plan, up to 70% of women of childbearing age suffering from MG experience cyclic series of exacerbations that are associated with menses (Lekker, 1998, [Men's & Women's Issues and Myasthenia Gravis - Conquer Myasthenia Gravis](#) 2018). Failure to consider this substantial divergence in disease burden would skew the analysis in a manner that could underestimate treatment benefit and over-estimate incremental treatment cost in Black women disproportionately experiencing early MG onset.

ICER appears to have eliminated consideration of the significant impact MG has on patient quality of life and productivity, including employment potential. BWHI notes that ICER's model input chart included entries of "N/A" for the productivity inputs associated with "labor market earnings lost," "cost of unpaid lost productivity due to illness," and "cost of uncompensated household production." We provide ICER with references to registry studies and meta-analyses, including that of US MG patients in the Cutter study, Guastafierro's meta-analysis of MG (refractory and non-refractory) and employment,

and *Schneider-Gold's* review highlighting the burden of disease and unmet needs in patients with refractory MG (Cutter, 2019; Guastafierro, 2020; Schneider-Gold, 2019).

- Younger patients tend to be more severely impaired in their health-related quality of life than those over 65 years of age, and women were more affected by their MG symptoms;
- MG remains a disease that may significantly affect the disease-specific quality of life of patients despite conventional treatments;
- Younger patients and women generally report more symptoms and limitations, and poorer disease-specific QOL;
- Patients may suffer disproportionately during their younger active years due to clinician reluctance to provide more aggressive treatment to such patients, given the significant acute side effects and long-term risks related to immunosuppressive therapies;
- Underlying practice patterns may vary to the point that, despite significant disease burden, some patients are not prescribed standard of care treatment, underscoring the added value FDA-approved MG treatments can bring to under-served populations without access to MG-specific experts;
- The burden of refractory disease is poorly understood and may be underestimated - clinically these patients experience extreme fatigue, considerable disability from uncontrolled symptoms, and frequent myasthenic crises and hospitalizations;
- Patients with refractory MG can have symptoms including severe bulbar weakness impacting swallowing and speech, and even necessitating a feeding tube, muscle weakness, dysphagia, dysarthria, and dyspnea. Some patients are disabled to the point that they are bedridden or mechanically ventilated;
- Nearly a quarter of the eculizumab study population had previously required ventilator support due to their MG symptoms;
- Symptom severity can require MG patients to modify the amount of physical work, reduce working hours or to limit their work activities, despite availability of conventional treatments;
- One study revealed that 41.2% of employed patients used 9 or more weeks of sick leave in a year;
- *Guastafierro's* meta-analysis revealed that just 50% of MG patients were employed despite an average age of 48. It is important to note that (1) this analysis included a general MG patient population; (2) employment impact is likely, if not certain, to be greater in refractory patients; and (3) MG has a greater impact on productivity than chronic conditions generally.

The MG disease impacts on productivity and QoL described above are profound; BWHI's outreach to MG clinicians and patient groups confirmed what we view as a fact – refractory MG can, if not adequately treated, determine the life course for Black women and girls and other underserved populations without resources and flexibility to absorb the financial consequences and care needs associated with MG. Our discussions with clinicians and patients, as well as real-world data, indicate that these treatments have great potential for transformative impact on the lived experience of Black women and girls with MG.

BWHI urges ICER to provide greater transparency on its model to enable stakeholders to understand how factors related to subpopulation divergence on disease burden are incorporated into the review.

BWHI appreciates that ICER acknowledged racial disparities in myasthenia gravis (MG) diagnoses and outcomes by stating, “[w]e also will pay attention to race/ethnicity differences.” Similarly, ICER

acknowledged the importance of considering the impact of MG on childbearing potential in women, particularly Black women, as well as the younger age of onset for Black patients. Beyond these statements however, it is unclear how ICER has addressed racial and ethnic disparities in disease burden and/or health outcomes. We urge ICER to consider using patient-specific data - either collected by a survey or through Medicare/Medicaid data. In the current analysis, ICER used network meta-analysis using some potentially nonrepresentative patient populations from incomparable studies.

Stakeholders and ICER would benefit from the type of dialogue that could result from increased model transparency, including:

- Whether and how the model accounted for several outcomes important for patients such as return to work and fatigue.
- How delayed childbearing and/or increased morbidity/mortality due to MG in pregnancy, delivery and post-partum was incorporated into model inputs. MG experts recommend a high-risk obstetrician for all pregnant MG patients; Black women and other women of color may have restricted access to these specialists that lead to additional MG-related poor health outcomes and increased costs.
- Although ICER acknowledges the effects of MG on caregivers, it is unclear how these indirect costs would be included in the model or in the voting questions. Again, patient/caregiver surveys would improve the accuracy and validity of ICER's review.
- Rationale for selecting a Semi-Markov Model cycle length of one month, as well as insight into the model parameters for each subpopulation and transition cycle.
- ICER does not explain the rationale for including data based on ADAPT trial or the impact of the missing data. An explanation would be useful.
- It would be helpful for ICER to explain how the transition probabilities affect the overall cost.
- Clearer explanation for the assumptions for using mixed model repeated measure (MMRM) analysis. It would be helpful for ICER to explain (See Table D2.1.).

BWHI is concerned that the cost inputs appear to rely on outdated data. ICER reports an outdated average cost of care per patient for MG, including the cost for inpatient hospitalization. We assume ICER was unable to obtain recent health utilization data from the MG Foundation of America and the Agency for Healthcare Research and Quality. It is also unlikely that the ICER-reported average cost of care per patient includes patient out-of-pocket costs, other indirect costs, and caregiver costs. These additional costs are important to fully assess economic impact and could be acquired through patient/caregiver survey instruments.

BWHI urges ICER to examine real-world data on eculizumab and project use of efgartigimod to ensure that the model reflects the importance of reduced steroid and immunosuppressive therapy exposure. Corticosteroid use contributes to development or worsening of health conditions that already disproportionately impact Black and Latinx patients, including hypertension, obesity, diabetes, and osteoporosis (Draft Evidence Report). High-dose steroids are also associated with a wide array of side effects impacting overall health and quality of life, including mental health issues, weight gain, and changes in appearance. Moreover, the costs of managing adverse events associated with longer-term use of corticosteroids (60 days or more) can be higher than disease-related medical costs (Draft Evidence

Report). We strongly urge ICER to incorporate real world data into its analysis, and to augment that information with discussions with and/or surveys of MG clinician experts.

Although BWHI hopes that the COVID-19 pandemic, including emergence of the Delta variant, will resolve within the short-term, MG patients have unique disease- and treatment-related considerations that must be included in ICER's analysis. MG patients are particularly vulnerable to poor outcomes due to COVID-19 infection.

- Patients with neuromuscular disorders, especially patients with autoimmune myasthenia gravis, might be at greater risk of worse outcomes than otherwise healthy people because of the combination of an immunocompromised state related to immunotherapy and MG-associated respiratory and bulbar muscular weakness.
- Infection, including COVID-19, is a well-recognized trigger for MG symptom exacerbation;
- A Brazilian study of MG patients hospitalized for COVID-19 revealed a severe disease course associated with MG: 87% were admitted to ICU, 73% needed mechanical ventilation, and 30% died (Camelo-Filho, 2020).

Although MG patients can safely receive COVID-19 mRNA vaccines, the treatments within conventional treatment regimens (e.g., prednisone, azathioprine, mycophenolate mofetil, etc.) can interfere with antibodies so that MG patients may NOT be fully protected even if they are fully vaccinated. The Delta variant and variable social distancing protections, as well as hospital, ICU, and ventilator capacity constraints within the various states create an urgency for MG patients. This urgency is particularly profound for people of color who have suffered disproportionately throughout the pandemic. It is, therefore, imperative that MG patients:

- Adequately manage disease symptoms without reducing vaccine efficacy; and
- Receive a treatment that is effective at reducing MG exacerbations and crises that could lead to hospitalization.

We urge ICER to reach out to MG clinical experts and the Myasthenia Gravis Foundation so the MG review considers and incorporates the urgencies associated with the COVID-19 pandemic.

We urge ICER to include language in its final evidence report that highlights the potential imprecisions in its analysis due to divergence between clinical trial populations and real-world patient demographics.

BWHI appreciates the opportunity to continue our dialogue with ICER through comments to the Draft Evidence Report. We look forward to continuing to engage with your team on intentional refinements and mechanisms that improve ICER's ability to capture the value of emerging treatments on the lived experience of women of color.

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HEALTH EQUITY COLLABORATIVE



BLACK WOMEN'S
HEALTH IMPERATIVE



Center for Black Equity



August 18, 2021

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The undersigned organizations, referred to collectively as the Diversity Stakeholders, appreciate the opportunity to comment on ICER's Draft Evidence Report entitled "Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis: Effectiveness and Value" (the Draft Report).

Each of the Diversity Stakeholder organizations listed below has been committed to helping improved the lives of Black Americans and members of other marginalized communities in the United States. Healthcare disparities are major a barrier to this goal. The purpose of this letter, in light of Institute for Clinical and Economic Review's (ICER) apparent role in the determination of "value" in the health care system, is to express our concern about ICER's review process -- specifically whether it accounts appropriately for the real-life experiences of patients and health disparities in its analysis of cost effectiveness or value, including ICER's current review of new therapies to treat Myasthenia Gravis (MG).

As you know, health conditions that lower both life expectancy and quality of life disproportionately affect Black Americans. The HIV epidemic, mental health and substance abuse disorders, cancers, diabetes, childhood obesity, and the ongoing COVID-19 pandemic all disproportionately affect the lives and health of Black communities and other communities of color. Although the U.S. healthcare system is well-equipped to ensure maternal and newborn health and safety, Black women die from childbirth at rates similar to those

seen in developing nations. MG, for which treatments are currently under review by the ICER, is a life-limiting, and potentially life-threatening condition. Black women have an earlier age of onset, and present with more serious symptoms than their white counterparts. Given the continuing impact of historic inequities on education, housing, career opportunities, and access to health care, any barriers to access to effective treatments will likely further disproportionately impact Black patients and exacerbate health inequities.

ICER has noted the lack of clinical trial data capturing disease burden and treatment impact in Black patients -- a fact that both reflects and perpetuates health inequities resulting from systemic racism. The Black community has long been sidelined and relegated to a health care system that was not designed to meet their care needs, and that relies on disease-specific standards of care developed without their inclusion. We understand that fully incorporating the lived experience of non-white patients into the value calculations designed to guide payers in defining the contours of access is neither simple nor easy. The Diversity Stakeholders believe, however, that ICER has the ability to review emerging treatments with model design and inputs that reflect the lived experience of divergent subpopulations and to quantify the benefits of new therapies within that context. In its review of Lupus Nephritis treatments, ICER demonstrated that it may also have the will to do so by creating a scenario analysis examining treatment impact in Black patients and:

- Applying general, rather than ethnicity-specific utility values, to avoid “discounting” treatment value to mirror race-specific differences in income; and
- Utilizing cost values that were independent of ethnicity rather than reflective of sub-optimal real-world care in Black populations.

While race-specific scenario analyses may not be informative of treatment value in each disease state subject to an ICER review, we have significant concerns that the Model and inputs outlined in the Draft Evidence Report drive conclusions that under-value the reviewed treatments, and ignore the lived experience of Black patients -- particularly Black women and girls with MG. We urge ICER to provide stakeholders with additional insight into the model and inputs used for the Draft Evidence Report, and offer the following comments and recommendations based on our understanding of the information contained in the report:

ICER should augment the clinical trial data with evidence and information on real-world use, and incorporate benefits related to reduction in steroid and immunosuppressive treatment use. Ideally, ICER would have all relevant information on how a reviewed treatment is used within the clinical setting before assessing its value. We understand that the timeline for review in MG necessitates reliance on clinical trial data alone in treatments that are not yet FDA approved. Eculizumab, however, has been available for use in MG since 2017 and there is no reason to ignore its real-world use, particularly with respect to reduction in concomitant use of drugs with known long-term adverse impact on health. This is particularly important in MG -- as corticosteroid use can trigger or exacerbate comorbidities that already disproportionately impact Black and Latinx patients, such as high blood pressure, obesity, diabetes, and osteoporosis. These medications also have an enormous impact on quality of life as side effects can include mental health issues and changes in appearance. Several of our organizations have had the opportunity to hear from patients and MG specialists, and we believe that, if ICER surveyed MG specialists, it would find that few patients receive eculizumab added to their existing treatment regimen over the long-term.

ICER’s model does not reflect the fact that MG is a chronic disease with acute episodes. The health states included in ICER’s model assume that the only health states are “improved” and “unimproved” based on a metric that is a snapshot in time. Ignoring the exacerbations and myasthenic crises that patients with refractory MG experience leads to a model that does not accurately reflect the potentially life-threatening

nature of poorly-managed refractory MG. Moreover, for young Black women in whom refractory disease with frequent acute episodes are common, any reduction in exacerbation frequency or avoidance of myasthenic crisis is an important outcome in assessing treatment impact and health care costs.

We are also concerned that ICER's model does not account for divergent disease burden based on age and gender. This is an important factor for menstruating patients, as they are likely to suffer acute episodes consistent with their menstrual cycle. This is a distinct disease manifestation that is not relevant to older, male MG patients. Aggregating treatment impact would, unfortunately, have the unintended effect of undervaluing treatment benefit in women, particularly in Black women who present with MG earlier.

ICER appears to have overlooked the impact MG has on productivity and quality of life. The Diversity Stakeholders find it troubling that ICER declined to consider the fact that MG is a debilitating and potentially disabling condition that can impact every facet of a patient's life. A cursory review of common MG symptoms and disease burden, particularly in younger patients and those that are refractory to conventional treatments, underscores that MG would have a clear and direct impact on a patient's ability to work and fulfill household responsibilities, including caring for their children. Some patients may find it difficult to live independently and/or complete the tasks of daily living. Functional limitations are, and should be treated as, health outcomes that are fully incorporated into quality adjusted life year (QALY) calculations. MG patients, including young Black women, who are within the workforce may not have sick leave to accommodate episodic worsening of MG symptoms. If employment includes significant activity, symptoms such as muscle weakness are often worsened. The physical and emotional stressors associated with struggling to maintain employment, or losing/decreasing employment can trigger MG exacerbations. These types of impacts and cycles are not contextual; they are the likely real-world experience for young Black women living with MG.

We strongly urge ICER to augment its data with information on quality of life and productivity impact of MG, through both patient interviews/survey instruments and published studies.

Although ICER acknowledged racial disparities and impact on childbearing in MG, it is unclear whether and how it incorporated these factors into its analysis. We note that ICER's Draft Evidence Report contended that ICER would "pay attention to race/ethnicity differences," and consider the impact of MG on women of childbearing potential. However, ICER provided no details on how these considerations were incorporated into the model or ICER's inputs. For example, we know that maternal morbidity and mortality in Black women without a chronic disease such as MG is disproportionately high. MG experts recommend that pregnant MG patients receive care from an obstetrician specializing in high-risk pregnancies and delivery, yet Black women and other women of color may have restricted access to this level of care. This is an important consideration for Black women and other underserved populations that is not addressed despite the fact that the average age of onset for Black women is well within the childbearing years.

Despite the continuing nature of the COVID-19 pandemic, ICER has not considered the impact of MG and its conventional treatments. We understand that MG patients are at extreme risk for poor outcomes due to COVID-19 infection. This, however, is not the only consideration relevant to MG patients within the context of the pandemic. Myasthenic crises and exacerbations can progress, with respiratory difficulties that require intubation and even ventilator support. In many geographic areas, the pandemic has stressed hospitals to the point where ICU care and ventilator support capacity is constrained, and MG patients could find that the care they need is unavailable locally. In addition, infection with COVID-19 (like other infections) can trigger symptom exacerbation and/or myasthenic crisis. Finally, conventional treatments for MG are now known to reduce efficacy of the COVID-19 vaccines.

Communities of color have been disproportionately impacted by the pandemic with respect to infection, mortality and finances. The Delta variant presents additional risk of infection and hospitalization that are particularly high for MG patients. We urge ICER to examine these factors more carefully in assessing the value of treatments that effectively reduce MG symptoms without impacting the COVID-19 vaccines.

Conclusion

We appreciate the opportunity to respond with comments to the Draft Report and look forward to continuing to engage with ICER to improve its ability to capture the value of emerging treatments on the lived experience of Black MG patients.

Sincerely,

Southern Christian Leadership Global Policy Initiative

National Organization of Black Elected Legislative Women

Health Equity Collaborative

Black Women's Health Imperative

Mana Action Fund

Black Idea Coalition

Frederick Douglass Foundation

Health Equality Leadership and Exchange Network

Center for Black Equity

Women Investing In Leadership Development (WIILD)

While the work that ICER does to review medications is of high importance so is the understanding of what it is like to live with a chronic rare disease. Therefore, I wanted to provide input on the burden and challenges of living with myasthenia gravis for the current ICER report. This is my personal experience of living with myasthenia gravis since age 5, as well as what I have experienced working with others who have been diagnosed in my role as Executive Director for the Myasthenia Gravis Association.

The journey from diagnosis to treatment generally is a very burdensome time for patients with myasthenia gravis. The time it takes to be diagnosed can be drawn out and patients may have multiple appointments with different specialists to get the actual diagnosis. Multiple medical appointments often leads to missed work and/or other personal obligations. Multiple medical appointments can also become a financial strain.

However much of the time, the burden does not end when a diagnosis comes. Coping with a chronic rare disease such as myasthenia gravis where fatigue and stress are factors that cause symptoms to worsen amplifies the situation at hand. A diagnosis with myasthenia gravis is like a full-time job. The length of time it takes to find a treatment that is going to possibly improve your condition while keeping the distraction in your life to a minimum all while knowing there is currently no cure is a heavy load to bear. Not to mention the impact of living with a chronic rare disease such as myasthenia gravis and what it has on your relationships, your family, your career and just about everything else you can think of. These are factors and burdens that cannot be dismissed and must valued when looking at the overall picture.

Allison Foss

Executive Director & Patient

Myasthenia Gravis Association



MGFA ICER Public Comments

The MG Patient Perspective of Value

MGFA appreciated the opportunity to collaborate with ICER by conducting patient interviews to gain insights into the lived experience of Myasthenia Gravis (MG). The patient group shared the life-altering challenges that MG patients and caregivers face. The unpredictability of disease progression and myasthenic crisis presents significant limitations that threaten the stability of careers, education, and the navigation of daily life. Patients and caregivers urge ICER to consider affordability and barrier-free access to effective treatments in its assessment.

MGFA recommends that ICER prioritize the patient voice and experience living with MG. The ICER assessment is encouraged to consider that MG is a rare, chronic, and ongoing disease with extreme exacerbations of difficult symptoms that vary from one patient to another. While there are multiple treatment paths, interventions are different for each patient, MG is a “snowflake” disease, meaning, the patient experience consists of long exacerbations, ongoing symptoms, inadequate response to treatment, and tolerability of various treatments may be very individual. Long exacerbations, acute crises and continuing disease symptoms are the rule rather than the exception.

ICER’s model should reflect these critical challenges. While symptom exacerbations may be chronic and complex, patients will have varying degrees of continuing MG symptoms that can negatively affect productivity and hinder their efforts to participate in the workplace and within their families fully. Many MG patients suffer job loss, loss of insurance coverage, and an unstable foundation to support themselves and their families. Communities of color experience higher rates of health inequities, less access to quality healthcare, and remain underrepresented in clinical research. Patients living in remote areas are subject to significant long-distance travel to access MG specialists, which strains their ability to work, afford transportation and lodging. Multiple hospitalizations and re-admissions to access urgent care present a dilemma of high medical costs that add a significant financial strain on MG patients and their families. The burden of MG poses an emotional toll on patients and caregivers.

Patients and their providers already face significant burdens in securing insurance coverage for treatment options other than corticosteroids. If ICER’s review leads to increased utilization management for patients who have benefited or may benefit from these

treatments, that burden will fall disproportionately on individuals in underserved and under-resourced populations.

Reducing exacerbations and myasthenic crises is an important outcome, but given the lifelong struggle MG patients face, reducing the daily impact of MG symptoms is also an essential parameter of treatment effectiveness.

QMG may be used in clinical trials, but it is not frequently used in clinical practice. MG-ADL is a reliable measure that treating providers generally rely upon to assess patient disease burden and response to treatment.

- The 4-week timeframe for assessing QMG improvement fails to account for the possibility that patients with less than a 3-point improvement may experience that level of improvement over 8, 12, or 16 weeks. Similarly, the 4-week response may not accurately capture the improvement in function and/or symptom reduction that would be experienced with continued treatment.
- An ICER review that could lead to payers requiring QMG results as a condition of coverage (to start or continue therapy) would present access issues, including treatment delays, beyond the already-burdensome prior authorization processes for all treatments.

ICER relies on clinical trial data to determine treatment effectiveness, and that the MG clinical studies did not withhold existing treatments. Still, MGFA urges ICER to consider real world data and information when it is available. Cost/benefit calculations that rely solely on the use of new treatments as an add-on to existing treatments over-states costs and fails to capture an essential benefit of newer treatments, i.e., reducing toxicities associated with long-term, high-dose steroids and immunosuppressive treatments. Providers individualize treatment to each patient's disease and treatment response, and many patients utilize newer treatments as monotherapy.

- Side effect burden and impact on the long-term health of treatment regimens involving high-dose corticosteroids are particularly important to younger MG patients.
- Corticosteroid use contributes to the development or worsening of health conditions that already exasperates health disparities and inequities.
- Costs of managing adverse events associated with longer-term use of corticosteroids (60 days or more) can be higher than disease-related medical costs.

Cost-effectiveness comparisons between therapies should not be made unless the treatments are indicated and studied in the same patient populations. For example, it would be essential to consider whether patients are refractory to other treatments and whether there are differences in treatment impacts dependent on demographic, disease onset, age, and other factors.

MGFA urges ICER to consider divergence in MG impacts on productivity between women at the peak of their childbearing and income potential years. This divergence is more than

contextual; it can be the key driver in whether an individual can meet their educational and income potential.

MG patients need new treatments to be effective, timely and affordable. Considering current and future treatments in the MG landscape, MGFA hopes that ICER will share its goal to remove risk and barriers to access for MG patients and develop solutions towards a better quality of life.

Thank you for the opportunity to share patient insights and perspectives on MG. MGFA appreciates ICER's invitation to provide public comments for consideration.

August 18, 2021

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for Myasthenia Gravis (MG). MG is a rare disease characterized by the fluctuating and weakness of patients' muscle systems that can greatly impair quality of life. Currently there is no cure for MG and there are very few available treatments. MG can present very differently in different patients, and it can often be difficult to find a treatment regimen that works for each patient. For this reason, availability of and choice between multiple treatments is very valuable to MG patients and physicians. With this in mind, we ask ICER to consider the following comments.

ICER's Model is Overly Simplified and Does Not Accurately Capture the Patient Experience with MG

ICER's model is too simplistic and does not capture the full spectrum of health improvements that matter to patients. The model has just three health states excluding death. These are improved MG on treatment, unimproved MG on treatment and unimproved MG off treatment. Using these broad health states limits the sensitivity of the model and does not allow the model to capture incremental improvements in health that matter to patients.

The model also excludes reference to a key aspect of the burden of MG, myasthenic crises. Myasthenic crises refer to a rapid deterioration in neuromuscular function with respiratory compromise due to ventilator muscle insufficiency or weakness of upper airway musculature or both. Regularity and severity of crises make a difference to patient quality of life, and this should have been included as a component of the model.

Typically, models developed to evaluate interventions in MG include frequency of myasthenic crisis as a key component in the model^{1,2,3} usually as a transitioning health state or at a minimum as a disutility. Many have also included mortality associated with myasthenic crisis into their model structure.

ICER's Model Does not Accurately Capture Patient Heterogeneity

¹ Chicaiza-Becerra LA, Garcia-Molina M, Gamboa O, Castañeda-Orjuela C. The cost-effectiveness of open or thoracoscopic thymectomy compared to medical treatment in managing Myasthenia gravis without thymomas. *Revista de Salud Pública*. 2012 Apr;14(2):260-70.

² Heatwole C, Johnson N, Holloway R, Noyes K. Plasma exchange vs. intravenous immunoglobulin for myasthenia gravis crisis: an acute hospital cost comparison study. *Journal of clinical neuromuscular disease*. 2011 Dec;13(2):85.

³ Canadian Agency for Drugs and Technologies in Health. CADTH Drug Reimbursement Review: Pharmacoeconomic Report on Eculizumab (Soliris). <https://www.ncbi.nlm.nih.gov/books/NBK567510/>. Published 2021

MG is a highly heterogeneous condition that affects patients in a host of different ways. Clinical presentations vary substantially, both for anti-AChR positive and negative MG, and accurate diagnosis and selection of effective treatment depends on recognition of less typical as well as classic disease phenotypes. Accumulating evidence suggests that clinical MG subgroups might respond differently to treatment.⁴ Despite this evidence in the research literature, ICER ran only two base case analyses: “refractory” anti-AChR antibody positive gMG and patients with gMG.

It has been suggested that heterogeneity on the autoantibody level may be associated with genetic heterogeneity and clinical phenotypes with different treatment responses.⁵ As a result, any interpretation of the relative effectiveness of new treatments for MG must be applied to treatments while reflecting this heterogeneity. To ignore this fact risks payers deciding to reduce or delay access to effective treatments for those who could benefit in an effort to prevent these therapies from being made available to all patients.⁶

This is an especially important element when evaluating treatments for MG, as the burden of a disease falls more acutely on Black women, a typically underserved population. Black women typically present with MG at younger ages and may have a more severe disease course than other patient groups.^{7,8} If patient heterogeneity is not captured by the study, payers referencing the study may choose to restrict coverage and exacerbate this existing health inequity.

The Model Does Not Accurately Represent Hospitalization Costs

The cost of patients experiencing MG-related hospitalizations was derived from a 2017 study.⁹ The study provides estimates of hospitalization cost in the period 2003-2013, while also concluding that costs of MG inpatient care rose 13-fold from 2003 to 2013. Based on this, it is reasonable to assume that the cost of MG inpatient care may have risen at a similar rate between then and now. Yet ICER has inflated cost estimates from this study by applying an inflation rate of 3%. This is very likely to be inaccurate, and we would suggest ICER look to a more recent study or claims data to derive a more accurate input for hospitalization cost.

ICER also does not use a unit cost for an MG-related emergency visit, instead using a mean cost for an emergency room (ER) visit in the US, obtained from the Healthcare Cost and Utilization Project

⁴ Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *The Lancet Neurology*. 2009 May 1;8(5):475-90.

⁵ Pal J, Rozsa C, Komoly S, Illes Z. Clinical and biological heterogeneity of autoimmune myasthenia gravis. *Journal of neuroimmunology*. 2011 Feb 1;231(1-2):43-54.

⁶ Basu A, Grieve R, Pritchard D, Stevens W. One size does not always fit all in value assessment. *Am J Manag Care*. 2019 Nov 1;25(11):540-2.

⁷ Bubuic AM, Kudabayeva A, Turuspekova S, Lisnic V, Leone MA. The epidemiology of myasthenia gravis. *Journal of Medicine and Life*. 2021 Jan;14(1):7.

⁸ Alshekhlee AM, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. *Neurology*. 2009 May 5;72(18):1548-54.

⁹ Omorodion JO, Pines JM, Kaminski HJ. Inpatient cost analysis for treatment of myasthenia gravis. *Muscle Nerve*. 2017;56(6):1114-1118

(HCUP). This produced a figure of \$563. HCUP data are net hospital costs, not costs to the healthcare system. A more realistic estimate from the literature is \$1,390.¹⁰

It should also be noted that there is significant heterogeneity for ER visit costs. The mean cost is much higher for people with severe health conditions than it is for visits for minor ailments among people who are not disabled or with a chronic condition. Unfortunately, overwhelming the ER has become a last line of defense for the uninsured, which means it sees many minor ailments from the generally healthy population. Most ER visits are for prescriptions or for basic care. A recent study suggests a little over 1% of attendees at the emergency room require ‘immediate and urgent’ attention. Less than 30% were in urgent need of care. If an MG patient visits an emergency room for a crisis, then it is for an urgent visit, not for a prescription, so using a mean cost for an ER visit is likely a very poor proxy for the cost to healthcare systems for an MG crisis.

ICER’s Model Relies on the Discriminatory Quality-Adjusted Life Year

In recent years, there has been a widespread questioning of several the assumptions on which traditional cost-effectiveness analysis is built.¹¹

The quality-adjusted life year (QALY) is known to discriminate by undervaluing the lives of people with disabilities and chronic illnesses, like MG.¹² Despite the known discriminatory implications of the QALY, ICER continues to use the metric. We believe this is inappropriate and would encourage ICER to identify and use alternative methods that do not discriminate.

The argument has also been made that we need to reassess the assumption that every unit of health gain – measured here in health-related quality of life - is equal in value.¹³ In other words, a single unit of health generates the same utility whether that health is accrued to someone with considerable disease burden, or to someone with minimal disease burden.¹⁴ In fact, several health technology assessment systems in Europe have backed away from direct use of strict cost-per-QALY estimates for this very reason, and incorporate the role of severity adjacent to the results to make a more context-relevant case for, or against, a new technology.^{15,16}

A system of evaluation that treats therapeutic innovations for highly disabling diseases as of similar relative value for unit of health gain in less severe conditions - and for patients who have minimal

¹⁰ Chang CF. Visitors to hospital emergency rooms: Who, why, and how much do they cost. The Methodist Le Bonheur Center for Healthcare Economics: Research Brief. 2015 Jul:1-6.

¹¹ Beresniak A, Medina-Lara A, Auray JP, De Wever A, Praet JC, Tarricone R, Torbica A, Dupont D, Lamure M, Duru G. Validation of the underlying assumptions of the quality-adjusted life-years outcome: results from the ECHOUTCOME European project. *Pharmacoeconomics*. 2015 Jan 1;33(1):61-9.

¹² https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf

¹³ Sund B, Svensson M. Estimating a constant WTP for a QALY—a mission impossible? *The European Journal of Health Economics*. 2018 Jul;19(6):871-80.

¹⁴ MacKillop E, Sheard S. Quantifying life: understanding the history of quality-adjusted life-years (QALYs). *Social Science & Medicine*. 2018 Aug 1;211:359-66.

¹⁵ Barra, M. and K. Rand-Hendriksen, *A missing cornerstone in the Norwegian Priority Commission’s weighting scheme—Sub-treatment balancedness is a necessary property for priority setting criteria*. *Nordic Journal of Health Economics*, 2016. 4(2): p. pp. 8-23.

¹⁶ Swedish Parliamentary Priorities Commission, *Priorities in health care: ethics, economy, implementation*. 1995, Stockholm: Swedish Government.

disease burden - is thought by many to be inherently unfair and unrealistic. Multiple studies¹⁷ have made this case.^{18,19} We would encourage ICER to explore these newer, more comprehensive approaches to modeling versus continuing to rely on traditional cost-effectiveness analyses.

Conclusion

ICER's model does not paint a full picture of the value of these treatments to the patient or society. It does not capture patient heterogeneity and omits outcomes that matter to patients and fails to capture accurate costs and burden of the disease. We urge ICER to make appropriate revisions to its model and to clearly communicate these limitations in its final report so that payers are not tempted to create one-size-fits-all coverage restrictions for new MG treatments.

Sincerely,



Tony Coelho
Chairman
Partnership to Improve Patient Care

¹⁷ Shirowa, T., et al., *WTP for a QALY and health states: More money for severe health states?* Cost Effectiveness and Resource Allocation, 2013. **11**(1): p. 22.

¹⁸ Lancsar, E., et al., *Deriving distributional weights for QALYs through discrete choice experiments.* Journal of health economics, 2011. **30**(2): p. 466-478

¹⁹ Richardson, J., A. Iezzi, and A. Maxwell, *How important is severity for the evaluation of health services: new evidence using the relative social willingness to pay instrument.* The European Journal of Health Economics, 2017. **18**(6): p. 671-683.

August 18, 2021

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Submitted electronically at: publiccomments@icer-review.org

Re: Request for Public Input on ICER's Draft Evidence Report, "Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis: Effectiveness and Value"

To Whom It May Concern,

UCB is a global biopharmaceutical company with nearly 8,500 employees globally, inspired by patients and driven by science. As an innovator company, UCB annually reinvests a quarter of its revenue back into research and development and is working to develop targeted immune therapies for generalized Myasthenia Gravis (gMG). As such, UCB welcomes the opportunity to provide feedback on ICER's assessment of new gMG treatments. UCB appreciates ICER's revision to its initial Scoping Document to reflect the prevalent use of intravenous immunoglobulin treatment (IVIg) as both chronic and acute therapy despite limited data on efficacy and its associated high costs. However, UCB would like to offer additional feedback for ICER's consideration, in the hope of improving the gMG assessment framework for existing and developing treatments. Specifically, UCB offers the following comments for ICER's consideration:

I. Patient and Caregiver Perspective

The value of a treatment is more than a mathematical calculation of efficacy and cost, and the value of a treatment differs according to the patient being treated. Patient perspectives provide critical insights about what is most important to patients, such as productivity, out-of-pocket (OOP) spending, ability to participate in activities of daily living, impact on caregiver burden, improvement over alternative treatments, impact on public health, and the promise of hope (among many other priorities). As such, it is vital to seek patient perspectives as part of value-assessment and to incorporate those perspectives into the assessment in a meaningful way. Incorporation of patient perspectives will help to account for a treatment's impact on the holistic patient experience and reflect individual patient viewpoints and disease journeys, not only population-level information. The Draft Evidence Report ("the Report") does not meaningfully incorporate patient and caregiver perspectives, and as a result, downplays the importance of disease management and the true lived patient experience. UCB acknowledges that data limitations can make it difficult to formally include value components important to the patient and/or caregiver; however, it is important to equally highlight these components in the context of value-assessment. As this data may not always be available, proxies or placeholders may need to be utilized as part of the assessment. To this end, UCB encourages ICER to have processes in place for, and to clearly elucidate any, uncertainties in the assessment or assumptions relied on to appropriately contextualize ICER's findings.

In the Report, ICER acknowledges that current treatment modalities and standards present a burdensome obstacle in gMG, such as suboptimal disease management, adverse effects (short-term and long-term toxicities), and disproportionate impact on patients. However, ICER does not formally incorporate these issues or the value



associated with solutions to these issues into its value-assessment framework. Newer, more targeted therapies bring disease control faster and more consistently without the risk of adverse effects. It is important to consider these clinical attributes when assessing the value of a treatment. As such, UCB urges ICER to more meaningfully incorporate these patient perspectives into its value-assessment methodology. Specifically, UCB suggests that ICER consider the following:

- a. In the Report, ICER acknowledges that gMG is an extremely heterogenous disease, varying not just patient-to-patient but hour-to-hour within a single patient. The nature of the disease further complicates the already complex world of rare disease and the subjective nature of the treatment approaches from physician-to-physician and patient-to-patient. ICER does not seem to account for this dynamic in its assessment. UCB encourages ICER to do so in order to reinforce the need for more targeted therapies and solutions to meet the unique needs of gMG patients and providers.
- b. The incorporation of patient perspectives and use of real-world evidence (RWE) is imperative, as many of the tools developed to measure outcomesⁱ do not completely reflect the true lived patient experience, which includes the social, psychological, and emotional effectsⁱⁱ of living with the unpredictability of disease that is often not visible to others – including healthcare providers. Because gMG is a rare disease and there are limited therapies available, physicians are left to assume a patient’s disease is controlled as long as that patient is not experiencing a crisis or hospitalization. In reality, patients may still have direct and/or indirect symptoms of disease that may impact their employment,^{vii} activities of daily living, mental health, and may pose a burden on the patient’s family and/or caregiver—even when they are not experiencing a crisis or hospitalization.^{vii} Additionally, prescribers in clinical practice do not uniformly use the tools ICER utilizes in the Report (e.g., Myasthenia Gravis Activities of Daily Living [MG-ADL], Quantitative Myasthenia Gravis score [QMG]) to assess patients. As such, an assessment relying *only* on such tools is incomplete and sets the baseline for a treatment’s effectiveness in managing the disease much too low.

II. Comparative Clinical Effectiveness

Comparative clinical effectiveness research can generate better information about the benefits of different treatment options in order to provide healthcare decision makers—including patients, providers, purchasers, and policymakers—with up-to-date, evidence-based information about their treatment options so they can make informed healthcare decisions. UCB urges ICER to incorporate all available comparative clinical effectiveness and safety research into its assessments and reevaluate treatments as additional research and evidence becomes available. In the case of gMG treatments, conventional therapies are associated with side effects, treatment-related comorbidities, and long-term toxicities that can prevent those treatments from being suitable maintenance therapies. Additionally, conventional therapies may expose patients to disease exacerbations and poor quality of life—e.g., osteoporosis-related fractures, psychiatric disorders, renal failure, thrombotic events, aseptic necrosis, infection and gastrointestinal bleeding.^{iii,iv,v,vi,vii,viii} These are important considerations that should be included as a formal part of ICER’s evaluation.

Additionally, clinical effectiveness of “standard of care” or “best practice” therapy is limited and there is wide variability with respect to onset of action, patient response, and health outcomes. ICER’s analysis generalizes that all patients will have the same response to “standard of care” treatment. However, any assessment of gMG must recognize the heterogeneity of the disease and focus on a treatment’s impact in the subset of patients with inadequate disease control despite being on standard of care therapy. Approximately 50 percent of gMG patients are uncontrolled, despite the availability of conventional therapies. Uncontrolled gMG leads to crisis,

exacerbations and decreased patient quality of life.^{ix} For example, over a one-year period, refractory patients had a significantly greater chance of:

- a. Having at least myasthenic crisis (21.3%), compared with non-refractory patients (6.1%, $p < 0.001$);
- b. Having at least one exacerbation (71.2%), compared with non-refractory patients (32.4%, $p < 0.001$); and
- c. Hospitalization and/or have an emergency department visit compared with non-refractory patients and non-MG control patients ($p < 0.001$ for all).^x

III. Long-Term Cost-Effectiveness

Uncertainties and assumptions are a given in any assessment. However, there is a real paucity of clinical trial data and utility data for gMG. UCB encourages ICER to put its assessment in context by highlighting this dynamic in greater detail. Any time there is a reference to cost-effectiveness, the assessment should clarify any and all assumptions the assessor relied on, as well as any uncertainties around the data used to assess that output. For example, Quantitative Myasthenia Gravis (QMG) and Myasthenia Gravis Activities of Daily Living (MG-ADL) scores are widely used patient-reported outcomes in clinical trials and a good measure of clinical relevance; however, additional measures such as such a minimal symptom expression and use of rescue therapy should also be considered when evaluating correlation to clinical outcomes and cost-effectiveness of treatment. Additional context is necessary to make such an assessment complete. It is critical that decision-makers understand that:

- a. The cost-effectiveness of a treatment can vary significantly across patient segments due to different patient needs; and
- b. The cost-effectiveness of a treatment is based on significant assumptions about the data.

Assuming a linear relationship between cost, utility, and QMG score represents a major limitation to an assessment of gMG treatments and leads to potential validity issues. For example, any patient with a QMG score greater than 33 would have a utility weight below zero ('state worse than death'). Uncontrolled gMG patients have more healthcare utilization and spend and, as such, these patients may derive greater benefit from novel treatments; thus, novel treatments may have greater cost effectiveness in those patients. Additionally, ICER's model assumptions may be underestimating the impact of disease improvement. Specifically, ICER's assessment of gMG treatments did not consider long-term consequences, such as complications associated with episodes of crisis which can alter the long-term outcomes in patients and increase mortality risk. There is additional secondary spend that should be taken into consideration, such as the impact of gMG exacerbation and crisis, which may require utilization of IVIg (80% of which is administered in an outpatient setting and may not be captured in this assumption) or plasma exchange (PLEX). These long-term consequences and the increased mortality risk related to these events should be incorporated in order to better capture the value of interventions that reduce risk of exacerbation and crisis.

Additionally, UCB would like to make the following points about the model structure and parameterization for ICER's consideration. First, the model schematic indicates that patients can move back to the unimproved-on-



initial-treatment state from the improved-on-initial-treatment state. However, the Report does not clearly state how this parameter was estimated and implemented. UCB encourages ICER to be more transparent about its assumptions by more clearly detailing this aspect of the model. Second, the use of a four- or eight-week assessment point for eculizumab does not seem to be justified as being reflective of current clinical practice and may have introduced additional uncertainty to the model. As such, UCB suggests that ICER refine the model to be more reflective of current clinical practice or, if this is not possible, to clearly explain its process and any uncertainties or assumptions relied on. Third, the model relies upon a sampling technique (i.e., bootstrapping) to impute the efficacy parameters for the treatment interventions; it would be useful to explore the possible implications and limitations of this approach on the model outputs through structural scenario analysis. Lastly, we note that the model does not appear to account for the potential additional benefit to patients by accounting for depth of response—i.e., patients who have a greater than three-point QMG response. This omission may underestimate the population-level treatment benefit.

Finally, it is important to note that a “substantial discount” cannot solve issues arising from an assessment that is based on significant uncertainties or assumptions. In the Report, ICER acknowledges that the treatments assessed have potential for a significant health benefit. The Report also acknowledges that conventional therapies present significant limitations that can be addressed by newer, more innovative therapies. UCB urges ICER to go one step further in its assessment to better understand the cohort of patients that can achieve the greatest benefit from the treatment while also working to get additional clinical evidence needed to clarify assumptions. This will improve the assessment’s ability to understand the true value of a treatment. Simply reducing the price of a treatment does not articulate its value.

* * *

UCB appreciates this opportunity to comment on ICER’s Draft Evidence Report and welcome further discussion with ICER on this matter. Please contact Amanda Ledford, Associate Director of U.S. Public Policy, at Amanda.Ledford@UCB.com or 202-893-6194 with any questions or feedback on our comments.

Sincerely,

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ⁱ E.g., Myasthenia Gravis Composite (MGC), Myasthenia Gravis Activities of Daily Living (MG-ADL), Quantitative Myasthenia Gravis Score (QMG)



- ⁱⁱ The physical symptoms of gMG can have a psychological impact on patients and often lead to social withdrawal and reduced social positivity. Reference: Nagane Y, et al. *BMJ Open* 2017;7:e013278; Richards HS, et al. *Orbit* 2014;33:263–9; A case-controlled study of Danish patients revealed an association between suicide risk and presence of gMG and highlighted the vulnerability of patients with neurological diseases. There was a 4-fold increase in the risk of suicide attempt for people with MG, compared with controls. Reference: Eliassen A, et al. *J Neurol* 2018;265:1303–9.
- ⁱⁱⁱ Lee I, Kaminski HJ, McPherson T, et al. Gender differences in prednisone adverse effects: Survey result from the MG registry. *Neurol Neuroimmunol Neuroinflamm* 2018;5:e507.
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