Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis
Response to Public Comments on Draft Evidence Report

September 10, 2021

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Manufacturers		
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1.	***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 same[1]. 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.	ICER published its value assessment framework for 2020-2023 and makes modifications for ultra-rare diseases. By our definition, this evaluation did not fall within the considered modifications for ultra-rare diseases. ICER's approach to value assessment provides a range of commonly cited thresholds as a decision tool (not rule). Further, we provide evidence and deliberations (during the public meeting) on contextual considerations and other potential benefits of treatment. Therefore, we allow decision makers the opportunity to account for disease severity and many other factors in value assessment deliberations.
2.	***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 expenditures. 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.	Publications on the burden of MG are helpful in providing context. There is no known evidence linking treatment improvements to their potential impact on work productivity or caregivers. Research is recommended in this space to better capture the societal perspective.

3.	***All rare diseases assessed to date have resulted in negative ICER assessment.*** 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 benefits – 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.	This statement is false, and the referenced conference abstract used to support this statement makes many false statements about ICER reviews, including the number of reviews completed in 2019, the timing of our assessments, and the outcomes of ICER evaluation on rare disease treatments. Please review our assessments on treatments for spinal muscular atrophy and hemophilia A. As previously stated, ICER published its value assessment framework and modifications for ultra-rare disease (last updated in 2020). We disagree that population-based average estimates are less meaningful in rare diseases. We were hoping to engage with Alexion throughout the value assessment process in our development of this Report. However, Alexion opted not to accept ICER's invitations to engage around the clinical and economic evidence in gMG. Through other stakeholder engagement, we learned of the highly heterogeneous nature of gMG. And yet, the status quo pricing remains broken. We would welcome Alexion to share evidence to support the current pricing for eculizumab and how the current pricing scheme is reflective of the highly heterogeneous nature of gMG. Finally, we do not have any one defined threshold or any one formula that we use in estimating a treatment's value. We provide a range of commonly cited thresholds alongside contextual considerations and other potential benefits of treatment in the deliberation of a treatment's value. This deliberation happens in public. Perhaps manufacturer pricing should follow suit by holding public deliberations and discussions about the value the treatment brings to patients and their health.
4.	**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 disease[4]. gMG patients experience exacerbations and crises throughout their lifetimes and this is not adequately captured in the current ICER model[5]. 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.*	We have acknowledged that gMG is a chronic condition and have modeled it as such. There have been no long-term beneficial effects of therapies relative to a comparator. It is unclear which long-term effects need to be considered by a more complex model. The design of this Markov model, typically used for modeling chronic processes, adequately projects the costs and quality of life observed in clinical trials to longer time horizons. Although the base-case analysis was conducted over a 2-year time horizon, a scenario analysis was run for 5 years. The results of this analysis demonstrated that the incremental cost-effectiveness analysis was stable at 2 years, changing very little from the longer analysis. Furthermore, the model designed is similar to the model that Alexion submitted to the Canadian Agency for Drugs and Technologies in Health in their review of eculizumab.

5.	**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 is 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.*	We agree that conducting an analysis from the societal perspective is important when evaluating new treatments. Unfortunately, there is inadequate evidence available to include a societal perspective. We encourage manufacturers and researchers to conduct studies further elucidating the impact of new therapies for gMG on model inputs such as productivity, caregiver burden, and patient out-of-pocket direct and indirect costs.
6.	**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.*	Reliable results from well-designed, controlled, real-world studies are not available. Therefore, the results from clinical trials were the best available evidence for the effectiveness of the treatments evaluated. We utilized the full available results from clinical trials in estimating the effectiveness of all treatments included. The effectiveness of eculizumab was maximal and appeared to stabilize at 8 weeks, while efgartigimod's response was maximal at 4 weeks. IVIG and rituximab trials had longer-term data, which was used to estimate their effectiveness in the model. With regard to the timeline with which physicians assess patient responses or for how long patients are treated before treatments are discontinued, we were unable to find evidence supporting a longer treatment trial. Note that treating patients for a longer time with ineffective treatments would add cost, while providing little benefit, making the cost-effectiveness ratio appear worse than was estimated in our model.

7.	**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.*	We stand by our results, and everything you request is in the Report. As noted in the Report, we used data from the subset of patients in the ADAPT trial who met the inclusion/exclusion criteria of the REGAIN trial (AChR Ab+, REGAIN definition of refractory). The patient characteristics were quite similar (data in confidence), and the endpoint compared with the same outcome assessed at the same time point. The statistical methods for the NMA are described in the report supplement in section D.1. page 18. Although the evidence for a direct comparison between eculizumab and efgartigimod was determined in the evidence review to be inconclusive, treatment with eculizumab was expected to be more costly when using the placeholder price for efgartigimod and was less effective than efgartigimod at 4 weeks in the network meta-analysis. These results have been moved from table 4.8 and included in the text.

8.	**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.).*	In tables 4.3 and E2.2, we included the mean change in QMG among responders to eculizumab and efgartigimod and comparators (the two base-case analyses), along with baseline utility and changes to the utility for each 1-point change in QMG score. Utility could be easily calculated from these estimates. We did not include changes to QMG in non-responders or estimates of variance. These have been added to table E2.2. In addition, utility values have been added to table E2.2.
9.	**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. 2017[6].*	We think that it is sophistry to make this distinction. The adverse event that led to the patient's death occurred while the patient was on active treatment in the trial. He was discontinued from the study because of the adverse event. Because he died after the discontinuation, the death is not counted as having occurred during the trial. We have made that clear by adding the following sentence: "Because the death occurred after the patient was discontinued from the study, it was not counted as a study death even though the death was directly due to an adverse event occurring while the patient was on active treatment."

Argenx		
1.	**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	Thank you. We appreciate the thoughtful discussion and additional data. We've discussed this widely within ICER, and some argued for a promising but insufficient rating (which is a lower rating than C++). However, our judgment remains that given the information on short-term benefits of efgartigimod in the clinical trial, but uncertainties about dosing, and consistent long-term benefits, and lack of data on long-term safety, the evidence rating on balance should remain C++ (moderate certainty of a comparable, small, or substantial net health benefit of efgartigimod added to conventional therapy with high certainty of at least comparable net health benefit).
2.	**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	We conducted a scenario analysis that more closely resembles the mean effect of individualized dosing schedules. We anticipate that individualized dosing schedules might lead to improved cost-effectiveness, as demonstrated in the scenario analysis. Importantly, the price of efgartigimod will be critical to a better understanding of the cost-effectiveness of efgartigimod. We have further adjusted our base-case and scenario analysis to provide threshold annual prices for both situations.

	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.	
3.	**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.	We have reviewed the data from open-label clinical trials provided by argenx. The data supports our initial estimates of treatment effectiveness with repeated dosing of efgartigimod. With regards to utilities, we used a deidentified data source of 252 patients to estimate the relationship between QMG and EQ5D sub-scores. While other findings from this study have been published by Dr. Barnett, the association between QMG and EQ5D has not been published. A published US-based valuation set (Pickard et al. 2019) was used to estimate utility from the EQ5D sub-scores. We have evaluated utility data provided by argenx for inclusion in the model. However, there are certain unexplained and concerning inconsistencies in this unpublished data. Specifically, patients with a 3-point or greater reduction in QMG in the ADAPT control population had a worse utility score than those without a 3-point QMG reduction in those receiving efgartigimod. These results do not make intuitive sense. Until a satisfactory explanation as to why patients with inadequate response to therapy would have such a large utility improvement is provided, we are unable to use this data in the model.

4.	**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 non-responders than what has been considered in the clinical trial. Specifically, all non-responders 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 ≥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.	While 12% of patients not responding in the first cycle eventually became responders, either a similar number of patients either become non responders or change in QMG became less over time in responders. This is evidenced by a plateauing of the effect of treatment with subsequent doses of efgartigimod. The response plateaus at a mean change in QMG equivalent to what was observed at 4 weeks. As such, we believe that our estimate of treatment effect beyond 4 weeks is consistent with the true benefits of treatment. While the clinical trial evaluating IVIG (NCT02473952) did maintain patients on IVIG for 36 weeks, we believe that patients would not continue treatment with IVIG beyond 4 weeks if it was not effective. This same assumption was applied to all treatments, including eculizumab and efgartigimod. Continuing an ineffective treatment would increase the incremental cost-effectiveness ratio. This is true for all treatments. Given that efgartigimod dominated eculizumab in our analysis, the described scenario is unnecessary. A combination of efgartigimod, followed by eculizumab would dominate eculizumab alone.

5.	**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.	If and until efgartigimod has a US FDA-approved label, we will continue to have uncertainty in the eligible patient population. We appreciate the feedback on the potential eligible populations for efgartigimod. Because the ICER potential budget impact method does not assume 100% uptake until the last year within a 5-year time horizon, the average annual findings from the potential budget impact approximate the 3rd year findings where we have assumed 60% uptake. Because the ICER average annual estimates are comparable to the argenx internal analysis related to those requiring additional MG treatments and because of uncertainty in an approved label, we retained the original estimates of 46,870 being potentially eligible for efgartigimod treatment.
6.	**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.	Thank you for your comment. Based on our evaluation, we have insufficient to distinguish the net health benefits of efgartigimod from eculizumab. And we also have insufficient evidence to distinguish both treatments from Rituximab and IVIG. However, we have clearly stated in the voting questions that if the panel votes to say there is adequate evidence to distinguish the net health benefit of eculizumab from that of efgartigimod, we will plan to take separate votes on eculizumab and efgartigimod on their comparative clinical effectiveness versus rituximab and IVIG.

7.	**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).	In talking to patients and experts we heard of patients being treated with rituximab who were not MuSK antibody positive. There is no indication for rituximab and it hasn't been carefully studied in any of the relevant populations. We expect the judgement of the panel to be that the evidence is inadequate for rituximab in all situations. In the MGFA guidelines, they note that the efficacy of rituximab is uncertain, but that it is an option for those who fail or are intolerant of other options. In addition, the Beat MG trial enrolled AChR+ patients, not patients who were MuSK+.
8.	**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 ≥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	As you note, IVIG does not have an indication for gMG. In our evidence assessment, we did not consider Zinman or Barth relevant when considering IVIG as maintenance therapy as they were trials in the acute setting. The only trial for maintenance therapy failed to meet its primary endpoint. We agree that there are limited data, thus the "I" rating and inclusion only as a scenario analysis within the economic modeling.

	results have not been able to establish an effect that leads to an FDA label for the treatment of MG.	
9.	**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.	We acknowledge that there is limited data on mortality and costs associated with myasthenic crisis. However, we heard from experts that mortality from myasthenic crisis is becoming increasingly rare. To date, there is no evidence suggesting that efgartigimod reduces the incidence of mortality. With regards to the costs associated with myasthenic crisis, there was low certainty in our hospitalization cost estimates, which includes hospitalization for myasthenic crisis. We had heard from clinical experts that a period of deteriorating clinical status often precedes myasthenic crisis. We have therefore expanded the range evaluated in our one-way sensitivity analysis for the cost of hospitalization to a broader range of values (between $74,495 and $151,395 per hospitalization), to account for these potential increased costs leading up to myasthenic crisis. This sensitivity analysis had some impact on the incremental cost-effectiveness, decreasing the incremental cost-effectiveness ratio of eculizumab to $5.12 million (from the base-case $5.21 million) per QALY gained and of efgartigimod to $2.06 million (from the base-case $2.01 million) per QALY gained (at the placeholder price for efgartigimod). These values are included in the revised Report.
10.	**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.	The referenced conference abstract used to support this statement makes many false statements about ICER reviews, including the number of reviews completed in 2019, the timing of our assessments, and the outcomes of ICER evaluation on rare disease treatments. Please review our assessments on treatments for spinal muscular atrophy and hemophilia A. As previously stated, ICER published its value assessment framework and modifications for ultra-rare disease (last updated in 2020). We do not have any one defined threshold or any one formula that we use in estimating a treatment's value. For this review, we provided an estimate of time spent in treatment response (defined using an improvement of at least 3 points on the QMG instrument) within the cost-effectiveness results. For all reviews, we provide a range of commonly cited thresholds alongside contextual considerations and other potential benefits of treatment in the deliberation of a treatment's value. This deliberation happens in public.

UCB		
1.	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… 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.	We agree with you that patient perspectives are an important part of value assessment. As such, we have a section of the Report devoted to patient perspectives, and we directly spoke to and incorporated feedback from patients at every study of the process. Because of a lack of data, some of those elements could not be incorporated into the economic model and those are highlighted in the potential other benefits and contextual considerations sections of the Report. The panel evaluating the value of these two therapies incorporates those elements into their judgments. In the future, if you have data that would allow us to incorporate these elements into the economic model, it would be helpful if you provided them to us during the open input period, comments on the scope, or in the comments on the draft report. We have made many changes to the modeling in this Report based on feedback from stakeholders.
2.	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 become available.	Thank you for your comment. We believe we have evaluated the effectiveness and safety of eculizumab and efgartigimod using the best available evidence. Please point us to any data you think we may be missing.
3.	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.	We have described assumptions in Table 4.2 and the impact of uncertainties in section 4.3., under the subheading "Uncertainty and Controversies."
4.	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	The methods clearly describe the paths and probabilities for each model: "*Those patients with less than a three-point improvement in QMG by week eight (two model cycles) discontinued the initial treatment and transitioned to the "Unimproved MG off-treatment" state. All living patients remained in the "Improved MG on initial treatment" or "Unimproved MG off-treatment" for all future cycles.*" The model did allow for movement between improved and unimproved states only in the scenario

	be more transparent about its assumptions by more clearly detailing this aspect of the model.	analysis evaluating the effectiveness of efgartigimod, with re-dosing occurring at 8 weeks, where a substantial number of patients would be expected to fall below the 3-point QMG cutoff that we used for determining who was in the "Improved" state. This scenario is described more completely in the supplemental materials.
5.	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.	We do not have data or expert commentary suggesting that the 4- and 8-week assessment points are problematic for eculizumab. We would be willing to consider any evidence provided. See our response to the comment above regarding the use of 4- and 8-week assessment points for eculizumab. Specifically, treating patients for a longer time with ineffective treatments would add cost while providing little or no benefit, making the cost-effectiveness ratio appear worse than was estimated in our model. We believe that the model and processes are clearly explained.
6.	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.	While we would rather use direct outcomes data from clinical trials, manufacturers did not provide estimates from clinical trials for the proportion of respondents or the mean QMG change in respondents and non-respondents. Bootstrapping was the next best option for estimating these needed data. We assumed a normal distribution and inputted (paired) standard error estimates, where reported in clinical trials. When standard error was not reported, we imputed results from the next best estimate. We validated our bootstrapped results against whatever data was available from manufacturers. The mean QMG values for each of the bootstrapped samples approximated the reported means from clinical trials, within 0.01 points. Regarding the model's accounting of depth of patient response. The bootstrapping was used to estimate the meant change in QMG for responders and non-responders. In other words, we did <u>not</u> apply only a 3-point reduction in QMG to responders. We applied the QMG reduction that was reported in tables 4.3 and E2.2. For example, eculizumab responders had a mean 6.95-point reduction in QMG, while efgartigimod responders had a mean 8.94 point QMG reduction.
7.	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	The base-case of this model estimates the incremental cost-effectiveness of eculizumab and efgartigimod using the best available evidence, given necessary model assumptions. While there are uncertainties regarding the actual real-world use of treatments and impact on longer-term outcomes, such as a possible steroid-sparing effect with some therapies, the effects of treatment on these outcomes have not been demonstrated. We

	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.	encourage the submission of quality evidence of these effects of treatments that not included in our analysis for future inclusion in the model. Given the current available evidence, and acknowledging limitations in the analysis, the annual price of eculizumab would need to be substantially lower (i.e. less than 1/20th of its current price) than it currently is to be considered a cost-effective option. It is highly unlikely that uncertainties in the model inputs could overcome such a large discrepancy between the list price and one that is considered cost-effective.
Patient Groups		
Black Women's Health Imperative		
1.	***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	We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. QALYs are also only one component of the value assessment. Specifically, many of the issues you raise such as severity, rarity, and heterogeneity may be addressed in the Other Benefits and Contextual Considerations section, which are essential in assessing value. Further, ICER seeks evidence on a treatment's impact on caregivers and where known, has included such impacts (see modified societal perspective of aducanumab review). We raise BWHI's concerns related to young Black women and girls within the contextual considerations section of the report.

	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).	
2.	**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).	Thank you for providing newly published data on steroid use. One study, Katyal 2021, is a case series of 15 patients initiated on eculizumab in which steroid doses were reduced over time. This data somewhat contrasts a larger study (Nowak. Front Neurol. 2020 Nov 24;11:556104. doi: 10.3389/fneur.2020.556104) of patients in the REGAIN Open-Label Extension Study that we had previously identified. In this single-armed, open-label study, 45/94 (47.9%) patients had a steroid dosage decrease, while 10/94 (10.6%) had their dosage increased, and 3/94 (3.2%) had both increases and decreases over time. Our understanding from experts and patients is that myasthenia gravis symptoms and treatment often change over time. These changes frequently include reductions (or attempts at reductions) in steroid use. Therefore, uncontrolled (real-world) studies are inadequate for assessing the impact of treatments on changes in steroid use over time.
3.	***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.	Our initial conceptual model included additional health states. Unfortunately, there was insufficient data to adequately specify the proposed model. We believe that the current model adequately captures the impact of therapies on patient quality of life. The model includes the impact of treatment on changes to AMG and resulting changes to utility. The model also incorporates the impact of hospitalizations, which include those for myasthenic crisis, on quality of life and cost of care.

4.	***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).	We agree that MG is likely to have a significant impact on employment potential, productivity, caregiver burden, and indirect health costs. Treatment may provide some benefits to patients for all of these costs typically included in the societal perspective. Unfortunately, the potential economic benefits of treatment cannot be determined from the included studies, which were included in our original systematic review of the literature.
5.	***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.	The network meta-analysis was not used in our base-case estimates of the cost-effectiveness of eculizumab or efgartigimod. The base-case analyses included the patient populations enrolled in clinical trials and considered by the FDA for drug approval. We evaluated the possibility of using primary data collected by other organizations and included these analyses where they were compatible with our model design and would provide significant improvements to our cost-effectiveness estimates. We did analyze primary data to determine the association between QMG score and utility. Other datasets that we considered did not have sufficient information to be useful in our analysis. These limitations were generally due to datasets, such as Medicare/Medicaid, no having any information on patient disease severity or health status.
6.	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	Please see previous comments regarding our desire, but inability, to conduct an analysis from the societal perspective. Similarly, insufficient data exists to conduct analyses on patient subgroups or to assess the impact of restricted access to treatments on health outcomes. Regarding the model structure, a full accounting of both the Markov structure and model inputs is provided in the study methods in the main Report and in the supplement. The impact of transition probabilities on cost-effectiveness were assessed in one-way sensitivity analyses and displayed as a tornado diagram.

	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.).	
7.	***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.	We utilized the best available evidence when identifying hospitalization costs for the model. The study (Omorodion 2017) utilized data from 2003 to 2013. We did use the most recent estimates (2017) from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUP) when estimating costs for admission to the emergency department (ED). However, these estimates were problematic as HCUP data combined patients with myasthenia gravis with other patients with neurological conditions. Note that all included costs were inflated to 2021 values.
8.	***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.	See above response regarding limitations of current real-world data on steroid use.

9.	***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.	Thank you for this input. We agree and have added it to the contextual considerations that should be kept in mind when judging the value of therapies for MG. We have added the following text under the acuity of need for treatment: "Patients with gMG are particularly vulnerable during the COVID-19 pandemic as they are typically on immunosuppressive medications (poor vaccine response, higher risk for severe disease) and because infection is a known trigger for MG exacerbations." We have spoken extensively with numerous MG expert clinicians and researchers as well as the Myasthenia Gravis Foundation and patients with MG. Their input has been invaluable in the structure of our review and our conclusions.

10.	***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.***	We agree that the estimates used in the clinical evidence section and the inputs to the model likely overestimate the real-world effectiveness of these therapies. In part, that is why we do detailed sensitivity analyses in the economic analyses and why we highlight the broad range of potential net benefits in our evidence ratings (for instance C++ for efgartigimod, I for rituximab and IVIG). Your comment applies to every ICER review and the voting members of the panels assessing the therapies under review always keep this consideration in mind.
Diversity Stakeholders		
1.	**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.	Thank you for your input. We specifically searched the literature and found no published real world evidence on eculizumab, nor did the manufacturers provide us with any. In speaking with clinical experts, their consistent message was that eculizumab was frequently being used inappropriately. If you have any citations, we will welcome them, but ideally you should direct us to them in the open input period or in your comments on the draft report.
2.	**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	See more detailed response to similar comment above. The Markov model used in the analysis adequately captures changes over time. It also characterizes the impact of treatments on both acute events (e.g. hospitalization, including myasthenic crisis) and long-term changes to patient quality of life.

	of myasthenic crisis is an important outcome in assessing treatment impact and health care costs	
4.	**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.	See above responses to similar comments. We agree that conducting an analysis from a societal perspective would be beneficial and are equally frustrated by the lack of evidence of the impact of myasthenia gravis and treatments on patient outcomes germane to the societal perspective.
5.	**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.	It is challenging when there are a lack of data. The trials of the novel therapies included very few Black patients which precluded subgroup analyses by race/ethnicity. It is important to bring pressure to bear on both the FDA, who can mandate inclusion of relevant subgroups in trials, and on the companies who design the trials so that there is adequate evidence to explore potential differences by race / ethnicity, sex, or other important subgroups. We have highlighted the differential impact of gMG in Black women in Table 5.2.

6.	**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.	Thank you. We have added a paragraph about this in the Patient Perspectives section and added this as an important contextual consideration (Table 5.1).

MG Association		
1.	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 value when looking at the overall picture.	Thank you for your perspective. Many of the sentiments that you express have been highlighted in Section 2 of the Report: Patient and Caregiver Perspectives. We had an extended conversation with five patients living with MG and have updated the patient perspective section to reflect their input and yours. Many of these elements are not fully captured in the modeling and should be emphasized in the section on contextual considerations and potential other benefits or disadvantages, which influence the value assessment.
Myasthenia Gravis Foundation of America		
1.	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.	We agree wholeheartedly. We start by talking to patients and patient representatives. Please see Section 2: Patient and Caregiver Perspectives as well as Tables 5.1 and 5.2.
2.	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,	See above responses to comments regarding the inability to conduct an analysis from the societal perspective or in patient subgroups not studied in the clinical trials. We agree that there are challenges that are unique to certain patient groups. These are highlighted in other sections of the Report.

	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.	
3.	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.	ICER's commitment is to "Fair Pricing, Fair Access, Future Innovation." If the therapies are priced at a level commensurate with their value in improving patient's health, then there should be no barriers to appropriate patients accessing the therapies. And the price needs to be high enough to promote continued innovation to bring more effective therapies to market. Your comment is particularly germane to the policy round table discussion in the second half of the meeting when we discuss pricing and access and policies to ensure fair and equitable access.
4.	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.	The model incorporates the effects of exacerbations and myasthenic crisis (as ED visits and hospitalizations), as well as the impact of treatments on daily quality of life. However, the average effect of these important outcomes is modeled.
5.	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.	We considered using MG-ADL as our primary outcome measure when trying to estimate utility. However, after consultation with clinical experts, we determined that the MG-ADL was a potentially unreliable measure for estimating utility due to significant floor and ceiling effects. The QMG was believed to better characterize the full range of impact on utility. Our decision to use QMG to estimate utility is unlikely to translate into payers requiring it. Also note that the QMG and MG-ADL are highly correlated.

6.	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.	See above response regarding limitations of current real-world data on steroid use.
7.	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.	See above responses to comments regarding the inability to conduct an analysis from the societal perspective or in patient subgroups not studied in the clinical trials.

Other		
Partnership to Improve Patient Care		
1.	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 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.	The model does incorporate the effects of exacerbations and myasthenic crisis (as ED visits and hospitalizations), as well as the impact of treatments on daily quality of life. Note that few models have included mortality benefits of treatments. Those that have included mortality have been severely criticized for the estimates that were used (e.g. the Canadian Agency for Drugs & Technologies in Health assessment of Alexion's eculizumab submission).
2.	**ICER's Model Does not Accurately Capture Patient Heterogeneity** 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. 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. 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	There is insufficient data on the effectiveness of treatments to model heterogeneity in patient on the autoantibody level. Where such data existed and manufacturers were willing to share study results, we did attempt to model certain differences (e.g. efgartigimod in refractory AChR Ab+ patients).

	from being made available to all patients. 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. , If patient heterogeneity is not captured by the study, payers referencing the study may choose to restrict coverage and exacerbate this existing health inequity.	
3.	**The Model Does Not Accurately Represent Hospitalization Costs.** The cost of patients experiencing MG-related hospitalizations was derived from a 2017 study. 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 (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.	See comment above regarding the use of the best available data. We were unable to identify a better source for the costs of MG-related ER visits. The reference provided is not specific to any health condition, nor does it describe the methodology used to determine the cost of ER visits. Note that we applied broad ranges to these estimates in one-way sensitivity analyses to address these concerns. Varying ED costs from $280 to $2,250 had minimal impact on incremental cost-effectiveness ratios. Varying hospital cost from $74,500 to $151,400 had more of an effect, but given the high incremental cost-effectiveness ratios, the overall impact was still small.
4.	**ICER's Model Relies on the Discriminatory Quality-Adjusted Life Year.** The quality-adjusted life year (QALY) is known to discriminate by undervaluing the lives of people with disabilities and chronic illnesses, like MG. 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. 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. In fact,	We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment. Specifically, many of the issues you raise such as severity are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value.

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