

April 2, 2021

Alexion appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft scoping document for the assessment of efgartigimod and eculizumab for the treatment of myasthenia gravis (MG).

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. The 2017 approval of eculizumab for generalized MG (gMG) patients who are anti-acetylcholine receptor antibody-positive (AChR+) represented the first FDA-approved treatment for this devastating disease in approximately 60 years. Prior to the approval of eculizumab, patients often underwent a long journey to diagnosis only to find the therapies available to them were limited to supportive care that addressed acute symptoms and did not address the underlying cause of the disease, with a subset of patients finding they did not respond to or could not tolerate these medicines.

We are deeply committed to addressing the unmet needs and burden of gMG and support the development of interventions that benefit patients, their support network and society overall. To this end, we have several concerns with the draft scoping document:

- 1. The gMG population studied in the pivotal trial for eculizumab (REGAIN) represents a subset of the total gMG population.**
  - a. The scoping document uses 20,000 as the number of gMG patients who are intolerant or have inadequate response to conventional treatment. In our view, this is an overstatement.
  - b. Based on epidemiological estimates, ~15% of treated AChR+ patients are refractory to treatment<sup>i</sup> (5,000-8,000 patients). This aligns with the inclusion criteria of the studied patient population in our Phase 3 REGAIN study.
  - c. At the end of 2020, Alexion reported ~2,600 patients in the U.S. who were taking eculizumab for all approved neurology indications, which includes gMG and neuromyelitis optica spectrum disorder (NMOSD).
- 2. ICER's comparative clinical effectiveness review should give more weight to long-term data and real-world effectiveness data.** These data further validate the efficacy observed in the randomized controlled trial. It is unclear if the current ICER evidence rating matrix gives added weight for such data.
  - a. Eculizumab has 3+ years of clinical trial data plus real world effectiveness data.**
    - **Long-term efficacy data:** Safety and efficacy of eculizumab is established based on an initial 26-week randomized controlled trial (REGAIN)<sup>ii,iii</sup> followed by an open label extension resulting in ~3 years of data<sup>iv,v,vi,vii,viii</sup>. Improvements with eculizumab in activities of daily living, muscle strength, functional ability and quality of life in REGAIN were maintained through 3 years.
    - **Real-world effectiveness data:** The efficacy of eculizumab, established in a clinical trial, is also reflected in the real-world setting. Clinically meaningful improvement in Myasthenia Gravis-Activities of Daily Living (MG-ADL) scores were observed at 3 months and maintained up to 12 months<sup>ix</sup> and reduction in exacerbations, crisis and related hospitalizations were observed for patients treated with eculizumab compared to baseline over a six month period.<sup>x</sup>

**3. Patient populations for the eculizumab and efgartigimod clinical trials are not directly comparable, as they were different with respect to disease severity and prior treatments.**

- a. It is inappropriate to compare eculizumab with published data on efgartigimod because of inherent differences between the patient populations in the two trials as well as different endpoints and different treatment approaches. These factors make indirect treatment comparison challenging and will likely produce potentially misleading results, negatively impacting input parameters in the economic model.
- **Patient population:** Eculizumab was studied in a specific patient population (failed prior therapies  $\geq 2$  ISTs or  $\geq 1$  IST and chronic IVIg or PLEX in 12 months) whereas efgartigimod was evaluated in a broader patient population in which patients did not have to fail prior therapy.
  - **Endpoints:** Efficacy of eculizumab was evaluated as change from baseline to week 26 for MG-ADL & Quantitative Myasthenia Gravis (QMG). Efficacy of efgartigimod was evaluated as % responders (MG-ADL  $\geq 2$  point improvement, QMG  $\geq 3$  point improvement) sustained for 4+ consecutive weeks during an 8-week period.
  - **Treatment approach:** The two treatments are fundamentally different in their dosing schedule. Eculizumab is given as continuous therapy to help gMG patients manage their symptoms in a consistent manner, which we feel is a preferred approach over cyclical therapies. Efgartigimod, if approved, will be given to patients on-demand/as needed basis, with re-treatment triggered by the re-emergence of symptoms.

**4. Chronic IVIg is not an approved therapy and efficacy is inconclusive.**

- a. It is inappropriate to compare the efficacy of eculizumab with chronic IVIg in AChR+ gMG patients who have failed to see improvement while on multiple therapies because IVIg is not an approved therapy for gMG, and the efficacy in this patient population is sparse and inconclusive. Additionally, there is no clear guidance on how IVIg is administered in a maintenance setting.

**5. Burden of disease may differ greatly between clinicians' and patients' perspective.** The scoping document did not adequately address the true burden of the disease in patients. This is an essential component when assessing value of a transformative therapy.

- a. **MG is a debilitating chronic, progressive rare neuromuscular disease:** Attributed to complement mediated destruction of the neuromuscular junction, it can significantly impact a person's life.
- b. **Patient burden of disease:**
- Clinician-based scoring typically focus on preventing crisis, i.e. controlling bulbar symptoms. Patients who failed on prior therapies continue to suffer from significant unresolved disease symptoms such as difficulties seeing, walking, talking, swallowing, and breathing. Eculizumab has been proven to improve muscle strength across ocular, bulbar, respiratory and limb/gross motor muscle groups, which were sustained through 2.5 years<sup>v</sup>.
  - Fatigue is an important disease symptom that is often neglected in patient care; a primary characteristic of MG is fatigable weakness. Eculizumab improves fatigue in gMG patients.<sup>xi</sup>
  - Unpredictable exacerbations can mean patients live in constant fear and must adapt and modify their plans. This burden cannot be easily quantified. Symptom fluctuations can have a huge emotional, social and physical impact on patients' lives. Since MG affects people of working age, this also has significant limitations in daily life activities including employment where they may have to modify their work, reduce their working hours or even be forced to retire early.
  - There are limited data on patient reported MG-related health utilities by disease severity and symptom type. This poses a challenge when measuring the impact of clinical benefit from

transformative therapies like eculizumab on patients' quality of life, and quality adjusted life years (QALYs) do not adequately capture this.

- c. **Medical costs:** Medical costs in patients who do not respond to conventional treatments are higher than reported in the draft scoping document. The risk of crisis and exacerbations are higher in patients who do not respond to treatments resulting in higher healthcare resource utilization.

**6. ICER's framework is inadequate to assess the value of medicines that address the life-long disease impact and burdensome journey that people with rare and ultra-rare diseases experience.**

- a. Ultra-rare diseases tend to be highly heterogeneous with diverse patient symptomatology making diagnosis challenging – on average it takes a rare disease patient 4.8 years and 7.3 specialists to receive an accurate diagnosis. It also makes measuring and adequately capturing full treatment impact challenging and population-based predictions less meaningful using mean values.
- b. It is widely recognized that cost effectiveness analysis (CEA) significantly undervalues treatment for severe and chronic conditions, which is often the case for rare disorders<sup>xii</sup> and certainly relevant in MG. In fact, ICER's methodology, using CEA, has yielded negative results for all rare diseases previously assessed<sup>xiii</sup>, despite significant clinical benefit from robust Phase 3 trials and long-term data with positive health benefit.
- c. ICER's framework excludes the costs of patients, caregivers, employers and society, undervaluing the ability of new treatments to offset the significant burden of rare disease.
- d. The unmet need in rare diseases continues to be significant. There are 400 million people around the world who are affected by a rare disease, half of whom are children. More than 95% of rare diseases lack an approved treatment option. Sustained investment in rare diseases continues to be critical to addressing these patients' needs. The use of CEA's that undervalue rare disease medicines brings with it the risk of discouraging scientific progress and investments along with the hope for a better future that they bring. Alexion has invested in numerous clinical programs with this hope, realizing that some of these programs may not be successful.

**7. Finally, ICER's framework does not allow for the numerous factors that must be considered for optimal patient access.**

- a. Each public and private payer in the United States needs to consider the uniqueness of their individual circumstances when making formulary decisions. These are likely to differ depending on the stakeholders, the specificities of the decision-making context they operate in, the elements of value they are considering and the relative importance they attach to each.
- b. Value evolves over time as more evidence is generated via clinical trials and in the real world. Value also varies based on the decision makers' perspective and from stakeholder to stakeholder. At Alexion, people living with rare and devastating diseases are our Guiding Star. We believe it is our responsibility to listen to, understand and change the lives of patients and those who work tirelessly to help them. The patient experience is paramount and must influence decision making. We support an environment where the interests of all stakeholders, including healthcare professionals and patients, are better balanced within pricing and coverage decision making systems. We remain committed to advancing our goal of both developing transformative medicines and ensuring optimal access in rare diseases, including gMG.

## References

- <sup>i</sup> Suh J, Goldstein JM, Nowak RJ Clinical characteristics of refractory myasthenia gravis patients. *Yale Journal of biology and medicine* 2013; 86: 255-260
- <sup>ii</sup> Howard JF Jr, Freimer M, O'Brien F, et al. QMG and MG-ADL correlations: Study of eculizumab treatment of myasthenia gravis. *Muscle Nerve*. 2017;56(2):328-330
- <sup>iii</sup> Vissing J, O'Brien F, Wang JJ, Howard JF Jr. Correlation between myasthenia gravis-activities of daily living (MG-ADL) and quantitative myasthenia gravis (QMG) assessments of anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis in the phase 3 regain study. *Muscle Nerve*. 2018;58(2):E21-E22
- <sup>iv</sup> Muppidi S, Utsugisawa K, Benatar M et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle & Nerve* 2019; 60 (1): 14-24
- <sup>v</sup> Mantegazza R, O'Brien FL, Yountz M, Howard JF; REGAIN study group. Consistent improvement with eculizumab across muscle groups in myasthenia gravis. *Ann Clin Transl Neurol*. 2020;7(8):1327-1339. doi:10.1002/acn3.51121
- <sup>vi</sup> Vissing J, Jacob S, Fujita KP, O'Brien F, Howard JF; REGAIN study group. 'Minimal symptom expression' in patients with acetylcholine receptor antibody-positive refractory generalized myasthenia gravis treated with eculizumab. *J Neurol*. 2020;267(7):1991-2001
- <sup>vii</sup> Jacob S, Murai H, Utsugisawa K, et al. Response to eculizumab in patients with myasthenia gravis recently treated with chronic IVIg: a subgroup analysis of REGAIN and its open-label extension study. *Ther Adv Neurol Disord*. 2020;13:1756286420911784. Published 2020 May 6.
- <sup>viii</sup> Nowak R, Muppidi S, Beydoun S, O'Brien F, Yountz M, Howard J; REGAIN study group. Concomitant immunosuppressive therapy use in eculizumab-treated adults with generalized myasthenia gravis during the REGAIN open-label extension study. *Front Neurol*. 2020;11:556104.
- <sup>ix</sup> Katyal N, Narula N, Govindarajan R. Clinical experience with eculizumab in treatment-refractory acetylcholine receptor antibody-positive generalized myasthenia gravis. *J Neuromuscul Dis*. 2021;8(2):287-294.
- <sup>x</sup> Muppidi S, Klink AJ, Parthan A et al. Real-world use of eculizumab in generalized myasthenia gravis in the United States: Results from a pilot retrospective chart-review study. 73<sup>rd</sup>, American Academy of Neurology, 2021 Abstract
- <sup>xi</sup> Andersen H, Mantegazza R, Wang J et al. Eculizumab improves fatigue in refractory generalized myasthenia gravis. *Quality of Life Research*, 2019; 28:2247-2254
- <sup>xii</sup> Lakdawalla DN, Doshi JA, Garrison LP, et al. Defining elements of value in health care – A health economics approach: An ISPOR special task force report [3]. *Value in Health*. 2018. 21(2):131-139.
- <sup>xiii</sup> <https://www.prmaconsulting.com/wp-content/uploads/2021/03/Magazine-US-booklet.pdf>

**RE: argenx Response to ICER's Draft Scoping on the Assessment of Treatments for Myasthenia Gravis**

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

argenx is a global immunology company with the goal of developing differentiated antibody-based therapies. The company is committed to improving the lives of people suffering from severe autoimmune diseases and cancer and aims to translate immunology breakthroughs into an innovative portfolio of novel medicines.

Below are the key points that argenx would like to emphasize as the scope of the MG review is finalized:

1. Anxiety and depression are common in patients with MG and can significantly impact their outcomes.
2. There is a need for updated medical cost data for MG, with specific need for information about the costs associated with exacerbations and myasthenic crises.
3. The Myasthenia Gravis Activity of Daily Living (MG-ADL) scale is a measure of MG symptoms and functional status rather than a quality of life measure.
4. Although ICER correctly reflects the consensus treatment guidelines for MG, these therapies lack empirical data supporting their effectiveness.
5. There is a substantial burden associated with current treatments due to side effects and long-term risks.
6. Intravenous immunoglobulin (IVIg) should be included as an intervention in both the Clinical Evidence Review and Comparative Value Analyses.
7. Efgartigimod reduces IgG antibody levels beyond 50%.
8. The cost-effectiveness model will require clearly defined health states.
9. Clarification is needed on how studies with 4-week efficacy data will be incorporated into the cost-effectiveness analysis given the use of 3-month cycles in the model.

The remainder of this letter provides a more detailed discussion of these points.

**Anxiety and depression are common in patients with MG and can significantly impact their outcomes.**

Anxiety and fear of a possible onset of MG crisis or a flare can diminish a patient's quality of life. In a survey conducted of MG patients, 50% have been diagnosed with depression or anxiety (Qiu 2010), and a separate cross-sectional study showed that higher MG severity is correlated to a higher likelihood of having symptoms of depression and anxiety (Aysal 2013). Furthermore, results from a survey of 118 patients with MG showed that quality of life is highly correlated with Patient Health Questionnaire-9 scores, and depressive symptoms can impact quality of life; uncontrolled MG status, relapse within the past year, and a higher number of current MG therapies were significantly associated with worsened quality of life (Alanazy 2020). There is a substantial body of evidence suggesting that the presence of depression significantly increases patient costs; one retrospective study demonstrated that patients with depression had nearly double the annual healthcare costs compared to those without (\$20,046 vs \$11,956,  $P < 0.01$ ; Unützer 2009). The impact of depression and anxiety should be considered as a Potential Other Benefit (ICER scoping pg. 5) of reducing MG severity.

**There is a need for updated medical cost data for MG, with specific need for information about the costs associated with exacerbations and myasthenic crises.**

In the background section, ICER states: "The average annual cost per patient for MG-specific care paid by a private health plan was \$15,675 in 2009" (pg. 1). Medical cost data from 12 years ago is unlikely to provide accurate data for the current cost of care. Additionally, this claims data study does not include patient copayments, patient-paid deductibles, third-party paid coinsurance amounts, or indirect costs (Guptill 2012). Other published cost data is also outdated or too limited in scope to be useful for this assessment. As MG is a

heterogeneous population, it is important that cost data specific for patients who experience exacerbations and myasthenic crisis be included. Argenx is completing a medical cost of MG study in a large US insurance claims database and would be happy to provide a complete report to ICER to inform this review.

**The MG-ADL scale is a measure of MG symptoms and functional status rather than a quality of life measure.**

In the Outcomes section of the draft scoping under Patient-Important Outcomes, the MG-ADL is listed as a quality of life measure (pg. 4). However, the MG-ADL is a physician-captured 8-item scale that measures MG symptoms and functional status that can be used as an efficacy measurement in clinical trials (Wolfe 1999). Items from the MG-ADL include talking, chewing, swallowing, breathing, impairment of ability to brush teeth or comb hair, impairment of ability to arise from a chair, double vision, and eyelid droop. The MG-ADL has been used as a primary outcome in many phase 3 clinical trials to measure response to treatment. MG-ADL was used as the primary efficacy outcome in eculizumab's Phase 3 REGAIN trial (Howard 2017) as well as efgartigimod's Phase 3 ADAPT trial (Howard 2020). Therefore, the MG-ADL should be included as a measure of MG symptoms and functional status rather than quality of life, and should be considered for defining health states in the Comparative Value Analysis.

**Although ICER correctly reflects the consensus treatment guidelines for MG, these therapies lack empirical data supporting their effectiveness.**

ICER's draft scoping indicates that first-line treatment of generalized MG is pyridostigmine, followed by corticosteroids and non-steroidal immunosuppressants (NSITs) with progressive disease (pg. 1). We are pleased that these treatment recommendations follow the consensus treatment guidelines for MG (Sanders 2016; Narayanaswami 2021). However, it should be noted that there is a lack of data supporting most treatments included in the guidelines, with only 2 treatments (pyridostigmine and eculizumab) approved by the Food and Drug Administration (FDA) for the treatment of MG. Additionally, many MG treatments have extensive adverse effects that create substantial burden and barriers to effective short- and long-term treatment. These are all factors that should be considered in the Clinical Evidence Review when reviewing the literature for multiple off label treatments to accurately characterize the treatment landscape. Additionally, in the Comparative Value Analysis ICER needs to consider that MG is not a progressive disease and many patients will enter periods of needing more aggressive treatments but these periods are not necessarily lifelong.

**There is substantial burden associated with current treatments due to side effects and long-term risks.**

We agree with the perspective that patients experience significant side effects from current therapies and that side effects can contribute as much to patient disability as the disease itself, as noted in the Stakeholder Input section (pg. 2). In a qualitative survey, patients diagnosed with MG reported experiencing side effects related to MG treatments, the most commonly reported being weight gain (57.1%), diarrhea/GI upset (42.9%), and headaches/migraines (35.7%) (Bacci 2019). The need for novel treatments due to the intolerability of current treatments should be considered as a Contextual Consideration for the assessment.

Significant side effects of corticosteroids often limit their usage and, thus, their effectiveness. In particular, long-term use of corticosteroids is associated with serious adverse events, such as diabetes, osteoporosis, hypertension, gastrointestinal effects, and psychological effects (Liu 2013; Schneider-Gold 2019). The current Patient-Important Outcomes (pg. 4) include side effects specific to corticosteroids that should be expanded to include side effects of other therapies as well. The long-term side effects of NSITs like methotrexate or azathioprine can include liver and bone marrow toxicities, malignancies, and increased risk of infection (Hsu 2009); IVIg therapy is associated with headaches in over 50% of patients, thrombotic events in 1% to 16.9% of patients, and flu-like symptoms in up to 87.5% of patients (Guo 2018). Additionally, eculizumab is associated with an increased risk of meningococcal disease, which can occur even in patients receiving the meningococcal vaccine (McNamara 2017; Soliris PI). Therefore, ICER should consider the cost of side effects, for which specific cost in MG are not available but could be estimated from the literature on other conditions treated with corticosteroids and NSITs (Manson et al. 2009; Shah et al. 2013, Rice et al. 2017).



## **IVIg should be included as an intervention in both the Clinical Evidence Review and Comparative Value Analyses.**

In the Scope of Comparative Value Analyses section, ICER notes that "...it is unlikely that IVIg would be widely adopted due to limitations in its supply" (pg. 5). However, treatment guidelines indicate that IVIg as maintenance therapy should be considered for patients contraindicated for corticosteroids and/or NSITs and for patients whose post-intervention status was unchanged or worse after treatment with corticosteroids and at least 2 NSITs (Sanders 2016; Narayanaswami 2021). A recent claims data analysis found that maintenance IVIg treatment, defined as >6 cycles in 12 months, was used by approximately 3% of MG patients, a rate 5 times greater than eculizumab in the same analysis (argenx data on file). Additionally, in the Background section of the draft scoping it is reported that "[t]he average annual cost per patient for MG-specific care paid by a private health plan was \$15,675 in 2009 (Guptill 2012). The largest costs were home health services and *intravenous immunoglobulin (IVIg) infusions*" (pg. 1, emphasis added). Given that IVIg was one of the largest costs for MG care 12 years ago, it seems reasonably likely that it has already been widely adopted. Furthermore, patients highlighted the use of IVIg as maintenance therapy in the Stakeholder Input section of the scoping document (pg. 2). Therefore, although there are supply issues with IVIg, that are periodic and due in part to increased demand for IVIg (FDA 2019, Guo 2018, Privigen PI 2017); IVIg should be included as an intervention in ICER's Comparative Value Analysis.

## **Efgartigimod reduces IgG antibody levels beyond 50%.**

The Background section states that efgartigimod "reduces IgG antibody levels by about 50%" (pg. 1); however, the clinical trials showed that the mean total IgG reduction in patients treated with efgartigimod was 70% in phase 2 (Howard 2019) and 61% in phase 3 (argenx data on file).

## **The cost-effectiveness model will require clearly defined health states.**

In the Scope of Comparative Value Analyses, ICER states: "The model will consist of health states including 1) symptomatic MG (multiple states based on quality of life); 2) remission or minimal manifestation; 3) myasthenic crisis; 4) death" (pg. 6). Symptomatic MG and remission or minimal manifestation are better thought of as a single continuum, particularly if the Quantitative Myasthenia Gravis or MG-ADL is used to define these constructs. Change in both the QMG and MG-ADL have been found to map well to changes in HRQoL (data on file) and ICER should consider using these scales to define health states across the continuum; we would be happy to provide further data on this mapping. Additionally, myasthenic crisis can occur within other health states and should not be considered a health state; rather, it should be considered a health event and modeled as such.

## **Clarification is needed on how studies with 4-week efficacy data will be incorporated into the cost-effectiveness analysis given the use of 3-month cycles in the model.**

ICER states that evidence on intervention effectiveness and harms will be derived from studies of at least 4 weeks duration (pg. 4) and indicates the use of predetermined 3-month cycles in the cost-effectiveness analyses (pg. 6). Given the inclusion of studies with 4-week efficacy data, modeling 3 month cycles will miss benefits and harms that occur in as little as 4 weeks. ICER should consider using a 1 month cycle in the Comparative Value Analysis.

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,

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## References

- Alanazy MH, Binabbad RS, Alromaih NI, et al. Severity and depression can impact quality of life in patients with myasthenia gravis. *Muscle Nerve*. 2020;61(1):69-73.
- Aysal F, Karamustafalıoğlu O, Özçelik B, et al. The relationship of symptoms of anxiety and depression with disease severity and treatment modality in myasthenia gravis: a cross-sectional study. *Noro Psikiyatr Ars*. 2013;50(4):295-300.
- Bacci ED, Coyne KS, Poon JL, Harris L, Boscoe AN. Understanding side effects of therapy for myasthenia gravis and their impact on daily life. *BMC Neurol*. 2019;19(1):1-13.
- Caremark. Soliris (eculizumab) Prior-approval requirements. Accessed March 25, 2021. [https://www.caremark.com/portal/asset/FEP\\_Criteria\\_Soliris.pdf](https://www.caremark.com/portal/asset/FEP_Criteria_Soliris.pdf)
- Food and Drug Administration (FDA). Information about immune globulin (human) product shortage. August 12, 2019. Accessed March 1, 2021. <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-about-immune-globulin-human-product-shortage>
- Gavrilov YV, Alekseeva TM, Kreis OA, Valko PO, Weber KP, Valko Y. Depression in myasthenia gravis: A heterogeneous and intriguing entity [published online ahead of print March 5, 2020]. *J Neurol*. 2020;267(6):1802-1811. doi: 10.1007/s00415-020-09767-7
- Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. *Front Immunol*. 2018;9:1299.
- Guptill JT, Sharma BK, Marano A, Soucy A, Krueger A, Sanders DB. Estimated cost of treating myasthenia gravis in an insured U.S. population. *Muscle Nerve*. 2012;45(3):363-366.
- Harris L, Aban IB, Xin H, Cutter G. Employment in refractory myasthenia gravis: A Myasthenia Gravis Foundation of America Registry analysis. *Muscle Nerve*. 2019;60(6):700-706.
- Howard J. Treatment of patients with myasthenia gravis with efgartigimod: Results of the Phase 3 ADAPT study. Presentation at the Myasthenia Gravis Foundation of America Virtual Scientific Session; October 3, 2020.
- Howard JF Jr, Bril V, Burns TM, et al. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. *Neurology*. 2019;92(23):e2661-e2673.
- 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. *Lancet Neurol*. 2017;16(12):976-986.
- Hsu DC, Katelaris CH. Long-term management of patients taking immunosuppressive drugs. *Aust Prescr*. 2009;32:68-71.
- Liu D, Ahmet A, Ward, L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9(1):30.
- Manson SC, Brown RE, Cerulli A, et al. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respir Med*. 2009;103:975-994.
- McNamara LA, Topaz N, Wang X, Hariri S, Fox L, MacNeil JR. High risk for invasive meningococcal disease among patients receiving eculizumab (Soliris) despite receipt of meningococcal vaccine. *MMWR Morb Mortal Wkly Rep*. 2017;66(27):734-737.
- Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology*. 2021;96(3):114-122.
- Privigen (immune globulin intravenous [human]) [package insert]. Kankakee, IL: CSL Behring; 2017.
- Qiu L, Feng HY, Huang X, et al. Study of incidence and correlation factors of depression, anxiety and insomnia in patients with myasthenia gravis. *Zhonghua Yi Xue Za Zhi*. 2010;90(45):3176-3179.



- Rice JB, White AG, Scarpatti LM, Wan G, Nelson WW. Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clinical Therapeutics*. 2017;39(11):2216-2229. doi:10.1016/j.clinthera.2017.09.011
- Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology*. 2016;87(4):419-425.
- Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. *Ther Adv Neurol Disord*. 2019;12:1756286419832242.
- Shah M, Chaudhari S, McLaughlin TP, Kan HJ, Bechtel B, Dennis GJ, Molta CT. Cumulative burden of oral corticosteroid adverse effects and the economic implications of corticosteroid use in patients with systemic lupus erythematosus. *Clin Ther*. 2013 Apr;35(4):486-97. doi: 10.1016/j.clinthera.2013.03.001.
- Soliris (ecuzliumab) [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc.; 2020.
- Tworok S, Wiesmeth S, Klewer J, Pöhlau D, Kugler J. Quality of life and life circumstances in German myasthenia gravis patients. *Health Qual Life Outcomes*. 2010;8:129.
- Unützer J, Schoenbaum M, Katon WJ, et al. Healthcare costs associated with depression in medically ill fee-for-service Medicare participants. *J Am Geriatr Soc*. 2009;57(3):506-510.
- Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology*. 1999;52(7):1487-1489.



## **BLACK WOMEN'S** HEALTH IMPERATIVE

**The Black Women's Health Imperative (BWHI) appreciates the opportunity to write in response to ICER's Draft Scoping Document for its 2021 review entitled "Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis."** Myasthenia Gravis (MG) exacts a substantial toll on the lives of Black women, who tend to receive a diagnosis and an opportunity for treatment later in the disease course than their white counterparts. BWHI appreciated the opportunities ICER afforded for a substantive and continuing dialogue in connection with its review of Lupus Nephritis and is eager to collaborate with ICER on the MG review to enable consideration of the lived experience of Black women diagnosed with, and determining best treatment approach for, MG. We ask that ICER accept this response to the Draft Scoping as our request for inclusion in stakeholder engagement activities related to Model development and the Model Analysis Plan. While our participation in ICER's LN review challenged our ability to fully review, research, and respond to the Draft Scoping document within the tight timeline between its publication and close of the comment period, we are committed to fully participating in the MG review and expect to provide ICER with a more detailed set of recommendations and data resources in the coming weeks.

**MG is a serious, chronic, life-limiting syndrome that can present potentially fatal respiratory complications requiring hospitalization.** Until October 2017, there were no FDA approved drugs for the treatment of MG. Off-label treatment regimens have offered clear improvement with respect to decreased mortality and an increased number of patients experiencing some level of therapeutic response. Unfortunately, these treatment approaches have not moved the needle to increase the small proportion of patients achieving remission or reduced the percentage of patients refractory to treatment. The unmet need for incorporation of newer treatments is, therefore, high.

**BWHI strongly urges ICER to include lost or delayed childbearing potential within its set of outcomes for assessing the value of treatment options for MG.** This is a particularly important consideration for women of color who face disproportionate risk of pregnancy-related death and for whom postponing pregnancy beyond age 30 is associated with a 4-5 times higher mortality risk in comparison to white women. The maternal mortality risk disparity continues to widen with age and is most pronounced in older women with advanced degrees. We recognize that preservation of fertility and childbearing potential are not specific outcomes included in clinical trials, and are eager to explore with ICER the potential to extrapolate from data on patient age, gender, use of treatments contraindicated in pregnant individuals or those intending to become pregnant, and sufficient response to treatment to enable safe pregnancy and childbirth.

**BWHI agrees that treatment goals of therapy include enabling patients to achieve sufficient response to reach and maintain a health status of minimal manifestations of disease or better, with minimal side effects.** We also agree that the quality of life impact of both the condition and its treatments are important outcomes for consideration, as are fatigue, hospitalizations, myasthenia crisis, and ability to return to work. BWHI expects to provide increased granularity on the lived experience of Black women with MG to further inform ICER's assessment.

**We support ICER's inclusion of corticosteroid side effects and other adverse events in its model, and urge ICER to adjust its analyses on comparative efficacy between new treatments and control arms of clinical trials to reflect patient feedback that "the side effects can contribute as much to patient disability as the disease itself" and prevalence of patient-initiated discontinuation of those therapies.** Side effect burden and impact on long-term health of treatment regimens involving high-





dose corticosteroids are particularly important to people of color with MG due to the earlier age of onset in these patients.

- Corticosteroid use contributes to development or worsening of health conditions that already disproportionately impact Black and Latinx patients, including hypertension, obesity, diabetes, and osteoporosis;
- Costs of managing adverse events associated with longer-term use of corticosteroids (60 days or more) can actually be higher than disease-related medical costs;
- Immunosuppressive medications are associated with minor side effects such as nausea, as well as very serious and relatively common adverse events such as ovarian failure in 38-52% of women, severe opportunistic infections, and higher risk of cancer with 2-3 years of use.

**BWHI urges ICER to consider the impact of MG and its treatment options in individuals under 18 years of age and to recognize that the quality of life impact of a life-limiting, potentially disabling condition in young women is not sufficiently captured by multiplying the impact in the elderly by a life expectancy adjustment factor.** Black patients are more likely to be diagnosed with MG before 40 years of age, and the age of onset is approximately 18 years younger than in white patients. Moreover, although white patients show a gradual increase in the number of patients in each decade up to the seventh, Black men and women show a gradual decrease in number of patients in each decade after the fourth. Similarly, we note that ICER includes several contextual considerations, and suggests that data could be collected using the Work, Productivity and Activity Impairment Instrument, as well as the Health-Related Quality of Life measure in addition to Quality Adjusted Life Year measure.

**ICER's assessment must give significant weight and consideration to the race-specific variability in MG prevalence, disease severity at diagnosis, age at onset, and treatment response, and assess each treatment from the lens of real-world experiences in patient subpopulations.** This includes accounting for tendency toward later diagnosis in people of color and the fact that side effects, adverse events, reliable access to a standard of care, and inadequate treatment response can further widen the gap in health outcomes based on race and/or ethnicity.

**The quality adjusted life-year (QALY) use, without separate subpopulation analyses and significant adjustments to the underlying model and its inputs, will distort the resultant value determination and perpetuate race-specific health inequities for MG patients.** The QALY framework ICER uses in assessing treatment options was crafted before racial inequities in care access and delivery were recognized as drivers of health outcomes and does not capture differences in burden of disease, outcome preferences, or viability of comparative treatments. BWHI appreciates ICER's inclusion of a discussion on QALY shortcomings within its reviews and urges it to consider:

- QALYs generally fail to account for non-health benefits and indirect costs that can have a greater impact on future health outcomes in communities of color given the existing health inequities patients encounter, potentially high prevalence of food and housing insecurity, and reduced access to care due to loss of employer-sponsored health coverage. This is especially relevant during and in the wake of the COVID-19 pandemic. These non-health benefits and indirect costs include ability to continue or return to work, better school performance, costs of caregiving,



## BLACK WOMEN'S HEALTH IMPERATIVE

mental health challenges, daily functioning, time accessing medical care, income loss, loss of productivity, and travel costs to access care;

- QALYs utility scores also tend to disadvantage patients with progressive chronic conditions. For MG patients, the baseline QALY (and MG patient inability to reach a state approximating full health) fails to capture both the full impact of the condition and the true value of each assessed treatment. The earlier age of onset in non-white patients further complicates calculation of an aggregated baseline QALY, particularly in light of the persistent challenges to enrolling clinical trial populations that reflect complete disease demographics.
- BWHI suggests that ICER utilize methods such as multiple criteria decision analysis (MCDA) to enhance the relevance of QALY to MG patients, across the age spectrum, likely to benefit from treatment or suffer from having it withheld.

**The MG assessment should prioritize effective management of chronic conditions like MG. The differential burden of the COVID-19 pandemic has made it clear that health disparities can have severe consequences.** MG patients have faced difficult treatment decisions throughout the COVID-19 pandemic to balance the risk of serious COVID-19 disease associated with MG with the similarly heightened risk associated with MG treatments incorporating high-dose steroids and immunosuppressants.

**ICER should consult with clinicians and patient advocacy stakeholders to ensure that its model includes all relevant MG disease states and treatment responses.**





## REFERENCES (BWHI Comments to ICER Draft Scoping Document for MG)

Bacci, E.D., Coyne, K.S., Poon, J.L. et al. Understanding side effects of therapy for myasthenia gravis and their impact on daily life. BMC Neurol 19, 335 (2019). <https://doi.org/10.1186/s12883-019-1573-2>

Bailey ZD, Krieger N, Agénor M, Graves J, Linos N, Bassett MT. Structural racism and health inequities in the USA: evidence and interventions. Lancet 2017;389:1453–63.

CDC, Racial and Ethnic Disparities Continue in Pregnancy-Related Deaths - Black, American Indian/Alaska Native women most affected. <https://www.cdc.gov/media/releases/2019/p0905-racial-ethnic-disparities-pregnancy-deaths.html>

CDC. Disparities in Incidence of COVID-19 Among Underrepresented Racial/Ethnic Groups in Counties Identified as Hotspots During June 5–18, 2020 — 22 States, February–June 2020. (early release, August 14, 2020). <https://www.cdc.gov/mmwr/volumes/69/wr/mm6933e1.htm>

CDC. Health equity considerations and racial and ethnic minority groups. Atlanta, GA: US Department of Health and Human Services, CDC; 2020. <https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/race-ethnicity.html>

[Gender and Ethnicity Based Differences in Clinical and Laboratory Features of Myasthenia Gravis \(hindawi.com\)](https://www.hindawi.com/)

Hutchins SS, Fiscella K, Levine RS, Ompad DC, McDonald M. Protection of racial/ethnic minority populations during an influenza pandemic. Am J Public Health. 2009;99 Suppl 2(Suppl 2):S261-S270. doi:10.2105/AJPH.2009.161505.

ICER Statement on Racism in America (June 3, 2020). [https://icer-review.org/blog/race\\_in\\_america/](https://icer-review.org/blog/race_in_america/)

National Minority Quality Form White Paper: Traditional Value Assessment Methods Fail Communities of Color and Exacerbate Health Inequities. <https://www.nmqf.org/nmqf-media/traditional-value-assessment-methods>

Oh SJ, Morgan MB, Lu L, Hatanaka Y, Hemmi S, Young A, Claussen GC. Racial differences in myasthenia gravis in Alabama. Muscle Nerve. 2009 Mar;39(3):328-32. doi: 10.1002/mus.21191. PMID: 19127534; PMCID: PMC2814330.

Selden TM, Berdahl TA. COVID-19 and racial/ethnic disparities in health risk, employment, and household composition. Health Aff (Millwood) 2020. Epub July 14, 2020.

Wortham JM, Lee JT, Althomsons S, et al. Characteristics of persons who died with COVID-19—United States, February 12–May 18, 2020. MMWR Morb Mortal Wkly Rep 2020;69:923–9

Yancy CW. COVID-19 and African Americans. JAMA. Published online April 15, 2020.







## **Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis Draft Background and Scope: Comments from the Myasthenia Gravis Foundation of America (MGFA)**

**Overview:** The Myasthenia Gravis Foundation of America is first and foremost a patient advocacy organization for people living with the rare and life-altering disease of MG. Until eculizumab was approved for use in MG in 2017, it had been more than 6 decades since any treatment had been approved for myasthenia gravis, and this was the first actual disease modifying therapy. The lived experience with MG can vary greatly from one patient to another. Finding a treatment regimen that works for a particular patient is as much art as science. People with MG need options with greater efficacy and fewer short and long-term side effects.

### **Stakeholder Input:**

***Quote from ICER Background and Scope:*** “Stakeholders highlighted that eculizumab is very expensive. They also noted that the Phase 3 pivotal trial of eculizumab studied patients with refractory disease, but that the FDA label was broader. This has led to widespread use of the drug in patients who have not received an adequate trial of conventional immunosuppressive therapy, which is much less expensive.”

**MGFA Response:** Eculizumab IS very expensive. For this very reason, we do not see evidence that there is “widespread use” of eculizumab in patients who have not had an adequate trial of other therapies—though that is certainly true for some patients.

The high cost of the drug is most certainly an impediment to access for many patients who might benefit. (Nancy Law, MG Patient, Chair, MGFA Board of Directors, former MGFA CEO)

### ***Quote from ICER “Population”***

*“As data permit, we will evaluate the evidence on the following subpopulations:*

- *Patients with anti-acetylcholine receptor antibodies*
- *Patients without anti-acetylcholine receptor antibodies”*

**MGFA Response:** We would suggest that you include 3 subpopulations:

- Patients with anti-acetylcholine receptor antibodies
- Patients with anti-MuSK antibodies
- Patients without either anti-acetylcholine receptor antibodies or anti-MuSK antibodies (seronegative)

It may be better to look at people with anti-MuSK MG separately from people with anti-AChR antibodies, and those who do not test positive for either MuSK or AChR. Treatment of MuSK MG is very different from that for people who have AChR mediated disease, and eculizumab should not be used with MuSK patients. But, while people with anti-MuSK antibodies would not be expected to respond to drugs that inhibit complement, that is not necessarily the case with people who do not show either anti-AChR or MuSK antibodies in testing (seronegative). In fact, we have seen some people who are seronegative and refractory to other treatments who have

responded remarkably well to treatment with Soliris. It may be more accurate to describe patients who do not test positive to either anti-AChR antibodies or anti-MuSK antibodies as “sero-undetectable” rather than seronegative. (*Nancy Law*)

#### **Quote from “Scope of Comparative Value Analyses**

*“We will not be comparing eculizumab and efgartigimod to conventional therapy plus IVIG as it is unlikely that IVIG would be widely adopted due to limitations in its supply.”*

**MGFA Response:** We believe that this protocol must be included in your study. In fact, it may be the most important one for you to examine in comparison to the use of eculizumab and efgartigimod. IVIg is already being used extensively in maintenance therapy for many people with MG, and people with MG report that often it is given in combination with steroids and/or Imuran or Cellcept—not as a substitution. One survey of MG patients in 2018 (Ra Pharma—now a part of UCB) showed that as many as 30% of responders (from MGFA database) were treated with IVIg as often as monthly—sometimes with 2-3 infusions. As you note, IVIg has been for years the largest expense in MG treatment. We think it is very important to include this comparison in your study, especially as most of the studies on this expense are from 10 years ago or longer, while the use of immunoglobulin in maintenance of MG patients has been on the rise—now with subcutaneous infusion (e.g., Hizentra) as an option in addition to IVIg. While this SubQ option increases convenience for patients, there does not appear to be any accompanying cost savings. (*Nancy Law*)

April 2, 2021

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Submitted electronically at: [publiccomments@icer-review.org](mailto:publiccomments@icer-review.org)

**Re: Request for Public Input on ICER's Draft Background and Scoping Document for Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis**

To Whom It May Concern,

UCB appreciates the opportunity to provide comments on the above referenced Scoping Document. UCB is a global biopharmaceutical company with nearly 7,500 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).

With current “standard of care” therapy, most gMG patients fail to achieve complete stable remission.<sup>i</sup> However, the landscape for gMG is evolving quickly, with promising treatments expected to transform the lives of people living with this chronic, unpredictable, and often debilitating neuromuscular disease. This will represent a fundamental shift from simply addressing disease symptoms using conventional therapy to innovative therapeutic options with the potential to reduce underlying disease pathology. Ensuring patients have appropriate access to those therapies will significantly enhance the treatment paradigm for gMG, allowing more patients to achieve and maintain control of their disease, while reducing damage at the neuromuscular junction.

**As such, disease assessment frameworks need to be designed to be forward-looking in order to shift the treatment paradigm to maximize the benefits of newer therapies in extending the period of minimal gMG manifestations.** UCB offers the following feedback for ICER's consideration.

[Evaluating disease burden](#)

gMG is a rare, chronic and clinically heterogeneous neuromuscular disease, with symptoms including chronic muscle weakness and fatigue.<sup>ii,iii</sup> gMG is characterised by severe and fluctuating skeletal muscle weakness and fatigability upon repeated movement, which can result in highly unpredictable episodes of severe muscle weakness for patients.<sup>iv</sup> However, the disease is highly variable both in its severity and its presentation across patients. Patients may also experience a life-threatening, sudden and unpredictable worsening of gMG symptoms resulting in respiratory failure and requiring mechanical ventilation, referred to as a myasthenic crisis.<sup>v</sup> **Myasthenic crisis is not a rare event, it is estimated that 15–20% of all gMG patients experience at least one myasthenic crisis during their lifetime, typically within the first two years after diagnosis.**<sup>vi,vii</sup>

For these reasons, it is an understatement to characterize gMG as a symptomatic disease, as this characterization minimizes its negative impact on patients and diminishes the value of treatments that address the debilitating effects of its chronic pathology and unpredictable symptoms. Up to 80% of patients with gMG will fail to achieve complete stable remission on current standard of care treatments,<sup>viii,ix</sup> demonstrating a high unmet need for well-tolerated, effective, fast onset treatments that achieve predictable and sustained control of symptoms and improve patients' treatment-related burden. **We recommend that ICER build a gMG disease framework that assesses the impact that newer gMG therapies can have on the severe and fluctuating nature of the disease.**

#### Evaluating treatment burden

Current standard of care therapies follow a consistent treatment algorithm of escalating drug classes, cycling within drug classes, and/or increasing drug dosages.<sup>x</sup> Despite current treatment, as many as 50–75% of MG patients do not achieve complete symptomatic relief and experience uncontrolled disease.<sup>xi, xii, xiii</sup> Treatment-associated comorbidities can negatively impact gMG patients' mobility, respiratory function and quality of life (QoL), as well as treatment adherence.<sup>xiv,xv,xvi,xvii</sup> Additionally, gMG patients spend years progressing through different lines of suboptimal treatment with significant adverse events, before resorting to invasive treatments requiring hospital administration and substantial healthcare resource utilisation.<sup>xviii</sup> **UCB recommends an evaluation framework that considers the current risk for these long-term toxicities and treatment-associated comorbidities alongside their associated healthcare resource utilization and costs.**

#### Evaluating economic burden

UCB recommends a thorough assessment of plasma exchange (PLEX) and IVIg due to its common use as rescue therapy and its association with high healthcare resource use and costs. **UCB recommends that ICER clearly define and differentiate “maintenance therapy” versus “acute use / emergency use” and appropriately capture the clinical and economic burden of these approaches in the evaluation of overall cost of care.** The costs for patients requiring assistance with activities of daily living are four-fold higher than estimates for those who do not need assistance. gMG manifests inconsistently, leading to different thresholds of disability, which drives considerable differences in total cost of care for gMG patients and highlights the importance of appropriately stratifying estimates of costs for gMG treatment to across patient segments (i.e., age and disease severity).

Additionally, UCB has concerns that references to treatment costs that are not representative of current established treatment costs will introduce a bias and diminish relevance, serving to minimize the unmet needs in gMG and the cost-effectiveness of newer therapies.<sup>xix</sup>

#### Comparator Groups and Line of Therapy Assumptions

Comprehensive evaluation of gMG treatments should include appropriate comparator therapies and be flexible in assessing multiple treatment sequence, treatment cycling and/or combination therapy scenarios.<sup>xx,xxi</sup> To this end, perspectives and insights from multiple stakeholders, including patients and

caregivers need to be considered to ensure that new innovative therapies are not being assessed within the confines of older treatment frameworks.

UCB encourages ICER to thoroughly state assumptions and definitions with such specificity that stakeholders clearly understand the methodology and perspective shaping ICER’s evaluation. For example, the scoping document refers to “patients with refractory disease” but does not specify what is meant by “refractory disease.”<sup>xxii</sup>

Data regarding the clinical effectiveness of standard of care therapy is limited and those therapies are associated with poor disease control as evidenced by high rates of gMG exacerbations.<sup>xxiii</sup> **That said, existing therapies’ patterns of use should not bias the perspectives of newer innovative therapies and focus on delivering the best outcomes for the patient. Rather, the value of newer therapies should stand on their own volition, based on their clear efficacy and safety profile and not be biased toward last-line use.** New therapies offer improved benefit, such as faster onset of action, favorable side effect profile, and the potential for a sustained and long-term remission of disease.<sup>xxiv</sup>

### Questions on the Modeling Approach

#### *Model Parameters:*

- How will the model account for variability in treatment combinations and/or sequences seen in real-world practice?
- Many gMG patients lose 18-24 months of their lives waiting for the right steroid dose and IST cycling. How does ICER intend to value therapies that have more rapid onset of action? What if the onset of action of newer therapies is faster than three months?
- Soliris® (eculizumab, Alexion) and efgartigimod (in development, Argenyx) are (will be) indicated for two distinct patient populations (ACHR+ versus ACHR+ and MuSK+).
  - What are the clinical assumptions that will be made if data does not permit for a prespecified subgroup analysis?
  - Additionally, Soliris®, based on trial design, is for treatment of moderate-to-severe and refractory patients, while the trial for efgartigimod is not limited to refractory patients. How does ICER plan to consider these segments of patients?
  - Will the value and/or cost-effectiveness of each therapy be assessed by baseline disease severity?

#### *Appropriateness and priority of model outcomes*

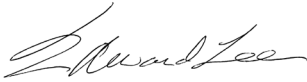
UCB urges ICER to prioritize those outcomes which are most important to patients and work toward improving their quality of life and ability to complete activities of daily life – such as faster time-to-treatment onset, appropriate treatment, and minimal manifestation status. These outcomes should drive clinical and economic decision-making and should guide policy that improves patients’ care.<sup>xxv</sup>

Lastly, randomized controlled trial data supporting the efficacy and safety of ISTs is limited and many of the outcomes included in ICER’s draft scoping document may not be available. UCB requests additional clarity regarding how ICER plans to report on those outcomes for which there is no trial data.

\* \* \*

UCB appreciates this opportunity to comment. We welcome further discussion with ICER on improvements to its scoping document to evaluate treatments for gMG. Please contact Amanda Ledford, Associate Director of U.S. Public Policy, at [Amanda.Ledford@UCB.com](mailto:Amanda.Ledford@UCB.com) or 202-893-6194 with any questions or feedback on our comments.

Sincerely,



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<sup>i</sup> Baggi F, Andreetta F, Maggi L, et al. Complete stable remission and autoantibody specificity in myasthenia gravis. *Neurology*. 2013.;80:188-195.

<sup>ii</sup> MG patients initially present with muscle weakness limited to the eyes (known as ocular MG), and 80–85% of these patients then progress to generalised MG (gMG) within two years from symptom onset, where additional muscle groups are affected.

<sup>iii</sup> UCB. Disease Area Review: Myasthenia Gravis (DAR).

<sup>iv</sup> UCB. DAR.

<sup>v</sup> UCB. DAR.

<sup>vi</sup> It is estimated that 15–20% of all gMG patients experience at least one myasthenic crisis during their lifetime, typically within the first two years after diagnosis. UCB. DAR.

<sup>vii</sup> UCB. DAR.

<sup>viii</sup> UCB. DAR.

<sup>ix</sup> Patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted. UCB. DAR.

<sup>x</sup> This includes AChEIs, corticosteroids (CS) and non-CS ISTs, which are either symptomatic or act through broad non-specific immunosuppression.

<sup>xi</sup> Standard of care therapies are associated with significant concerns regarding the treatment's tolerability, side effects, long-term toxicities and treatment-associated comorbidities. After failing to achieve adequate symptom control with AChEIs and low-dose CS, patients are often escalated to high-dose CS, non-CS ISTs or off-label combination therapies of CS and non-CS ISTs. Sathasivam S. Steroids and immunosuppressant drugs in myasthenia gravis. *Nature Clinical Practice Neurology* 2008;4:317-27.

<sup>xii</sup> Safety is also concerning as long-term high-dose CS use is associated with complications and the development of comorbidities, usually within 12 months of diagnosis, including infections, diabetes, hypertension, glaucoma, gastrointestinal toxicities, hepato- and nephrotoxicities. Rice JB, White AG, Scarpatti LM, et al. Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clinical Therapeutics* 2017;39:2216-2229.

<sup>xiii</sup> Gilhus N. Myasthenia gravis. *New England Journal of Medicine*. 2016;375:2570-2581.

<sup>xiv</sup> Sathasivam S. Steroids and immunosuppressant drugs in myasthenia gravis. *Nature Clinical Practice Neurology* 2008;4:317-27.

<sup>xv</sup> Rice JB, White AG, Scarpatti LM, et al. Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clinical Therapeutics* 2017;39:2216-2229.

<sup>xvi</sup> Gilhus N. Myasthenia gravis. *New England Journal of Medicine*. 2016;375:2570-2581.

<sup>xvii</sup> Schneider-Gold C, Hagenacker T, Melzer N, et al. Understanding the burden of refractory myasthenia gravis. *Therapeutic Advances in Neurological Disorders*. 2019;12:1756286419832242.

<sup>xxvi</sup> This subpopulation has, on average, higher resource needs and costs compared with younger individuals. Secondly, the use of non-steroidal immunosuppressants and thymectomy in young adults in their 20s and 30s may be worthy of further analysis.

<sup>xviii</sup> UCB. DAR.

<sup>xix</sup> UCB. DAR.

<sup>xx</sup> Trends indicate that more recent cost estimates are significantly higher than in 2009, as noted in the scoping document.

<sup>xxi</sup> Patients commonly begin treatment with AChEIs, usually pyridostigmine, an on-label treatment for MG. Whilst AChEIs are able to improve gMG symptoms in many patients, only a subset will experience complete symptomatic relief through AChEI therapy alone. Patients with uncontrolled disease transition from first line AChEIs and low-dose CS, and are then treated with higher doses of CS and other non-CS ISTs, which are associated with a risk of systemic and harmful adverse effects with chronic use and a high treatment burden. Due to these harmful adverse effects associated with high-dose CS therapy, these treatments are often used in combination with other non-CS ISTs, such as azathioprine or mycophenolate mofetil, to achieve a CS-sparing effect. However, there is often a delay between treatment initiation and therapeutic onset of non-CS ISTs, in some cases taking 6–12 months before a clinical benefit is demonstrated. Additionally, the clinical evidence for the efficacy of non-CS ISTs in gMG is limited. The therapeutic effects of non-CS ISTs are often minimal, which causes patients to progress to other treatments. Patients who experience uncontrolled disease following treatment with AChEIs, CS and non-CS ISTs, will further progress to either episodic or chronic, last-line treatments with IVIg, PLEX or rituximab. UCB. DAR.

<sup>xxii</sup> Based on current literature, refractory patients can range from 10% up to 40% of gMG patients; providing a clear definition

and estimation of this patient population will assist greatly with the understanding of the evaluation.

<sup>xxiii</sup> In a real-world evidence study, 27% of patients experience exacerbation with an annualized mean of 4.96 exacerbations while on first-line therapy of AChEIs and/or steroids. In addition, that rate of exacerbation increased by 40% while on non-steroid immunosuppressive therapy (data on file). Further, studies have shown that 20% of gMG patients will experience a myasthenic crisis – which is much more severe than exacerbation and requires hospitalization and mechanical ventilation. This is further corroborated by a 2019 analysis of MGFA patient registry data that showed many gMG patients who exhibited significant disease burden had not yet been treated with multiple immunosuppressive agents. The unpredictable nature of gMG means that patients may experience a serious exacerbation shortly after standard of care therapy initiation.

<sup>xxiv</sup> Deepak Menon, Carolina Barnett and Vera Bril. Novel Treatments in Myasthenia Gravis. *Front. Neurol.*, 30 June 2020.

<sup>xxv</sup> UCB would like to suggest that ICER also consider the Quality of Life in Neurological Disorders (Neuro-QOL) assessment in its evaluation. A short form Neuro-QOL Fatigue subscale is available and recently validated in patients with gMG Andersen, H., Mantegazza, R., Wang, J.J. *et al.* Eculizumab improves fatigue in refractory generalized myasthenia gravis. *Qual Life Res* 28, 2247–2254 (2019).