Single Technology Appraisal

Ravulizumab for treating generalised myasthenia gravis [ID4019]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ravulizumab for treating generalised myasthenia gravis [ID4019]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Alexion:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Myaware-Muscular Dystrophy UK
   b. Association of British Neurologists
   c. NHS England

4. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre (SHTAC)

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6. **Technical engagement response from company**
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7. **Technical engagement responses and statements from experts:**
   a. Jennifer Spillane, Consultant Neurologist – clinical expert, nominated by Alexion
   b. Amanda Hayes – patient expert, nominated by Muscular Dystrophy UK
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8. **Technical engagement responses from stakeholders:**
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ravulizumab for treating antibody-positive generalized myasthenia gravis [ID4019]

Document B

Company evidence submission

November 2022

File name	Version	Contains confidential information	Date
ID4019_Alexion Ravulizumab_STA Document B		**Yes**	**03/11/2022**

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This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

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In this template any information that should be provided in an appendix is listed in a box.

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Abbreviations

Abbreviation	Definition
Ach	Acetylcholine
AChR	Acetylcholine receptor
AE	Adverse event
A&E	Accident and Emergency
AUC	Area under the curve
COVID-19	Coronavirus disease
CPRD	Clinical Practice Research Datalink
DSP	Disease Specific Programme
EPAR	European Public Assessment Report
FAS	Full analysis set
gMG	Generalized myasthenia gravis
HES	Hospital Episode Statistics
HRQL	Health-related quality of life
IPW	Inverse-propensity weighting
IST	Immunosuppressive therapy
ITC	Indirect treatment comparison
IVIg	Intravenous immunoglobulin
LSM	Least squares mean
mAB	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post-Intervention Status
MG-QoL15	MG-Quality of Life 15
MG-QoL15r	MG-Quality of Life 15 revised
MHRA	Medicines and Healthcare products Regulatory Agency
MuSK	Muscle-specific kinase
NMJ	Neuromuscular junction
Neuro-QoL	Quality of Life in Neurological Disorders
OLE	Open-label extension
OR	Odds ratio
PBO	Placebo
QMG	Quantitative Myasthenia Gravis scale
RAV	Ravulizumab
RCT	Randomized controlled trial
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation

Abbreviation	Definition
SEM	Standard error of the mean
SLR	Systematic literature review
SmPC	Summary of product characteristics
VAS	Visual analogue scale
WPAI	Work Productivity and Activity Impairment

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorization for this indication. A summary of how the decision problem is addressed in this submission is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with gMG	Adult patients with anti-AChR antibody-positive gMG. Ravulizumab is indicated as an add-on to standard therapy	The decision problem addressed by the company is aligned with the licensed population and clinical evidence available for ravulizumab
Intervention	Ravulizumab	As per scope	NA
Comparator(s)	Established clinical management without ravulizumab including corticosteroids and immunosuppressive therapies with or without intravenous immunoglobulin or plasma exchange	As per scope	NA
Outcomes	The outcome measures to be considered include: • Improvement in myasthenia gravis • Hospitalizations • Mortality • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Improvement in myasthenia gravis – Change in MG-ADL score – Change in QMG score • Mortality • MG exacerbations and crises • Number of hospitalizations • Adverse effects of treatment • Health-related quality of life	MG exacerbations and crises are a relevant outcome for consideration in this appraisal due to their impact on patient health-related quality of life, mortality and engagement with NHS services (healthcare resource use)
Economic analysis	The reference case stipulates that the cost effectiveness of treatments	A cost-effectiveness model will be developed in Microsoft Excel, in line	NA

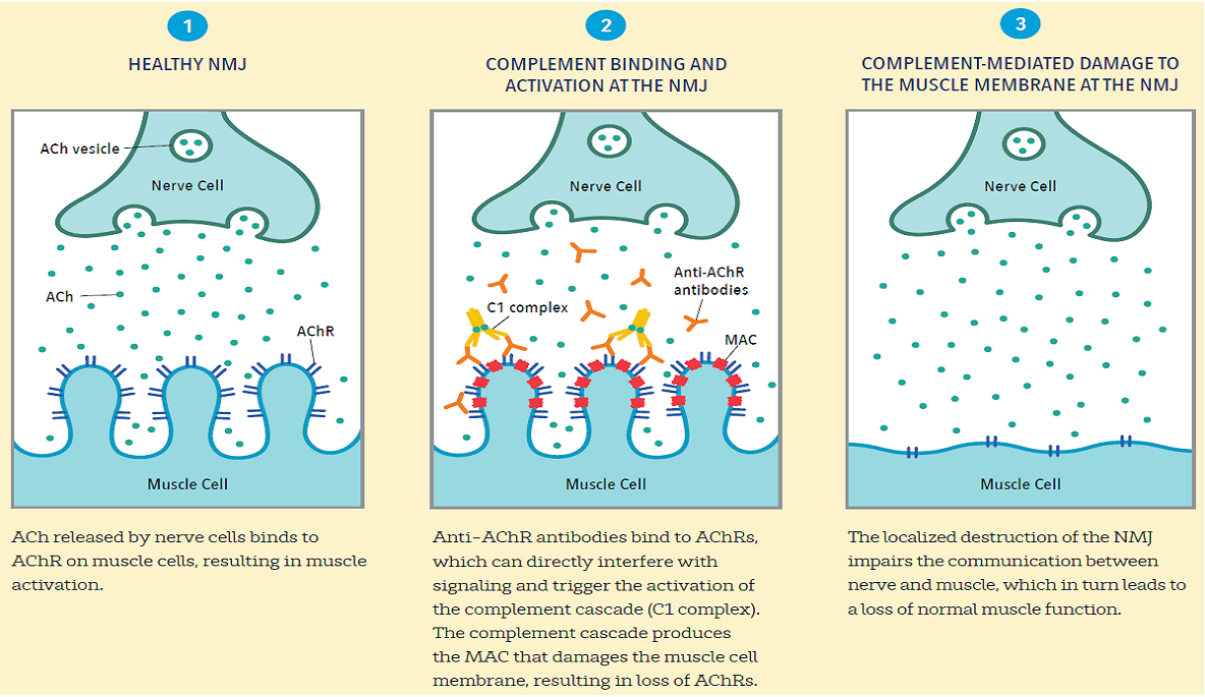
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered. The availability of any managed access arrangement for the intervention will be considered.	with the reference case and NICE methods for health technology evaluation. [redacted] A managed access arrangement is not anticipated and is therefore not considered.	
Special considerations including issues related to equity or equality	The availability and cost of biosimilar and generic products should be considered. Guidance will only be issued in accordance with the marketing authorization. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that	As per scope	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	has underpinned the marketing authorization granted by the regulator.		

B.1.2. Description of the technology being appraised

Ravulizumab is a long-acting terminal complement inhibitor that specifically binds to the complement protein C5 in the terminal complement pathway, inhibiting the activation of the terminal complement cascade. The activation of this cascade is responsible for localized destruction of the postsynaptic membrane of the neuromuscular junction (NMJ), which leads to generalized myasthenia gravis (gMG; Figure 1).

Figure 1: Schematic of binding of anti-AChR autoantibodies at the neuromuscular junction in patients with MG



Key: ACh, acetylcholine; AChR, acetylcholine receptor; MAC, membrane attack complex; NMJ, neuromuscular junction.
Source: Meriggioli et al. 2009[13]; Conti-Fine et al. 2006[1]; Engel et al. 1977[14].

This destruction interrupts the communication between nerves and the muscles at the NMJ, which relies on the release of a neurotransmitter, acetylcholine (ACh), into the synaptic cleft (the space between the neuron and muscle cell). Normal muscle contraction occurs when ACh binds to the ACh receptor (AChR) on the postsynaptic membrane.[1, 2]

According to feedback from UK clinical experts, 90% of patients with gMG in the UK are anti-AChR antibody-positive.[3] These patients have autoantibodies directed against the nicotinic AChR on the post-synaptic membrane[4-11], which reduces the availability of AChR in several ways, including damaging the receptors via the complement system.[2] This in turn results in muscle weakness or fatigue, and causes a range of disabling symptoms including decreased ability to move independently, impaired swallowing, risk of choking, disorienting vision, slurred speech, dysarthria, and episodes of pulmonary failure, necessitating hospitalization and mechanical ventilation.[12]

Ravulizumab is a monoclonal antibody treatment that received UK marketing authorisation via the European Commission Decision Reliance Procedure in September 2022 as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-AChR antibody-positive.

Ravulizumab is an effective therapy that demonstrates rapid and sustained improvements in symptoms and minimizes functional impairment, alongside a side effect and adverse-event profile that did not limit treatment in adults with anti-AChR antibody-positive gMG. Following an initial loading dose, ravulizumab requires dosing once every 8 weeks, meaning only six infusions a year are needed to be given in a broad range of patients with anti-AChR antibody-positive gMG.

Table 2 summarizes ravulizumab for the gMG indication being appraised. The summary of product characteristics (SmPC) and the European Public Assessment Report (EPAR) is presented in Appendix C.

Table 2: Technology being evaluated

UK approved name and brand name	Ravulizumab (ULTOMIRIS®)
Mechanism of action	Ravulizumab is a monoclonal antibody IgG2/4K that binds to complement protein C5, preventing cleavage of C5 to C5a and C5b and subsequent generation of the terminal complement complex C5b-9
Marketing authorisation/CE mark status	UK MHRA approval was granted on 29 September 2022 following European Commissioning approval was granted on 23 September 2022

<table>
<tr><td>Indications and any restriction(s) as described in the summary of product characteristics</td><td>Ravulizumab is indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-AChR antibody-positive</td></tr>
<tr><td>Method of administration and dosage</td><td>Ravulizumab is administered by intravenous infusion. Dosage is determined by weight as detailed below.
The dosing schedule consists of an initial loading dose, followed by maintenance dosing, starting 2 weeks after the loading dose and every 8 weeks thereafter:
<table>
<tr><th>Body weight (kg)</th><th>Loading dose (mg)</th><th>Maintenance dose (mg)</th><th>Maintenance dosing interval</th></tr>
<tr><td>≥ 40 to < 60</td><td>2,400</td><td>3,000</td><td rowspan="3">Every 8 weeks</td></tr>
<tr><td>≥ 60 to < 100</td><td>2,700</td><td>3,300</td></tr>
<tr><td>≥ 100</td><td>3,000</td><td>3,600</td></tr>
</table></td></tr>
<tr><td>Additional tests or investigations</td><td>No additional tests or investigations are required; however, all patients must be vaccinated against meningococcal infections at least 2 weeks before initiating ravulizumab therapy, unless the risk of delaying ravulizumab therapy outweighs the risk of developing a meningococcal infection. If ravulizumab therapy is initiated less than 2 weeks after receiving a meningococcal vaccine, patients must receive treatment with appropriate prophylactic antibiotics until two weeks after vaccination.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>List price:
£4,533 for 3 mL vial (100 mg/mL)
£16,621 for 11 mL vial (100 mg/mL)
Cost per mg: £15.11 (for all vial sizes)
Average cost of treatment per month: £27,619</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>A simple PAS is offered to the NHS.
PAS price:
1. [redacted] for 3 mL vial (100 mg/mL)
2. [redacted] for 11 mL vial (100 mg/mL)
Cost per mg: [redacted] (for all vial sizes)
Average cost of treatment per month: [redacted]</td></tr>
<tr><td colspan="2">Key: AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; PAS, patient access scheme.</td></tr>
</table>

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

Myasthenia gravis (MG) is a rare, chronic, autoimmune disorder of neuromuscular transmission, which causes weakness in the skeletal muscles that control breathing, swallowing and movement of the body. It is associated with severe, debilitating symptoms that have a significant impact on patients' physical functioning and health-related quality of life (HRQL).[1, 2, 13, 15, 16]

MG is classified as ocular MG, where only the eye muscles are affected (eyelid droop, double vision), or gMG, when one or more (non-ocular) muscle groups in the head, neck, trunk and/or limbs are affected.[17] The Myasthenia Gravis Foundation of America (MGFA) classification is based on the predominant muscle group(s) involved as well as the severity of symptoms (Table 3).[1, 18-20] An estimated 75–90% of patients with ocular MG progress to gMG within two years of disease onset.[1, 12, 19, 21-24] As a result, gMG accounts for a large proportion of the MG population.

Table 3: MGFA clinical classification of myasthenia

Class	Description
I	Ocular muscle weakness
II	**Mild** weakness affecting other than ocular muscles; may also have ocular muscle weakness of any severity
IIa	Predominantly affecting limb, axial muscles, or both; may also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both; may also have lesser or equal involvement of limb, axial muscles, or both
III	**Moderate** weakness affecting other than ocular muscles; may also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb, axial muscles, or both; may also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both; may also have lesser or equal involvement of limb, axial muscles, or both
IV	**Severe** weakness affecting other than ocular muscles; may also have ocular muscle weakness of any severity
IVa	Predominantly affecting limb, axial muscles, or both; may also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both; may also have lesser or equal involvement of limb, axial muscles, or both

Class	Description
V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in Class IVb
Key: MGFA, Myasthenia Gravis Foundation of America. **Source**: Jaretzki et al. 2000[18].	

B.1.3.2. Epidemiology

gMG can affect anyone at any age.[21, 25] Literature estimates of the mean age of onset of gMG differ across studies, but these studies have demonstrated that women are more likely to have early-onset gMG (< 50 years of age), while men are more likely to have late-onset gMG (> 50 years of age).[21, 26-30]

Limited UK-specific epidemiological studies are available, which are mainly of poor quality. Based on an MG prevalence rate of 15 per 100,000 people and an estimated UK population size of 59,597,300 (England and Wales Census 2021), there could be an estimated 8,940 patients living with MG in the UK.{Spillane, 2012 #68;GOV.UK, 2022 #69} Based on feedback from UK clinical experts that 75% of MG patients have gMG, and 90% of these patients are anti-AChR antibody-positive,[3] there are approximately 6,034 patients with anti-AChR antibody-positive gMG in the UK. For further information on estimated patient numbers, please refer to the budget impact analyses report.

B.1.3.3. Pathophysiology

B.1.3.3.1. Neuromuscular junction signalling

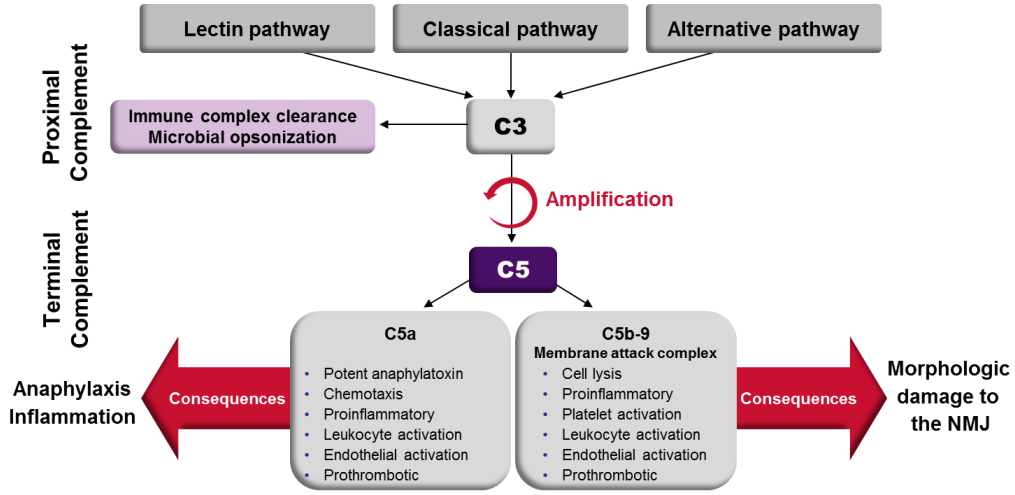
gMG interrupts the communication between nerves and muscles at the NMJ (Figure 1).[1, 2] For the nerve to signal muscle contraction, the neuronal action potential (signal) travels down the neuron to the axon, to the NMJ (the junction between the neuron and the muscle), and stimulates the release of ACh into the synaptic cleft (the space between the neuron and the muscle). Normal muscle contraction is initiated when ACh is released by the nerve terminals (pre-synaptic boutons) into the NMJ and binds to the AChR on the postsynaptic membrane.[1, 2] AChR activation allows small, positively charged sodium ions to enter the muscle cell and generate a muscle action potential that ultimately results in muscle contraction.[1, 2] In patients

with anti-AChR antibody-positive gMG, anti-AChR autoantibodies binding to the ACh binding site causes functional AChR blockade. When anti-AChR autoantibodies cross-link to AChRs, AChR endocytosis and degradation (antigenic modulation), as well as complement activation, is accelerated.[1, 33-35]

B.1.3.4. The role of complement activation

Three stimuli-dependent pathways (lectin, classical and alternative) can initiate complement activation. All complement activation pathways converge on complement component C3, cleaving C3 to complement proteins C3a and C3b.[36] Complement protein C3b cleaves the C5 molecule into the terminal complement proteins C5a (proinflammatory and prothrombic peptide) and C5b.[37] The terminal complement proteins C5b-9 form the membrane attack complex (MAC) that causes localized destruction of the postsynaptic membrane of the NMJ.[38, 39] Anti-AChR antibodies activate the classical pathway, which initiates the complement cascade.[40] Approximately 85% of patients with MG have autoantibodies directed against the nicotinic AChR on the post-synaptic membrane of the NMJ.[4-11] Antibodies reduce AChR numbers in several ways, including damaging the receptors via the complement system.[2] In patients with gMG who are anti-AChR antibody-positive, anti-AChR antibodies bind to AChR at the NMJ which can impair signal transduction and trigger activation of the complement cascade.[1, 2] A major pathogenic mechanism in patients with gMG who are anti-AChR antibody-positive is complement-dependent lysis of the postsynaptic membrane of the NMJ (Figure 2).[14, 41-44] The subsequent muscle weakness or fatigue causes a range of disabling symptoms, including decreased ability to move independently, impaired swallowing, risk of choking, disorienting vision, slurred speech, dysarthria, and episodes of pulmonary failure, necessitating hospitalization and mechanical ventilation.[12]

Figure 2: Complement activation



Key: C3, complement component 3; C5, human complement component 5; MAC, membrane attack complex; NMJ, neuromuscular junction.
Notes: Several studies have demonstrated that complement-dependent lysis of the NMJ is the primary driver of disease in patients with anti-AChR antibody-positive gMG.[44] The complement components C3 and C9, and the C5b-9 MAC, have been detected at the NMJ in patients with gMG.[14, 41-43] Complement inhibition mediated by blocking cleavage of C5 into C5a and C5b prevents both inflammatory cell chemotaxis and MAC activity in patients with MG.[1, 45, 46] Terminal complement inhibition has been demonstrated to improve clinical symptoms of gMG.[37]
Source: Rother et al. 2007[42]; Tegla et al. 2011[39]; Noris et al. 2012[47]; Owen 2013[38].

B.1.3.5. Clinical features of disease

The condition is diagnosed by reviewing symptoms (muscle fatigue and weakness), medical history, physical examination, serological tests (serum antibody assay), electrodiagnostic tests to confirm muscle fatigue, and/or anticholinesterase tests to examine a patient's response to an injection of edrophonium or an oral cholinesterase inhibitor.[1, 6, 48-50] Electrodiagnostic tests, such as single-fibre electromyography or repetitive nerve stimulation,[51] measure the electrical activity that travels between the brain and muscle, and are used to confirm a postsynaptic defect in neuromuscular transmission.[49, 50] Anticholinesterase tests (also known as Tensilon tests) examine clinical response to an injection of edrophonium, a short-acting acetylcholinesterase inhibitor.[50] A sudden, although temporary, improvement in muscle strength is an indication of MG.[52] Serological tests to detect circulating antibodies can provide laboratory confirmation of an MG diagnosis, and identify antibody-related subgroups.[48, 50, 53]

Patients with gMG experience considerable disease burden due to the symptoms of disease. Most patients (96%) have debilitating variations and fluctuations in their

symptoms, and this has a major impact on all aspects of their daily lives, encompassing work, family and social activities.[54, 55] These symptoms often persist despite treatment and include muscle weakness after physical strain (75.4%), upper limb weakness (71.3%), walking problems (69.6%), difficulty swallowing (43.9%), and difficulty chewing (39.1%), resulting in diminished HRQL.{Twork, 2010 #30}

In addition, patients with suboptimal disease management are at risk of myasthenic exacerbations and life-threatening crises. A myasthenic exacerbation is a clinical deterioration (worsening) of gMG symptoms, sometimes resulting in emergency treatment.[57] Myasthenic crisis is a severe, life-threatening, sometimes fatal, exacerbation that results in an inability to swallow or breathe and requires mechanical ventilation.[58, 59] These severe and potentially life-threatening clinical events result in increased use of healthcare resources, with patients requiring Accident and Emergency (A&E) department visits and admission to intensive care units (ICUs) (see Section B.1.3.6.4).

Due to the rarity of the condition and heterogeneity in clinical presentation, limited published evidence on the natural history of gMG is available. Feedback from UK clinicians indicates that patients with gMG will generally experience fluctuations in the severity of their symptoms. When symptoms fluctuate within a manageable range, patients are considered ‘controlled’, and when these fluctuations move outside of the manageable range, they are considered ‘uncontrolled’. The clinicians noted that exacerbations in gMG can happen even in patients who have been stable and controlled for long periods of time, particularly when linked to infections or stress. The underlying cause of an exacerbation is likely to impact the trajectory of a patient’s return to baseline or rate of stabilization following the exacerbation.[3] The clinicians also confirmed that patients who experienced a clinical event (such as an MG crisis or exacerbation) were likely to experience future clinical events, as these patients are more fragile. Some patients in clinical practice therefore experience recurrent exacerbations or crises.

B.1.3.6. Disease burden

B.1.3.6.1. Clinical burden

Living with gMG can be debilitating and symptoms can negatively impact the most basic aspects of daily life, including speaking, eating, breathing, mobility and vision (Figure 3).[60] Symptoms and severity can vary, and affect from as little as one muscle to being generalized or resulting in respiratory failure that requires ventilation.[61, 62] Patients with gMG and increased levels of fatigue were more likely to have more severe disease,[63] comorbidities including other autoimmune disease, and treatment with steroids.[64]

Several measures have been designed to evaluate outcomes in gMG by monitoring symptoms. Two common disease-specific measures are the Myasthenia Gravis Activities of Daily Living (MG-ADL) and the Quantitative Myasthenia Gravis Score (QMG). MG-ADL has eight items, each scored from 0 to 3 (higher scores indicate greater disease severity) and combines two items on daily life activities (ability to brush teeth or comb hair, and limitations in the ability to rise from a chair) with six items reflecting other gMG symptoms: diplopia, ptosis, chewing, swallowing, voice/speech problems and respiratory symptoms. [65] The QMG has 13 items, each scored from 0 to 3 (higher scores indicate greater disease severity), that measure endurance or fatigability.[65]

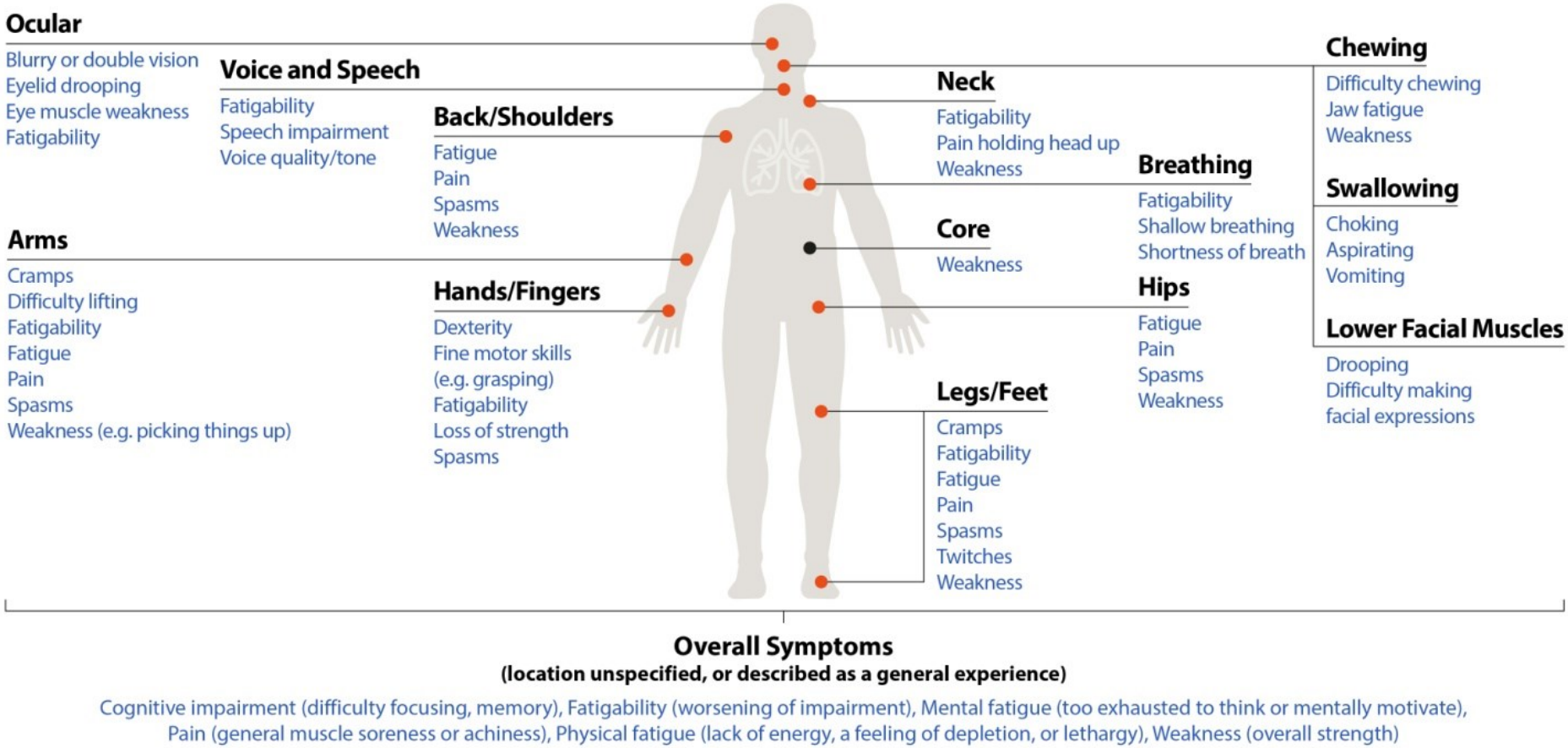
Symptoms often persist despite treatment. In a study of 150 US patients who had been living with gMG for 10 years, the majority had persistent symptoms despite receiving an average of 2.3 treatments to control gMG symptoms, including fatigue (83%), limb weakness (76%), brain fog (74%), difficulty sleeping (69%), blurred/ double vision (63%), drooping eyelids (61%), difficulty standing or walking (58%), depression (51%) and anxiety (48%).[66] Similar findings were reported in a US analysis using an Adelphi Disease Specific Programme (Adelphi DSP) that identified 456 patient records completed by 78 physicians. The records showed the mean number of symptoms was the same following treatment as at diagnosis (n = 5).[67] The most commonly reported symptoms were ocular myasthenia (53%), drooping eyelid (49%), fatigue (47%), weakness in the arms (37%) and double vision (31%), with fatigue being reported as the most troublesome symptom in 25% of patients.[67]

More than half of patients will experience at least one myasthenic exacerbation over the course of the disease. Patients with uncontrolled disease are 4.7 times more likely to have an exacerbation than patients whose disease is better controlled.[68] Myasthenic crisis occurs in 15% to 30% of patients and can lead to respiratory tract infection, aspiration pneumonia and death.[12, 59, 61, 62, 68-77]

In addition to the burden of gMG symptoms, exacerbations and crises, patients with gMG are further impacted by comorbidities including diabetes, depression, malignancy, and other autoimmune diseases.[62, 68, 78-80]. Comorbid autoimmune diseases that patients with gMG are more likely to experience include arthritis, coeliac disease, pernicious anaemia, Sjögren's syndrome, systemic lupus erythematosus and thyroiditis.[62] In 1,288 patients with gMG enrolled in seven US insurance companies and identified in the Accordant Health Services disease management database, a number of comorbidities were reported, including hyperlipidaemia (49.9%), hypertension (45.3%), diabetes (24.2%), autoimmune thyroid disease (20.2%), asthma (17.1%), coronary artery disease (13.0%), chronic obstructive pulmonary disease (7.1%) and osteoporosis (5.7%).[81] In a longitudinal cohort study of English patients with gMG, patients with refractory disease were more likely to experience renal disease (33% versus 22%), hypertension (24% versus 14%), psoriasis (6% versus 2%) and psoriatic arthritis (3% versus < 1%) compared with patients with non-refractory gMG.[82]

Studies have reported that up to 73% of patients with gMG have comorbidities, and comorbidities are associated with a worse prognosis, more frequent A&E visits and more frequent myasthenic crises than patients without comorbidities.[16, 83] In a retrospective analysis of patient-level data from the Adelphi MG DSP study, over two-thirds of patients (69%) had at least one comorbid condition, with cardiovascular (43%) or psychiatric/neurological conditions (27%) being the most common.[84] Patients who had used corticosteroids were more likely to have a comorbidity versus corticosteroid-naïve patients (74% versus 65% were diagnosed with a comorbidity, respectively).[84] These results suggest that comorbidities in gMG can be secondary to and/or exacerbated by corticosteroids, which are often used to manage gMG.

Figure 3: An overview of symptoms of gMG



Key: gMG, generalized myasthenia gravis.
Source: Jackson et al. 2021[60].

The mortality rate of patients with gMG has improved in recent years as a result of improved diagnosis, care and treatment. However, given the risk of severe clinical events, such as MG crises, and the high rate of comorbidities, gMG still incurs a considerable mortality burden.[85] Overall in-hospital mortality for patients with gMG ranges from 2.2% to 4.5%, but mortality rates as high as 15% have been reported for patients hospitalized with myasthenic crisis.[68, 85-91]

Data analysis from the US Nationwide Inpatient Sample (NIS) determined that overall in-hospital mortality for patients with gMG during the period 2000–2005 was 2.2%.[87] Mortality rates for hospitalized patients with gMG and myasthenic crises were higher and ranged from 4.5% to 18%.[85, 87] Another US-based study found a higher unadjusted mortality rate in patients who experienced a myasthenic crisis compared with patients who did not (4.44% versus 0.44%; $p < 0.001$).[91]

Comorbidities have been identified as a risk factor for mortality in patients with gMG.[91] A study of patients with gMG (N = 5,502) in the US (from the NIS database) found that the risk of death increased in patients with gMG if they were hospitalized with respiratory failure (odds ratio [OR] 10.8, 95% confidence interval [CI] 7.5, 15,7), sepsis (OR 7.3, 95% CI 2.5, 21.4), and cardiac complications (OR 7.32, 95% CI 2.4, 6.0).[87] For patients with gMG who were mechanically ventilated, in-hospital mortality rates were estimated to be 13% during the period 2001–2002.[85]

B.1.3.6.2. Humanistic burden

Patients with symptomatic gMG have severely impaired HRQL when compared with the general population. In a German study, patients with gMG (n = 4,216) had lower physical functioning and mental health and reported lower 36-item Short Form Survey (SF-36®) scores (adjusted difference: 25 and 5, respectively), compared with matched controls.[92]

Several studies have investigated predictors of poor HRQL in patients with gMG, and found that older age, lower income, female gender, depression, anxiety, fatigue, increased disease severity and comorbidities, a higher body mass index and a self-perceived lack of social support were associated with poorer HRQL.[56, 92, 93]

Fatigue is common among patients with gMG and negatively impacts activities of daily living and HRQL. In a German study of 200 patients with MG (119 of whom had gMG), over half (56%) experienced fatigue. This study also found that fatigue was significantly more common among patients with gMG compared with those in pharmacological remission (72% versus 32%; $p < 0.001$).[94] Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15) and MG-ADL scores were significantly higher, indicating more severe symptoms, among patients with fatigue ($p < 0.001$).[94]

For many patients, HRQL remains poor even with the use of available therapies. In another German study (n = 1,518), patients with gMG, particularly those with severe disease, had reduced HRQL, despite receiving treatment.[56] In an Italian study (n = 41), a higher dose of corticosteroid therapy was significantly associated with poorer HRQL.[95] A US-based study reported that, despite taking an average of 2.3 treatments for gMG, most patients (87%) experienced negative effects on their personal lives and 68% were worried that limitations caused by their disease were having a negative impact on their relationships.[66]

B.1.3.6.3. Caregiver burden

Limited evidence on caregiver burden in gMG is available in the literature. However, patients with gMG, particularly those with comorbidities or who experience exacerbations, often require additional care. In an analysis of a cross-sectional survey of patients with gMG and physicians across Europe, the UK and the US in 2020, a total of 119 out of 987 patients required a caregiver and had completed a self-reported Work Productivity and Activity Impairment (WPAI) form.[96] These patients reported that over half (55%) of their daily activities had been impaired by their condition in the past week using the WPAI form, and most of these patients (84%) relied on a non-professional caregiver. The remaining patients either received care from a professional caregiver (13%) or received care from both non-professional and professional caregivers (3%).[96]

In a community survey of Australian patients with gMG (n = 165), 15% received part-time care and a further 15% received full-time care. In an independent analysis conducted by the Australian Centre for International Economics, survey results from 190 patients living with gMG indicated that 32% of patients experienced symptoms

severe enough to necessitate assistance with daily activities (15% full-time care, 17% part-time care), with families or carers providing 21 hours of care per week.

In the Adelphi DSP study, patients without professional care often relied on the support of a partner/spouse as a caregiver (82%), and physicians reported that 42% of these informal caregivers had changed their working patterns, with 14% stopping work altogether, to be able to care for the patient.[96] Patients required the support of a caregiver to complete daily activities including walking (50%), help with shopping (45%), emotional support (41%), travelling outside of the home (36%), and help with preparing meals (32%).[96] In a US analysis, 19% of caregivers (n = 38) reported changing or reducing their working hours or stopping work altogether because they were caring for a patient with gMG.[97] Providing informal care can place considerable mental and physical strain on family members, and can restrict their time available for social or family activities as well as work. As a result, a caregiver may face negative impacts on their career, finances, health and quality of life.

B.1.3.6.4. Economic burden

Patients with gMG who experience persistent symptoms and uncontrolled disease that result in severe clinical events, such as MG exacerbations or crises, require substantial healthcare resource use, which significantly increases medical costs.[91, 98] In addition to this, gMG incurs a wider economic burden to patients and society through indirect costs. As a result of the fluctuating nature of the condition, and the potential for severely debilitating symptoms, gMG negatively affects both patient and carer employment opportunities and work productivity.[56, 99, 100]

A study of healthcare resource use in patients with gMG in England using data collected between 1997 and 2016 from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) databases found that patients with refractory and non-refractory gMG are significantly more likely to visit healthcare providers and A&E departments, in addition to being hospitalized, compared with age-matched, sex-matched and general practice-matched controls (Table 4).

Table 4: Rates of all-cause healthcare resource use during the follow-up period

Healthcare resource use, visits per person-years	Refractory gMG (n = 66)	Non-refractory gMG (n = 1,083)	Control (n = 252)
GP visit	13.6	9.5	6.4
Other healthcare professionals	11.5	6.9	4.2
GP phone calls and other admin	44.2	30.6	16.8
Outpatient hospital visits	7.1	4.8	2.1
ER visits	0.4	0.3	0.2
Inpatient visits	1.5	0.8	0.4

Key: ER, emergency room; gMG, generalized myasthenia gravis; GP, general practitioner.
Notes: Rates of all-cause healthcare professional visits during the follow-up period for the refractory gMG, non-refractory gMG and non-gMG control cohorts. For all categories show, the rate of healthcare resource use per person-year was significantly higher ($p < 0.001$) for the refractory gMG cohort compared with the non-refractory gMG and non-gMG control cohorts.
Source: Harris (2019)[101].

The median total length of stay in hospital was significantly longer in the refractory gMG cohort (33 days) versus the non-refractory and non-gMG cohorts (16 and 8 days, respectively; $p < 0.001$). However, in both gMG groups, patients experienced a substantially longer hospital stay than non-gMG controls.[101]

Patients with gMG who experience myasthenic crises or exacerbations are at increased risk of hospitalization, often requiring A&E visits, admission to ICUs, mechanical ventilation, lengthy hospital stays and additional support following discharge.[16, 68, 71, 79, 85, 88] Patients experiencing myasthenic crises or exacerbations often require treatment with intravenous immunoglobulin (IVIg) or plasma exchange; these treatments impose a substantial economic burden.[102] Relevant resource use and costs data for patients with gMG in UK settings is lacking. To identify this data, UK clinicians with experience of treating patients with gMG were surveyed (Appendix I).

gMG negatively impacts employment and work productivity.[56, 99, 100] A population-based matched-controlled study conducted in Denmark found that 41% of patients with gMG took ≥ 9 weeks of sick leave in their first year following diagnosis. In a group of matched controls, only 3% took a similar length of long-term sick leave.[99] In a survey of 1,518 patients with MG identified through the German Myasthenia Association, 69% of respondents reported being unemployed. Additionally, 21%

reported difficulties at work as a result of gMG, 9% had changed jobs, and 8% felt that their choice of career had been limited by their condition.[56]

B.1.3.7. Current management of patients with gMG

B.1.3.7.1. Treatment pathway

Currently available treatment options for gMG aim to control symptoms by suppressing the immune system, which eliminates the production of autoantibodies directed at the NMJ. Available options include acetylcholinesterase inhibitors such as pyridostigmine, corticosteroids, and/or immunosuppressive treatments (ISTs), such as azathioprine, ciclosporin, methotrexate, mycophenolate mofetil and tacrolimus. Eculizumab – another C5 inhibitor with the same mechanism of action and over 99% homology with ravulizumab – is also approved as a treatment for gMG; however, it is not reimbursed for use in the NHS in gMG and therefore is not used in UK clinical practice.

The available treatment options differ in terms of time to onset of action, effectiveness in relieving disease symptoms, ability to slow the course of the disease, durability of effect, side effect profile, and the level of evidence supporting use for the treatment of gMG. Further details are presented in Section B.1.3.7.2. Evidence supporting the use of steroids and non-steroidal ISTs as management options has primarily been derived from retrospective, observational studies and case reports.[103-105] Results from trials that have been conducted for IST and non-IST therapies, such as rituximab or IVIg, have been mixed, and reporting is limited.[48, 106, 107]

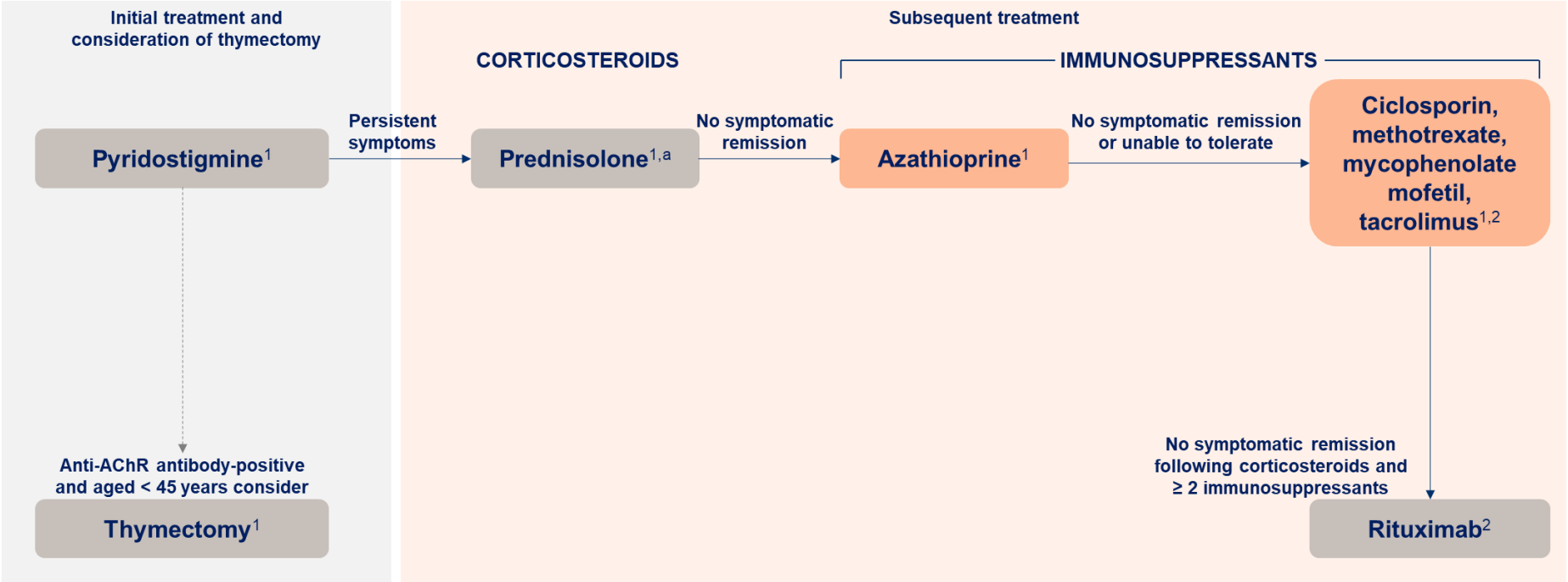
The Association of British Neurologists' (ABN) management guidelines for MG provide physicians and general neurologists with guidance to manage gMG, based on available evidence and the experience of experts where well-established treatments lack evidence (Figure 4).[108] In the UK, pyridostigmine is used as a first-line treatment, and corticosteroids (with or without ISTs) are reserved as second-line and later treatment options for patients who continue to experience symptoms on pyridostigmine.[108] The ABN management guidelines recommend IVIg and plasma

exchange for acute use in inpatient or ICU management of gMG, with IVIg being the preferred choice as it is often easier and faster to administer.[108]

UK clinicians who were consulted as part of an advisory board confirmed that they would consider prednisolone as a second-line treatment, but in severe cases it could be given in combination with azathioprine. Azathioprine would otherwise be reserved as a third-line treatment option.[3] For patients considered refractory to azathioprine, the most commonly used treatments in the UK are methotrexate or mycophenolate mofetil where immunosuppression is required.

In line with the NHS England Clinical Commissioning Policy statement published in 2018 on the use of rituximab biosimilars for the treatment of gMG,[109] rituximab is used in later lines of therapy as a last resort for patients who have received all other treatment options. As rituximab can interact with coronavirus disease (COVID-19) symptomology and the vaccine, it is generally reserved as a treatment for patients who have severe disease.[3] There is little robust trial data that supports the use of rituximab in anti-AChR antibody-positive patients; most evidence is available in anti-muscle-specific kinase (MuSK) antibody-positive populations. Studies supporting the effectiveness of rituximab in refractory gMG are mostly in the form of case reports, open-label studies and retrospective analyses involving small numbers of patients.[103-105, 110, 111] Most studies demonstrate clinical improvement in refractory gMG patients who are treated with rituximab. However, at least two studies have suggested that it is not as effective in patients who are anti-AChR antibody-positive compared with patients with anti-MuSK antibody-positive gMG. Because of this, it is used primarily for patients with anti-MuSK antibody-positive gMG, which is in line with clinical feedback obtained from treating physicians at a UK advisory board.[104, 112]

Figure 4: Recommended prophylactic treatment pathway for gMG



Key: AChR, acetylcholine receptor; gMG, generalized myasthenia gravis.
Notes: These recommendations are based on guidance from the British Neurologists' management guideline (2015)[1] and the NHS England Clinical Commissioning Policy Statement (2018)[2] on the use of rituximab biosimilars for the treatment of gMG. Treatments shaded in grey indicate those that are not relevant comparators for ravulizumab.
[a]Guidelines recommend seeking expert opinion on use of plasma exchange, intravenous immunoglobulin or immunosuppression in the event of failure to respond or side effects on corticosteroids.
Source: 1. Sussman et al. (2015);[108] 2. NHS England (2018)[109].

B.1.3.7.2. Key limitations of current standard of care

Currently available treatments for gMG are associated with various limitations, which are discussed below.

B.1.3.7.2.1. Insufficient response to conventional therapies

A retrospective, longitudinal cohort study of adult patients with treatment-refractory or non-refractory gMG conducted in England found that current treatments for gMG do not adequately manage patients' symptoms. As a result of this, out of 1,149 patients with gMG identified using data recorded between 1997 and 2016 in the CPRD and the HES databases:

- 18% of patients experienced a myasthenic crisis, with an average (mean [standard deviation, SD]) of 1.4 (4.3) events per year in affected patients
- 25% of patients experienced an MG exacerbation, with an average of 2.8 (10.3) events per year in affected patients
- 39% of patients experienced an MG-related inpatient hospitalization, with an average of 2.2 (9.1) events per year in affected patients.[82]

Current maintenance therapies do not sufficiently control gMG, and many patients therefore rely on acute and costly rescue therapies. Patients whose disease is considered difficult to treat (i.e. patients with persistent symptomology) may require repeat plasma exchange or IVIg. However, these are not long-term solutions, as they only alleviate symptoms temporarily, and there can be challenges with venous access (plasma exchange) and price and supply shortages with IVIg.[3] In a US analysis of real-world data from 456 patient record forms completed by 78 physicians, 44% of patients (n = 200/456) required acute treatment, with 36 patients receiving acute treatment at the time of survey completion.[67] Most of these patients were being treated with acute treatment as a result of exacerbation (n = 24/36) or myasthenic crisis (n = 5/36).

Given the fluctuating nature in disease severity with gMG and the potential for debilitating symptoms, including MG exacerbations and crises, a need remains for a treatment that demonstrates a deep and durable response, allowing patients to maintain their ability to perform activities of daily living.

B.1.3.7.2.2. Slow speed of onset with current standard of care

Patients treated with azathioprine can wait up to a year for the full effects of this treatment to be reached. While rituximab is not considered a relevant comparator for this submission (as discussed in Section B.1.3.7.1), it is used in patients who have exhausted all alternative treatment options. However, clinical experts advised that in practice, it may take up to 2 years of treatment to begin to observe a clinical benefit with rituximab in patients with anti-AChR antibody-positive gMG. This highlights a need for more effective treatment options with rapid onset of action for use earlier in the treatment pathway.

When treatments have such a slow onset of action, patients may feel demoralized because they do not know whether their symptoms will eventually be alleviated; this uncertainty can impact on their quality of life. This means that there is a clear unmet need for a treatment that exhibits a rapid onset of action and achieves symptom response in a short period of time to provide that certainty of response and thereby avoid patient anxiety and negative impact on HRQL.

B.1.3.7.2.3. Current treatments have various acute and long-term side effects

Side effects of currently available gMG treatments can contribute as much to patient burden as the disease itself, and these side effects have a significant impact on patients' lives.[113] Side effects associated with existing gMG treatments include diarrhoea, bronchial secretions, flu-like symptoms, weight gain, and potentially serious side effects associated with immunosuppression.[114-116]

Corticosteroids (particularly if used at high doses or over prolonged periods) are associated with cataracts, Cushingoid appearance, osteoporosis and fractures, glucose intolerance and diabetes, hypertension, infections, mood disturbances and weight gain.[16, 116, 117] One study found that significant cognitive deficits were present in patients with gMG and depression who used corticosteroids.[118] Clinical experts also advised that prolonged use of steroids, particularly among patients with steroid-induced diabetes, can be associated with a greater mortality risk (hazard ratio: 3.738; $p < 0.001$),[119] as these patients have a higher risk of heart attack, thrombosis and infection.[3]

Azathioprine, mycophenolate and methotrexate impact the immune system and may also cause problems with blood clotting.[16, 115, 116] Ciclosporin and tacrolimus can lead to renal complications as well as hypertension.[120] A clinician consulted as part of an advisory board suggested that he would not use ciclosporin or tacrolimus because of these complications.[3]

While rituximab is not considered a relevant comparator for this submission (as discussed in Section B.1.3.7.1), it is used in patients who have exhausted all alternative treatment options, and it is associated with adverse events, including infusion-related events, hypertension, dyspnoea, infections, bradycardia and cytopenia.[105, 121-123] Each round of rituximab treatment presents a risk of progressive multifocal leukoencephalopathy, which, although rare, is untreatable and often fatal.[124] This risk has created reluctance among UK clinicians in treating all but the most severe patients with rituximab.[3]

B.1.3.7.2.4. Current treatment options are inconvenient with regards to administration, dosing and frequent monitoring

In addition to side effects, patients may experience treatment burden caused by inconveniences associated with treatment regimens, administration or testing requirements. A cross-sectional cohort study from Brazil found that more complex treatment regimens (more daily pills) were associated with poor adherence to gMG treatments and resulted in increased symptoms and reduced HRQL.[125]

The ideal dosing and tapering regimens for corticosteroid treatment have still not been established because it depends on various factors, including symptoms, symptom exacerbation and side effects, which complicates treatment.[126, 127]

Treatments (e.g. azathioprine and cyclosporin) associated with haematological issues result in frequent monitoring, which can be inconvenient for patients.[16, 115, 116]

Varying disease course, and fluctuating muscular weakness and fatigability, creates a chronically impaired state for patients with gMG.[59, 76] In contrast, stable disease course has a positive impact on physical and mental health.[56] gMG treatments that can control symptoms consistently over a long period of time with a more convenient dosing schedule can therefore be beneficial to patients with gMG.

B.1.3.7.2.5. Current treatment options exacerbate comorbidities

ISTs used to treat gMG can contribute to comorbidity.[116] Some gMG treatments may cause comorbid conditions such as cardiac arrhythmias, diabetes, dyslipidaemia, obesity and osteoporosis,[16] which exacerbate gMG and increase patient burden.[25, 74, 128] Drug interactions between gMG therapies (particularly cyclosporin) and therapies used to treat comorbid conditions can undermine effective gMG management.[16, 107] The presence of comorbid conditions may limit or preclude the use of conventional gMG therapies, which may complicate the management of gMG for these patients (see Section B.1.3.6.1 for further information).

B.1.3.7.3. Proposed positioning of ravulizumab

Ravulizumab is indicated as an add-on to standard therapy for the treatment of adult patients with anti-AChR antibody-positive gMG (Figure 5). The approved label for ravulizumab is broad, with the potential to use ravulizumab early in the treatment pathway as a second-line treatment option. Research with UK clinical experts indicates that ravulizumab is likely to be used as a later-line treatment option in UK clinical practice, particularly for patients who remain symptomatic despite active treatment.

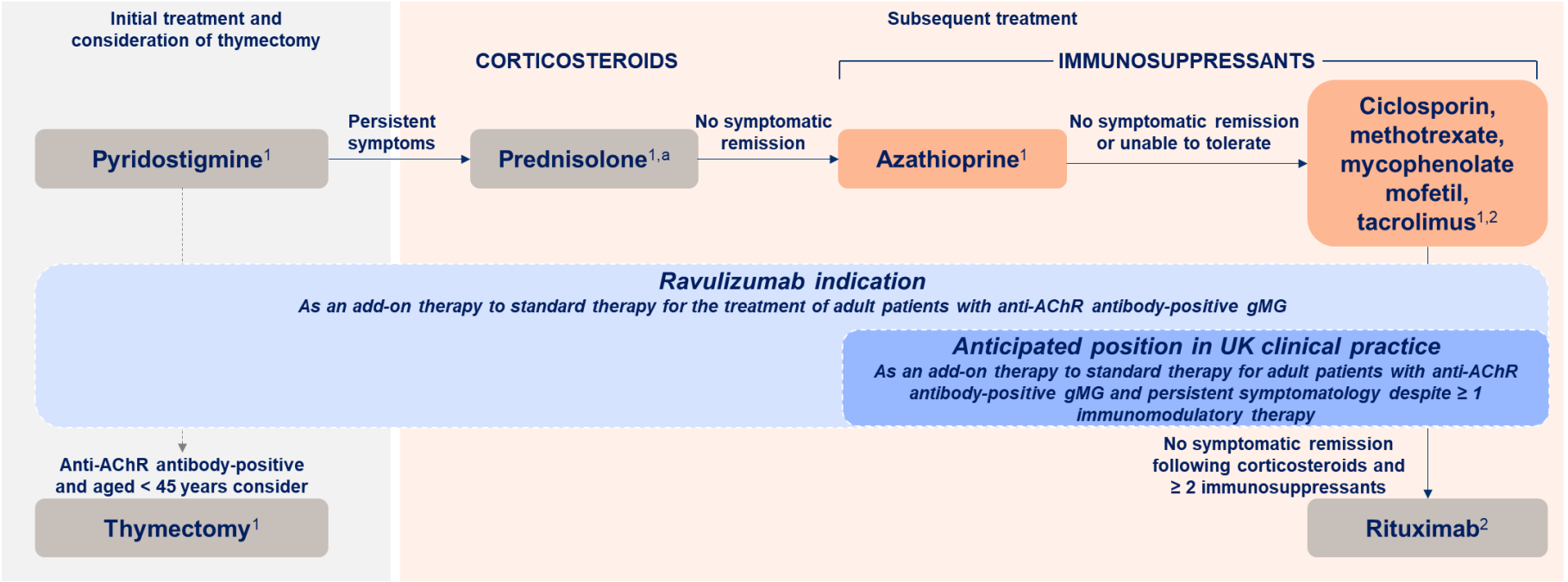
These patients with difficult-to-treat disease may be refractory to current care and require IVIg and plasma exchange. However, these treatments are reserved for acute use in inpatient or intensive care settings, rather than as maintenance treatment.[108] As a result, patients often receive ineffective treatments on a long-term basis, with some acute use of IVIg or plasma exchange as part of background care when symptoms reach more severe levels.

B.1.4. Equality considerations

No equality issues are expected. However, it is important to know that:

- Women tend to develop gMG at an earlier age, with one study reporting a mean age at onset of 53 to 55 years for women versus 59 to 64 years for men[129]
- Patients with gMG who are female, or older, or on low incomes have been identified as being at greater risk of poor HRQL (described in Section B.1.3.6.2).[56, 92, 93]

Figure 5: Proposed positioning of ravulizumab



Key: Ab, antibody; AChR, acetylcholine receptor; gMG, generalized myasthenia gravis.
Notes: These recommendations are based on guidance from the British Neurologists' management guideline (2015)[1] and the NHS England Clinical Commissioning Policy Statement (2018)[2] on the use of rituximab biosimilars for the treatment of gMG. Treatments shaded in grey indicate those that are not relevant comparators for ravulizumab.
[a]Guidelines recommend seeking expert opinion on use of plasma exchange, intravenous immunoglobulin or immunosuppression in the event of failure to respond or side effects on corticosteroids.
Source: 1. Sussman et al. (2015);[108] 2. NHS England (2018)[109].

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify publications that described the efficacy and safety of currently available therapies for patients with gMG who are anti-AChR antibody-positive. The searches were conducted on 4 February 2022. In total, the SLR identified 43 publications, corresponding to 19 studies. This SLR was conducted from a global perspective, with a broader remit than the decision problem presented in this submission. We performed an additional screening step to identify the studies that were relevant to this submission, using the criteria defined in the NICE scope. This resulted in the identification of four studies (five publications) that were relevant to this submission. Full details of the process and methods used to identify and select the clinical evidence relevant to this appraisal are provided in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

The pivotal evidence supporting ravulizumab for the treatment of adult patients with anti-AChR antibody-positive gMG comes from the CHAMPION-MG study, presented in Section B.2.6 to Section B.2.10. In addition, as ravulizumab has been derived from eculizumab, allowing the effective half-life of the molecule to be extended, while retaining the efficacy and safety profile of eculizumab, we also present evidence from the eculizumab REGAIN study and its open-label extension (OLE) period, as it provides supportive evidence of the long-term efficacy and safety of C5 inhibitor treatment in gMG (efficacy presented in Section B.2.6.2 and safety in Section B.2.10.2). Key details of these randomized controlled trials (RCTs) are presented in Table 5.

Table 5: Clinical effectiveness evidence

Study	**CHAMPION-MG (NCT03920293)**	**REGAIN (NCT01997229)**
Study design	Phase III, multicentre, double-blind RCT	Phase III, multicentre, double-blind RCT
Population	Adult patients with anti-AChR antibody-positive gMG (MGFA Class II–IV) and MG-ADL score of ≥ 6	Adult patients with anti-AChR antibody-positive gMG (MGFA

Study	CHAMPION-MG (NCT03920293)		REGAIN (NCT01997229)	
			Class II–IV) and MG-ADL score of ≥ 6	
Intervention	Ravulizumab		Eculizumab	
Comparator	Placebo		Placebo	
Indicate if study supports application for marketing authorisation	Yes	✓	Yes	
	No		No	✓
Indicate if study used in the economic model	Yes	✓	Yes	✓
	No		No	
Reported outcomes specified in the decision problem	• **Change in MG-ADL total score** • MG-QoL15r • Neuro-QoL Fatigue • **Incidence of hospitalizations / MG-related hospitalizations** • **Safety and tolerability**		• Change in MG-ADL total score • MG-QoL15r • Incidence of hospitalizations	
All other reported outcomes	• **MG-ADL ≥ 3-point improvement** • Change in QMG total score • QMG ≥ 5-point improvement • **Change in EQ-5D-5L** • **Incidence of clinical deterioration / MG crisis**		• MG-ADL ≥ 3-point improvement • Change in QMG total score • QMG ≥ 5-point improvement • Incidence of MG exacerbations • Rescue therapy use	
Published reports	Vu et al. Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. NEJM. 2022.[130]		Howard 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[131] Muppidi et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. Muscle Nerve. 2019[132]	
Regulatory materials	European Public Assessment Report[133]		-	
Clinical study reports	CHAMPION-MG clinical study report[134] 60-week data addendum[135]		-	

Key: AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MGFA-PIS, Myasthenia Gravis Foundation of America Post Intervention Status; MG-

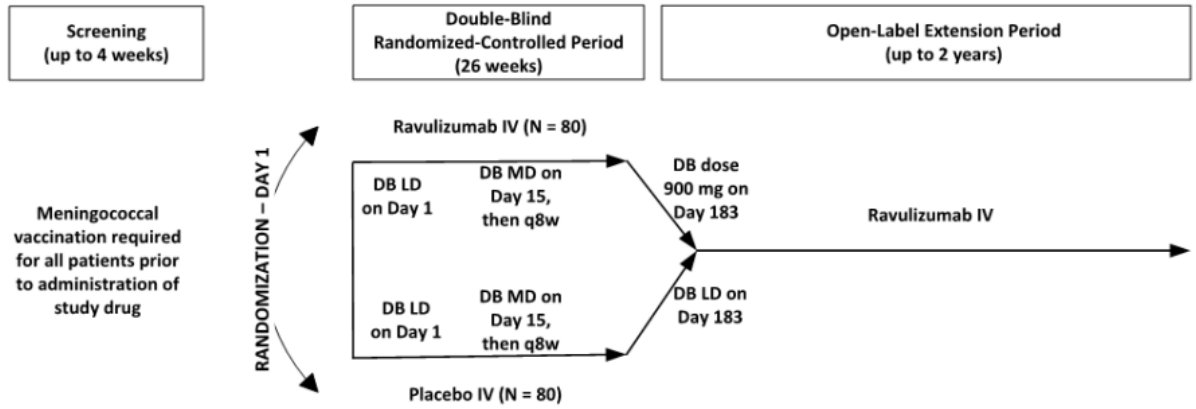
Study	CHAMPION-MG (NCT03920293)	REGAIN (NCT01997229)
QoL15r: MG-Quality of Life 15 revised; Neuro-QoL, Quality of Life in Neurological Disorders; RCT, randomized controlled trial. **Notes:** Outcomes in bold are those directly used in the economic modelling.		

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. CHAMPION-MG

CHAMPION-MG is a Phase III, randomized, double-blind, parallel-group, placebo-controlled, multi-centre study investigating the safety and efficacy of ravulizumab in adult patients with gMG who were naïve to complement inhibitor treatment (Figure 6). The trial was conducted at 85 sites across 13 countries, including 8 sites in Europe. While the trial was placebo-controlled, patients using ISTs at baseline were permitted to continue using ISTs as background therapy during the study. As a result, this trial compared ravulizumab as an add-on to standard of care (SoC) (subsequently referred to as ravulizumab) versus placebo plus SoC (subsequently referred to as placebo).

Figure 6: CHAMPION-MG study design



Key: DB, double-blind; IV, intravenous; LD, loading dose; MD, maintenance dose.
Note: see Table 6 for study drug dosing regimens.

During the randomized, placebo-controlled period of the study, patients were randomized 1:1 to 26 weeks of double-blind treatment with ravulizumab or placebo. Randomization was stratified by region (North America, Europe, Asia-Pacific and

Japan). Patients received a weight-based loading dose of ravulizumab (Table 6) or placebo on Day 1, followed by maintenance doses of ravulizumab or placebo on Day 15 and then every 8 weeks thereafter.

Table 6: Ravulizumab dosing regimen for the randomized controlled period

Body weight (kg)	Loading dose (mg) Day 1	Maintenance dose (mg) Day 15; administered q8w
≥ 40 to < 60	2,400	3,000
≥ 60 to < 100	2,700	3,300
≥ 100	3,000	3,600
Key: q8w, every 8 weeks.		

After 26 weeks, patients who completed the randomized controlled period were able to enter an OLE period of up to 2 years, which started with a blinded dose for each patient that was specifically designed to maintain the blinded treatment assignment from the randomized controlled period. Patients in the study were permitted to continue receiving standard care for gMG during the RCT, as such the placebo arm provides a standard care comparison. It is also important to note that the CHAMPION-MG trial was conducted during the COVID-19 pandemic, which may have impacted overall HRQL results, presented in Sections B.2.6.1.4 and B.2.6.1.5.

The MG-ADL 8-point questionnaire was used to assess the impact of ravulizumab on relevant symptoms and functional performance of activities of daily living in patients with gMG. The eight items forming this questionnaire were derived from the symptom-based components of the original 13-item QMG scale to assess disability secondary to ocular, bulbar, respiratory and gross motor/limb impairment relating to effects from MG. The range of the total MG-ADL score is 0–24, based on each response to the eight items being graded 0 (normal) to 3 (most severe).

The 13-item QMG scoring system was also used (range of total QMG score: 0–39; each item graded 0 [normal] to 3 [most severe]), as recommended by the MGFA task force.[136]

The patient-reported MG-ADL questionnaire uses patients' recollections from the previous week, capturing a longer period than the physician-reported QMG measure,

which is recorded at a single point in time. By capturing a longer period, the MG-ADL questionnaire may be more sensitive in detecting disease fluctuations.[137]

Two global amendments were made to the protocol, with the latest amendment (25 October 2019) revising secondary and exploratory endpoints, to decrease burden to patients by reduction in assessment and visit frequency and to provide additional guidance for supplemental dosing and provide clarification on minor operational aspects of the protocol. To better characterize disease parameters associated with gMG and to gain a clearer assessment of the impact of ravulizumab, change from baseline in MG-Quality of Life 15 (revised; MG-QoL15r), Quality of Life in Neurological Disorders (Neuro-QoL) Fatigue scores, and MG-ADL and QMG responder outcomes were moved from exploratory to secondary endpoints. Exploratory endpoints were expanded to include change from baseline in MG-ADL and QMG subcomponent scores as well as incidence of hospitalizations, MG-related hospitalizations, and clinical deterioration and MG crisis.

B.2.3.2. REGAIN

REGAIN was a Phase III, randomized, double-blind, placebo-controlled, multi-centre study investigating the safety and efficacy of eculizumab in adult patients with anti-AChR antibody-positive refractory gMG. Eligible patients were aged ≥ 18 years, with an MG-ADL score of ≥ 6, MGFA Myasthenia Class II–IV disease, vaccination against *Neisseria meningitides*, and previous treatment with two or more ISTs (or at least one IST with IVIg or plasma exchange given at least 4 times per year), for 12 months without symptom control. The trial was conducted at 76 sites in 17 countries across North America, Latin America, Europe and Asia.

Further details on the REGAIN methodology are presented in Appendix L. A brief summary of the methods used in both CHAMPION-MG and REGAIN is presented in Table 7.

Table 7: Summary of CHAMPION-MG and REGAIN methodology

Trial	CHAMPION-MG (NCT03920293)	REGAIN (NCT01997229)
Location	85 sites across 13 countries including: Canada, Czech Republic, Denmark, France, Germany, Israel, Italy, Japan, the Netherlands, South Korea, Spain, Switzerland, and the United States	76 sites across 17 countries across North America, Latin America, Europe and Asia
Trial design	Phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study The study consisted of: • Screening period: 4 weeks • Placebo-controlled period: 26-week double-blinded • Extension period: up to 2 years, and a safety follow-up visit 8 weeks after the last dose of study drug	Phase III, randomized, double-blind, placebo-controlled, multicentre study The study consisted of: • Screening period: 2–4 weeks • Placebo-controlled period: 26-week double-blinded • Extension period: up to 208 weeks including a 4-week blinded induction phase
Eligibility criteria for participants	**Key inclusion criteria** • Patients aged ≥ 18 years diagnosed with gMG at least 6 months prior to screening and confirmed positive by serologic testing for anti-AChR antibodies • MGFA Class II–IV with a MG-ADL profile ≥ 6 at screening and randomization (Day 1) • Vaccinated against meningococcal infection • Stable doses of ISTs prior to screening were permitted **Key exclusion criteria** • Active or untreated thymoma, history of thymic carcinoma or thymic malignancy or history of thymectomy within the 12 months prior to screening • MG crisis/exacerbation or clinical deterioration between screening and Day 1	**Key inclusion criteria** • Patients aged ≥ 18 years diagnosed with gMG at least 6 months prior to screening and confirmed positive by serologic testing for anti-AChR antibodies • Impaired activities of daily living defined as MGFA Class II–IV with a MG-ADL profile ≥ 6 • Had to have received treatment with ≥ 2 ISTs with IVIg or plasma exchange given ≥ 4 times per year, for 12 months without symptom control **Key exclusion criteria** • History of thymic neoplasms or thymectomy within the 12 months prior to screening • Exclusively ocular MG (MGFA Class I) • Myasthenic crisis (MGFA Class V)

Trial	CHAMPION-MG (NCT03920293)	REGAIN (NCT01997229)
		• Use of IVIg or plasma exchange within 4 weeks before randomization or rituximab within 6 months before screening
Trial drugs **Permitted and disallowed concomitant medication**	• Ravulizumab (n = 86) administered by IV infusion on Day 1 (loading dose) and subsequently on Day 15 and then q8w thereafter (maintenance doses). Weight-based dosing was used (Table 6) • Placebo (n = 89) administered by IV infusion **Concomitant medication** • Patients being treated with IST at the time of screening visit could continue receiving ISTs throughout the study; however, the dosage was not allowed to be changed and no new ISTs were allowed to be added during the randomized controlled period unless deemed medically necessary by the investigator • Rescue therapy (e.g. high-dose corticosteroid, plasma exchange/plasmapheresis, or IVIg) was allowed if a patient experienced a protocol-defined clinical deterioration[a] **Disallowed medication** • Use of rituximab, chronic plasma exchange/ plasmapheresis, chronic IVIg, and eculizumab (or other complement inhibitors) was prohibited during the study	• Eculizumab (n = 62) administered by IV infusion on Day 1 and Weeks 1–3 at 900 mg, followed by 1,200 mg at Week 4, subsequently followed by 1,200 mg every 2 weeks thereafter (maintenance doses) • Placebo (n = 63) administered by IV infusion **Concomitant medication** • Patients receiving previous treatment with a cholinesterase inhibitor, oral corticosteroid, or other IST were to maintain the dose and schedule of these medications throughout the study unless there was a compelling medical need for adjustment • Rescue medication (high-dose corticosteroids, IVIg or plasma exchange) was allowed
Primary outcomes	Change from baseline in MG-ADL total score at Week 26	Change from baseline in MG-ADL total score at Week 26
Other outcomes used in the economic model/ specified in the scope	<u>Secondary outcomes</u> • Change from baseline in QMG total score at Week 26 • Change from baseline in the MG-QoL15r score at Week 26	<u>Secondary outcomes</u> • Change from baseline in QMG total score at Week 26 • Change from baseline in the MG-QoL15 score at Week 26

Trial	CHAMPION-MG (NCT03920293)	REGAIN (NCT01997229)
	• Change from baseline in Neuro-QoL Fatigue score at Week 26 • Improvement of at least 3 points in the MG-ADL total score from baseline at Week 26 • Improvement of at least 5 points in the QMG total score from baseline at Week 26 <u>Exploratory outcomes</u> • Incidence of hospitalizations/MG-related hospitalizations • Incidence of clinical deterioration/MG crisis <u>Safety outcomes</u> • Incidence of adverse events and serious adverse events over time	• Improvement of at least 3 points in the MG-ADL total score from baseline at Week 26 • Improvement of at least 5 points in the QMG total score from baseline at Week 26 <u>Exploratory outcomes</u> • Incidence of hospitalizations • Incidence of MG exacerbations <u>Safety outcomes</u> Incidence of adverse events and serious adverse events over time

Key: AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; IST, immunosuppressive therapy; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15r, Revised Myasthenia Gravis Quality of Life 15-item scale; Neuro-QoL, Quality of Life in Neurological Disorders; QMG, Quantitative Myasthenia Gravis.
Notes: [a]A clinical deterioration was defined as any of the following: (1) patients who experience an MG crisis, which is defined as weakness from MG that is severe enough to necessitate intubation or to delay extubation following surgery. The respiratory failure is due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness often accompanies the respiratory muscle weakness, or may be the predominant feature in some patients; (2) significant symptomatic worsening to a score of 3 or a 2-point worsening from baseline on any of the individual MG-ADL items other than double vision or eyelid droop; (3) administration of rescue therapy to a patient whose, in the opinion of the investigator or investigator-designated physician, health would be in jeopardy, if rescue therapy were not given (e.g. emergent situations).

B.2.3.3. Baseline characteristics

Details of key baseline demographics, clinical characteristics and previous treatments for patients included in CHAMPION-MG and REGAIN are presented in Table 8.

Table 8: Key baseline characteristics of patients in CHAMPION-MG and REGAIN

Trial	**CHAMPION-MG (NCT03920293)**		**REGAIN (NCT01997229)**	
Baseline characteristic	**Ravulizumab (n = 86)**	**Placebo (n = 89)**	**Eculizumab (n = 62)**	**Placebo (n = 63)**
Male, N (%)	42 (49)	44 (49)	21 (34)	22 (35)
Age at infusion, years	58.0 (13.8)	53.3 (16.1)	47.5 (15.7)	46.9 (18.0)
Race, N (%)				
White	67 (78)	61 (69)	53 (85)	42 (67)
Asian	15 (17)	16 (18)	3 (5)	16 (25)
Black or African American	2 (2)	5 (6)	0	3 (5)
Not reported	2 (2)	4 (5)	-	-
Other	0 (0)	3 (3)	6 (10)	2 (3)
Body weight (kg), mean (SD)	91.6 (23.4)	90.9 (29.5)	-	-
BMI (kg/m^2)	-	-	31.4 (9.0)	30.5 (8.4)
Age at MG diagnosis (years), mean (SD)	48.6 (18.5)	43.7 (19.0)	38.0 (17.8)	38.1 (19.6)
Duration of MG (years), mean (SD)	9.8 (9.7)	10.0 (8.9)	-	-
Baseline MG-ADL score, mean (SD)	9.1 (2.6)	8.9 (2.3)	10.5 (3.1)	9.9 (2.6)
Baseline QMG score, mean (SD)	14.8 (5.2)	14.5 (5.3)	17.3 (5.1)	16.9 (5.6)
MGFA class IIa or IIIa, N (%)[a]	44 (52)	58 (65)	30 (48)	32 (51)
MGFA class IVa, N (%)	2 (2)	4 (4)	4 (6)	2 (3)
MGFA class IIb or IIIb, N (%)[a]	36 (42)	26 (29)	25 (40)	26 (41)
MGFA class IVb, N (%)	4 (5)	1 (1)	3 (5)	3 (5)

Trial	CHAMPION-MG (NCT03920293)		REGAIN (NCT01997229)	
Baseline characteristic	**Ravulizumab (n = 86)**	**Placebo (n = 89)**	**Eculizumab (n = 62)**	**Placebo (n = 63)**
Any prior intubation since diagnosis (MGFA class V), N (%)	8 (9)	9 (10)	-	-
Any prior ventilator support since diagnosis, N (%)	[redacted]	[redacted]	15 (24)	14 (22)
N of patients with prior MG crisis since diagnosis, N (%)	21 (24)	17 (19)	13 (21)	10 (16)
No IST use at baseline, N (%)	10 (12)	8 (9)	-	-
Any IST use at baseline, N (%)[b]	76 (88)	81 (91)	-	-
N of patients receiving glucocorticoids at baseline, N (%)	56 (65)	65 (73)	46 (76)	51 (81)
N of patients receiving other stable IST agents at baseline, N (%)	56 (65)	63 (70.8)	-	-
N of patients receiving ≥ 2 IST agents at baseline, N (%)	36 (42)	47 (53)	61 (98)	62 (98)

Key: IST, immunosuppressive therapy; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; QMG, Quantitative Myasthenia Gravis scale; SD, standard deviation.
Notes: [a] Due to small patient numbers, the REGAIN study presented patients MGFA Class at baseline in the groupings presented. In the CHAMPION-MG trial the following numbers of patients in the ravulizumab (RAV) and placebo (PBO) arms were: MGFA Class IIa (RAV: 22, PBO: 24); MGFA Class IIIa (RAV: 22, PBO: 34); MGFA Class IIb (RAV: 17, PBO: 15); MGFA Class IIIb (RAV: 19, PBO: 11).[130] [b] Corticosteroids, azathioprine, ciclosporin, methotrexate, mycophenolate mofetil, tacrolimus.
Sources: CHAMPION-MG clinical study report (2021);[134] Vu *et al* (2022);[130] Howard *et al* (2017)[131].

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Statistical considerations related to the CHAMPION-MG study are summarized in Table 9.

In CHAMPION-MG, the full analysis set (FAS) population used for the efficacy analysis included all randomized patients who received at least one dose of study drug grouped by randomized treatment arm for reporting efficacy data. The safety set was defined as all patients who received at least one dose of study drug grouped by treatment actually received (for reporting exposure and safety data). For a patient to be analysed according to the treatment they actually received and not according to the randomization schedule, they would have to receive that treatment for the entire duration of the randomized controlled period. All patients who received at least 1 dose of ravulizumab starting from Week 26 onward were included in the OLE set.

A patient Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the CHAMPION-MG study is presented in Figure 7.

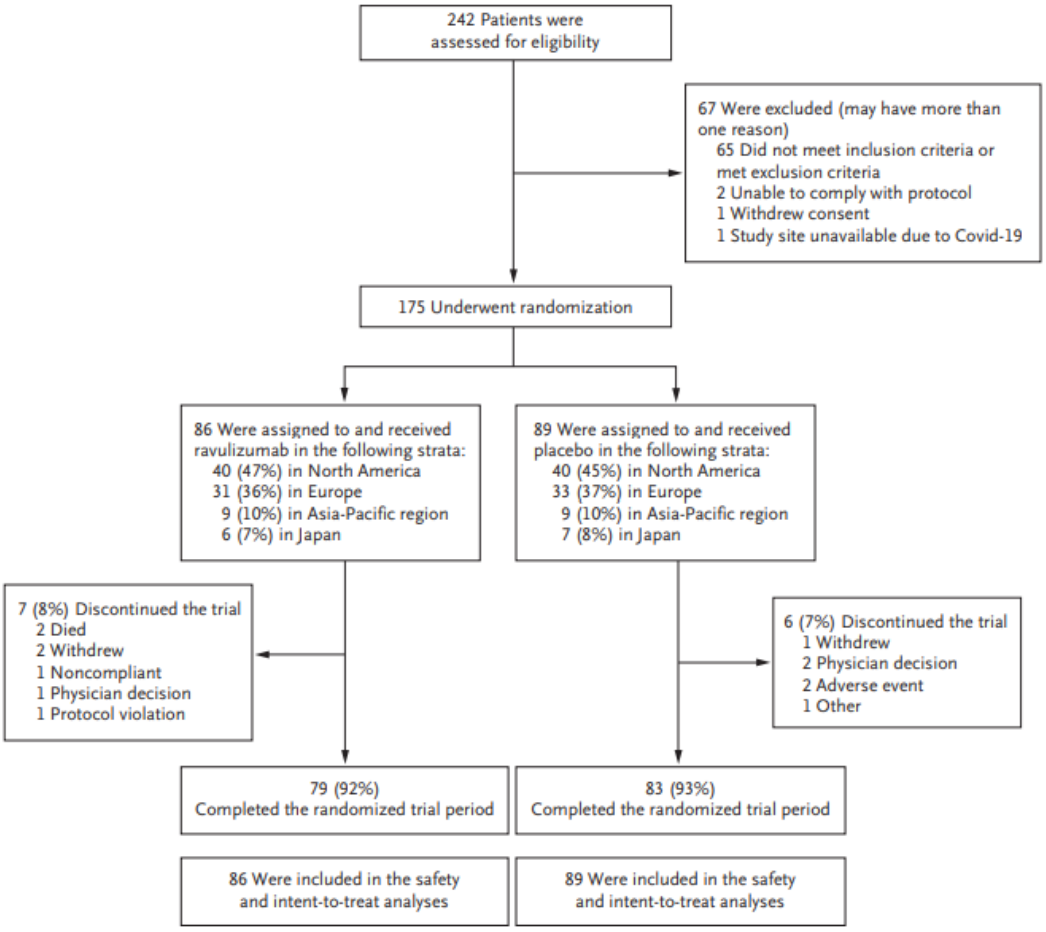
Table 9: Summary of statistical analyses in CHAMPION-MG

Trial	CHAMPION-MG (NCT03920293)
Hypothesis objective	The primary hypothesis for this study was that ravulizumab is superior to placebo in improvement of MG-ADL total score at Week 26. The treatment effect based on the primary endpoint was estimated by the difference in means between ravulizumab and placebo arms in the change from baseline in MG-ADL total score at Week 26, irrespective of rescue therapy. A lower value of the corresponding estimate indicated a beneficial treatment effect. Secondary hypotheses were included in study-wise multiplicity adjustment (provided the null hypothesis for the primary endpoint was rejected): • Ravulizumab is superior to placebo in improvement of QMG total score at Week 26 • Ravulizumab is superior to placebo in QMG 5-point response at Week 26 • Ravulizumab is superior to placebo in improvement of the MG-QoL15r total score at Week 26 • Ravulizumab is superior to placebo in improvement of Neuro-QoL Fatigue total score at Week 26 • Ravulizumab is superior to placebo in MG-ADL 3-point response at Week 26
Statistical analysis	MMRM analysis was used for the primary efficacy endpoint using al available longitudinal data regardless of whether patients received a rescue therapy. The model included MG-ADL change from baseline score at each prespecified timepoint as the response variable, fixed categorical effects of treatment, study visit and treatment-by-study visit interaction, region; as well as fixed covariate of baseline MG-ADL total score. The treatment effect was evaluated via contrast for the treatment-by-visit term at Week 26. An unstructured covariance matrix was used to model the correlations among repeated measurements within each patient. Two sensitivity analyses were performed for the primary efficacy endpoint to explore the robustness of the MMRM results for the primary efficacy analysis: • Placebo-based sensitivity analysis: considers the Missing Not at Random mechanism for the missing data, where it will be assumed that patients who discontinue early from ravulizumab will follow the trajectory of outcomes similar to the one in the placebo arm after discontinuing ravulizumab, considering observed values prior to discontinuation • Tipping point sensitivity analysis: assumes that patients who discontinue ravulizumab experience worsening defined by a prespecified adjustment in the primary efficacy endpoint All continuous secondary and exploratory endpoints related to change from baseline were analysed similarly as the primary endpoint. The QMG 5-point and MG-ADL 3-point responder endpoints were analysed using a mixed effect repeated measures model.

Trial	CHAMPION-MG (NCT03920293)
	The model included response variable at each pre-specified time point as the dependent variable, fixed categorical effects of treatment, study visit and treatment-by-study visit interaction, and region; as well as fixed covariate of baseline QMG or MG-ADL total score (depending on the response variable). The treatment effect was evaluated via contrast for the treatment-by-visit term at Week 26. An unstructured covariance matrix will was used to model the correlations among repeated measurements within each patient. Clinical deterioration/MG crisis and hospitalizations/ MG-related hospitalizations were analysed using a logistic regression model with treatment arm, region. Long-term efficacy data will be summarized descriptively based on OLE set. The study was designed to strongly control the overall 2-sided Type I error of $\alpha = 0.05$. The primary null hypothesis was tested first at $\alpha = 0.05$. If statistically significant, 5 secondary hypotheses were planned to be tested for superiority using a closed-testing procedure with the following order: • Change from baseline in QMG total score at Week 26 • Proportion of patients with improvement of at least 5 points in the QMG total score from baseline at Week 26 • Change from baseline in MG-QoL15r at Week 26 • Change from baseline in Neuro-QoL Fatigue at Week 26 • Proportion of patients with improvement of at least 3 points in the MG-ADL total score from baseline at Week 26 The testing proceeded from (#1) to (#5) and if statistical significance was not achieved ($p \leq 0.05$), then subsequent endpoints were not considered to be statistically significant. Estimates and confidence intervals were computed for all secondary endpoints regardless of the outcome of the closed testing procedure. No interim analysis was planned during the randomized controlled period. Periodic analysis and reporting will be performed during the OLE period (ongoing) based on regulatory requirement. Final analysis and reporting will be conducted at the conclusion of the study.
Sample size, power calculation	To ensure at least 90% nominal power to reject the null hypotheses of no treatment difference for the primary and secondary endpoints based on 2-sided Type 1 error (α) = 5%, 175 patients were randomly assigned to ravulizumab and placebo in a 1:1 ratio stratified by region (North America, Europe, Asia-Pacific, and Japan). Assumptions related to statistical power were based on REGAIN (details are presented in Appendix L).
Missing data	Missing data was not imputed for the primary analysis. No further data was collected from patients who withdrew or withdrew consent from the study, and such patients were not replaced. With patient consent, the investigator would attempt to perform assessments specified for the early termination

Trial	CHAMPION-MG (NCT03920293)
	visit, of if not possible, a follow-up phone call to be conducted 8 weeks after the last dose of the study drug. Attempts would also be made to follow all patients for safety for a total of 8 weeks from the last dose of study drug administration.
Key: MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL15r, Myasthenia Gravis Quality of Life questionnaire revised; MMRM, mixed model repeated measures; Neuro-QoL, Quality of Life in Neurological Disorders; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis scale.	

Figure 7: Patient CONSORT flow diagram for CHAMPION-MG



Notes: Patients were stratified by region (North America, Europe, Asia-Pacific, and Japan). The full analysis set (intent-to-treat analysis) included all randomized patients with at least one dose of trial agent grouped by randomized treatment arm. The safety set (safety analysis) included all patients with at least one dose of trial agent, grouped by treatment actually received.
Key: AE, adverse event; CONSORT, Consolidated Standards of Reporting Trials; COVID-19, coronavirus disease; FAS, full analysis set.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

CHAMPION-MG was a multicentre, double-blind Phase III RCT. A summary of the quality of this study is presented in Table 10 with a full quality assessment using the Cochrane Risk of Bias tool presented in Appendix D. Overall, the CHAMPION-MG trial had a low risk of bias across all domains.

Table 10: Quality assessment results

Trial	**CHAMPION-MG (NCT03920293)**
Was randomization carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

The CHAMPION-MG trial did not include patients treated in the UK. However, UK clinical experts confirmed that the baseline characteristics of the CHAMPION-MG trial population aligned with the patients they see in clinical practice. For example, most patients included in the study were classified as MGFA Class II or III, which captures most of the gMG population.[3] Patients were not required to have been previously treated with ISTs at baseline (approximately 10% were not receiving ISTs at baseline), which meant that patients who were earlier in their disease progression could have been recruited. Despite this, enrolled patients had been living with gMG for an average of 10 years, which suggests that many patients will have been pre-treated. This is aligned with both the decision problem that is addressed in this submission and with the patient population that ravulizumab is expected to be used for in clinical practice.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. CHAMPION-MG

The efficacy results relevant to the decision problem for this submission from the RCT FAS and the OLE set are presented below (Table 11). The results start with the primary and secondary endpoints in order of hierarchical testing, followed by exploratory outcomes relevant to the decision problem for this submission.

Table 11: CHAMPION-MG trial endpoints presented in this section

Decision problem outcomes	Endpoint	Week 26	Week 60
Improvement in MG	• Change from baseline in MG-ADL total score • Change from baseline in QMG total score • ≥ 5-point improvement in QMG • ≥ 3-point improvement in MG-ADL	B.2.6.1.1 B.2.6.1.2 B.2.6.1.3 B.2.6.1.6	B.2.6.1.1 B.2.6.1.2 NA NA
Mortality	• Summary of AEs	B.2.10.1.2	B.2.10.1.3
MG exacerbations and crisis	• Incidence of clinical events, including clinical deterioration (exacerbations), MG crises and use of rescue therapy	B.2.6.1.7.2	B.2.6.1.7.2
Number of hospitalizations	• Number of all-cause and MG-related hospitalizations	B.2.6.1.7.2	NA
Adverse effects of treatment	• Summary of AEs	B.2.10.1.2	B.2.10.1.3
Health-related quality of life	• MG-QoL15r • Neuro-QoL Fatigue • EQ-5D-5L	B.2.6.1.4 B.2.6.1.5 B.2.6.1.7.1	B.2.6.1.4 B.2.6.1.5 NA[a]

Key: AE, adverse event; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL15r, Myasthenia Gravis Quality of Life questionnaire revised; NA, not applicable; Neuro-QoL, Quality of Life in Neurological Disorders; QMG, Quantitative Myasthenia Gravis scale.
Notes: [a]EQ-5D-5L data were not analysed in the interim analysis of the open-label extension study at Week 60.

The OLE period of the CHAMPION-MG study is ongoing; data are presented below from a 60-week clinical study report addendum based on a database lock from 4 February 2022.[135] A total of 161 patients received at least one dose of ravulizumab in the OLE period and were included in the OLE set, including 79 patients who had been on placebo and 91 patients who received ravulizumab during the randomized controlled period. The results of the extension period support the deep and sustained

impact of ravulizumab on symptom control, both for patients continuing on ravulizumab treatment and those switching from placebo.

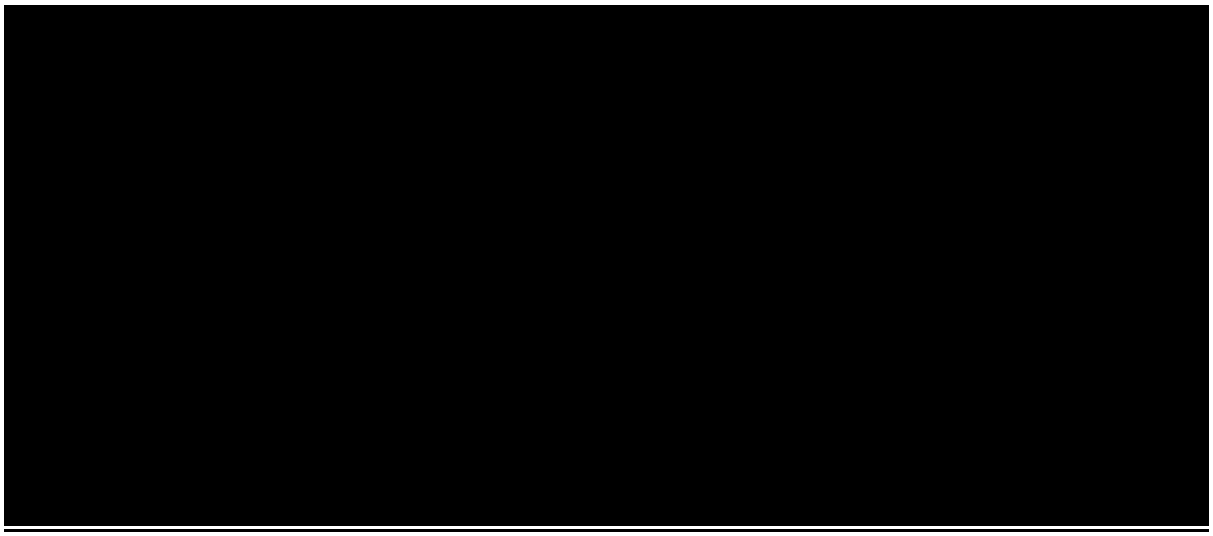
B.2.6.1.1. Change from baseline in MG-ADL total score

Treatment with ravulizumab was associated with a statistically significant and clinically meaningful improvement in MG-ADL total score (least squares mean [LSM] reduction [standard error of the mean, SEM]) at Week 26 versus placebo (-3.1 [0.38] versus -1.4 [0.37] ; $p < 0.001$; Figure 8).[130]

The treatment effect of ravulizumab was demonstrated as early as Week 1 ($p = 0.0265$) and was sustained through to Week 26.[130, 134] The mean treatment difference in change from baseline was -1.6 (SEM: 0.49; 95% CI: -2.6, -0.7; $p = 0.0009$).[130]

Improvement in the MG-ADL total score observed during the randomized controlled period was sustained in the ravulizumab/ravulizumab (RAV/RAV) arm from Week 26 to Week 60 (LSM change at Week 60: [redacted]; Figure 8).[135] In the placebo/ravulizumab (PBO/RAV) arm, a similarly rapid and sustained improvement to that seen in the RAV/RAV arm during the randomized controlled period was observed for MG-ADL total score through to Week 60 (LSM change at Week 28[redacted]; LSM change at Week 60: [redacted]; Figure 8).[135]

Figure 8: Change from randomized controlled period baseline in MG-ADL total score (LSM and 95% CI) up to Week 60



Key: CI, confidence interval; LSM, least squares mean; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MMRM, mixed model repeated measures; PBO/RAV, placebo/ravulizumab; RAV/RAV, ravulizumab/ravulizumab.
Source: CHAMPION-MG clinical study report – 60-week addendum[135].

B.2.6.1.2. Change from baseline in QMG total score

The LSM QMG change from baseline was significantly greater with ravulizumab versus placebo at Week 26 (ravulizumab LSM: -2.8 [95% CI: -3.7, -1.9] versus placebo LSM: -0.8 [95% CI: -1.7, 0.1]; P < 0.001).[130]

Improvement in the QMG total score observed during the randomized controlled period in the RAV/RAV arm was sustained from Week 26 through to Week 60 during the OLE period (LSM change at Week 60:).[135] A rapid and sustained improvement of a similar magnitude to that seen in the RAV/RAV arm was observed in the QMG total score during the OLE period up to Week 60 following transition of placebo patients to ravulizumab (LSM change at Week 28: ; LSM change at Week 60:).[135]

Figure 9: Change from randomized controlled period baseline in QMG total score (LSM and 95% CI) up to Week 60

Key: CI, confidence interval; LS, least square; MMRM, mixed model repeated measures; PBO/RAV, placebo/ravulizumab; QMG, Quantitative Myasthenia Gravis; RAV/RAV, ravulizumab/ravulizumab.
Source: CHAMPION-MG clinical study report – 60-week addendum[135].

B.2.6.1.3. Proportion of patients with ≥ 5-point improvement in QMG

During the randomized controlled period of the trial, a significantly greater proportion of patients who received ravulizumab achieved a ≥ 5-point improvement in their QMG score at Week 26 compared with patients receiving placebo. In total, 35.5% (n = 27/76) of patients in the ravulizumab arm and 12.8% (n = 10/78) of patients in the placebo arm experienced an improvement of 5 points or more in their QMG score at Week 26 (adjusted percentages: 30.0% [95% CI: 19.2, 43.5] versus 11.3% [95% CI: 5.6, 21.5], respectively; P = 0.0052; adjusted relative risk for ravulizumab/placebo: 2.7 [95% CI: 1.4, 5.3]).[130]

B.2.6.1.4. Change from baseline in MG-QoL15r total score

The LSM (SEM) reduction from baseline to Week 26 in the MG-QoL15r total score was numerically greater in the ravulizumab arm (-3.3 [0.71]) versus the placebo arm (-1.6 [0.70]). However, this difference was not statistically significant (p = 0.0636; Figure 10).[130, 134]

The improvement between treatment arms became statistically significant (p = 0.0424) when patients who had experienced a significant impact due to COVID-19 were excluded from the analysis (ravulizumab n = 6; placebo n =4).[130]

Improvement in the MG-QoL15r total score observed during the randomized controlled period in the RAV/RAV arm was sustained from Week 26 through the OLE period to Week 60 (LSM change at Week 60: [redacted]; Figure 10).[135] A rapid and sustained improvement in MG-QoL15r total score to Week 60 was observed in the PBO/RAV arm (LSM change at Week 30: [redacted]; LSM change at Week 60: [redacted]; Figure 10).[135]

Figure 10: Change from randomized controlled period baseline in MG-QoL15r score (LSM and 95% CI) up to Week 60

Key: CI, confidence interval; LS, least square; MG-QoL15r, Revised Myasthenia Gravis; MMRM, Mixed Model Repeated Measures; PBO/RAV, placebo/ravulizumab; RAV/RAV, ravulizumab/ravulizumab.
Source: CHAMPION-MG clinical study report – 60-week addendum[135].

B.2.6.1.5. Change from baseline in Neuro-QoL Fatigue score

The LSM (SEM) reduction from baseline to Week 26 in the Neuro-QoL Fatigue total score was numerically greater in the ravulizumab arm (-7.0 [1.92]) versus the placebo arm (-4.8 [1.87]). However, this difference was not statistically significant (p = 0.3734; Figure 11).[130, 134]

Improvement in the Neuro-QoL Fatigue score observed during the randomized controlled period in the RAV/RAV arm was continuously sustained from Week 26 to Week 60 during the OLE period (LSM change at Week 60: [redacted]; Figure 11).[135] A rapid and sustained improvement in Neuro-QoL Fatigue scores to Week 60 was observed in the PBO/RAV arm (LSM change at Week 30: [redacted]; LSM change at Week 60: [redacted]; Figure 11).[135]

Figure 11: Change from randomized controlled period baseline in Neuro-QoL Fatigue score (LSM and 95% CI) up to Week 60

Key: CI, confidence interval; LS, least square; Neuro-QoL, Quality of Life in Neurological Disorders; PBO/RAV, placebo/ravulizumab; RAV/RAV, ravulizumab/ravulizumab.
Source: CHAMPION-MG clinical study report – 60-week addendum[135].

B.2.6.1.6. Proportion of patients with ≥ 3-point improvement in MG-ADL

Overall, 60.3% (n = 47/78) and 36.6% (n = 30/82) of patients in the ravulizumab and placebo arms, respectively, achieved an improvement of ≥ 3 points in the MG-ADL total score from baseline at Week 26.[130] These percentages were adjusted, with estimates based on a generalized linear mixed model that included treatment arm stratification factor, region, and endpoint score at baseline, at trial visit and at trial visit multiplied by treatment arm interaction to give adjusted percentages of 56.7% (95% CI: 44.3, 68.3) for ravulizumab and 34.1% (95% CI: 23.8, 46.1) for placebo.[130]

By Week 60, 67.9% of patients in the OLE study achieved an improvement of ≥ 3 points in the MG-ADL total score from baseline (Table 25).

B.2.6.1.7. Exploratory outcomes relevant to the decision problem

B.2.6.1.7.1. EQ-5D-5L

Of patients with EQ-5D-5L data at baseline and at the end of the randomized controlled period, a statistically significant improvement in Health State Index score was observed in the ravulizumab arm versus placebo (p = 0.0486), and a numerical

improvement in health-related quality of life was reported with a mean treatment difference in the visual analogue scale (VAS) score of 1.3 (Table 12).[134]

Table 12: Change from baseline to Week 26 in EQ-5D-5L VAS and Health State Index

EQ-5D-5L outcomes	Ravulizumab (N = 86)	Placebo (N = 89)
Change from baseline to Week 26 in VAS (LSM [SEM])	[redacted]	[redacted]
Mean treatment difference (LSM [SEM]; 95% CI, p-value)	[redacted]	
Change from baseline to Week 26 in Health State Index (LSM [SEM])	[redacted]	[redacted]
Mean treatment difference (LSM [SEM]; 95% CI, p-value)	[redacted]	

Key: CI, confidence interval; LSM, least squares mean; SEM, standard error of the mean; VAS, Visual Analogue Scale.
Source: CHAMPION-MG clinical study report (2021)[134].

B.2.6.1.7.2. Incidence of clinical events, including clinical deterioration (exacerbations), MG crises and MG-related hospitalization

Overall, fewer patients in the ravulizumab arm experienced a clinical deterioration event during the randomized controlled period (ravulizumab: 9%; placebo: 17%), and fewer patients required rescue therapy for clinical deterioration (ravulizumab: 9%; placebo: 16%; Table 13).[130, 134]

Table 13: Clinical deteriorations during the randomized controlled period

	Ravulizumab (N = 86)	Placebo (N = 89)
Total number of patients reporting clinical deterioration, n (%)	8 (9)	15 (17)
MG crisis	[redacted]	[redacted]
Significant symptomatic worsening	[redacted]	[redacted]
Rescue therapy, for health in jeopardy	[redacted]	[redacted]
Total number of clinical deteriorations, n	[redacted]	[redacted]
MG crisis	[redacted]	[redacted]
Significant symptomatic worsening	[redacted]	[redacted]
Rescue therapy, for health in jeopardy	[redacted]	[redacted]
Total number of patients requiring rescue therapy, n (%)	8 (9)	14 (16)
High-dose corticosteroids		

	Ravulizumab (N = 86)	Placebo (N = 89)
Plasmapheresis/plasma exchange	[redacted]	[redacted]
IVIg	[redacted]	[redacted]
	[redacted]	[redacted]
Total number of clinical deterioration events requiring rescue therapy, n	10	24
High-dose corticosteroids	[redacted]	[redacted]
Plasmapheresis/plasma exchange	[redacted]	[redacted]
IVIg	[redacted]	[redacted]

Key: IVIg, intravenous immunoglobulin; MG, myasthenia gravis; SD, standard deviation.
Notes: One patient in the ravulizumab arm experienced a clinical deterioration under the per protocol criteria of 'Significant symptomatic worsening' which was also reported as a serious adverse event of MG crisis.
Source: CHAMPION-MG clinical study report (2021);[134] Vu *et al* (2022)[130].

The incidence of MG-related hospitalization was lower in the ravulizumab arm compared with the placebo arm, with a shorter average duration of stay (ravulizumab: n = 4; mean 5.8 days; placebo: n = 9; mean 6.8 days; Table 14).[134]

Table 14: Hospitalizations during the randomized controlled period

	Ravulizumab (N = 86)	Placebo (N = 89)
Number of patients hospitalized during the randomized controlled period, n (%)	16 (19)	19 (21)
Number of patients with MG-related hospitalizations during the randomized controlled period, n (%)	3 (3)	7 (8)
Total number of all-cause hospitalizations	23	21
MG-related hospitalizations	4	9
Duration of all-cause hospitalizations, days (mean [SD])	8.2 (6.61)	5.9 (4.94)
Duration of MG-related hospitalizations, days (mean [SD])	5.8 (6.24)	6.8 (6.22)

Key: MG, myasthenia gravis; SD, standard deviation.
Source: CHAMPION-MG clinical study report (2021)[134].

In the CHAMPION-MG OLE, a total of [redacted] patients reported clinical deteriorations that met protocol criteria (RAV/RAV: [redacted]; PBO/RAV: [redacted]) and required rescue therapy for clinical deterioration events.[135]

B.2.6.2. REGAIN

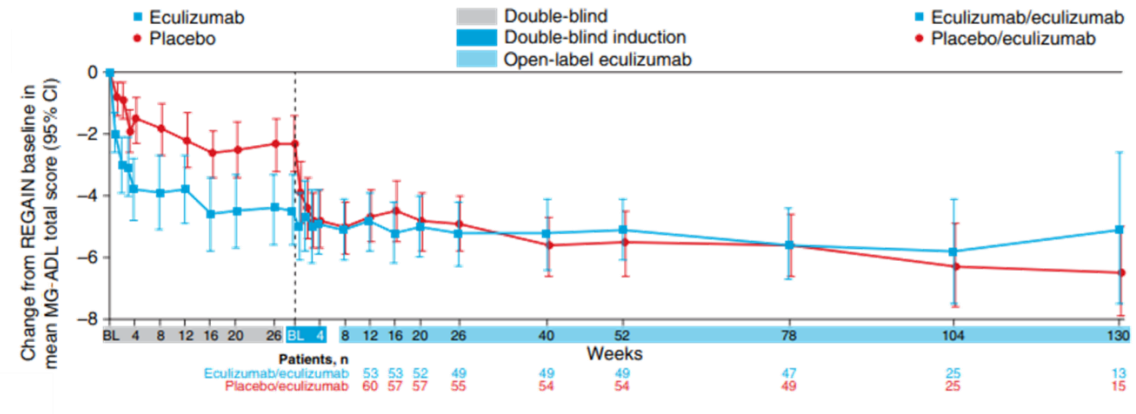
This section presents long-term data (equating to up to 3 years of eculizumab treatment duration in the eculizumab/eculizumab arm) available from the OLE of the REGAIN study,[132] which is substantially longer than data available from CHAMPION-MG (60 weeks).[135] Given the similarities between eculizumab and ravulizumab, this longer-term data can be used to inform our understanding of how ravulizumab is expected to perform with respect to long-term patient outcomes and time on treatment. To support the clinical understanding of the similarities between these drugs, an indirect treatment comparison (ITC) was performed, which showed that there were no statistically significant differences between ravulizumab and eculizumab in efficacy (MG-ADL, QMG) or HRQL (Neuro-QoL Fatigue and EQ-5D™) outcomes (presented in Section B.2.9). Results from the randomized controlled period (26-week data period) are presented in Appendix L, Section L.2.

In total, 117/118 patients who completed REGAIN enrolled in the open-label study (eculizumab/eculizumab: 56; placebo/eculizumab: 61). At a data cut-off on 31 December 2017, study participation was ongoing for 73% of patients.[132]

B.2.6.2.1. Change from baseline in MG-ADL total score

The treatment effect observed with 6 months of blinded eculizumab in REGAIN was sustained over a treatment duration of 3 years in the open-label study. The mean MG-ADL total score from open-label baseline did not change significantly in the eculizumab/eculizumab arm at each assessment (Figure 12).[132]

Figure 12: Change from REGAIN baseline up to Week 130 in the open-label extension study in MG-ADL total score

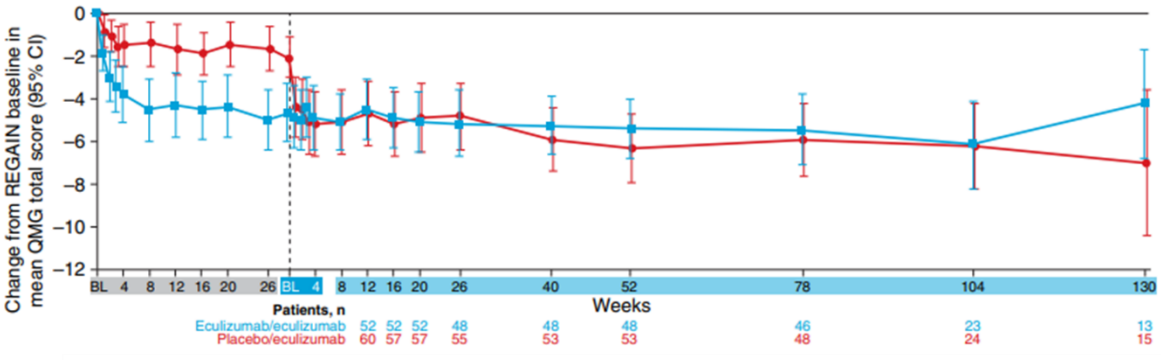


Key: BL, baseline; CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living.
Notes: Change from REGAIN baseline to Week 130 in the open-label Myasthenia Gravis extension study in MG-ADL total score (mean [95% CI]) by treatment arm over time (full analysis set).
Source: Muppidi *et al.* (2019)[132].

B.2.6.2.2. Change from baseline in QMG total score

The statistically significant treatment effect observed in the QMG total score during the randomized controlled period was sustained in the open-label study (Figure 13).[132]

Figure 13: Change from REGAIN baseline up to Week 130 in the open-label extension study in QMG total score

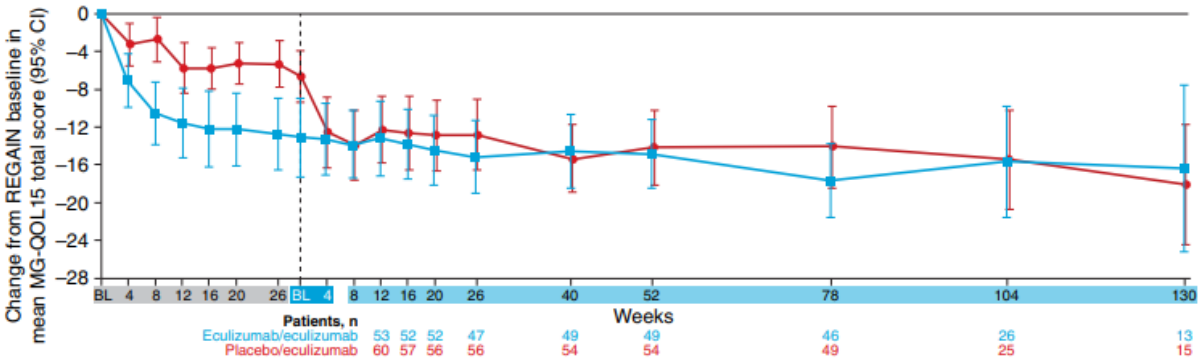


Key: BL, baseline; CI, confidence interval; QMG, Quantitative Myasthenia Gravis scale.
Notes: Change from REGAIN baseline to Week 130 in the open-label Myasthenia Gravis extension study in QMG total score (mean [95% CI]) by treatment arm over time (full analysis set).
Source: Muppidi *et al.* (2019)[132].

B.2.6.2.3. Change from baseline in MG-QoL15 total score

The statistically significant treatment effect observed in the MG-QoL15 total score during the randomized controlled period was sustained in the open-label study (Figure 14).[132]

Figure 14: Change from REGAIN baseline up to Week 130 in the open-label extension study in MG-QoL15 total score



Key: BL, baseline; CI, confidence interval; MG-QoL15, Myasthenia Gravis Quality of Life 15.
Notes: Change from REGAIN baseline to Week 130 in the open-label Myasthenia Gravis extension study in MG-QoL15 total score (mean [95% CI]) by treatment arm over time (full analysis set).
Source: Muppidi *et al.* (2019)[132].

B.2.6.2.4. Incidence of clinical events, including exacerbations, MG crises and use of rescue therapy

59 MG exacerbations (including MG crises, substantial symptomatic worsening and health in jeopardy if rescue therapy not given) were reported by 29 patients during the open-label study period.[132] Compared with the year before the trial started, the exacerbation rate was reduced by 75% (pre-trial: 102.4 exacerbations per 100 patient-years; open-label: 25.4 exacerbations per 100 patient-years; $p < 0.0001$). This exacerbation rate was also significantly lower than that observed in the REGAIN placebo arm (73.5 exacerbations per 100 patient-years; $p = 0.0061$).[132]

Similarly significant reductions were reported in the rates of rescue therapy use (open-label: 23.1 events per 100 patient-years; REGAIN placebo arm: 67.5 events per 100 patient-years; $p = 0.015$) and MG-related hospitalizations (open-label: 13.7 hospitalizations per 100 patients-years versus: pre-trial: 81.3 hospitalizations per 100

patient-years [p < 0.0001]; and REGAIN placebo arm: 48.4 hospitalizations per 100 patient-years [p = 0.0228]).[132]

B.2.7. Subgroup analysis

Subgroup analyses were conducted for the CHAMPION-MG primary and key secondary endpoints at Week 26 based on sex, race, geographic region, age, IST use at baseline, years from diagnosis to informed consent, baseline MGFA clinical classification and baseline body weight. No sensitive subgroups were identified for MG-ADL total score. The point estimates across all subgroups generally favoured ravulizumab. There were some non-significant differences; however, this is largely expected to be due to small patient numbers.

No sensitive subgroups were identified for QMG total score, QMG 5-point response, MG-QoL15r, or MG-ADL 3-point response. The point estimates for most groups favoured ravulizumab. In the subgroup analysis of the Neuro-QoL Fatigue score, point estimates for most groups favoured ravulizumab. Patients in the randomization strata of Asia-Pacific and in the baseline body weight category ≥ 40 kg to < 60 kg favoured placebo; however, the populations of these groups were small, so no inferences could be made.

While formal subgroup analyses based on MG-ADL response status (i.e. ≥ 3-point improvement in MG-ADL) were not performed, the proportions of patients with various point reductions in MG-ADL total score at Week 26 were used to assign proportions of patients to sub-states in the economic model (see Section B.3.3 for further information).

B.2.8. Meta-analysis

A meta-analysis is not required for this submission, as the only evidence available in support of ravulizumab in adult patients with gMG who are anti-AChR antibody-positive comes from the pivotal CHAMPION-MG study, which compared ravulizumab as an add-on to SoC versus placebo plus SoC.

B.2.9. Indirect and mixed treatment comparisons

The CHAMPION-MG trial was placebo-controlled, whereby the majority of patients in both treatment arms were receiving trial treatment as add-on to existing gMG therapy, in line with current UK SoC. Therefore, an ITC is not required to develop evidence of ravulizumab effectiveness versus UK SoC.

In the absence of long-term outcomes data for ravulizumab, given the same mechanism of action and over 99% homology with eculizumab, an ITC was performed to demonstrate the similarity in outcomes between the two drugs and support the use of long-term eculizumab data as a proxy for ravulizumab.

B.2.9.1. Rationale for indirect treatment comparison with eculizumab

Eculizumab and ravulizumab have the same mechanism of action and over 99% homology. Ravulizumab was re-engineered from eculizumab to create a C5 inhibitor with longer half-life, resulting in a longer-acting drug with a less frequent dosing regimen (every 8 weeks versus every 2 weeks with eculizumab).

A previous NICE appraisal of ravulizumab (technology appraisal [TA] 710 for atypical haemolytic uremic syndrome) concluded that it was biologically plausible that ravulizumab and eculizumab may be similarly effective because of their mechanisms of action. The NICE appraisal of ravulizumab in paroxysmal nocturnal haemoglobinuria (TA698) also concluded that ravulizumab and eculizumab are similarly effective with a similar adverse event profile, based on data from two non-inferiority Phase III trials comparing the safety and efficacy of ravulizumab with eculizumab. The Committee noted that the point estimates favoured ravulizumab, but that there was no statistically significant difference between the two treatments for any reported outcomes in either trial. We therefore assume that, given the biological similarities of the treatments and prior determination of equivalence in effect in alternative disease areas, the eculizumab REGAIN study could be a useful source of evidence for helping to predict long-term outcomes for patients treated with ravulizumab. To confirm that the similarities of these treatments extend to similar clinical benefit in the gMG setting, an ITC was performed.

B.2.9.2. Summary of indirect treatment comparison with eculizumab

B.2.9.2.1. Objective

This analysis aimed to assess the relative efficacy of ravulizumab compared with eculizumab for the management of patients with anti-AChR antibody-positive gMG.

The primary objective was to compare changes in MG-ADL and QMG total scores. The secondary objective was to compare changes in MG-ADL subdomains, as well as Neuro-QoL Fatigue, EQ-5D and EQ-5D VAS scores. Comparing the MG-QoL15 scores was not feasible as the trials used two different versions of the tool.

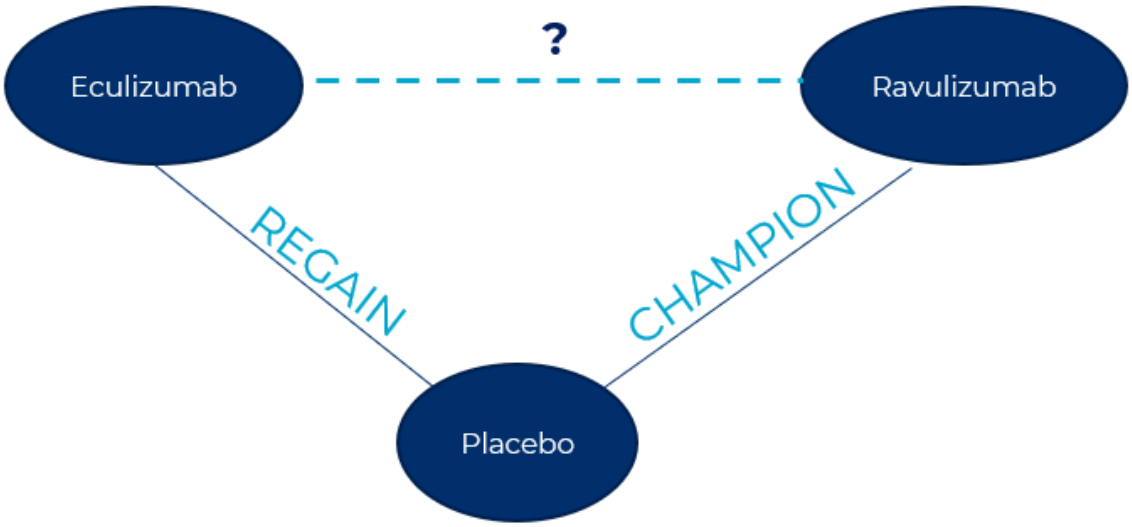
To achieve these objectives, the following analyses were conducted:

- An 'unadjusted' analysis, adjusted only through anchoring on placebo arms
- A matching-adjusted indirect comparison (MAIC)
- An analysis adjusted with inverse-propensity weighting (IPW).

B.2.9.2.2. Methods

This study was an indirect comparison of the efficacy of ravulizumab (CHAMPION-MG) relative to eculizumab (REGAIN) and relied on the placebo-controlled trials (Figure 15).

Figure 15: Network of an indirect comparison of eculizumab and ravulizumab



The indirect comparison was based on change from baseline in endpoint scores at Week 26 and over 26 weeks. In addition, the percentage of patients achieving each point improvement in MG-ADL and QMG total scores at Week 26 was compared with estimates of relative risk (RR) and ORs. An 'unadjusted' comparison (adjusted only by anchoring on placebo arms) was undertaken, as well as a MAIC and an IPW analysis.

The MAIC was conducted following the recommendations of the NICE Decision Support Unit (DSU) Technical Support Document (TSD) on population-adjusted indirect comparisons. In particular, baseline characteristics of the populations were compared before undertaking the MAIC. Imbalances across those baseline characteristics were identified, as well as the subset of those characteristics expected to be prognostic of outcome or treatment-effect modifiers. The subset of baseline characteristics available for both populations that were identified as either prognostic of survival or a treatment-effect modifier were selected for adjustment.

In the IPW analysis, propensity scores were used to balance observable characteristics between studies. Propensity scores are defined as the conditional probability of treatment assignment, given observed covariates. The IPW analysis was conducted following the recommendations of the NICE DSU TSD on observational data. In particular, a predictive equation was applied to model the relationship between trial membership and baseline characteristics. From this model, each patient's conditional probability of belonging to their trial was calculated, i.e. their propensity score. Patients were then weighted by their inverse propensity scores to balance out characteristics between trials.

Further details of the methods used to conduct these analyses are presented in Appendix D.

B.2.9.2.3. Overview of results

Bucher ITC results are summarized in Table 15. Point estimates favouring ravulizumab are denoted with a dagger symbol (†). Results with statistically significant confidence intervals are denoted with a double dagger symbol (‡). As expected, the efficacy of ravulizumab and eculizumab is similar across most

outcomes, with the exception of a few scenarios. Statistically significant results favouring eculizumab are observed for: change from baseline at Week 26 in Neuro-QoL Fatigue score in the unadjusted analysis; and change from baseline at Week 26 and area under the curve (AUC) up to Week 26 in EQ-VAS in the MAIC analysis. Given that the CHAMPION-MG trial was conducted during the COVID-19 pandemic, it is possible that these differences in HRQL results are impacted by COVID-19.

Table 15: Summary of results across all scenarios and outcomes

Outcome	**Unadjusted**	**MAIC**	**IPW**
	Ravulizumab - eculizumab Mean (95% CI)	**Ravulizumab - eculizumab Mean (95% CI)**	**Ravulizumab - eculizumab Mean (95% CI)**
MG-ADL			
Change from baseline at week 26	[redacted]	[redacted]	[redacted]
AUC (baseline to week 26)	[redacted]	[redacted]	[redacted]
≥2 point improvement, OR	[redacted]	[redacted]	[redacted]
≥3 point improvement, OR	[redacted]	[redacted]	[redacted]
QMG			
Change from baseline at week 26	[redacted]	[redacted]	[redacted]
AUC (baseline to week 26)	[redacted]	[redacted]	[redacted]
≥3 point improvement, OR	[redacted]	[redacted]	[redacted]
≥5 point improvement, OR	[redacted]	[redacted]	[redacted]
Neuro-QoL Fatigue			
Change from baseline at week 26	[redacted]	[redacted]	[redacted]
AUC (baseline to week 26)	[redacted]	[redacted]	[redacted]
EQ-5D (score range 0–1)			
Change from baseline at week 26	[redacted]	[redacted]	[redacted]
AUC (baseline to week 26)	[redacted]	[redacted]	[redacted]
EQ-VAS			
Change from baseline at week 26	[redacted]	[redacted]	[redacted]

Outcome	Unadjusted	MAIC	IPW
	Ravulizumab - eculizumab **Mean (95% CI)**	**Ravulizumab - eculizumab** **Mean (95% CI)**	**Ravulizumab - eculizumab** **Mean (95% CI)**
AUC (baseline to week 26)	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; IPW, inverse-probability weighting; MAIC, matching-adjusted indirect comparison; MG-ADL, myasthenia gravis activities of daily living; Neuro-QoL, Quality of Life in Neurological Disorders; QMG, quantitative myasthenia gravis; VAS, Visual Analogue Scale.
Notes: Estimates of change from baseline and AUC for MG-ADL, QMG, and Neuro-QoL Fatigue favour ravulizumab when negative and favour eculizumab when positive. The reverse is true for EQ-5D. Estimates of ORs favour ravulizumab when they are above 1 and favour eculizumab when they are below 1. Estimates of change from baseline and AUC are statistically significant if their CI does not cross 0, while estimates of ORs are statistically significant if their CI does not cross 1.
†Point estimate favours ravulizumab.
‡Statistically significant CI.

In the absence of head-to-head RCTs, the results from this ITC indicate similar treatment benefits between ravulizumab and eculizumab after matching CHAMPION-MG trial patients to REGAIN trial patients on demographic, clinical and treatment characteristics at baseline. Statistically significant differences were not observed for most of the patient-reported measures (MG-ADL, EQ-5D and Neuro-QoL Fatigue) or clinician-reported measures (QMG) in either the MAIC or IPW analyses. While a statistically significant difference in favour of eculizumab was observed in the mean change from baseline in Neuro-QoL Fatigue scores at Week 26 in the unadjusted analysis, this effect may reflect pre-existing differences between the CHAMPION-MG and REGAIN trial populations or impacts of the COVID-19 pandemic on CHAMPION-MG data, rather than a treatment benefit of eculizumab.

This ITC confirms that the similar clinical benefit between ravulizumab and eculizumab demonstrated in previous NICE appraisals also applies to the gMG setting. As a result, the long term efficacy data for eculizumab have been used to inform the model as a proxy for ravulizumab.

B.2.9.2.4. Strengths and limitations

The study findings are limited by the extent of data availability, the comparability of the trials and sample size considerations. A key limitation is differences in trial populations that could not be adjusted for due to lack of information. For example, data were not available to allow for adjustment by failure on prior treatment in

CHAMPION-MG. Additionally, after applying patient-level weights in the MAIC and IPW analyses, effective sample sizes were reduced, limiting the ability to detect differences.

Considering these limitations, a strength of the analysis was that it produced estimates of comparative efficacy, while maximizing the use of available data to conduct a fair and reliable comparison. In the absence of head-to-head RCTs, the results from this analysis allowed the efficacy of ravulizumab and eculizumab to be compared after adjusting for differences in patient characteristics at baseline. As individual patient data were available from both trials, MAIC and IPW-adjusted analyses could be carried out. These analyses adjusted for differences in demographic, clinical and treatment characteristics at study entry. The similarity in trial design and outcome reporting for the CHAMPION-MG and REGAIN trials facilitated a reliable indirect comparison. Anchoring comparisons of ravulizumab and eculizumab on a common comparator (placebo) using the Bucher ITC approach, ensured randomization was maintained in the trials. The follow-up period of 26 weeks for both trials enabled a more robust comparison of change from baseline scores to be carried out. Uncertainty in results was accounted for with the reporting of 95% CIs.

B.2.10. Adverse reactions

B.2.10.1. Summary of adverse reactions associated with ravulizumab

B.2.10.1.1. Summary of safety from SmPC

The most common adverse drug reactions include diarrhoea, upper respiratory tract infection, nasopharyngitis and headache. The most serious AEs in patients in clinical trials are meningococcal infection and meningococcal sepsis. The most commonly reported AEs observed in the clinical trials, and post-marketing studies for paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome (other conditions that can be treated with ravulizumab), are presented in Table 16. Meningococcal infections were reported as uncommon (≥ 1/1,000 to < 1/100) AEs.

Table 16: Summary of very common and common adverse events

Intervention	Key adverse events	
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**
Ravulizumab	• Upper respiratory tract infection • Nasopharyngitis • Headache • Diarrhoea • Nausea • Fatigue	• Dizziness • Abdominal pain • Vomiting • Dyspepsia • Rash • Pruritus • Urticaria • Arthralgia • Back pain • Myalgia • Muscle spasms • Pyrexia • Influenza-like illness • Asthenia • Infusion-related reaction
Source: Ravulizumab SmPC (2022)[133].		

B.2.10.1.2. Initial evaluation period

Similar proportions of patients experienced AEs between the ravulizumab and placebo treatment arms. The most frequent AE was headache, experienced by 19% of patients in the ravulizumab arm and 26% in the placebo arm. A tabulated summary of AEs reported in the randomized controlled period is presented in Table 17.

Serious AEs were reported for 23% of patients in the ravulizumab arm and 16% of patients in the placebo arm.[130] The most frequent serious AEs related to worsening of MG (one patient receiving ravulizumab and three receiving placebo) and COVID-19 (two patients receiving ravulizumab and one patient receiving placebo). There were no cases of meningococcal infection during the randomized controlled period. Two deaths were reported in the ravulizumab arm: one due to COVID-19, and one due to cerebral haemorrhage.[130]

Table 17: Summary of AEs reported in CHAMPION-MG at Week 26

Adverse event	Ravulizumab (n = 86)		Placebo (n = 89)	
	No. of events	No. of patients (%)	No. of events	No. of patients (%)
Any adverse event	350	78 (91)	341	77 (87)
Related to trial agent[a]	56	29 (34)	61	30 (34)
Any adverse event, by severity[b]				
Grade 1	223	65 (76)	250	66 (74)
Grade 2	85	39 (45)	70	30 (34)
Grade 3	36	19 (22)	20	14 (16)
Grade 4	4	4 (5)	1	1 (1)
Grade 5 (death)	2	2 (2)	0	0
Any SAE	35	20 (23)	16	14 (16)
MG crisis	1	1 (1)	0	0
Worsening of MG	0	0	3	3 (3)
Related to trial agent[a]	2	2 (2)	4	4 (4)
Death	2	2 (2)	0	0
Adverse event leading to discontinuation of agent		2 (2)		3 (3)
Adverse events reported in ≥ 10% of patients				
Headache	19	16 (19)	27	23 (26)
Diarrhoea	14	13 (15)	15	11 (12)
Nausea	13	9 (10)	10	9 (10)

Key: MG, myasthenia gravis; SAE, serious adverse event
Notes: [a] As determined by the investigator. [b] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
Sources: Vu *et al* (2022)[130].

B.2.10.1.3. Extension period

Table 18 presents a tabulated summary of treatment-emergent AEs based on 169 patients in the ravulizumab treated set, including patients treated with RAV/RAV and PBO/RAV during the OLE period. Most AEs were not considered to be related to ravulizumab, and were Grade 1 or 2 in severity.[135] Four patients died during the ravulizumab treatment period: one due to cerebral haemorrhage and three due to

COVID-19.[135] No meningococcal infections were reported as of the 60-week data cut-off date.[135]

Table 18: Summary of AEs reported in the open-label extension period of CHAMPION-MG at Week 60[a]

Adverse event	Patients (n = 169)	
	No. of events	No. of patients (%)
Any adverse event	[redacted]	[redacted]
Related to trial agent[b]	[redacted]	[redacted]
Any adverse event, by severity[c]		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]
Related to trial agent[b]	[redacted]	[redacted]
Death[d]	[redacted]	[redacted]
Adverse events reported in ≥ 10% of patients		
Headache	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]

Key: MG, myasthenia gravis; OLE, open-label extension; SAE, serious adverse event
Notes: [a] Includes data available for all patients up to Week 60 at data cut-off (November 9, 2021). [b] As determined by the investigator. [c] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. [d] Two deaths occurred during the RCP and two during the OLE.
Sources: CHAMPION-MG clinical study report 60-week data addendum (2022)[135].

B.2.10.2. Summary of adverse reactions associated with eculizumab

Table 18 presents a tabulated summary of treatment-emergent AEs with eculizumab during the OLE period. Three patients had died at the time of the interim analysis presented.[132] One patient was concomitantly receiving azathioprine, and their death was attributed to haemophagocytic lymphohistiocytosis associated with cytomegalovirus infection of the liver resulting in multiple organ failure. The second death was attributed to end-stage liver disease in a patient with cryptogenic liver

cirrhosis and a medical history of fatty liver. The third death was due to pulmonary embolism that occurred in a patient who was in hospital recovering from cardiogenic shock secondary to sepsis complicated by deep vein thrombosis. No meningococcal infections were reported as of the interim data cut-off date; however, one case, which was resolved with antibiotic treatment, occurred after this date.[132] A summary of the adverse reactions reported during the randomized controlled period of REGAIN is presented in Appendix L, Section L.3.

Table 19: Summary of AEs reported in the open-label extension period in patients with up to 3 years of eculizumab treatment[a]

Adverse event	Patients (n = 117)		
	No. of events	No. of patients (%)	Events per 100 PY
Any adverse event	1,816	113 (96.6)	800
Adverse events reported in > 10% of patients			
Headache	71	44 (37.6)	31.3
Nasopharyngitis	76	37 (31.6)	33.5
Diarrhoea	40	27 (23.1)	17.6
Upper respiratory tract infection	55	27 (23.1)	24.2
Worsening of MG	40	23 (19.7)	17.6
Arthralgia	29	22 (18.8)	12.8
Nausea	26	21 (17.9)	11.5
Pain in extremity	21	18 (15.4)	9.3
Cough	21	17 (14.5)	9.3
Fatigue	21	17 (14.5)	9.3
Urinary tract infection	32	17 (14.5)	14.1
Influenza	24	16 (13.7)	10.6
Gastroenteritis	15	14 (12.0)	6.6
Bronchitis	22	13 (11.1)	9.7
Pyrexia	17	13 (11.1)	7.5
Fall	24	12 (10.3)	10.6
Any SAE	147	52 (44.4)	64.8
MG- and infection-related SAEs reported in ≥ 2% of patients			

Adverse event	Patients (n = 117)		
	No. of events	No. of patients (%)	Events per 100 PY
Worsening of MG	28	15 (12.8)	12.3
Death	3	3 (2.6)	1.3
MG crisis	3	3 (2.6)	1.3
Pyrexia	3	3 (2.6)	1.3
Gastroenteritis	3	3 (2.6)	1.3
Pneumonia	3	3 (2.6)	1.3
Sepsis	3	3 (2.6)	1.3
Bronchitis	3	2 (1.7)	1.3
Influenza	2	2 (1.7)	0.9
Upper respiratory tract infection	2	2 (1.7)	0.9
Urinary tract infection	3	2 (1.7)	1.3
Aspiration pneumonia	2	2 (1.7)	0.9

Key: MG, myasthenia gravis; OLE, open-label extension; SAE, serious adverse event
Sources: Muppidi *et al* (2019)[132].

B.2.11. Ongoing studies

No additional studies are investigating ravulizumab in gMG; however, the OLE period of CHAMPION-MG is ongoing. We do not anticipate that any additional evidence relevant to the appraisal will become available during the evaluation.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings from the clinical evidence

Ravulizumab is an innovative monoclonal antibody that was developed by re-engineering eculizumab. It has demonstrated significant improvements in treating gMG, as measured by the MG-ADL and QMG scores at Week 26 in the pivotal Phase III CHAMPION-MG trial. The statistically significant improvements observed at Week 26 in CHAMPION-MG continued for patients up to Week 60, with ravulizumab being associated with longer-term stabilization of patient symptoms,

while other treatments are typically associated with only minor and transient improvements.[3, 135]

CHAMPION-MG compared ravulizumab as an add-on to SoC versus SoC through a placebo-controlled trial design to maintain blinding, in which patients were permitted to continue using SoC therapies in both arms. As a result, the placebo arm provides a reasonable comparison to SoC in the target population for this submission.

Ravulizumab has demonstrated a rapid onset of action, with improvements in MG-ADL scores seen within 1 week of adding ravulizumab to a background treatment regimen. This allows patients to quickly regain function in routine activities.[138] In addition, ravulizumab's sustained efficacy, including beneficial effects on the incidence of clinical deterioration and use of rescue therapy, is likely to reduce the burden of disease. Ravulizumab is expected to be used on an ongoing basis in those patients who continue to benefit from it. UK clinical experts confirmed that they would trial ravulizumab for 4 months (two cycles) and would continue treatment for patients who respond, based on patient and clinician observations, aided by MG-ADL and QMG scores (discussed further in Section B.3.3.3). For patients who remain on treatment and who find ravulizumab to be tolerable, the benefit of treatment is expected to continue, which is supported by the findings of the longer-term eculizumab data showing MG-ADL scores for up to 3 years.[3, 132]

HRQL (measured by changes in MG-QoL15r scores) was maintained with no statistically significant differences between ravulizumab plus SoC and placebo plus SoC reported.[138] Other studies in patients with MG have found a deterioration in HRQL, including worsening in MG-QoL15 scores, during the COVID-19 pandemic.[139, 140] This may have been a confounding factor in the CHAMPION-MG trial, which could have masked the true treatment effect of ravulizumab on HRQL. Post-hoc analyses of the CHAMPION-MG trial found that, when patients in the trial who had experienced a significant impact due to COVID-19 were excluded, there was a significantly greater improvement in HRQL for patients treated with ravulizumab compared to placebo, as measured by the MG-QoL15r score.[138]

A substantial placebo effect was observed during the initial evaluation period before patients were permitted to switch to ravulizumab. Reductions from baseline in

efficacy outcomes (MG-ADL, QMG, MG-QoL15, Neuro-QoL Fatigue) were observed in the placebo arm, despite patients remaining on a stable IST dose throughout the randomized controlled period.

UK clinical experts noted this placebo effect during the initial 26-week randomized period, particularly the decrease in MG-ADL total score. Given these patients were permitted their standard care, the reduction observed may represent part of a natural fluctuation. Given only 26 weeks of follow up were reported, it is plausible that these patients would have stabilized, meaning the placebo effect would not persist long-term.[17] In addition, as these data were presented as an average change from baseline, it is feasible that some patients in the placebo arm will have also declined over the same period, which is important to consider when interpreting the results.[17]

A well-tolerated safety profile consistent with that observed in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome was demonstrated in the CHAMPION-MG trial. No cases of meningococcal infection occurred during the randomized trial period.[138] There were two deaths in the ravulizumab arm; one due to COVID-19 and the other due to a cerebral haemorrhage. However, neither of these deaths were considered to be related to ravulizumab treatment.

B.2.12.2. Strengths and limitations of the evidence base

B.2.12.2.1. Applicability of the evidence base to the decision problem

The CHAMPION-MG trial supporting the use of ravulizumab as an add-on therapy in patients with anti-AChR antibody-positive gMG is reflective of the decision problem outlined in Section B.1.1 and the gMG population seen in UK clinical practice.[3] The CHAMPION-MG RCT was designed to compare ravulizumab as an add-on to SoC with placebo plus SoC, with SoC in line with UK clinical practice.

The trial outcomes are relevant parameters for the clinical care of patients in the real world, as both patient and clinician-reported assessments were used. UK clinical experts confirmed that they recognised the value of the MG-ADL scale – a quantitative patient-reported outcome score – alongside the QMG – a quantitative physician-reported outcome score – to assess or review patients' symptom severity..

The UK clinical experts reported that they would assess response to treatments using patient and clinician observations, likely aided by MG-ADL and QMG.[3]

Long-term data of the effectiveness of ravulizumab in gMG are not yet available. As longer-term data are available for eculizumab in gMG, to address this limitation, an ITC was performed comparing ravulizumab with eculizumab in the gMG setting to confirm similarity between the two drugs in this setting. The ITC confirmed comparative efficacy and safety between ravulizumab and eculizumab in the gMG setting. Based on this and the fact that eculizumab was evaluated in a refractory population (rather than a broader population as for ravulizumab), the long-term follow-up data from the REGAIN OLE period provide a conservative indication of the potential long-term treatment benefit expected with ravulizumab.

In the REGAIN open-label extension study, the rapid response to eculizumab was maintained for up to 3 years. This was demonstrated using several disease-specific measures, including MG-ADL and QMG total scores. These results demonstrated a sustained treatment effect, with significant reductions in the rates of MG exacerbations and MG-related hospitalizations when compared with pre-trial rates.[132] These long-term clinical benefits confirm that C5 complement inhibition has positive impacts on alleviating the burden of disease in patients with difficult-to-treat gMG, in addition to relieving the healthcare resource burden involved in managing serious clinical events such as MG exacerbations and crises. As eculizumab and ravulizumab have the same mechanism of action and over 99% homology, with ravulizumab engineered from eculizumab to provide a longer half-life, we would expect ravulizumab to have at least a similar, long-term effect.

A potential limitation of the evidence base relates to the CHAMPION-MG trial population. While this population was relevant to the decision problem (i.e. patients with anti-AChR antibody-positive gMG), not all randomized patients were reflective of the likely positioning of ravulizumab in UK clinical practice, with approximately 10% of patients not receiving ISTs at baseline. However, all patients received some gMG therapy before the trial started, which included symptomatic therapies. UK clinical experts agreed that the patients and outcomes in the CHAMPION-MG trial were reflective of those that they would expect to see in UK clinical practice. The experts

noted that the enrolled patients had lived with gMG for approximately 10 years on average, suggesting that most patients will have been heavily pre-treated.[3]

One limitation worth noting is the impact of the COVID-19 pandemic, in particular on HRQL assessments (MG-QoL15r).[138] COVID-19 may also have had wider impacts on the AEs reported in the trial (two patients receiving ravulizumab and one patient receiving placebo had COVID-19 during the trial). However, this impact is uncertain. Although mitigation measures were in place and allowed the trial to continue to collect data as planned, it is unclear what impact COVID-19 will have had on the outcomes measured. Based on previous studies and the results of the post-hoc analyses in patients who did not experience COVID-19, evidence suggests that COVID-19 may have been a confounding factor that masked the true impact of ravulizumab on treatment outcomes.

B.2.12.2.2. Generalizability of the CHAMPION-MG trial population to patients in clinical practice

The CHAMPION-MG trial enrolled patients with anti-AChR antibody-positive gMG, with a mean baseline MG-ADL score of 9 (inclusion criteria ≥ 6). This indicated that the patients enrolled in the trial were affected by gMG symptoms (total MG-ADL score range: 0 to 24; higher scores indicate more severe symptoms). All patients used MG therapy (including symptomatic therapies) before the trial started. The most common MG medications used were pyridostigmine bromide (77.7%), prednisone (51.4%), mycophenolate mofetil (32.6%), azathioprine (31.4%), and immunoglobulins not otherwise specified (28.6%). During the randomized controlled period, most (69.1%) patients were taking corticosteroids at the time of their first dose of the study drug, and 70% of these patients continued taking corticosteroids throughout the randomized controlled period. Almost half (47.4%) of patients were using only two ISTs (placebo: 52.8%; ravulizumab 41.9%); the most common (18.3%) combination was corticosteroids and mycophenolate mofetil (placebo: 22.5%; ravulizumab 14.0%). The CHAMPION-MG trial population is therefore largely aligned with the population outlined in the decision problem.

UK clinical experts reviewed the characteristics of patients enrolled in the CHAMPION-MG trial and found them to be largely aligned with those of patients in

UK clinical practice. One clinician noted that they would want to ensure treatments became available to younger patients and those with shorter disease duration (including as little as 6 months), as these are patients who theoretically should be leading more active lives and could therefore benefit the most from an efficacious treatment that would allow normal functioning.[3] Patients with gMG with recent diagnoses (6 months prior to screening) aged 18 years or older were permitted to participate in CHAMPION-MG. However, as most the gMG population is more heavily pre-treated with a MGFA Class II or III classification, the CHAMPION-MG trial was considered broadly aligned with clinical practice. A post-hoc analysis evaluating the effect of ravulizumab in patients who initiated treatment ≤ 2 years versus > 2 years after their MG diagnosis found statistically significant improvements in MG-ADL total scores from baseline to Week 26, regardless of when patients initiated ravulizumab after diagnosis:

- In the subgroup entering the study ≤ 2 years after diagnosis, the treatment difference between ravulizumab and placebo in change from baseline MG-ADL total score was -2.9 (95% CI: -4.9, -0.9; p = 0.0046)
- In the subgroup entering the study > 2 years after diagnosis, the treatment difference in change from baseline MG-ADL total score was -1.4 (95% CI: -2.4, -0.5; p = 0.0035).[141]

There was a trend towards greater improvement in MG-ADL total score in patients who initiated ravulizumab earlier (≤ 2 years versus > 2 years) following MG diagnosis.[141] These data suggest that treatment with ravulizumab earlier in the disease course may provide greater therapeutic benefits for patients.

B.2.12.3. Clinical effectiveness conclusion

When used as an add-on to existing treatment, ravulizumab offers rapid and sustained alleviation of gMG symptoms, demonstrated by statistically significant improvements in MG-ADL and QMG total scores, which resulted in trends of improvement in HRQL and fatigue scores from baseline to Week 26. These trends continued into the OLE study. Patients who continued with ravulizumab treatment maintained their substantial improvement in disease-specific outcomes, and patients who previously received SoC plus placebo were able to switch to receive

ravulizumab treatment and go on to experience similar deep and lasting improvements in outcomes. Alongside a well-tolerated safety profile with generally manageable side effects, ravulizumab offers patients with anti-AChR antibody-positive gMG an effective and fast-acting treatment option, which addresses the clear unmet need in the gMG setting.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

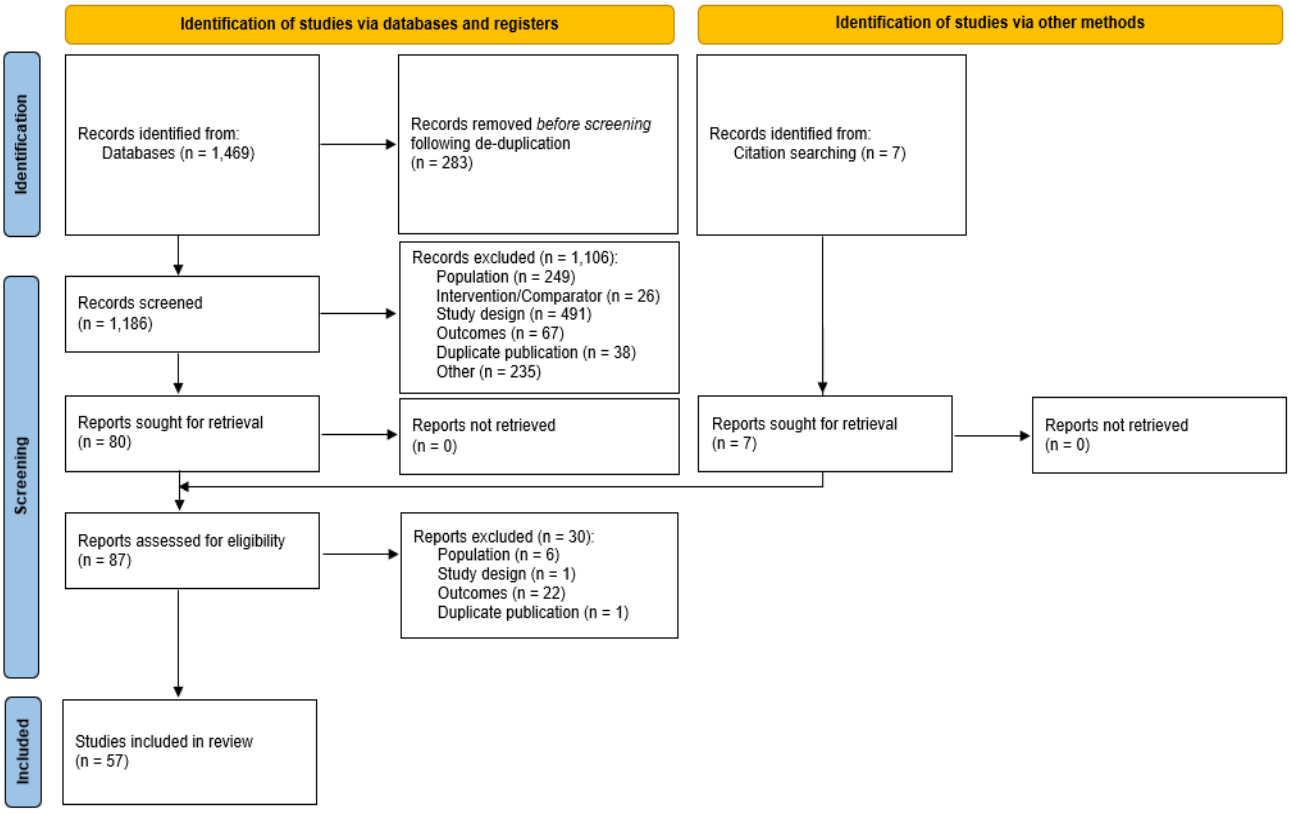
- In appendix G, describe and compare the methods and results of any published cost-effectiveness analyses available for the technology and/or the comparator technologies (relevant to the technology evaluation).
- See section 3.1 of the user guide for full details of the information required in appendix G.

An SLR of existing economic evaluations did not identify any previous cost-effectiveness studies for ravulizumab in gMG in a UK setting. The search was run on 28 March 2022. Full details of the search and findings are reported in Appendix G. The search identified 57 studies that met the inclusion criteria relating to population, intervention, comparator and study design. The details of the identified studies are presented in a PRISMA flow diagram (Figure 16). Of these, six studies related to adults with anti-AChR antibodies, including two cost-effectiveness studies (comparing eculizumab or efgartigimod with SoC) [142-82], two RCTs (comparing ravulizumab or eculizumab with placebo) [3, 131] and two cross-sectional studies (describing SoC).[143, 144]

Markov model structures were used in both of the published cost-effectiveness studies (Table 20) in adults with anti-AChR antibodies. One of the identified studies, set in the US[82], conducted two comparisons. Eculizumab plus conventional therapy versus conventional therapy alone and compared efgartigimod plus conventional therapy with conventional therapy alone. Health states in the model were defined by QMG score, with all patients entering the model in the 'unimproved MG on (initial) treatment' state. Patients whose QMG score improved by three or more points at 8 weeks transitioned to the 'improved MG on initial treatment' state, while other patients transitioned to the 'unimproved MG off-treatment' state. The second model, which compared eculizumab plus SoC with SoC alone in a Canadian setting[142], defined health states by change in MG-ADL score after 6 months of therapy. In that

model, non-response was defined as an MG-ADL score decrease of fewer than 3 points at 6 months.

Figure 16: PRISMA flow diagram for economic studies



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 20: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Tice et al.[113]	2022	Markov model 2-year time horizon Health system perspective	eculizumab plus conventional therapy vs conventional therapy alone in patients with refractory anti-AChR antibody-positive gMG as defined in the REGAIN trial. Baseline age: (47.15 years) Efgartigimod plus conventional therapy vs conventional therapy alone in patients with gMG, including those with or without anti-AChR antibodies. Baseline age: (45.9 years)	Eculizumab plus Conventional Therapy: 1.13 Conventional therapy alone: 0.98 Efgartigimod plus Conventional Therapy: 1.27 Conventional Therapy alone: 0.98	Eculizumab plus Conventional Therapy $855,400 Conventional Therapy alone: $95,500 Efgartigimod plus Conventional Therapy: $692,700 Conventional Therapy alone: $94,800	Comparison of eculizumab to conventional therapy: $5,210,000 Comparison of efgartigimod to conventional therapy: $2,076,000
CADTH 2020[142]	2020	Markov model Lifetime horizon Healthcare payer perspective	47.2 years	SoC alone: 15.03 Eculizumab plus SoC: 15.93	SoC alone: $3,690,170 Eculizumab plus SoC: $4,901,459	CDN$1,329,219

Key: MG-ADL, QALYs, quality-adjusted life years; QMG, quantitative myasthenia gravis; ICER, incremental cost-effectiveness ratio; vs, versus.

B.3.2. Economic analysis

None of the previous economic evaluations identified by the SLR compared ravulizumab with standard therapies in a UK setting. A de novo economic model was therefore developed in Microsoft Excel®. The model was developed to conduct a cost-utility analysis in line with the NICE reference case.[145]

B.3.2.1. Patient population

In September 2022, the MHRA authorized the use of ravulizumab for the treatment of adult patients with gMG who are anti-AChR antibody-positive. Ravulizumab is licensed as an add-on to SoC. As highlighted in Section B.1.3.7.3, the approved label for ravulizumab is broad, but research with UK clinical experts indicates that ravulizumab is likely to be used as a later-line treatment option in UK clinical practice, particularly for patients who remain symptomatic despite active treatment. This is broadly aligned to the population assessed in CHAMPION-MG, where the mean time from a patient's diagnosis to entering the trial was 10 years.[138]

B.3.2.2. Model structure

A cohort state-transition model was developed to assess the cost-effectiveness of ravulizumab compared with SoC. The analysis is conducted from the UK National Health Service (NHS) and Personal Social Services (PSS) perspective, in line with the NICE reference case.[146, 147]

Several factors were considered when selecting the most appropriate model structure:

- Accurately capturing the benefit of treating patients with gMG with ravulizumab, through reductions in the symptomology of the disease and improvements to patients' quality of life, in addition to reductions in the risk of experiencing clinical events such as myasthenia exacerbations or crisis
- Reflecting covariates that were shown to be predictors of clinical event prevalence and HRQL
- The availability of efficacy and treatment duration data for both C5 inhibitors (ravulizumab and eculizumab) and SoC in the treatment of gMG

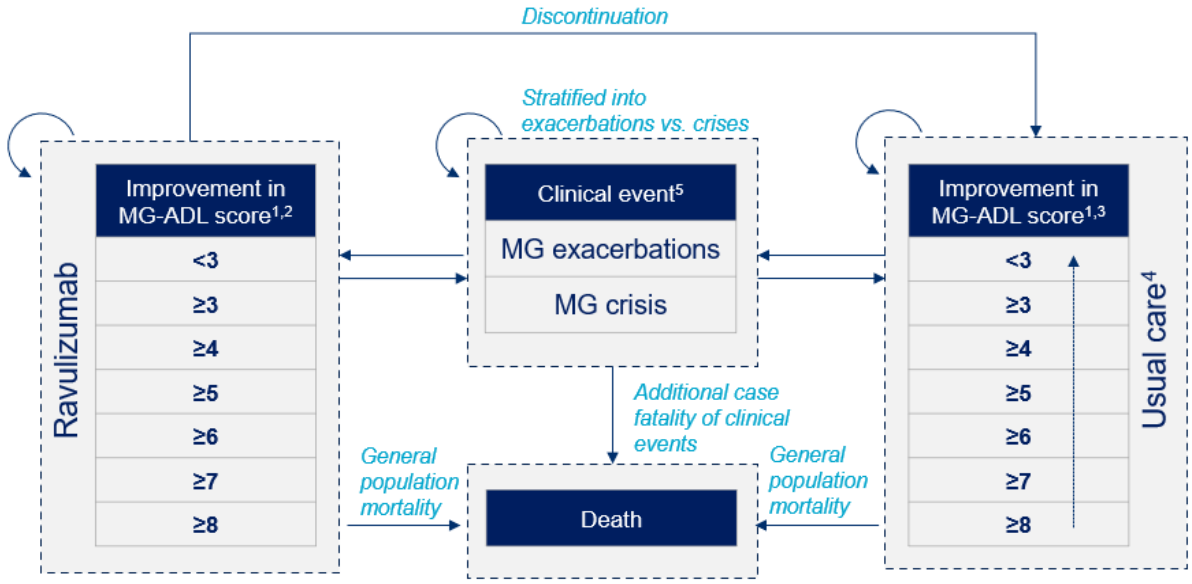
A cohort-level model was considered appropriate after considering these factors and the data available for ravulizumab and SOC. Given the available patient numbers within the relevant clinical trials, a patient level model was considered inappropriate due to the limited amount of data available to inform the parameters.

The cost-effectiveness modelling was primarily informed by two RCTs, CHAMPION-MG and REGAIN, with the methods and results of these studies described in Section B.2.

A three-state model was developed (presented in Figure 17) with two alive health states differentiated by treatment status (‘on ravulizumab’ and ‘on SoC’), and an absorbing state for death. Treatment arms were separated into distinct health states, as patients would be expected to remain on SoC once they had discontinued treatment with ravulizumab, and patients are also not expected to discontinue treatment with SoC. With no data to establish the long-term outcomes of patients who discontinue ravulizumab we assume that there is no enduring treatment effect once a patient discontinues treatment and transitions to the ‘On SoC’ state. This assumption simplifies the model structure but potentially underestimates the benefit associated with ravulizumab.

A key objective of the model was to reflect the improved gMG symptomology of patients receiving ravulizumab. Disease symptomology was measured in the primary endpoint of the CHAMPION-MG trial using MG-ADL scores. Data collected using this measure during the trial was then used to model patient experience in the cost-effectiveness model. The MG-ADL scoring system is an eight-item patient-reported outcome measure that assesses MG symptoms and functional activities related to activities of daily living. A reduction in MG-ADL score is associated with an improvement in patient outcomes. Results from CHAMPION-MG show that MG-ADL correlated well with patients’ HRQL, which is a critical component of the analysis.

Figure 17: Model structure



Key: MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; vs, versus.

The average number of clinical events that patients experienced in each cycle was estimated using a Poisson regression that was developed using CHAMPION-MG and REGAIN trial data. A Poisson regression analysis was selected as the most appropriate method to estimate the average number of clinical events because of its suitability to model count data. A Poisson distribution expresses the number of events occurring in a fixed interval of time, which was a 3-month cycle length in this instance.

Poisson regression analyses were conducted using the largest available dataset; a pooled dataset consisting of both arms of the randomized periods of CHAMPION-MG and REGAIN, along with the OLE of CHAMPION-MG, which captured an additional 34 weeks of follow-up on treatment with ravulizumab. The data was pooled because clinical events were infrequent, and conducting analyses on a single large dataset was an effective way to reduce uncertainty. Additionally, as highlighted in Section B.2.9, the ITC confirms that the similar clinical benefit between ravulizumab and eculizumab, as demonstrated in previous NICE appraisals, also applies in the gMG setting, so it is considered appropriate to pool this data.

As the reduction in MG-ADL scores was not normally distributed across patients in any arm of CHAMPION-MG or REGAIN, it was considered inappropriate to model

the MG-ADL score of patients using a single mean reduction. Each alive state is therefore divided into sub-states that reflect the differing levels of benefit experienced by patients on each treatment arm. Upon entering the model, patients are assigned to a sub-state within the treatment health states. The sub-states capture the reduction in a patient's disease severity following treatment. The first sub-state captures patients with a change from baseline MG-ADL of < 3 points. Each subsequent health state covers a change in the range of one unit. For example, the sub-state captures a reduction in MG-ADL score of ≥ 3 and < 4 points. The final sub-state captures patients with a reduction in MG-ADL score of ≥ 8 points. Patients do not move between sub-states following their initial MG-ADL score change, except for patients who discontinue treatment with ravulizumab. The average number of clinical events and HRQL is then estimated for each of these sub-states, rather than the entire treatment group, as this best reflects the variability in response to treatment. A summary of the key features of the economic analysis is presented in Table 21.

Table 21: Features of the economic analysis

	Current evaluation	
Feature	**Chosen values**	**Justification**
Time horizon	48 years (lifetime)	A lifetime time horizon was used to capture all of the health and cost outcomes associated with gMG, which is a chronic disease. A 48-year time horizon was assumed to represent the lifetime of patients based on the average age (52.2 years) of patients within CHAMPION-MG and REGAIN.
Discounting	3.5% for costs and QALYs	In line with the NICE reference case.[145]
Type of economic analysis	Cost-utility analysis	There is expected to be a difference in both cost and health outcomes when treating gMG patients with ravulizumab as an add-on to standard of care compared to standard of care alone
Severity modifier	1.0	gMG is not eligible for any severity modifiers based on the proportional and absolute QALY shortfall measures
Sources of efficacy	Change in MG-ADL score is the key measure of treatment effect and a main predictor of HRQL. Change in MG-ADL is informed by the primary endpoint of CHAMPION-MG and REGAIN, change in MG-ADL from baseline at 26 weeks	MG-ADL is a recognized measure of severity of MG symptoms and the key measure of treatment effectiveness in the RCT investigating ravulizumab in gMG
	A Poisson regression estimating the average number of clinical events experienced in each cycle. The regression model is informed by data from the CHAMPION-MG and REGAIN trials.	Poisson regression is the most appropriate modelling count data and provides a good fit to the observed data. The efficacy analysis is informed by two Phase III, randomized, double-blinded, placebo-controlled trials. One exploring ravulizumab and the other eculizumab, which is seen as an appropriate proxy for ravulizumab to supplement the analyses.
Source of utilities	EQ-5D-5L data from CHAMPION-MG and REGAIN mapped to EQ-5D-3L equivalent values, using the Hernández Alava et al. methodology.	In line with the best practice specified in the NICE reference case.[145]
Source of costs	Standard UK databases (e.g., BNF, eMIT, NHS schedule of reference costs, PSSRU)	Best available sources relevant to the NHS setting specified in the NICE reference case.[145]

	Current evaluation	
Feature	**Chosen values**	**Justification**
Key: BNF, British National Formulary; eMIT; drugs and pharmaceutical electronic market information tool; EQ-5D, EuroQol 5-level; gMG, generalized myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NHS, National Health Service; NICE, National Institute of Care and Health Excellence; QALY, quality-adjusted life year; RCT, randomized controlled trial.		

B.3.2.3. Intervention technology and comparators

B.3.2.3.1. Ravulizumab treatment arm

The ravulizumab dosing schedule in the model is based on the licence, which is summarized in Table 22. Depending on a patient's weight, a loading dose is given via intravenous infusion, followed by the first maintenance dose 2 weeks after the loading dose and subsequent maintenance doses every 8 weeks. The dosing schedule for ravulizumab is consistent with the dosing schedule used in the CHAMPION-MG clinical trial.

Table 22: Ravulizumab dosing bands

Body weight	Loading dose (day 1)	Maintenance dose (Day 15 and q8w thereafter)
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg
Key: q8w, every 8 weeks.		

B.3.2.3.2. SoC arm

The comparator arm of the model is SoC, which is modelled as a basket of relevant steroids and non-steroidal ISTs to be aligned with the expected clinical pathway in England. The foundation of the basket of treatments was based on the distribution of therapies administered in both arms of CHAMPION-MG. These distributions were then amended following consultation with UK clinicians, who believed that tacrolimus and cyclosporin were not part of UK SoC and that the use of methotrexate was more prominent.[3] To address this, the percentages assigned to tacrolimus and cyclosporin were moved to methotrexate. The distribution of treatments from CHAMPION-MG and the distributions expected in UK clinical practice are both reported in Table 23.

Patients could receive multiple therapies as part of SoC, so the percentages presented do not sum to 100%.

Table 23: SoC therapy distribution

Therapy	CHAMPION-MG* (n = 175)	UK clinical practice
Pyridostigmine	92.0%	92.0%
Azathioprine	31.4%	31.4%
Mycophenolate mofetil	32.6%	32.6%
Cyclosporin	6.9%	0.0%
Tacrolimus	12.6%	0.0%
Methotrexate	1.7%	21.2%
Cyclophosphamide	1.1%	1.1%
Prednisone	51.4%	51.4%
Prednisolone	32.0%	32.0%
Note: *, clinical study report Tables 14.1.5.2-3		

B.3.3. Clinical parameters and variables

The CHAMPION-MG trial was the key trial used to inform clinical model parameters. As discussed previously in Sections B.2.2 and B.2.9.1, data from REGAIN, which investigated the efficacy and safety of eculizumab in the treatment of gMG, were used to supplement the results from CHAMPION-MG, with ravulizumab and eculizumab assumed to be equivalently efficacious and tolerable. Data from the 26-week double-blind phases of CHAMPION-MG and REGAIN provide evidence that demonstrates the efficacy of ravulizumab (or the equivalent, eculizumab) and SoC in the management of gMG. An OLE of CHAMPION-MG provides an additional 34 weeks of evidence for patients receiving ravulizumab, including those who switched from SoC.

B.3.3.1. Allocation to MG-ADL sub-states

As referenced in Section B.3.2, the reduction in MG-ADL score associated with treatment was not normally distributed. Sub-states were therefore used to follow the outcomes of patients experiencing increasing levels of treatment benefit. The allocation of patients to the sub-states in each treatment arm was informed by the results of the CHAMPION-MG trial. Specifically, the distribution of patients across substates reflected the change in total MG-ADL score at 18 weeks for ravulizumab

patients and 26 weeks for SoC patients, considering the change as a categorical variable. The proportion of patients assigned to each sub-state is reported in Table 24. Different time-points are used for each arm due to the difference in the speed of onset between the two treatments. This is described in more detail in Section B.3.3.3.

Table 24: Distribution of patient by magnitude of treatment effect in CHAMPION-MG at 18-weeks for ravulizumab and 26 weeks for SOC

Change in total MG-ADL score	Ravulizumab (n = 86)	SoC (n = 89)
Change < 3	41.90%	65.20%
3 ≤ Change < 4	58.10%	34.80%
4 ≤ Change < 5	45.30%	25.80%
5 ≤ Change < 6	34.90%	16.90%
6 ≤ Change < 7	24.40%	7.90%
7 ≤ Change < 8	14.00%	3.40%
Change ≥ 8	9.30%	1.10%
Key: MG-ADL, Myasthenia Gravis Activities of Daily Living scale.		

A patient's MG-ADL score would be expected to fluctuate a small amount in clinical practice. However, in the absence of longer-term data, a simplifying assumption that patients do not move between change in MG-ADL score sub-states for the duration of treatment is implemented in the model. The categorical distribution from the OLE of CHAMPION-MG suggests that this assumption is appropriate, with the percentage of patients experiencing each level of benefit remaining relatively stable over time. Additionally, UK clinical experts consulted at an advisory board noted that a patient's MG-ADL score does not progressively improve or worsen over time, which confirms that outcomes are expected to remain relatively constant over time.

Table 25: Distribution of patient by magnitude of treatment effect in CHAMPION-MG at 60 weeks

Change in total MG-ADL score at 60 weeks	Ravulizumab (n = 78)
Change < 3	[redacted]
3 ≤ Change < 4	[redacted]
4 ≤ Change < 5	[redacted]
5 ≤ Change < 6	[redacted]
6 ≤ Change < 7	[redacted]
7 ≤ Change < 8	[redacted]
Change ≥ 8	[redacted]
Key: MG-ADL, Myasthenia Gravis Activities of Daily Living scale.	

The only time patients transition between sub-states is when they discontinue ravulizumab. These patients are modelled to receive SoC as subsequent therapy, so once they discontinue treatment with ravulizumab, they are modelled as experiencing the treatment efficacy associated with SoC. This means that the distribution of patients between sub-states changes over time in the ravulizumab arm of the cost-effectiveness model, with the distribution between sub-states in the ravulizumab arm being equal to the distribution in the SoC arm once all patients have discontinued ravulizumab.

Based on the data available, it is unclear if in reality patients who discontinue treatment with ravulizumab would retain some benefit from treatment for a period of time. However, the approach to modelling the long-term efficacy of both treatment arms ensures that the modelled treatment effect is, if anything, a potential underestimate of reality.

Time on treatment (ToT) is modelled independently of the magnitude of treatment effect (change in MG-ADL score sub-state). This is because there is insufficient data to robustly stratify treatment discontinuation by all model sub-states. ToT and treatment discontinuation due to non-response is described in Sections B.3.3.2 and B.3.3.3.

B.3.3.1.1. MG-ADL reduction

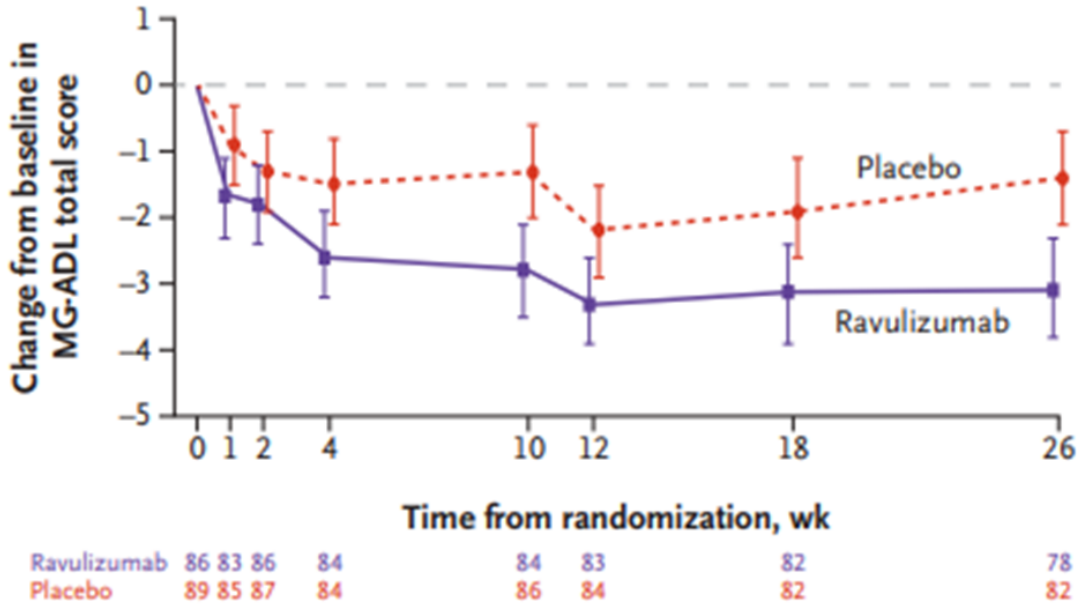
Patients enter the model with a baseline MG-ADL score of 9.53. This reflects the mean MG-ADL score of patients in both arms of CHAMPION-MG and REGAIN. The reduction in MG-ADL experienced by patients is then dependent on the sub-state they are in. The reductions for patients in the MG-ADL score reduction < 3 units and ≥ 9 units sub-states are treatment arm specific. The reductions are informed by the mean reduction in MG-ADL of patients who fell into these bands in CHAMPION-MG and REGAIN and are reported in Table 26. The reduction for patients in the sub-states capturing 1-unit intervals is assumed to be the midpoint value. For example, in the substate capturing a reduction in MG-ADL score of 3-4 units the reduction is assumed to be 3.5 units.

Table 26: Reduction in MG-ADL in unbounded sub-states

Change in total MG-ADL score	**Ravulizumab**	**SoC**
Change < 3	-0.40	0.02
Change ≥ 8	-9.17	-8.33
Key: MG-ADL, Myasthenia Gravis Activities of Daily Living scale; SoC, standard of care.		

As referenced in B.2.12.1, there was a substantial placebo effect in the control arms of CHAMPION-MG. A significant decrease in MG-ADL score from baseline was observed in patients in the placebo arm Figure 20. This reduction occurred despite patients remaining on a stable dose of IST that was in line with their treatment prior to entering the trial.

Figure 20: Mean change in MG-ADL from baseline



Key: MG-ADL, Myasthenia Gravis Activities of Daily Living scale; wk, week.

Maintaining this treatment effect long-term would result in a substantial underestimation of ravulizumab's relative effectiveness versus SoC and in turn its cost-effectiveness. Therefore, it is assumed that patients in the SoC arm experience the treatment effect observed in the trial for the first year of the model before returning to baseline. When consulted at an ad-board, clinical experts believed it was plausible that the MG-ADL scores of patients in the SoC arm would stabilize, meaning the placebo effect would not persist long-term.[17]

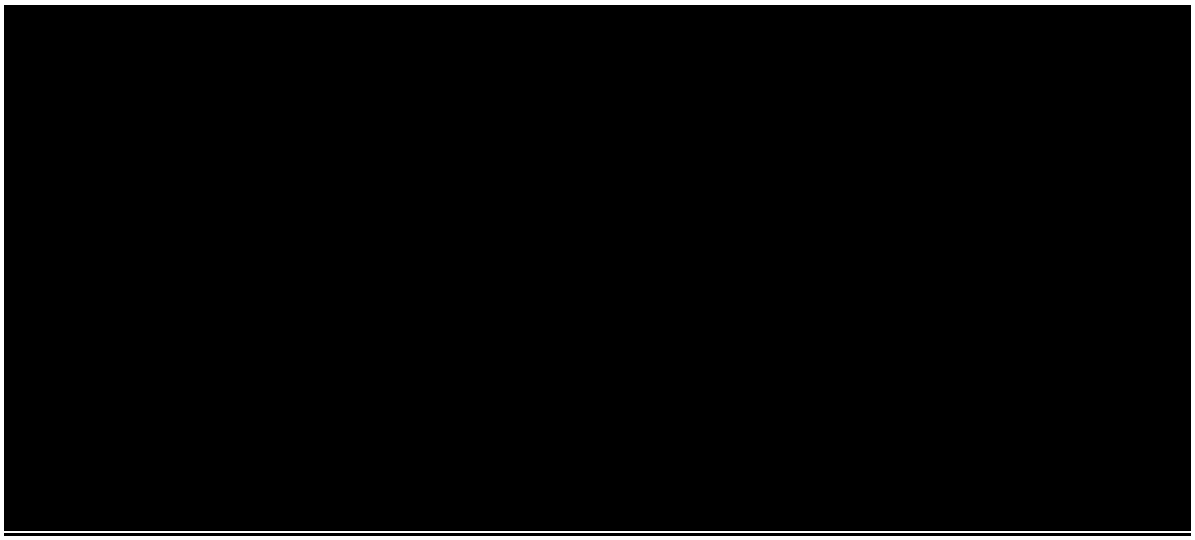
B.3.3.2. Time on treatment

gMG is a chronic condition that requires constant disease management, so patients are expected to receive treatment for their whole lives. Ravulizumab was well tolerated in CHAMPION-MG with a low-impact toxicity profile. It also has a fast onset of action; this means that response can be assessed quickly, and most adverse reactions occur soon after treatment initiation. These factors led clinical experts to believe that, after an initial period, where patients may discontinue treatment due to non-response or adverse reactions, there are few reasons why patients would stop treatment. This means that ToT is expected to extend beyond the follow-up of any of the trials investigating ravulizumab or eculizumab for the treatment of gMG. CHAMPION-MG has a maximum follow-up of [redacted] years, at which point [redacted] of patients remained on ravulizumab. REGAIN, reported that [redacted]% of patients remained on treatment at the maximum follow-up time of [redacted] years.

Longer-term discontinuation rates with ravulizumab may be lower than with eculizumab, given the improved convenience associated with the longer dosing interval of ravulizumab. The open-label eculizumab data may also underestimate long-term ToT, because patients only remained on eculizumab in the OLE study until the drug became commercially available in their country of residence. After this patients exited the trial but may have continued to receive eculizumab through their health service. This causes a significant drop-off in patient numbers after 3 years, which does not align with the plateau in discontinuations seen between Year 1 and Year 3.

Despite this, to make effective use of the available patient-level data, ToT was pooled from CHAMPION-MG and REGAIN, which provided a larger data set to which parametric survival curves could be fitted. Figure 18 presents overlaid ToT Kaplan–Meier data from the CHAMPION-MG and REGAIN studies. The figure shows that, up to the point of maximum follow-up in the CHAMPION-MG study, the discontinuation of ravulizumab and eculizumab follows a similar trend. This suggests that it is appropriate to pool the patient-level ToT data to before extrapolating with parametric models.

Figure 18: Time on treatment Kaplan–Meier data from CHAMPION-MG and REGAIN



Seven standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalized gamma) were fitted to the pooled CHAMPION-MG and REGAIN ToT data. The best-fitting model was selected based on statistical best fit using the Akaike information criterion (AIC) and Bayesian information criterion (BIC), in addition to visual fit to the observed ToT and the plausibility of long-term predictions.

All the models fit the initial 2 years of data well, but none follow the plateau and subsequent spike in treatment discontinuation between Years 3 and 4. The plateaus in the Kaplan–Meier data were caused by the patient assessments being less frequent in the OLE than in the randomized control period up to 26 weeks. The only curve that has a noticeably poor visual fit is the log-normal, which is less influenced by the tail resulting in a more optimistic extrapolation.

The AIC and BIC statistics for each model are reported in Table 26. The results show that the exponential model provides the best statistical fit to the data when measured with either AIC or BIC. The Gompertz and gamma models then provide the second- and third-best statistical fits, but the AIC and BIC scores of the three models are close enough together to suggest they would all be appropriate.

Assessing the long-term plausibility of the available ToT data for ravulizumab specifically is challenging, as the 4-year follow-up in REGAIN is the longest period of time that gMG patients have been treated with ravulizumab or eculizumab. However, the OLE of REGAIN suggests that C5 inhibitors are well tolerated and provide a durable long-term benefit. The log-logistic and log-normal predict a plateau in treatment discontinuation and although this is not implausible it was not considered most appropriate for the base case.

The exponential is used to model long-term ToT in the model base case. It has similar long-term outcomes to the gamma, Weibull and generalized gamma models, but has superior statistical fit. The impact of other extrapolations on model results are investigated in a scenario analysis.

Figure 19: Parametric models fitted to pooled CHAMPION-MG and REGAIN time on treatment data

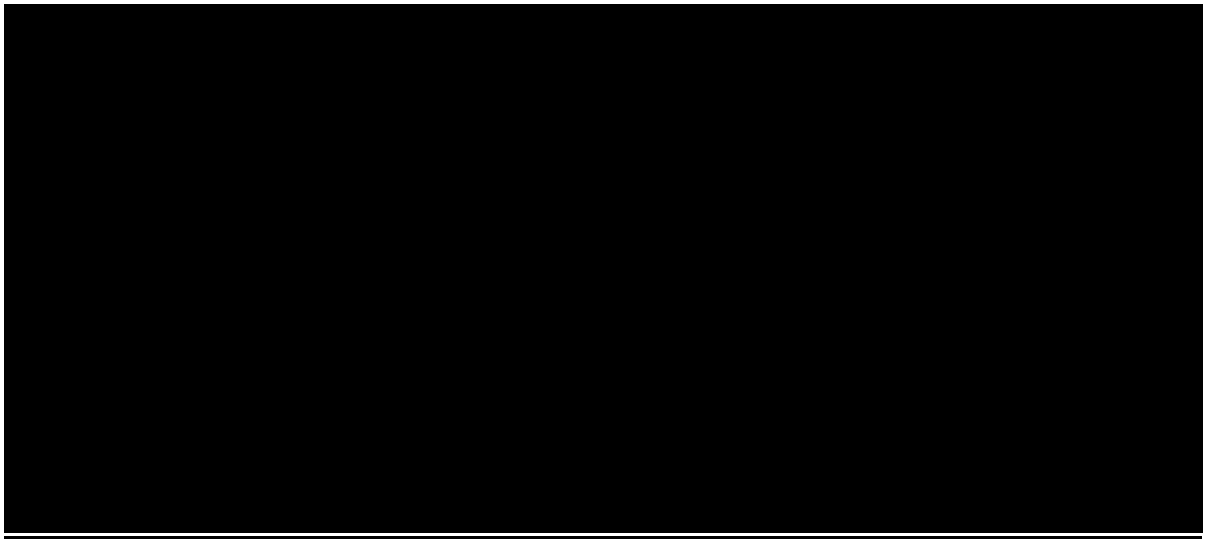


Table 27: Statistical fit of time on treatment parametric models

Model	AIC	BIC
Exponential	227.544	230.541
Gamma	229.242	235.236
Generalized gamma	231.202	240.193
Gompertz	229.193	235.187
Log-logistic	229.681	235.676
Log-normal	230.138	236.132
Weibull (AFT)	229.254	235.248

Key: AFT, accelerated failure time; AIC, Akaike information criterion; BIC, Bayesian information criterion.

B.3.3.3. Treatment discontinuation due to non-response

At a UK advisory board, clinical experts noted that one of the key benefits of ravulizumab was its speed of onset following treatment initiation. Clinicians believe that they could assess whether a patient was responding, or likely to respond to treatment, after approximately two treatment cycles (16 weeks). A patient would then be transitioned onto a different therapy if they were not responding. Comparatively, patients often spend over a year receiving SoC therapy before response can be accurately assessed.[3]

The model does not explicitly capture one particular benefit of ravulizumab: the peace of mind for patients that they can avoid receiving a long-term treatment that does not benefit them. However, the model does include the discontinuation of non-responders as per the expectation of clinical experts. The proportion of patients defined as non-responders was informed by the number of patients who did not achieve a reduction in MG-ADL score of at least 3 points at 18 weeks in CHAMPION-MG. A 3-point reduction is greater than the reduction that is recognized as a clinically meaningful improvement in MG symptomology.[148]

Patients were not assessed in CHAMPION-MG before their third treatment cycle at 16 weeks, so data from the 18-week assessment was used in the model. The mean change in MG-ADL plotted in Figure 20, along with the long-term follow-up at 60 weeks from the OLE of CHAMPION-MG (presented in Table 25), suggest that patient response remained stable beyond 12 weeks. It was therefore deemed

appropriate to use the measure at 18 weeks as a proxy for the assessment that would usually be conducted at 16 weeks in clinical practice.

After 18 weeks of the CHAMPION-MG study, 53.5% of patients had experienced a reduction of ≥ 3 points in MG-ADL score, resulting in 46.5% of patients being categorized as non-responders. In the model, all patients in the MG-ADL score reduction < 3 sub-state are assumed to discontinue as non-responders. However, some may have already discontinued because of reasons other than a lack of response, with treatment discontinuation being applied uniformly across all changes in MG-ADL score sub-states.

B.3.3.4. Clinical event rates

Along with a patient's MG symptomology affecting their daily quality of life, patients can also experience significant, rapid and devastating deteriorations in symptoms. These clinical events are classified by severity and described as either MG exacerbations or MG crises. The severity of an event can vary, but more severe exacerbations and all crises are associated with significant management costs. These events severely impact a patient's quality of life and, in some cases, can lead to death.

The number of clinical events that occur in a 3-month model cycle are estimated using a Poisson regression model. A Poisson model was selected as it is designed to estimate count data within a fixed interval. The model estimates the overall number of clinical events in a given treatment cycle, which are then subdivided into exacerbations or crises. The clinical events are divided using a fixed proportion, with [redacted]% of clinical events being crises and the remaining [redacted]% being exacerbations. These proportions were based on the number of crises observed in the 26-week randomized controlled period of CHAMPION-MG and REGAIN across all arms ([redacted] clinical events were crises and [redacted] were exacerbations).

The clinical regressions were informed using pooled data from the OLE of CHAMPION-MG, supplemented with the randomized controlled period of REGAIN. With 36 events occurring in the randomized control period of CHAMPION-MG, a further 15 events occurring in the OLE and 34 occurring in REGAIN, giving a total of

85 events. These events occurred at a rate of 0.35 per patient year (85 events in 246.28 patient years).

The dataset was then amended to account for the discontinuation of non-responders in the ravulizumab arm. This was done because clinical events were most common in patients who did not meet the exclusion criteria. If the dataset had not been amended, the treatment effect associated with ravulizumab would be underestimated. Ravulizumab patients in CHAMPION-MG (up to 60 weeks) or REGAIN who did not achieved a reduction in MG-ADL of > 3 points from baseline at 18 weeks were removed from the dataset. As discussed previously, observations at 18 weeks are considered a justifiable proxy for assessing patients after two treatment cycles. This left [redacted] events in 166.51 patient years.

A simple Poisson model using only treatment arm as a predictor was implemented in the model. The specification of this model is outlined in Table 27. As this model approach was parsimonious while also providing a good fit to the observed data, it was judged that a more complex approach would yield little additional value. The treatment covariate for ravulizumab is not applied to patients who are considered non-responders (a reduction of > 3 MG-ADL points from baseline) prior to them discontinuing ravulizumab. Non-responders in CHAMPION-MG (up to 60 weeks) or REGAIN experienced [redacted] clinical events in 79.77 patients years compared to [redacted] events in 81.125 patient years in the placebo arm, suggesting this is a conservative assumption.

Table 28: Poisson regression for responders

Parameter	Estimate	Standard error	p-value
Intercept	[redacted]	0.1459	< 0.001
Ravulizumab	[redacted]	0.4051	< 0.001

The model predicts [redacted] and [redacted] clinical events per patient year in the ravulizumab and SoC arms, respectively. This reflects CHAMPION-MG and REGAIN well, where clinical event rates of [redacted] and [redacted] per patient year were observed in the respective arms.

B.3.3.5. Mortality

No evidence was identified in the clinical SLR to suggest that well-managed gMG led to excess mortality. This opinion was reflected by clinical experts when they were consulted during an advisory board. The model therefore uses age-matched general population mortality rates estimated from UK life tables to inform the transitions to the death state in each cycle. However, when gMG is not well controlled, patients can experience an MG crisis, which is associated with an increased rate of mortality. A study reviewing a US database on inpatient treatments reported a mortality rate of 4.42% associated with MG crises.[87] The model assumes that all MG crises that occur in each cycle are managed as an inpatient hospital stay, and the mortality rate is applied to all patients experiencing a crisis. MG crisis is the only clinical event associated with increased mortality. No evidence of exacerbation-related mortality was identified in the literature, so it was assumed that exacerbations did not impact survival in the model.

B.3.4. Measurement and valuation of health effects

Daily life can be severely impacted by gMG symptoms, exacerbations and crises (Section B.1.3). As described above, myasthenic exacerbations are clinical deteriorations of MG symptoms that may result in emergency treatment. Myasthenic crises are severe, life-threatening exacerbations that lead to patients requiring mechanical ventilation. Common symptoms of gMG include chronic fatigue, severe weakness, difficulty sleeping, anxiety and depression. Patients who suffer from muscle weakness report challenges with eating, breathing and walking, in addition to ocular symptoms causing double or blurred vision, which further impact daily life through the inability to drive or read, for example. These symptoms are common despite the current SoC being well established in the UK. This suggests a clear unmet need for new treatments that offer long-term benefits to patients.

The HRQL impact of MG exacerbations or MG crises is uncertain. Only two crises were observed across the randomized periods of CHAMPION-MG and REGAIN. Although there were significantly more exacerbations (n = 68), limitations are associated with using an HRQL survey to capture the impact of one-off events. Patients are unlikely to complete EQ-5D surveys during an event, particularly in the

case of a MG crisis where treatment often includes ventilation or intubation. The true, devastating effect of these events is therefore not well captured which has the potential to underestimate the true value of ravulizumab in improving patients' quality of life. Ravulizumab used as an adjunctive to current therapies has demonstrated the potential to improve patients' HRQL. In line with the NICE reference case, to incorporate the impact of ravulizumab on HRQL, the EQ-5D data collected from the CHAMPION-MG and REGAIN trials were analysed and incorporated into the economic model. Additional decrements to account for adverse events and age adjustment to HRQL were considered in line with the NICE reference case.

B.3.4.1. Health-related quality-of-life data from clinical trials

HRQL data were collected in both CHAMPION-MG and REGAIN trials. In CHAMPION-MG, EQ-5D-5L questionnaires were completed at baseline, then at 4, 12, 18 and 26 weeks. Similarly, EQ-5D-5L questionnaires were completed at baseline, then at 4, 12, 16 and 26 weeks in REGAIN.

B.3.4.2. Mapping

The EQ-5D-5L data collected in CHAMPION-MG and REGAIN were mapped onto the 3L scale using the algorithm developed by Hernandez-Alava et al. (2017) in line with the NICE reference case.[145, 149]

B.3.4.3. Health-related quality-of-life studies

An SLR of existing HRQL studies in gMG was conducted. The search was run on 28 March 2022. Full details of the search and findings are reported in Appendix H. The search identified 57 studies that met the inclusion criteria relating to population, intervention, comparator and study design. The details of the identified studies are presented in a PRISMA flow diagram (Figure 16) (see details in Appendix H).

In total, 20 studies reported SF-36 scores and seven reported EQ-5D scores (Appendix H). Among studies that described patients with anti-AChR antibodies, only one cross-sectional study reported SF-36 scores[143] while four studies of patients with anti-AChR or anti-MuSK antibodies had SF-36 scores. Mental Component Summary (MCS) scores were generally higher than Physical Component Summary (PCS) scores, suggesting that the impact was greater on patients' physical health than their

mental health. In one Serbian cross-sectional study that stratified SF-36 scores by antibody status, mean (SD) MCS scores (49.4 [21.3]) were lower than PCS scores (53.8 [21.4]) among patients with anti-AChR antibodies, while the opposite was the case for patients with anti-MuSK antibodies (MCS score: 65.4 [25.9]; PCS score: 61.8 [25.6]).[150] A longitudinal study from Serbia observed patients with anti-AChR or anti-MuSK antibodies on SoC therapies over a 10-year period and noted a decrease in PCS (baseline: 67.3 [20.7], last assessment: 63.5 [22.8]) and an increase in MCS over time (baseline: 65.4 [23.3], last assessment: 70.3 [20.0]).[151]

B.3.4.4. Adverse events

In line with the NICE reference case, the impact of adverse events (AEs) on HRQL is incorporated in the economic model. All events occurring in ≥ 2% patients in either arm of the CHAMPION-MG trial were included regardless of grade.

The percentage of patients experiencing each AE included in the model in the first 6 months of the CHAMPION-MG trial is reported in Table 29. The average duration and one-off disutility applied for each AE are presented in Table 30.

Table 29: Included adverse event risks, based on data from CHAMPION-MG

Adverse event	Ravulizumab (N = 86)	SoC (N = 89)
Headache	19%	26%
Diarrhoea	15%	12%
Nasopharyngitis	3%	6%
Upper respiratory tract infection	3%	2%

Table 30: Adverse event disutility and duration

Event	Disutility	Duration (days)
Headache	-0.027[152]	2.0[152]
Diarrhoea	-0.047[152]	2.4[152]
Nasopharyngitis	-0.010[153]	5.0[154]
Upper respiratory tract infection	-0.014[152]	14.0[152]

Total quality-adjusted life years (QALYs) lost due to AEs are calculated by multiplying the duration of each AE by its disutility and the proportion of patients expected to experience it. This is then applied to patients in the first cycle of the model.

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

The HRQL data from REGAIN were used to supplement CHAMPION-MG HRQL data, with the assumption that eculizumab and ravulizumab are equivalent. Regression models were fitted to utility values that were based on EQ-5D-5L measurements. A total of 1368 questionnaires were completed by 175 patients in the

CHAMPION-MG trial and 125 patients in the REGAIN trial throughout the 26-week study periods. Models were fitted for all patients in the intention-to-treat population without missing values for MG-ADL reduction. In these trials, EQ-5D measures captured the change in EQ-5D score from baseline measurements. MG-ADL was included in the regression in order to capture the impact of the severity of the underlying disease while patients were not experiencing an exacerbation or crisis, not only does it align with the primary outcome of the trial but when tested in the regression it was found to be a statistically significant covariate, indicating it is a good predictor of HRQL.

In the base case, a regression model is used with MG-ADL score and baseline EQ-5D as independent variables (Table 31). Alternative regression model specifications were tested in a scenario analysis.

Table 31: MG-ADL score utility regression model used in the base case

Parameter	Estimate	Standard error	p-value
Intercept	[redacted]	0.0280	0.0000
MG-ADL Score	[redacted]	0.0018	0.0000
Baseline EQ-5D	[redacted]	0.0355	0.0000
Key: MG-ADL, Myasthenia Gravis Activities of Daily Living scale.			

In addition to modelling utilities based on MG-ADL score changes, the impact of events can be separately included using direct estimation. All data from Weeks 1 to 26 were used to regress patient-reported EQ-5D data on whether the assessment took place during or after the patient's first crisis or exacerbation, or before the patient's first crisis or exacerbation. Clinical event disutility for crises or exacerbations can be estimated from this regression, with the option to use a disutility based on CHAMPION-MG-only, REGAIN-only or pooled data.

The duration of a myasthenic exacerbation is calculated by assuming that 20% of patients are hospitalized and treated in the same way as a crisis as described by Neumann et al (2020)[88]. The remaining 80% of patients are treated over 7 days in an outpatient setting. This disutility is multiplied by the duration of crises to calculate a

total decrement for the event (Table 32).[155] This decrement is applied as a one-off to the proportion of patients experiencing each clinical event in a cycle.

Table 32: Clinical event patient disutility

Clinical event		Value	Source
Exacerbation	Disutility	[redacted]	Pooled CHAMPION-MG and REGAIN trial data
	Duration (days)	[redacted]	UK clinical opinion or Neumann et al
	Total decrement	-0.0022	Calculated
Crisis	Disutility	[redacted]	Pooled CHAMPION-MG and REGAIN trial data
	Duration (days)	[redacted]	Neumann et al. or HCRU survey
	Total decrement	-0.084	Calculated

Caregiver utilities

In addition to the HRQL effect of myasthenic exacerbations and crises on patients, there is also an impact on caregivers.[76] Applying caregiver disutilities reflects the application of patient disutilities; the total decrement is calculated by taking a disutility from the literature and multiplying it by the assumed duration of patient events.

Table 33: Clinical event caregiver disutilities

Clinical event		Value	Source
Exacerbation	Disutility	-0.03	Thomas et al[76]
	Duration (days)	11.8	Neumann et al.[88]
	Total decrement	-0.0009	Calculated
Crisis	Disutility	-0.3	Thomas et al[76]
	Duration (days)	31.1	Neumann et al.[88]
	Total decrement	-0.026	Calculated

B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR of existing cost and resource use studies in gMG was conducted. The search was run on 28 March 2022. Full details of the search and findings are reported in Appendix I. The search identified 57 studies that met the inclusion criteria relating to population, intervention, comparator and study design. The details of the identified studies are presented in a PRISMA flow diagram (Figure 16).

In total, 15 studies described costs for patients with MG, whether all-cause or MG-related. Across studies, the types of cost data reported varied widely, with some focusing on total or direct costs, and others specifying costs related to hospitalizations, treatments or crises. In a Bulgarian cross-sectional study of patients with anti-AChR antibodies, total all-cause costs were a median (range) of €4,047 (€862–9,544) per patient per year, while direct costs were €1,366 (€792–5,275) per patient per year. However, the types of treatments received were not reported.[144] In a Portuguese study of six patients with or without anti-AChR antibodies receiving rituximab, all-cause costs were reportedly €17,967 per patient per year.[156] Studies that described the costs associated with crises reported higher costs for patients who experienced crises compared with patients who did not.[91, 157]

16 studies reported outcomes related to healthcare resource utilization, such as the number and proportion of patients requiring a hospital visit, A&E visit, ICU stay or outpatient visit, and associated length of stay (LOS) for these visits. Hospital visits were reported in two Phase III RCTs of patients with anti-AChR antibodies. In the CHAMPION-MG trial, all-cause hospitalizations were less common but longer in duration in the ravulizumab arm compared with the placebo arm at the end of the randomized period. However, MG-related hospitalizations were less common and shorter in duration for ravulizumab-treated patients compared with placebo-treated patients, while non-MG hospitalizations were more common and longer for ravulizumab-treated patients than for placebo-treated patients.[3] In the REGAIN trial, the proportion of patients who required hospitalization decreased to a greater extent following eculizumab and placebo treatment. While 48% of patients required

hospitalization in the eculizumab group at baseline (N = 62), 15% had admissions following eculizumab treatment, and while 46% of patients in the placebo group (N = 63) required hospitalization at baseline, 29% had admissions following placebo treatment.[131]

In a German retrospective study that stratified outcomes by antibody status, patients with anti-AChR antibodies had shorter hospital and ICU LOS for crisis than patients with anti-MuSK antibodies. The mean hospital (SD) LOS was 28.8 (20.9) days for patients with anti-AChR antibodies, and the mean (SD) LOS was 55.9 (47.6) days for patients with anti-MuSK antibodies. The sample size for patients with anti-MuSK antibodies was considerably smaller than for patients with anti-AChR antibodies (15 versus 144, respectively).[158] Full SLR results are detailed in Appendix I.

To identify relevant resource use and cost estimates for patients with gMG in a UK setting, UK clinicians with experience of treating patients with gMG were surveyed (Appendix I).

NHS Reference Costs, the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care, the Monthly Index of Medical Specialities (MIMS), and the drugs and pharmaceutical electronic market information tool (eMIT) were used to inform unit costs in the model.

The following cost categories are incorporated into the economic model and described in this section:

- Drug acquisition costs
- Drug administration costs
- Vaccination costs
- Routine care costs
- Clinical event management costs
- AE costs

B.3.5.1. Intervention and comparators' costs and resource use

Total drug acquisition costs are calculated for all patients remaining alive in each arm of the model, based on label dosing regimens and list prices. Ravulizumab costs are applied to all patients remaining on treatment in the ravulizumab arm. Patients in the ravulizumab arm are assumed to receive SoC therapies as background treatment. Costs for these treatments are therefore applied to all surviving patients in both model arms throughout the modelled time horizon.

Ravulizumab is costed according to the label's dosing regime, with one loading dose applied at the beginning of the model and then a maintenance dose applied every 8 weeks starting on Day 15 (Table 36). In the first model cycle, costs for one loading dose and two maintenance doses of ravulizumab are applied to all patients. In subsequent cycles, one or two doses are administered depending on how the 8-week treatment cycle intersects with the 13-week model cycle. Ravulizumab dosing

is based on patient weight, which is based on the weight distributions observed in the CHAMPION-MG trial.

Acquisition costs in the SoC arm comprise a basket of treatments used to manage gMG. Unit costs for each treatment are calculated from list prices.[159, 160] Each treatment in the basket is costed (Table 37) and a treatment distribution (Table 23) determines the overall cost for all patients in the SoC arm.

Table 34: Dosing schedules used in the analysis

Drug		**Dosing per administration**	**Dosing frequency**
Ravulizumab	Loading dose	• 2,400 mg for patients < 60 kg • 2,700 mg for patients 60 < 100 kg • 3,000 mg for patients ≥ 100 kg	One-off (Day 1)
	Maintenance dose	• 3,000 mg for patients < 60 kg • 3,300 mg for patients 60 < 100 kg • 3,600 mg for patients ≥ 100 kg	Q8W (starting on Day 15)
Pyridostigmine		225 mg	Daily
Azathioprine		2 mg/kg	Daily
Mycophenolate Mofetil		1,000 mg	BID
Cyclosporin		4 mg/kg	Daily
Tacrolimus		0.1 mg/kg	Daily
Methotrexate		20 mg	Weekly
Cyclophosphamide		1.5 mg/kg	Daily
Prednisone		80 mg	Daily
Prednisolone		1.5 mg/kg	EOD

Table 35: Unit costs for each treatment included in the model

Treatment	**mg per unit**	**Units per pack**	**Cost per pack**	**Source**
Ravulizumab	300 mg	1	£4,533	MIMS[160]
Pyridostigmine	60 mg	200.0	£45.44	MIMS[160]
Azathioprine	50 mg	56.0	£1.57	eMIT[159]
Mycophenolate Mofetil	500 mg	50.0	£6.83	eMIT[159]
Cyclosporin	100 mg	30.0	£48.50	MIMS[160]
Tacrolimus	5 mg	50.0	£205.74	MIMS[160]
Methotrexate	130 mg	1.0	£61.40	eMIT[159]
Cyclophosphamide	50 mg	100.0	£52.46	eMIT[159]

Prednisone	20 mg	1000.0	£3.30	Assumed equal to prednisolone
Prednisolone	20 mg	28.0	£3.30	eMIT[159]
Key: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities.				

Table 36: Drug acquisition costs per treatment per model cycle

Treatment arm	Drug	Total cost per cycle
Ravulizumab	Ravulizumab	Model cycle 1: £146,491
		Subsequent model cycles: £82,574*
	Pyridostigmine	£25.45
	Azathioprine	£3.14
	Mycophenolate Mofetil	£15.30
	Cyclosporin	£181.07
	Tacrolimus	£230.43
	Methotrexate	£245.60
	Cyclophosphamide	£44.07
	Prednisone	£0.27
	Prednisolone	£8.57
SoC	Pyridostigmine	£25.45
	Azathioprine	£3.14
	Mycophenolate Mofetil	£15.30
	Cyclosporin	£181.07
	Tacrolimus	£230.43
	Methotrexate	£245.60
	Cyclophosphamide	£44.07
	Prednisone	£0.37
	Prednisolone	£11.55
Key: SoC, standard of care *Average cost in subsequent cycles with approximately 1.625 doses administered per 3 month cycle		

B.3.5.1.1. Treatment administration costs

Ravulizumab is administered by intravenous infusion. The cost of this infusion is assumed to be £281.11 (NHS Reference cost SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance as an outpatient).[109] However, beyond the first treatment cycle patients receive infusions at home through the homecare infusion

service funded by Alexion. Therefore, the model only includes the cost to the NHS of administering the loading dose and the first maintenance dose.

SoC therapies are assumed to incur no administration costs.

B.3.5.2. Health-state unit costs and resource use

Routine care costs in the model are based on UK clinical expert opinion (Appendix Q).[155] Unit costs of resources used (Table 39) are combined with frequency of resource use (Table 40) to generate a per-cycle cost of routine care for all patients of £[redacted].

Table 37: Unit costs for healthcare resource use during routine care and clinical events

Resource	Unit cost	Unit cost source/ description
GP visit	£3.70	PSSRU 21 – General Practitioner per minute of patient contact
Neurologist with specific interest in myasthenia	£2.05	PSSRU - Consultant: medical, Cost per hour £123
General neurologist	£2.05	PSSRU - Consultant: medical, Cost per hour £123
Specialist nurse	£90.27	NHS Reference Costs (2020-21): N29AF [Other specialist nursing, adult, face to face]
Physical therapist	£1.05	PSSRU 21 - Physiotherapist (advanced), Specialist physiotherapist (respiratory problems), Specialist physiotherapist (community), Cost per hour £63
Blood test	£3.63	NHS Reference Costs (2020-21): DAPS05 [directly accessed pathology services - Haematology]
Urinalysis	£3.61	NHS Reference Costs (2020-21): DAPS09 [directly accessed pathology services - Other]
Serum creatinine test	£3.63	NHS Reference Costs (2020-21): DAPS05 [directly accessed pathology services - Haematology]
IVIG	£2,014.86	NHS Reference Costs (2020-21): HICD0460 [intravenous human immunoglobulins] and
Key: IVIG, intravenous immunoglobulin		

Table 38: Routine care resource use

Resource	Annual frequency	Duration
GP visit	[redacted]	[redacted]
Neurologist with specific interest in myasthenia	[redacted]	[redacted]
General neurologist	[redacted]	[redacted]
Specialist nurse	[redacted]	[redacted]
Physical therapist	[redacted]	[redacted]
Blood test	[redacted]	[redacted]
Urinalysis	[redacted]	[redacted]
Serum creatinine test	[redacted]	[redacted]

Key: GP, general practitioner.

In addition to routine care, gMG clinical events, including exacerbations and crises, are assumed to incur costs. The survey of UK clinicians described in Appendix Q was used to inform resource use assumptions for clinical event management. Clinicians estimated that [redacted] of patients experiencing myasthenic exacerbations are treated in an outpatient setting, and [redacted] are treated in an inpatient setting.[155] Healthcare resource use during exacerbations is reported in Table 41. The expected cost per exacerbation is calculated to be £[redacted]. Resource use and costs during a myasthenic crisis are reported in Table 42. The cost per myasthenic crisis incorporated into the economic model is £[redacted]. Costs for clinical events are applied as a one-off in the cycle in which the event takes place.

Table 39: Myasthenic exacerbation healthcare resource use

Resource	Proportion of patients	Frequency per event	Duration
GP visit	[redacted]	[redacted]	[redacted]
General neurologist	[redacted]	[redacted]	[redacted]
Specialist nurse	[redacted]	[redacted]	[redacted]
Blood test	[redacted]	[redacted]	[redacted]
Urinalysis	[redacted]	[redacted]	[redacted]
Serum creatinine test	[redacted]	[redacted]	[redacted]
Inpatient stay	[redacted]	[redacted]	[redacted]
Intubation	[redacted]	[redacted]	[redacted]
ICU stay	[redacted]	[redacted]	[redacted]
Key: GP, general practitioner; ICU, intensive care unit.			

Table 40: Healthcare resource use during myasthenic crisis

Resource	Proportion of patients	Frequency per event	Duration
GP visit	[redacted]	[redacted]	[redacted]
General neurologist	[redacted]	[redacted]	[redacted]
Specialist nurse	[redacted]	[redacted]	[redacted]
Inpatient stay	[redacted]	[redacted]	[redacted]
Intubation	[redacted]	[redacted]	[redacted]
ICU stay	[redacted]	[redacted]	[redacted]
Intravenous immunoglobulin	[redacted]	[redacted]	[redacted]
Key: GP, general practitioner; ICU, intensive care unit.			

B.3.5.3. Adverse reaction unit costs and resource use

As reported in Section B.3.4, costs associated with AEs occurring in ≥ 2% patients were included regardless of grade. Costs of AE management are applied as a one-off in the first model cycle (Table 43). It was assumed that headache and nasopharyngitis would incur no cost.

Table 41: Adverse event costs applied in the model

Event	Cost	Description	Source
Headache	-	Assumed to incur no cost	Assumption
Diarrhoea	£686.81	Weighted average of Non-elective short stay costs (FD01C-FD01J) for Non-Malignant Gastrointestinal Tract Disorders without Interventions and Non-Malignant Gastrointestinal Tract Disorders with Single Intervention (all grades)	NHS Reference costs 2020-21
Nasopharyngitis	-	Assumed to incur no cost	Assumption
Upper respiratory tract infection	£292	Weighted average of Non-elective Short Stay, DZ19H-N, Other Respiratory Disorders	NHS Reference costs 2020-21
Key: NHS, National Health Service.			

B.3.5.4. Miscellaneous unit costs and resource use

B.3.5.4.1. Vaccination cost

Ravulizumab administration, and the associated complement system inhibition, may increase the risk of meningococcal infection. The SmPC for ravulizumab states that all patients must be vaccinated against meningococcal infections at least 2 weeks before receiving treatment, unless the risk of delaying treatment outweighs the risks of developing a meningococcal infection.[161] Costs and dosing for the two necessary vaccines, MenACWY and MenB, were derived from Hampstead Health Pharmacy.[162] Additionally, the MenACWY SmPC indicates that a booster vaccination is available up to 5 years after vaccination.[163] In the model, MenACWY vaccination is therefore given every 5 years for patients receiving complement-inhibitor treatment. In line with the approach used in other ravulizumab appraisals, the cost of giving a MenB booster vaccination every 5 years has also been incorporated.[164, 165] The total cost of meningococcal vaccination is outlined in Table 44.

Table 42: Costs of required vaccines for patients receiving ravulizumab

Vaccine	Cost per dose	Number of doses required	Source	Frequency of booster dose	Source
MenACWY	£70	1	Hampstead Heath Pharmacy[162]	5 years	MenAWCY SmPC[163]
MenB	£135	2		5 years (single dose)	Assumption (based on vaccination approach in PNH and aHUS)

Key: aHUS, atypical hemolytic-uremic syndrome; PNH, paroxysmal nocturnal hemoglobinuria; SmPC, summary of product characteristics.

B.3.6. Severity

This submission is not eligible for any severity multipliers.

B.3.7. Uncertainty

The literature that describes the long-term management of patients with gMG is limited, which means that there is little additional evidence relevant to the decision problem. Given the chronic nature of the condition, no trials have a long enough follow-up period to accurately capture patients' experiences over their lifetimes. Clinicians were consulted through an advisory board to understand the current treatment pathway in the UK and assumptions related to patient care that were relevant for the economic model. Similarly, there are significant gaps in the literature related to the healthcare resources used by gMG patients. In addition to the advisory board, clinicians were surveyed in an attempt to reduce the uncertainty in the treatment and management of gMG. No literature reports the HRQL impact of patients experiencing MG exacerbations or MG crises. As seen in CHAMPION-MG and REGAIN, obtaining robust estimates on the impact of these events is difficult because of their irregularity. The sudden onset of these events also means that they are difficult to capture using an EQ-5D survey. The overall impact of composite uncertainty on model outcomes is difficult to determine. Despite this, we have attempted to model using the most relevant available data and be guided by the feedback obtained from the clinical community to increase confidence in the

modelling approach used and the outputs produced. We have also developed scenarios to test some of the structural uncertainties in our modelling approach.

B.3.8. Summary of base-case analysis inputs and assumptions

All of the parameters used in the cost-effectiveness model are summarised in Appendix O. The table includes the mean value, standard error or confidence interval and probability distribution used to vary each parameter in sensitivity analysis.

B.3.8.1. Assumptions

Table 43: Assumptions made in the model

Topic	Assumption	Justification/Reason
Perspective and discounting	NHS and personal services; 3.5% discounting applied to cost and health outcomes	In line with NICE reference case
Population	Adults with gMG and confirmed anti-AChR antibodies.	In line with the marketing authorization.
Time horizon	50 years in the base case	In line with NICE reference case
Model structure	State-transition model	As detailed in Section B.3.2.2.
Meningococcal vaccination cost	Assumed to be paid by the manufacturer	
Adverse events	The most common AEs (≥2%) from either arm of the CHAMPION-MG trial were included.	
MG-ADL score	Patients MG-ADL score only changes over time if they discontinue ravulizumab and begin treatment with SoC. Patients on the SoC arm remain within the same MG-ADL change sub-state until death	There is insufficient data from CHAMPION-MG and REGAIN to robustly estimate patients MG-ADL score changing in each cycle. Evidence from the 60-week data cut of the CHAMPION-MG open-label extension support the assumption that once a patient responds to treatment their benefit remains stable.

Topic	Assumption	Justification/Reason
Clinical events	[redacted] of clinical events in each cycle are MG exacerbations, the remainder are MG crisis	This is reflective of the split in clinical events observed in CHAMPION-MG and REGAIN
Discontinuation	Patients who do not achieve a reduction in MG-ADL of three points by the end of two treatment cycles are discontinued.	The quick on-set of treatment effect is one of the key benefits of ravulizumab compared to SoC. Clinical experts believed two cycles would be sufficient to judge a patient's response to ravulizumab.
Key: AChR, acetylcholine receptor; AE, adverse event; gMG, generalized myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; SoC, standard of care.		

B.3.9. Base case results

Table 47 presents the base case results for ravulizumab versus SoC. In patients with gMG, treatment with ravulizumab results in an increase in a mean life years (LYs) of [redacted], and a mean increase in QALYs of [redacted] when compared with SoC in England. The base case economic results are reported with the current PAS discount of [redacted] applied. The base case incremental cost-effectiveness ratio (ICER) of ravulizumab compared with SoC is £[redacted] per QALY gained.

B.3.9.1. Base-case incremental cost-effectiveness analysis results

Table 44: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	£87,637	18.60	10.18				
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 45: Net health benefit

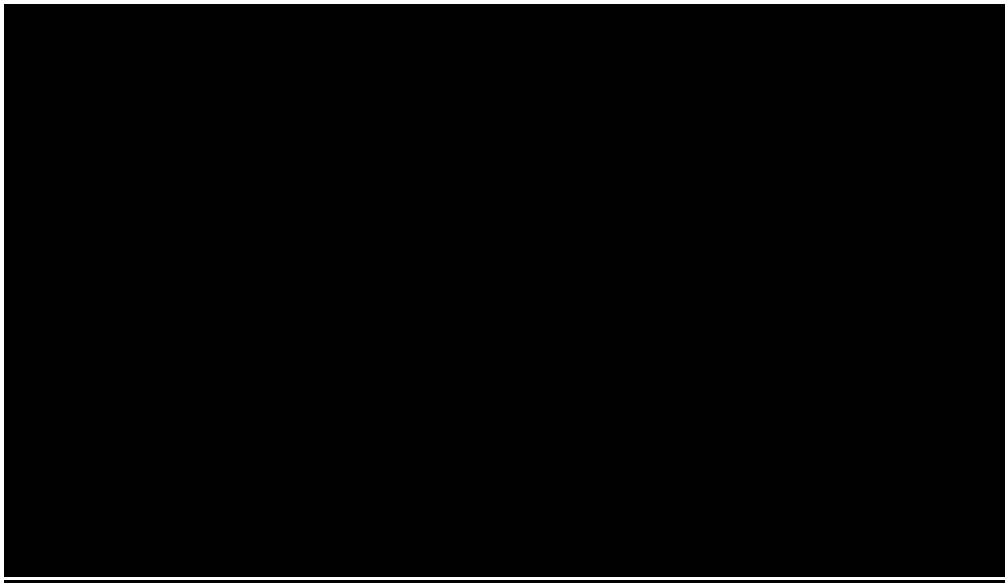
Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
SoC	£87,637	10.18				
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.						

B.3.10. Exploring uncertainty

B.3.10.1. Probabilistic sensitivity analysis

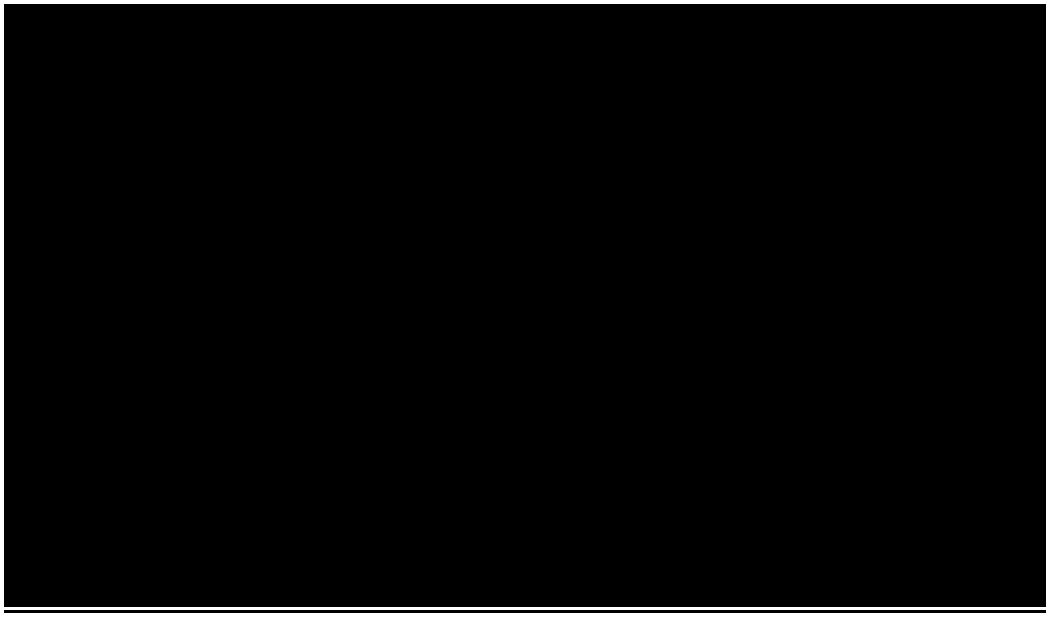
Probabilistic sensitivity analysis (PSA) was conducted where all inputs were varied simultaneously over 1000 iterations, based on reported uncertainty values and appropriate distributional information. Where uncertainty parameters (e.g. standard errors, confidence intervals) were not reported, a standard error of 10% around the mean value is assumed. Table 49 shows the mean results of all PSA iterations. The mean outcomes of the probabilistic iterations result in an ICER of [redacted] per QALY. The individual iterations are tightly grouped and the mean results are close to the deterministic results. This suggests that the model is not subject to significant levels of second order uncertainty.

Figure 21: Cost-effectiveness plane



Key: QALYs, quality-adjusted life years.

Figure 22: Cost-effectiveness acceptability curve



Key: QALYs, quality-adjusted life years.

Table 46: Mean PSA results, ravulizumab versus SoC – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	£87,582	18.60	10.19				
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.10.2. Deterministic sensitivity analysis

One-way sensitivity analyses (OWSAs) were conducted to evaluate the sensitivity of the model to individual inputs, holding all other parameters constant. In OWSA, the lower and upper bounds of a parameter were set to +/-20% of the base case value. No single parameter was identified as a significant driver of cost-effectiveness.

Figure 23: Tornado diagram of deterministic sensitivity analysis results

Key: MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; N/A, not applicable; RWE, real-world evidence.

B.3.10.3. Scenario analysis

Scenario analyses were performed to investigate uncertainty around the structural assumptions of the model. The deterministic results associated with each scenario are presented in Table 47.

Table 47: Scenario analysis results

Model assumption	Base case	Scenario	ICER (£/QALY)	NMB
Base case			[redacted]	[redacted]
Probabilistic			[redacted]	[redacted]
Time horizon	48 years	40 years	[redacted]	[redacted]
Discounting	3.5% for cost and health outcomes	1.5%	[redacted]	[redacted]
		5.0%	[redacted]	[redacted]
Time on treatment parametric model selection	Exponential	Gompertz	[redacted]	[redacted]
		Log-logistic	[redacted]	[redacted]
EQ-5D model	With baseline EQ-5D	Without baseline EQ-5D	[redacted]	[redacted]
Non-responder assessment timepoint for ravulizumab patients	16 weeks (using 18 week data from CHAMPION-MG)	26 weeks	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NMB, net monetary benefit.

B.3.11. Validation

B.3.11.1. Validation of clinical assumptions for cost-effectiveness analysis

The cost-effectiveness model was developed in line with the NICE reference case and guidance from the NICE DSU TSDs where appropriate. The cost-effectiveness model was quality-checked by health economists who were not involved in developing the cost-effectiveness model. They reviewed the technical implementation of calculations and checked inputs and settings for logical inconsistencies. The validation process included identifying any errors and applying the necessary corrections for the final cost-effectiveness model.

This is the first economic evaluation to assess the cost-effectiveness of ravulizumab for patients with gMG who have anti-AChR antibodies. No study assessing the UK cost-effectiveness of ravulizumab in the specified target population was identified from the SLR, so the results of the economic model developed in this appraisal could not be compared with previous studies.

B.3.12. Interpretation and conclusions of economic evidence

gMG is a condition where a clear unmet need remains for patients whose disease cannot be controlled using either corticosteroids or immunosuppressant regimens. Despite SoC being well established in the UK and internationally, there are still significant gaps in the evidence related to the long-term effectiveness of current care and patient experiences while receiving current care. Although C5 inhibitors demonstrate clear advantages in the treatment of patients with gMG, these evidence gaps ultimately make investigating the cost-effectiveness of new therapies challenging. The randomized controlled phases of CHAMPION-MG and REGAIN, two RCTs that explored the effectiveness of gMG treatment with C5 inhibitors, represent the only gold-standard evidence for the effectiveness of SoC. This means that there is a need to extrapolate lifetime outcomes from only 26 weeks of evidence in the management of a chronic disease with recognized standard practice. As

discussed in Section B.3.7, we have tried to mitigate the uncertainty of this wherever possible, by maximizing the use of the available evidence and engaging with practising clinicians to generate confidence in our approach.

The clinical evidence from CHAMPION-MG and REGAIN suggest that ravulizumab would provide a substantial and clinically meaningful benefit to gMG patients that, for most patients, would be maintained in the long term. Given the substantial unmet need, particularly for patients who have exhausted the current treatment options without long-term success, [redacted]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ravulizumab for treating antibody positive generalized myasthenia gravis [ID4019]

Summary of Information for Patients (SIP)

November 2022

File name	Version	Contains confidential information	Date
ID4019_Alexion Ravulizumab in gMG SIP		Yes/no	

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Ravulizumab (ULTOMIRIS®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The licensed population is adult patients with anti-acetylcholine receptor (AChR) antibody-positive generalized myasthenia gravis (gMG). Patients with anti-AChR antibody-positive gMG have autoantibodies directed against AChR, which reduces the availability of these receptors and disrupts the communication between nerve and muscle cells, ultimately causing muscle weakness and fatigue. These patients would use ravulizumab as an add-on to their standard therapy. In the UK, clinicians would likely use ravulizumab as a treatment option for patients who continue to experience symptoms despite receiving active treatment. Therefore, it is likely ravulizumab would be used as an add-on to standard therapy for patients who have tried at least one immunomodulatory therapy.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) approved ravulizumab in September 2022 as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-AChR antibody-positive.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Interaction between Muscular Dystrophy and Alexion UK

- Sponsorship of Muscular Dystrophy (MD) UK's Muscular Dystrophy Muscles Matter Seminar Series 2021 (£4,000)
- Discussion regarding clinical trials in gMG (2021)
- Corporate sponsor of the UCL-MD UK Neuromuscular Translational Research Conference on 26 and 27 April 2022 (£5,000)
- Check-in on gMG-related activities (June 2022)
- Check-in on patient engagement activities in gMG (internal learning session; August 2022)
- Corporate sponsor MD UK's Muscle Maters Series and Virtual Muscle Groups (2022-3; October/November 2022; £7,500)

Interaction between MyAware and Alexion UK

- Check-in on gMG-related activities (June 2022)
- Check-in on patient engagement activities in gMG (internal learning session; August 2022)

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Disease description

Myasthenia gravis (MG) is a rare, chronic, autoimmune disorder. It disrupts the communication between nerve and muscle cells, resulting in weakness in the muscles that control breathing, swallowing, and movement of the body. MG is classified as either ocular MG (only the eye muscles are affected) or gMG, where one or more muscle group (not including the eye muscles) in the head, neck, trunk and/or limbs are affected. Approximately 75–90% of patients with ocular MG progress to gMG, within 2 years of disease onset.[1-7]

How many people have gMG?

The epidemiology of MG in the UK is not well known. Estimates suggest that 15 in 100,000 people have MG[8], which could mean there are around 8,900 patients living with MG in the UK.[8, 9] If we assume that 75% of these patients have gMG, and based on feedback from UK clinical experts that 90% of patients with gMG in the UK have anti-AChR antibodies[10, 11], then there could be approximately 6,000 patients with anti-AChR antibody-positive gMG in the UK. The presence of autoantibodies directed against AChR[12-19] is a key part of the disease; it results in damage to the receptors caused by the complement system (part of the body's immune system).[20]

Main symptoms

Patients with gMG experience a significant and debilitating impact from their symptoms. The majority of patients (96%) have debilitating variations and fluctuations in their symptoms; these affect all aspects of their daily lives, encompassing work, family and social activities.[21, 22] These symptoms often persist despite treatment and include muscle weakness after physical strain (75.4%), weakness of upper limb (71.3%), walking problems (69.6%), difficulty swallowing (43.9%), difficulty chewing (39.1%), drooping of the upper eyelid (37.8%) and double vision (37.1%) – all of which result in a diminished health-related quality of life.[23]

Burden of disease

In addition to considerable symptoms, patients with suboptimal disease management are at risk of myasthenic exacerbations and life-threatening crises. A myasthenic exacerbation is a clinical deterioration (worsening) of gMG symptoms, sometimes resulting in emergency treatment in hospital.[24] More than half of patients will experience at least one myasthenic exacerbation over the course of the disease. Patients with uncontrolled disease are 4.7 times more likely to have an exacerbation than patients whose disease is better controlled.[25] Myasthenic crisis is a severe, life-threatening and sometimes fatal exacerbation that results in an inability to swallow or breathe. Patients experiencing crises require mechanical ventilation and therefore will need to be hospitalized.[26, 27] Myasthenic crisis occurs in 15–30% of patients and can lead to respiratory tract infection, aspiration pneumonia, and death.[1, 25, 27-38] These severe and potentially life-threatening clinical events result in increased use of healthcare resources, with patients requiring Accident and Emergency department (A&E) visits and admission to intensive care.

Patients with gMG are often further affected by comorbid conditions, including cardiovascular disease, diabetes, depression, and other autoimmune diseases.[25, 32, 39-41] These other autoimmune diseases include arthritis, celiac disease, pernicious anaemia, Sjögren's syndrome, systemic lupus erythematosus, and thyroiditis.[32] Some studies report that up to 73% of patients with gMG have comorbidities, and comorbidities are associated with a worse prognosis, more frequent A&E visits and more frequent myasthenic crises and associated hospitalizations than patients without comorbidities.[42, 43] In one study, over two-thirds of patients (69%) had at least one comorbid condition, with cardiovascular (43%) or psychiatric/neurological conditions (27%) being the most common.[44] Patients who had used corticosteroids were more likely to have a diagnosed comorbidity compared with patients who had never used corticosteroids (74% versus 65% were diagnosed with a comorbidity, respectively).[44] These results suggest that comorbid conditions in gMG can be secondary to and/or exacerbated by corticosteroids, which are often used to manage gMG.

Despite the availability of treatments for gMG, many patients continue to experience poor health-related quality of life. In a German study, patients with gMG (N = 1,518), particularly those with severe disease, had reduced health-related quality of life, despite receiving treatment.[23] In an Italian study (N = 41), a higher dose of corticosteroid therapy was significantly associated with poorer health-related quality of life.[45] A US-based study reported that, despite taking an average of 2.3 treatments for gMG, the majority of patients (87%) experienced negative effects on their personal lives, and 68% of patients worried that limitations caused by their disease have a negative impact on their relationships.[46]

Impact on caregivers

Patients with gMG, particularly those with comorbid conditions or experiencing an exacerbation, often require additional care. According to a survey of physicians and patients with gMG conducted in Europe and the US, patients reported that 55% of their daily activities had been impaired by their condition, and the majority of patients (84%) relied upon a non-professional caregiver.[47] Providing informal care can place considerable mental and physical strain on the family members responsible. It can also restrict their time available for work and for social and family activities. As a result, a caregiver may face negative impacts on their career, finances, health, and quality of life.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
Diagnosis is made by reviewing a patient's symptoms (muscle fatigue and weakness), reviewing their medical history, performing a physical examination, conducting serological tests (serum antibody assay), conducting electrodiagnostic tests to confirm muscle fatigue, and/or conducting anticholinesterase tests to examine response to injection of edrophonium or oral cholinesterase inhibitor.[3, 14, 48-50] No additional diagnostic tests will be required to be treated with ravulizumab.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - If there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - Are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatments are currently available?

The treatment options that are currently available for gMG all aim to control symptoms of the disease, either by 1) increasing the amount of acetylcholine available to offset the effect of the anti-AChR antibodies, or 2) suppressing the immune system. Available options include acetylcholinesterase inhibitors, such as pyridostigmine; and corticosteroids, with or without immunosuppressants such as azathioprine, ciclosporin, methotrexate, mycophenolate mofetil and tacrolimus.

In the UK, typically pyridostigmine is used as a first-line treatment. Corticosteroids with or without immunosuppressants is usually reserved as second-line and later treatment options for patients who continue to experience symptoms while receiving pyridostigmine.[51]

These treatments are associated with various limitations, which are discussed below.

Conventional therapies do not control gMG symptoms

A study of patients with gMG in England found that current treatments do not adequately manage patients' symptoms. Out of 1,149 patients with gMG identified through patient records from 1997 to 2016:

- 18% of patients experienced myasthenic crisis, with an average of 1.4 events a year
- 25% experienced an MG exacerbation, with an average of 2.8 events a year
- 39% experienced an MG-related hospitalization, with an average of 2.2 events a year

As a result of this lack of disease control, many patients rely on acute rescue therapies. These patients may require repeat plasma exchange or intravenous immunoglobulin. Plasma exchange involves using a machine called a cell separator, which separates the plasma from the blood to remove abnormal substances – in this case, auto-antibodies – circulating in the plasma. Intravenous immunoglobulin is a therapy that contains antibodies obtained from healthy blood donors, given to the patient through a drip. However, these are not long-term solutions, as they

only alleviate the symptoms temporarily. There are also challenges with administration (plasma exchange) and with price and supply shortages (intravenous immunoglobulin).[11] In a US analysis of real-world data from 456 patient record forms completed by 78 physicians, 44% of patients (N = 200/456) required acute treatment at some point, with 36 patients receiving acute treatment at the time of survey completion.[52] The majority of these patients were being treated with acute treatment as a result of exacerbation (n = 24/36) or myasthenic crisis (n = 5/36).

Current treatment options have a slow onset of action

Patients treated with azathioprine can wait up to a year for full effects of their treatment to be reached. In some cases, patients who have exhausted all alternative treatment options are offered rituximab. However, clinical experts have advised that in practice, it may take up to 2 years of treatment with rituximab to see a clinical benefit in patients with anti-AChR antibody-positive gMG. Being treated with therapies with such slow onset of action can be demoralizing for patients, as they have to continue to take these treatments for a long period of time without knowing whether or when symptom alleviation will occur.

Current treatment options are associated with various short- and long-term side effects

Side effects of currently available gMG treatments can contribute as much to patient burden as the disease itself and have a significant impact on patients' lives.[53] Side effects associated with existing gMG treatments include diarrhoea, bronchial secretions, flu-like symptoms, weight gain, and potentially serious side effects associated with immunosuppression. Examples of such side effects associated with corticosteroids and azathioprine, mycophenolate and methotrexate are provided below[54-56]:

- Corticosteroids (particularly if used at high doses or over prolonged periods) are associated with cataracts; Cushingoid appearance; osteoporosis and fractures; glucose intolerance and diabetes; hypertension; infections; mood disturbances; and weight gain.[42, 56, 57] One study found that significant cognitive deficits were present in patients with gMG and depression who used corticosteroids.[58] Clinical experts also advised that prolonged use of steroids, particularly among those with steroid-induced diabetes can be associated with some general mortality risk (hazard ratio: 3.738; $p < 0.001$),[59] with these patients being at higher risk of heart attack, thrombosis or infection[11]
- Azathioprine, mycophenolate and methotrexate all affect the immune system, and they can also cause problems with blood clotting.[42, 55, 56] Ciclosporin and tacrolimus can lead to renal complications as well as hypertension.[60] A clinician consulted as part of an advisory board suggested that he would not use ciclosporin or tacrolimus in patients with gMG due to these complications[11]

Current treatment options are associated with various inconveniences for patients with regards to administration, dosing and frequent monitoring

In addition to side effects, patients may experience treatment burden due to inconveniences associated with treatment regimens, administration, or testing requirements. A cross-sectional cohort study from Brazil found more complex treatment regimens (i.e. those that involved more daily pills) were associated with poor adherence to gMG treatments. These regimens also resulted in increased symptoms and reduced health-related quality of life.[61]

- The ideal dosing and tapering regimens for corticosteroid treatment have still not been established. It will vary from patient to patient, as it depends on various factors including symptoms, symptom exacerbation and side effects, which complicates treatment
- Treatments such as azathioprine and cyclosporin are associated with haematological issues. As a result, frequent monitoring is required, leading to patient inconvenience

When there is a varying disease course, with fluctuating muscular weakness and fatigability, this creates a chronically impaired state for patients with gMG.[27, 37] In contrast, a more stable disease course has a positive impact on physical and mental health.[62] Therefore, gMG treatments that can control symptoms consistently over a long period of time and that have a more convenient dosing schedule could be beneficial to patients with gMG.

Current treatment options can exacerbate comorbidities

Immunosuppressive therapies used to treat gMG can contribute to comorbidities.[56] Some gMG treatments may cause comorbid conditions such as cardiac arrhythmias, diabetes, dyslipidaemia, obesity and osteoporosis[42], which exacerbate gMG and increase the burden on the patient.[34, 63, 64] Drug interactions between gMG therapies (particularly cyclosporin) and those used to treat comorbid conditions can undermine effective gMG management.[42, 65] The presence of comorbid conditions may limit or preclude the use of conventional gMG therapies, which may complicate the management of gMG in these patients.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Living with gMG can be challenging. Varying disease severity, and fluctuating muscular weakness and fatigue creates a chronically impaired state for patients with gMG.[27, 37] As part of the fluctuating nature of gMG, these patients may face debilitating symptoms, severe clinical events (including MG exacerbations and crises), and comorbid conditions, which can occur as a result of gMG treatment.

Fatigue is common among patients with gMG and negatively affects activities of daily living and health-related quality of life. In a German study of 200 patients with MG (119 of whom had gMG), over half (56%) experienced fatigue. This study also found that fatigue was significantly more common among patients with gMG compared with those in pharmacological remission (72% versus 32%; $p < 0.001$).[66] The Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15) and Myasthenia Gravis Activities of Daily Living (MG-ADL) scores were significantly higher (indicating more severe symptoms) among patients with fatigue ($p < 0.001$).[66]

In a survey of physicians and patients with gMG in Europe and the US, it was found that patients without professional care often relied on the support of a partner/spouse as a caregiver (82%). Physicians reported that 42% of these informal caregivers had changed their working patterns, with 14% stopping work altogether, to be able to care for the patient.[47] Patients required the support of a caregiver to complete daily activities including walking (50%), help with shopping (45%), provide emotional support (41%), help with travelling outside of the home (36%), and help with preparing meals (32%).[47]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Ravulizumab is a long-acting inhibitor of a protein known as C5. It is administered every 8 weeks. By binding to the complement protein C5 in the terminal complement pathway (a part of the body's immune system) and preventing its activation, ravulizumab preserves the molecules involved in sending signals between nerve and muscle cells. This can prevent autoimmune damage and alleviates symptoms such as muscle weakness.

Please click here to view the summary of product characteristics and patient information leaflet for ravulizumab.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Yes, ravulizumab is intended to be used alongside patients' standard therapies. The CHAMPION-MG trial provides results for patients treated with ravulizumab in addition to the treatment they were using at the beginning of the trial (treatment options available in UK clinical practice are listed above in 2c).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Ravulizumab is administered by intravenous (via a vein) infusion. Dosage is determined based on the patient's weight, as detailed below.
The dosing schedule consists of an initial loading dose followed by maintenance dosing. Maintenance dosing starts 2 weeks after the loading dose and continues every 8 weeks thereafter.

Body weight	Loading dose	Maintenance dose	Maintenance dose interval
≥ 40 to < 60 kg	2,400 mg	3,000 mg	Every 8 weeks
≥ 60 to < 100 kg	2,700 mg	3,300 mg	
≥ 100 kg	3,000 mg	3,600 mg	

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Table 1 gives an overview of the CHAMPION-MG study supporting ravulizumab for the treatment of adult patients with anti-AChR antibody-positive gMG.

Table 1: Summary of CHAMPION-MG study

Study	**CHAMPION-MG (NCT03920293)**
Location	85 sites across 13 countries including: Canada, Czech Republic, Denmark, France, Germany, Israel, Italy, Japan, the Netherlands, South Korea, Spain, Switzerland, and the United States.
Population	Adult patients with anti-AChR antibody-positive gMG (MGFA Class II–IV) and an MG-ADL score of ≥ 6.
Patient group size	Ravulizumab (standard therapy allowed): N = 86 Placebo (standard therapy allowed): N = 89
Key inclusion criteria	• Patients aged ≥ 18 years diagnosed with gMG at least 6 months prior to screening and confirmed positive by serological testing for anti-AChR antibodies • MGFA Class II–IV (patients with mild, moderate, or severe weakness affecting more muscle groups than only eye muscles, who are not receiving emergency treatment) with a MG-ADL profile ≥ 6 at screening and randomization (Day 1) • Vaccinated against meningococcal infection • Stable doses of immunosuppressive therapies prior to screening were permitted
Key exclusion criteria	• Active or untreated thymoma, history of thymic carcinoma or thymic malignancy or history of thymectomy within the 12 months prior to screening • MG crisis/exacerbation or clinical deterioration between screening and Day 1
Completion dates	Blinded period (26 weeks): 11 May 2021 Open-label extension period (up to 2 years): Ongoing Estimated study completion date: 31 December 2023
Primary publication	Vu et al. 2022[67]

Key: AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The Phase III CHAMPION-MG study investigated ravulizumab (plus standard of care therapy) in patients with anti-AChR antibody-positive gMG. The comparator was placebo plus standard of

care therapy. As a result, although this trial was placebo-controlled to ensure patients and study investigators were not aware which patients were receiving ravulizumab, these results provide a reasonable comparison between ravulizumab as an add-on therapy to standard of care versus standard-of-care therapies used in the UK.

Most patients included in this study were Myasthenia Gravis Foundation of America (MGFA) Class II or III (patients with mild or moderate weakness affecting more muscle groups than only eye muscles), which captures the majority of the gMG population. Approximately 10% of patients were not receiving an immunosuppressive therapy at baseline, suggesting that these patients may have had early disease. However, on average, patients enrolled in this trial had an average duration of MG of approximately 10 years, suggesting that many patients will have been pre-treated. This is a similar patient population to the population in which ravulizumab is expected to be used in UK clinical practice.

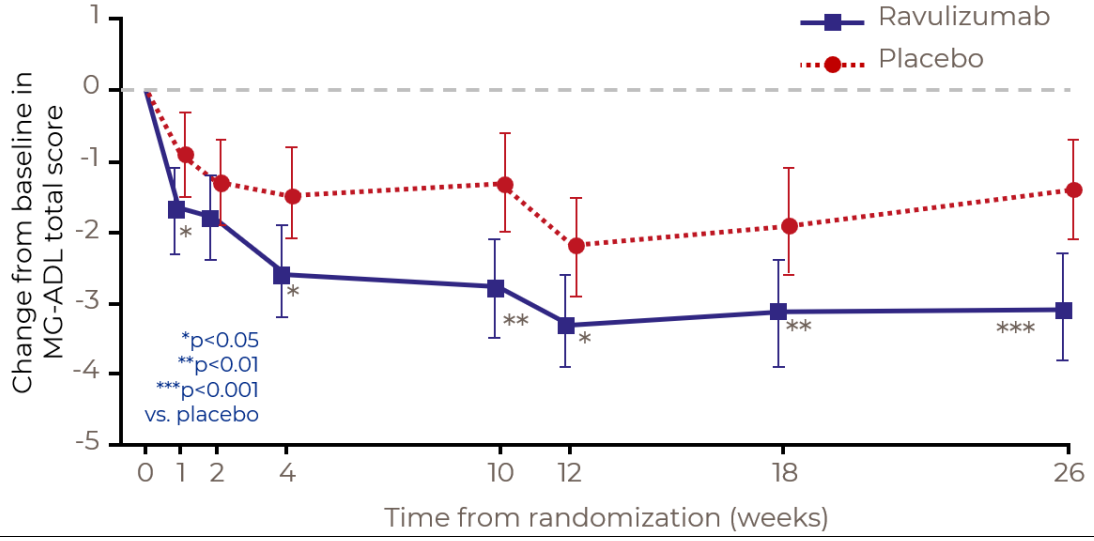
Ravulizumab treatment resulted in statistically significant improvements in MG-ADL total scores at Week 26 versus placebo

The primary endpoint of the CHAMPION-MG study was the change from baseline in MG-ADL total score at Week 26. This 8-point questionnaire includes questions to assess relevant symptoms and functional performance of activities of daily living in patients with gMG. This questionnaire is completed by patients and relies on patients recollecting their symptoms and functional performance over the previous week. This captures a longer period of time than the physician-reported Quantitative Myasthenia Gravis (QMG) score measure, which may make it more sensitive in detecting fluctuations in disease severity.[68]

A noticeable and clinically meaningful treatment effect with ravulizumab was demonstrated as early as Week 1 and sustained through Week 26. Ravulizumab was associated with a statistically significant improvement in MG-ADL total score (least squares mean [LSM] reduction [standard error of the mean, SEM]) at Week 26 versus placebo (-3.1 [0.38] vs -1.4 [0.37]; $p < 0.001$; Figure 1).

This improvement was sustained in patients treated with ravulizumab who remained on ravulizumab treatment in the open-label extension study at Week 60. Patients who were originally given placebo and then switched to ravulizumab in the open-label extension study experienced a rapid and sustained improvement of a similar magnitude to those patients treated with ravulizumab.

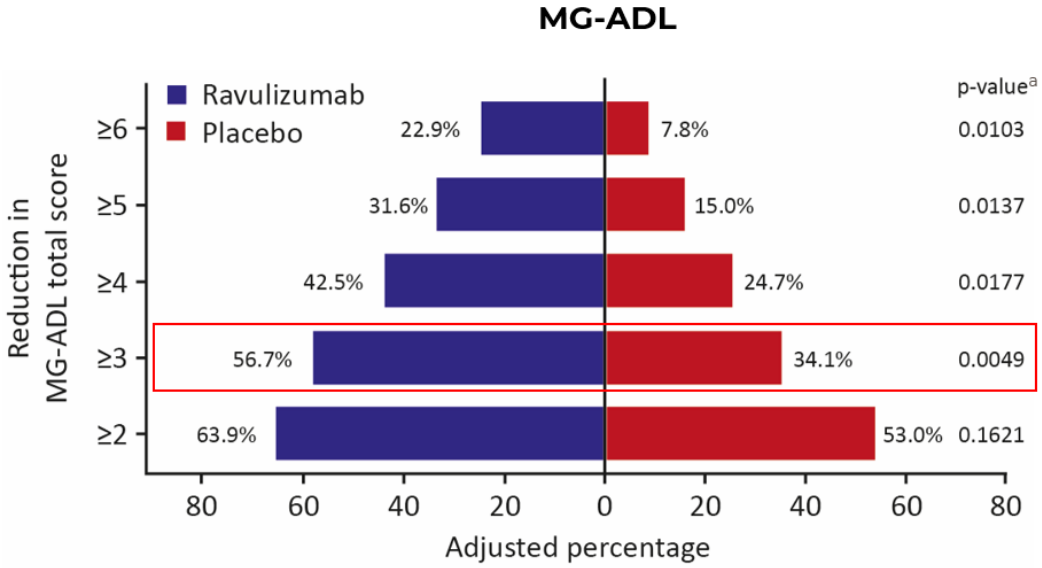
Figure 1: Change from baseline to Week 26 in MG-ADL total score



Key: MG-ADL, Myasthenia Gravis Activities of Daily Living.

There were more MG-ADL responders (MG-ADL ≥3-point improvement at Week 26) in the ravulizumab arm (56.7%) versus the placebo arm (34.1%; Figure 2)

Figure 2: Proportion of patients with various point reductions in MG-ADL total score at Week 26



Key: MG-ADL, Myasthenia Gravis Activities of Daily Living.

During the 26-week study period, there were fewer clinical deteriorations (9% versus 17%) and less rescue therapy use (9% versus 16%) in the ravulizumab arm compared with the placebo arm.

The incidence of MG-related hospitalization was also lower with ravulizumab treatment versus placebo (4 hospitalizations with ravulizumab versus 9 with placebo), with a shorter average duration of stay (5.8 days with ravulizumab versus 6.8 days with placebo).

Further information on the efficacy outcomes from CHAMPION-MG can be found in Document B (Section B.2.6.1).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The impact of ravulizumab on quality of life was assessed in the CHAMPION-MG trial using two quality-of-life measures:

- Myasthenia Gravis Quality of Life 15-item scale (**MG-QoL15**) – a 15-item questionnaire designed to assess the quality of life in patients with MG
- Quality of Life in Neurological Disorders (**Neuro-QoL**) Fatigue subscore – an eight-item self-reported survey with a possible 40 points, with higher scores indicating worse fatigue

Patients' quality of life was maintained during the CHAMPION-MG trial, with no statistically significant changes between the ravulizumab plus standard of care and placebo plus standard of care treatment groups.

The CHAMPION-MG trial was conducted during the COVID-19 pandemic. This may have had an effect on the results of the trial, potentially masking the true treatment effect of ravulizumab on quality of life. Other studies have found that patients with MG have experienced a decline in their quality of life during the COVID-19 pandemic, demonstrated by worsening in MG-QoL15 scores. [69, 70] Analyses performed on the results of the CHAMPION-MG study found that when patients who had been significantly impacted by COVID-19 were removed, there was a significantly greater improvement in quality of life for patients treated with ravulizumab compared with placebo, as measured by the MG-QoL15r scale.[71]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The most common adverse reactions associated with ravulizumab include diarrhoea, upper respiratory tract infection, nasopharyngitis and headache. The most serious adverse reactions in patients in clinical trials are meningococcal infection (a serious infection caused by the bacteria *Neisseria meningitidis*) and meningococcal sepsis (a serious condition caused by the spread of *Neisseria meningitidis* into the bloodstream and various organs). The most commonly reported adverse reactions observed in clinical trials and in post-marketing studies for other conditions that can be treated with ravulizumab are presented in Table 2. These other conditions are paroxysmal nocturnal haemoglobinuria, a rare blood disease that causes red blood cells to break apart; and atypical haemolytic uraemic syndrome, a disease that causes abnormal blood blots to form in small blood vessels in the kidneys. Meningococcal infections were reported as uncommon (≥ 1/1,000 to < 1/100) adverse reactions.

Table 2: Summary of very common and common adverse reactions

Intervention	**Key adverse reactions**	
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**
Ravulizumab	Upper respiratory tract infection Nasopharyngitis Headache Diarrhoea Nausea Fatigue	Dizziness Abdominal pain Vomiting Dyspepsia Rash Pruritus Urticaria Arthralgia Back pain Myalgia Muscle spasms Pyrexia Influenza-like illness

		Asthenia Infusion-related reaction

Source: Ravulizumab SmPC (2022).[72]

In the CHAMPION-MG study, across the ravulizumab and placebo arms, the proportion of patients who experienced adverse events was similar. The most frequent adverse event was headaches, experienced by 19% of patients in the ravulizumab arm and 26% in the placebo arm.

Serious adverse events were reported for 23% of patients in the ravulizumab arm and 16% of patients in the placebo arm.[67] The most frequent serious adverse events were worsening of MG (one patient receiving ravulizumab and three receiving placebo) and COVID-19 (two patients receiving ravulizumab and one patient receiving placebo). There were no cases of meningococcal infection during the randomized controlled period. Two deaths were reported in the ravulizumab arm: one due to COVID-19 and one due to cerebral haemorrhage.[67] Neither death was considered to be related to ravulizumab treatment.

In the open-label extension study, following up to 60 weeks of ravulizumab treatment, there were no meningococcal infections. Most of the adverse events that occurred in this extension study were mild in severity and considered to be unrelated to ravulizumab treatment.[73] Four patients died: one due to cerebral haemorrhage and three due to COVID-19.[73] None of these deaths was considered to be related to ravulizumab treatment.

As with any medicine, if patients experience any side effects, they should talk to their doctor or nurse. Patients can also directly report any side effects to the Yellow Card Scheme in the UK.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Ravulizumab is an effective and safe therapy that demonstrates rapid and sustained improvements in symptoms and minimizes functional impairment. Only six infusions a year need to be given to patients with anti-AChR antibody-positive gMG.

Ravulizumab has demonstrated significant improvements in treating gMG, measured by the MG-ADL and QMG total scores at Week 26 in the Phase III CHAMPION-MG trial.[71] The statistically significant improvements observed at Week 26 were sustained for patients who continued in the open-label extension study up to Week 60, suggesting that ravulizumab is associated with longer-term stabilization of patients' symptoms.

Patients treated with ravulizumab did not have to wait long to experience the benefit of treatment. In CHAMPION-MG, ravulizumab demonstrated a rapid onset of action, with improvements in MG-ADL total scores seen within 1 week of adding ravulizumab to a background treatment regimen. This allows patients to quickly regain function in routine activities.[71]

These treatment benefits extended to reductions in the incidence of clinical deterioration and use of rescue therapy, which will likely reduce the burden of gMG on patients, their carers, and the healthcare system.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Patients will only need to receive their treatment every 8 weeks. Ravulizumab treatments must always be administered by a healthcare professional. The first two doses of ravulizumab (the loading dose and the first maintenance dose) will likely be administered in hospital (in an outpatient clinic). Further doses can then be administered by a healthcare professional in the patient's home, as Alexion provides a Homecare service for ravulizumab.

Some patients may not want to receive an intravenous treatment. However, the drawbacks of intravenous administration may be outweighed by the benefits of a limited number of doses required each year (6 or 7 only) and a greater potential for rapid and sustained improvement in gMG symptoms compared with current standard-of-care treatment options.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects gMG

The cost-effectiveness model reflects the reduction in a patient's MG-ADL score when receiving ravulizumab or standard of care, with a greater reduction reflecting more improvement in symptoms. The model also captures the number of myasthenic exacerbations and myasthenic crises experienced by patients receiving each treatment.

The model is informed by data from the ravulizumab clinical trial CHAMPION-MG and the eculizumab clinical trial REGAIN. The model uses data related to MG-ADL scores to reflect a patient's response to treatment and their health-related quality of life. The model also uses the number of exacerbations and crises in the trials to predict the number of events patients will experience while receiving ravulizumab and their existing standard-of-care treatments.

Health outcomes

Ravulizumab has been shown to reduce a patient's MG-ADL score, which reflects an improvement in their symptoms and in turn increases their quality of life. Ravulizumab also reduces the risk of

experiencing myasthenic exacerbations or myasthenic crises. These events can have a significant impact on a patient's quality of life.

A myasthenic crisis can be fatal for a patient, so by reducing the risk of patients experiencing these events, ravulizumab reduces the risk of a patient dying from gMG.

Cost outcomes

Myasthenic exacerbations and crises are also associated with significant management costs. Therefore, reducing the risk of these events will result in cost savings for the health service, as well as improved quality of life for the patients.

Ravulizumab is administered via intravenous infusion every 8 weeks. The first two of these infusions need to be carried out in a hospital setting. However, after this Alexion provides infusions at the patient's home for the duration of their treatment. As ravulizumab is an add-on to standard of care, patients will continue to receive any prescribed corticosteroids or immunosuppressants.

Uncertainty

There is significant uncertainty around the long-term outcomes of gMG patients on standard of care. REGAIN and CHAMPION-MG are the only randomized control trials that provide evidence for patients on standard of care, and this only provides 26 weeks of comparative data. However, long-term follow-up data (without the standard of care comparison) from CHAMPION-MG (up to 60 weeks) are available. The long-term eculizumab data from REGAIN (up to 3 years) can be used to demonstrate the expected ravulizumab results, due to the similarity between the two drugs.

There was believed to be a placebo effect in the control arm of the trial, which is reflected in the model due to a lack of alternative evidence. Removing this effect using a simple assumption results in significantly improved cost-effectiveness results. This means that the economic model is likely to be conservative – i.e. it underestimates the comparative benefits of ravulizumab, meaning ravulizumab is likely to be more cost-effective than the results of the model suggest.

Results

Ravulizumab is associated with an improved quality of life, a minor extension in survival and cost-savings by reducing patient's risk of experiencing a myasthenic exacerbation or crisis.

Additional factors

This appraisal in gMG was not eligible for any severity multipliers. One benefit that is challenging to capture in the cost-effectiveness model is how quickly the treatment effect of ravulizumab occurs. A patient's response to ravulizumab is expected to be assessed after 16 weeks, compared with standard of care where response to treatment is often only assessed after a year or more on treatment. The financial aspect of this benefit is captured in the model. However, it is difficult to reflect the value of peace of mind for a patient knowing they are receiving a treatment that works quickly – rather than one that does not work until several months have passed.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Ravulizumab is an innovative monoclonal antibody that was developed by re-engineering eculizumab to create a longer half-life. This means that ravulizumab is a longer-acting drug. As a result, patients only need to receive their maintenance treatment once every 8 weeks compared with every 2 weeks for eculizumab.

Eculizumab is not reimbursed for use in the NHS and is therefore not available to patients in the UK. If ravulizumab is recommended for use by NICE, it would be the first complement inhibitor treatment to be used to treat patients with gMG in the UK.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality issues are expected.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Response: Information on ravulizumab: • Ultomiris (ravulizumab) information for patients: ULTOMIRIS (ravulizumab-cwvz) | Official Patient Website Information on generalized myasthenia gravis: • Myaware charity – providing support and advice for people affected by myasthenia: myaware • National Institute of Neurological Disorders and Stroke MG Factsheet: Myasthenia Gravis Fact Sheet | National Institute of Neurological Disorders and Stroke (nih.gov) • NHS MG Overview: Myasthenia gravis - NHS (www.nhs.uk) Further information on NICE and the role of patients: • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE

- EUPATI guidance on patient involvement in NICE: Guidance on Patient Involvement in HTA - EUPATI Toolbox
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: Health technology assessment: an introduction to objectives, role of evidence, and structure in Europe (who.int)

4b) Glossary of terms

- **ACh**, acetylcholine, is a neurotransmitter that acts at the neuromuscular junction and communicates between nerve and muscle cells
- **AChR**, acetylcholine receptors, exist on the neuromuscular junction. Acetylcholine binds to these receptors, which results in muscle contraction
- **gMG**, generalized myasthenia gravis, is a rare, chronic autoimmune disorder that disrupts the communication between nerve and muscle cells, resulting in weakness in the muscles that control breathing, swallowing, and movement of the body. In gMG, one or more muscle group (not including eye muscles) in the head, neck, trunk and/or limbs are affected
- **MG-ADL**, Myasthenia Gravis Activities of Daily Living, is a disease-specific measure consisting of eight items, each scored from 0 to 3 (higher scores indicate greater disease severity) and combines two items on daily life activities (ability to brush teeth or comb hair, and limitations in the ability to rise from a chair) with six items reflecting other gMG symptoms: diplopia, ptosis, chewing, swallowing, voice/speech problems and respiratory symptoms.[74] This questionnaire is completed by patients based on their recollections from the previous week
- **MG-QoL15**, Myasthenia Gravis Quality of Life 15-item scale, is a 15-item questionnaire designed to assess the quality of life in patients with MG. The revised version of this scale (MG-QoL15r) was used in the CHAMPION-MG study
- **NeuroQoL Fatigue**, Quality of Life in Neurological Disorders Fatigue score, is an eight-item self-reported survey with a possible 40 points. Higher points indicate worse fatigue
- **QMG**, Quantitative Myasthenia Gravis Score, is a disease-specific measure consisting of 13 items, each scored from 0 to 3 (higher scores indicate greater disease severity), that measures endurance or fatigability.[74] This questionnaire is completed by physicians at a single point in time

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ravulizumab for treating generalised myasthenia gravis [ID4019]

Clarification questions

April 2023

File name	Version	Contains confidential information	Date
ID4019 ravulizumab EAG clarification letter – Alexion response AIC CIC	1.0	Yes	28 April 2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Systematic literature review

A1. Please provide the list of studies excluded from the systematic literature review of clinical effectiveness [company submission (CS) Appendix D says this is available on request].

Please find a list of studies excluded from the global clinical systematic literature review in Table 1.

Table 1: List of studies excluded from the clinical systematic literature review

First author, year	Title	Reason for exclusion
Achiron et al., 2000	Immunoglobulin treatment in refractory myasthenia gravis	Study design
Akaishi et al., 2016	Response to treatment of myasthenia gravis according to clinical subtype	Study design
Bril et al., 2019	Proof-of-concept and safety of the anti-FCRN antibody rozanolixizumab in patients with moderate-to-severe generalized myasthenia gravis (GMG): a phase 2a study	Intervention/Comparator

First author, year	Title	Reason for exclusion
Chiu et al., 2000	The six year experience of plasmapheresis in patients with myasthenia gravis	Study design
Clinicaltrials.gov, 2019	A study to evaluate safety, tolerability, and efficacy of TAK-079 in participants with generalized myasthenia gravis	Outcomes
Diaz-Manera et al., 2012	Long-lasting treatment effect of rituximab in MuSK myasthenia	Study design
Dos Santos et al., 2020	Efficacy and safety of rituximab in myasthenia gravis: a French multicentre real-life study	Study design
Drachman et al., 2008	Rebooting the immune system with high-dose cyclophosphamide for treatment of refractory myasthenia gravis	Study design
Gamez et al., 2019	Intravenous immunoglobulin to prevent myasthenic crisis after thymectomy and other surgical procedures can be omitted: a randomized, controlled, double-blind trial	Study design
Guptill et al., 2020	A phase 2, multicentre, randomized, doubleblind, placebo-controlled study to evaluate the safety, tolerability, efficacy, PK, and PD of nipocalimab (m281) in adults with generalized myasthenia gravis	Intervention/Comparator
Guptill et al., 2021	Phase 2 RCT trial evaluating the fcrn antagonist nipocalimab in adults with generalized myasthenia gravis	Intervention/Comparator
Guptill et al., 2021	Vivacity-MG: a phase 2, multicentre, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of nipocalimab administered to adults with generalized myasthenia gravis	Intervention/Comparator
Han et al., 2015	Double filtration plasmapheresis combined with glucocorticoid treatment for myasthenia gravis: symptom remission and variation of immune antibodies	Other
Hanisch et al., 2009	Mycophenolate mofetil as second line immunosuppressant	Study design

First author, year	Title	Reason for exclusion
	in myasthenia gravis - A long-term prospective open-label study	
Hewett et al., 2018	Randomized study of adjunctive belimumab in participants with generalized myasthenia gravis	Intervention/Comparator
Howard et al., 2021	Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): A multicentre, randomised, placebo-controlled, phase 3 trial	Duplicate publication
Howard et al., 2019	Zilucoplan, a subcutaneously self administered peptide inhibitor of complement component 5 (C5), for the treatment of generalized myasthenia gravis: Results of a phase 2 randomized, double-blind, placebo-controlled trial	Duplicate publication
Howard et al., 2019	Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis	Duplicate publication
Howard et al., 2020	Clinical effects of the self-administered subcutaneous complement inhibitor zilucoplan in patients with moderate to severe generalized myasthenia gravis: Results of a phase 2 randomized, double-blind, placebo-controlled, multicentre clinical trial	Duplicate publication
Howard et al., 2019	Zilucoplan, a self-administered subcutaneous peptide inhibitor of complement component 5 (C5) for the treatment of generalized myasthenia gravis: Phase 2 results	Duplicate publication
Itoh et al., 2002	Sensitivity to vecuronium in seropositive and seronegative patients with myasthenia gravis	Study design
Jacob et al., 2020	'Minimal symptom expression' in patients with acetylcholine receptor antibody-positive refractory generalized myasthenia gravis treated with eculizumab	Duplicate publication
Jiang et al., 2020	Thymus-derived B cell clones persist in the circulation after thymectomy in myasthenia gravis	Population

First author, year	Title	Reason for exclusion
Katzberg et al., 2012	Predictors of response to immunomodulation in patients with myasthenia gravis	Outcomes
Konig et al., 2021	MuSK-antibodies are associated with worse outcome in myasthenic crisis requiring mechanical ventilation	Study design
Lee et al., 2020	Minimal manifestation status and prednisone withdrawal in the MGTX trial	Population
Li et al., 2019	Results of robotic thymectomy performed in myasthenia gravis patients older than 60 years at onset	Study design
Li et al., 2014	Serum IL-21 levels decrease with glucocorticoid treatment in myasthenia gravis	Population
Lipka et al., 2016	Ephedrine treatment for autoimmune myasthenia gravis	Intervention/Comparator
Mercedes et al., 2019	Eculizumab in refractory generalized myasthenia gravis	Other
Misra et al., 2006	A study of diagnostic yield, technical ease and patient discomfort of low rate repetitive nerve stimulation test in patients with myasthenia gravis	Intervention/Comparator
Narayanaswami et al., 2021	PROMISE-MG: A comparative effectiveness study of myasthenia gravis treatments: study design, demographics and baseline data	Study design
Onesti et al., 2019	Short-Term Ultramicronized Palmitoylethanolamide Therapy in Patients with Myasthenia Gravis: a Pilot Study to Possible Future Implications of Treatment	Intervention/Comparator
Rowin et al., 2004	Etanercept treatment in corticosteroid dependent myasthenia gravis	Intervention/Comparator
Sanders et al., 2015	A Double-Blinded, Randomized, Placebo-Controlled Trial to Evaluate Efficacy, Safety, and Tolerability of Single Doses of Tirasemtiv in Patients with Acetylcholine Receptor-Binding Antibody-Positive Myasthenia Gravis	Intervention/Comparator
Soliven et al., 2009	Terbutaline in myasthenia gravis: A pilot study	Intervention/Comparator

First author, year	Title	Reason for exclusion
Strijbos et al., 2017	A prospective, placebo controlled study on the humoral immune response to and safety of tetanus revaccination in myasthenia gravis	Intervention/Comparator
Tackenberg et al., 2018	Acetylcholine receptor antibody titers and clinical course after influenza vaccination in patients with myasthenia gravis: A double-blind randomized controlled trial (ProPATIent-Trial)	Intervention/Comparator
Tada et al., 2006	Long-term therapeutic efficacy and safety of low-dose tacrolimus (FK506) for myasthenia gravis	Duplicate publication
Tuzun et al., 2005	Myasthenia gravis patients with low plasma IL-6 and IFN-gamma benefit from etanercept treatment	Intervention/Comparator
Ulrichts et al., 2019	Efgartigimod in myasthenia gravis: Update on clinical development and phase 3 ADAPT study	Duplicate publication
Wolfe et al., 2016	Randomized trial of thymectomy in myasthenia gravis	Population
Yeh et al., 2000	Comparison between double-filtration plasmapheresis and immunoadsorption plasmapheresis in the treatment of patients with myasthenia gravis	Outcomes
Yoshikawa et al., 2012	Indication of extended thymectomy in patients with myasthenia gravis	Other
Zambelis et al., 2011	Repetitive nerve stimulation of facial and hypothenar muscles: Relative sensitivity in different myasthenia gravis subgroups	Outcomes
Zhao et al., 2021	Double-blinded, randomized, placebo-controlled phase 2 study of FCRN antagonist batoclimab in Chinese generalized myasthenia gravis	Intervention/Comparator

Key: Ab, antibody; AChR, acetylcholine receptor; FcRn, neonatal Fc receptor; gMG, generalised myasthenia gravis; MuSK, muscle specific kinase; NMOSD, neuromyelitis optica spectrum disorder; PD, pharmacodynamics; PK, pharmacokinetics.

CHAMPION-MG trial

A2. Please provide the tables of actual values and change from baseline to week 26 results for the EQ-5D-5L VAS and index score referred to in section 5.1.3.2 of the 2021clinical study report (CSR) (Tables 14.2.3.3.2.1 to 14.2.3.3.6.1).

The CSR supplemental tables 14.2.3.3.2.1 to 14.2.3.3.6.1 can be found in the zip folder labelled “A2_EQ5D5L_VAS_index”.

A3. The number of data available for analysis at week 26 for the MGQoL15r and the Neuro-QoL Fatigue score differ slightly between Figure 2 in the trial publication (Vu et al. 2022, reference 130) and CS Figure 10. Please explain this.

Thank you for highlighting this discrepancy, we included the wrong figures from the CSR for the 60 Week Addendum in the company submission. Please find the correct figures below:

Figure 1: Change from randomized controlled period baseline in MG-QoL15r score (LSM and 95% CI) up to Week 60 [Replacing CS Figure 10]

Key: CI, confidence interval; LS, least square; MG-QoL15r, Revised Myasthenia Gravis; MMRM, Mixed Model Repeated Measures; PBO/RAV, placebo/ravulizumab; RAV/RAV, ravulizumab/ravulizumab.
Source: CHAMPION-MG clinical study report – 60-week addendum.[1]

Figure 2: Change from randomized controlled period baseline in Neuro-QoL Fatigue score (LSM and 95% CI) up to Week 60 [Replacing CS Figure 11]

Key: CI, confidence interval; LS, least square; Neuro-QoL, Quality of Life in Neurological Disorders; PBO/RAV, placebo/ravulizumab; RAV/RAV, ravulizumab/ravulizumab.
Source: CHAMPION-MG clinical study report – 60-week addendum.[1]

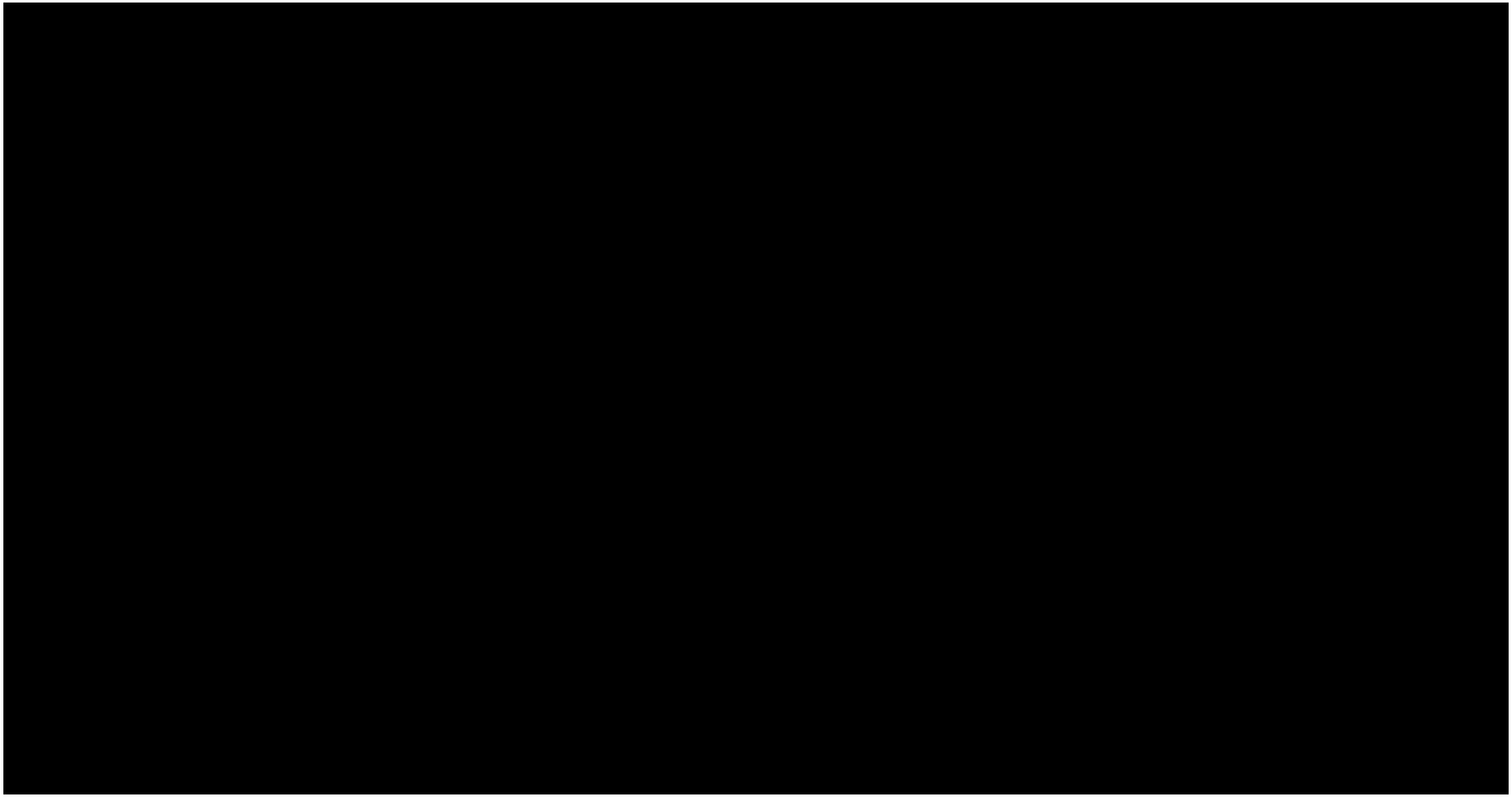
A4. CS section B.2.7 presents descriptive subgroup analysis results for the primary and key secondary outcomes analysed according to eight baseline characteristics. The text in CS section B.2.7 cites Howard et al. (reference 141) for the data but this reference only reports one subgroup analysis (time from diagnosis). Please provide quantitative data (e.g. forest plots) for all of the subgroup analyses described in CS section B.2.7.

Please find below forest plots from the CSR for subgroup analyses of the primary (Figure 3) and key secondary endpoints (Figure 4 to Figure 8). We also noted that Howard et al. is not cited in this section of the submission. Please could the EAG confirm this?

Figure 3: Forest plot of change from baseline to Week 26 in MG-ADL total score, overall and by subgroup (full analysis set)

Key: CI, confidence interval; DIFF, difference; IST, immunosuppressant therapy; LS, least square; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America.
Source: CHAMPION-MG clinical study report.[2]

Figure 4: Forest plot of change from baseline to Week 26 in QMG total score, overall and by subgroup (full analysis set)

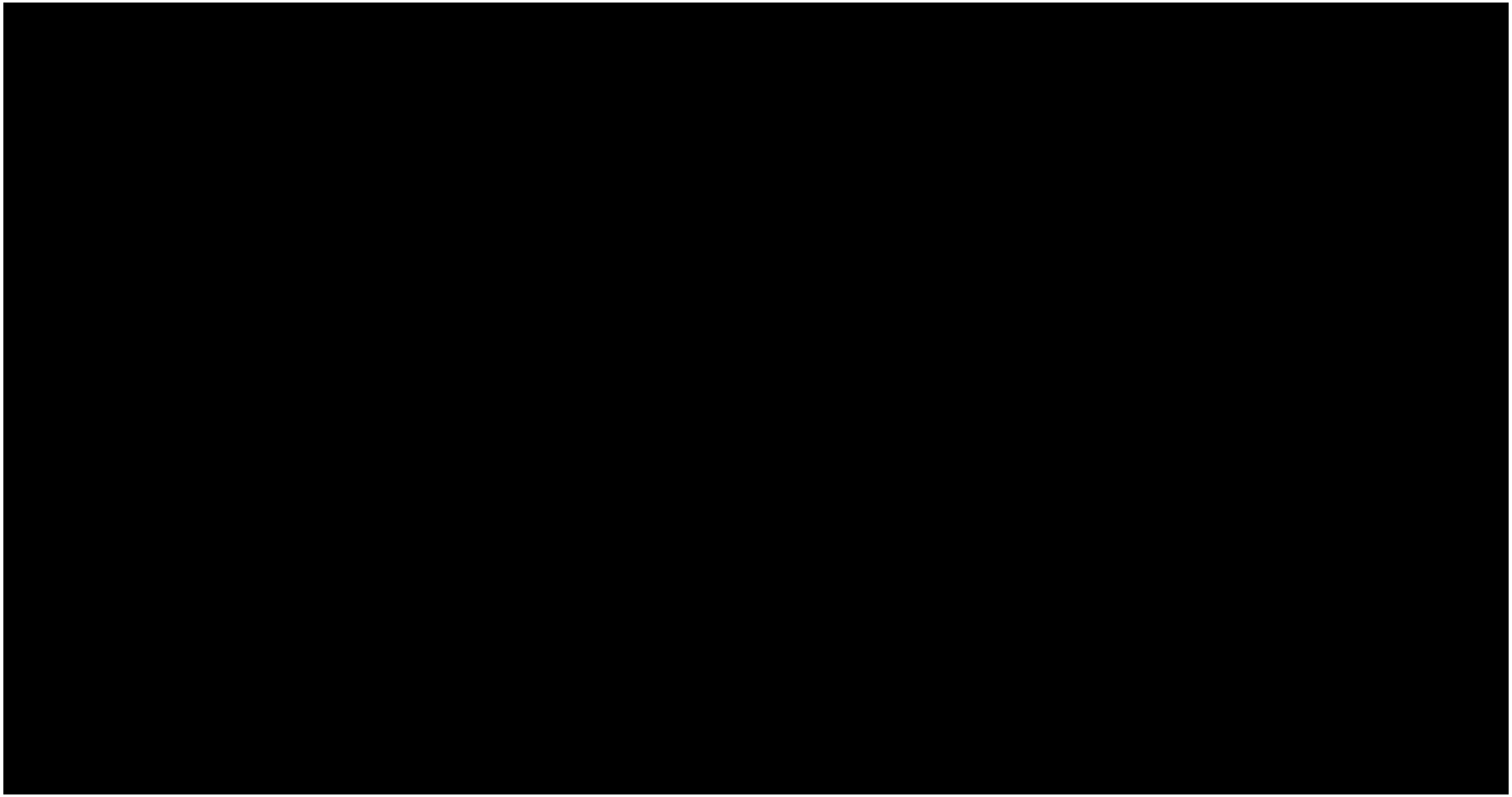


Key: CI, confidence interval; DIFF, difference; IST, immunosuppressant therapy; LS, least square; MGFA, Myasthenia Gravis Foundation of America; QMG, Quantitative Myasthenia Gravis.
Source: CHAMPION-MG clinical study report.[2]

Figure 5: Forest plot of at least 5-point improvement from baseline to Week 26 in QMG total score, overall and by subgroup (full analysis set)

Key: CI, confidence interval; IST, immunosuppressant therapy; LS, least square; MGFA, Myasthenia Gravis Foundation of America; QMG, Quantitative Myasthenia Gravis; OR, odds ratio.
Source: CHAMPION-MG clinical study report.[2]

Figure 6: Forest plot of change from baseline to Week 26 in MG-QoL15r score, overall and by subgroup (full analysis set)



Key: CI, confidence interval; DIFF, difference; IST, immunosuppressant therapy; LS, least square; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15r, Revised 15-Component Myasthenia Gravis Quality of Life.
Source: CHAMPION-MG clinical study report.[2]

Figure 7: Forest plot of change from baseline to Week 26 in NeuroQoL Fatigue score, overall and by subgroup (full analysis set)

Key: CI, confidence interval; DIFF, difference; IST, immunosuppressant therapy; LS, least square; MGFA, Myasthenia Gravis Foundation of America; NeuroQoL, Neurological Quality of Life.
Source: CHAMPION-MG clinical study report.[2]

Figure 8: Forest plot of at least 3-point improvement from baseline to Week 26 in MG-ADL total score, overall and by subgroup (full analysis set)

Key: CI, confidence interval; IST, immunosuppressant therapy; LS, least square; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; OR, odds ratio.
Source: CHAMPION-MG clinical study report.[2]

A5. The CHAMPION-MG trial CSR does not include the main data tables. Please provide the following tables:

(a) Full baseline characteristics: Table 14.1.1.1.1 (full analysis set), Table 14.1.1.1.2 (safety set), Table 14.1.1.1.5 (extension study).

(b) Previous medical history: Table 14.1.3.3.2 (safety set).

(c) Concomitant medications used during the randomized-controlled period: Table 14.1.5.9.2 (medications including IV immunoglobulin), Table 14.1.5.10.2 (plasma exchange/plasmapheresis), Table 14.1.5.12.2 (immunosuppressants).

(d) Changes in concomitant medications during the randomised controlled period: Table 14.1.5.14.2.

(e) Concomitant medications used during the extension study: Table 14.1.5.22.5 (IV immunoglobulin), Table 14.1.5.23.5 (plasma exchange/plasmapheresis), Table 14.1.5.24.5 (immunosuppressants).

(f) Changes in concomitant medication during the extension study: Table 14.1.5.25.5.

The main data tables missing from the CSR can be found in the zip folder labelled "A5_main data tables".

A6. The trial publication (Vu et al. 2022, reference 130) states that Alexion was responsible for analysing all trial data in CHAMPION-MG. According to CS Table 10, care providers, participants and outcome assessors were blinded to treatment allocation, but this does not explicitly cover all investigators, e.g. data analysts. Please clarify whether there were any people involved in the trial conduct, analysis, and reporting who were not blinded to the ravulizumab/placebo group assignments.

We can confirm that everyone involved in the CHAMPION-MG trial was blinded to treatment arm until database lock.

CHAMPION-MG extension study

A7. Please clarify when the next data cut for the CHAMPION-MG extension study will be available and, if possible, what the estimated sample size and length of follow-up for that data cut is likely to be.

Alexion do not anticipate that analysis from further data cuts will be available during the timeframe of this appraisal process.

A8. Please provide a critical appraisal of the CHAMPION-MG extension study to identify all potential sources of bias (i.e. systematic error) for each outcome assessed in this study. The EAG are not prescriptive in the tool(s) that we suggest the company should use, but we do request that:

> **(i) the focus should be on internal validity (i.e. risk of bias) (rather than undefined "quality" criteria),**
>
> **(ii) an attempt should be made to identify all potential sources of bias relevant to the study design, and**
>
> **(iii) a rationale should be concisely stated for each judgement made.**

Resources that may be helpful when considering where bias may arise in non-randomised cohort studies include a checklist for "non-randomised and non-controlled studies" provided in NICE's guidance for company submissions[3] and a paper by Bowers et al.[4] which discusses in detail the methodological issues encountered in trial extension studies.

Please find a critical appraisal of the open-label extension period of the CHAMPION-MG study in Table 2. The Downs and Black checklist has been used to assess the overall methodological quality of this part of the study.[5]

Overall, the CHAMPION-MG open-label extension period satisfied the relevant Downs and Black checklist criteria, excluding the questions around randomization. Patients included in the open-label extension study were initially randomized within the randomized controlled period, and received ravulizumab regardless of intervention assigned within the randomized controlled period. Patient disposition was reported as of the clinical data cut-off date (9 November 2021). Less than 10%

of the population (7%, n = 161) had discontinued from the study during the open-label extension period.

Table 2: Critical appraisal of the open-label extension period of CHAMPION-MG using the Down and Blacks checklist

Is the hypothesis/aim/objective of the study clearly described?	Yes Reason for the addendum to the CSR provided.
Are the main outcomes to be measured clearly described in the introduction or methods section?	Yes
Are the characteristics of the patients included in the study clearly described?	Yes Patients who enrolled into the open-label extension period completed CHAMPION-MG the randomized controlled period. Characteristics were summarized in the CHAMPION-MG CSR.
Are the interventions of interest clearly described?	Yes
Are the distributions of principal confounders in each group of patients to be compared clearly described?	Yes
Are the main findings of the study clearly described?	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes
Have all important adverse events that may be a consequence of the intervention been reported?	Yes
Have the characteristics of patients lost to follow-up been described?	Yes Reasons for withdrawal of the 11 patients who discontinued the open-label extension period presented.
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Not applicable
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes
Were the staff, places, and facilities where the patients were treated	Yes

representative of the treatment the majority of patients receive?	
Was an attempt made to blind study subjects to the intervention they have received?	Yes
Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes
If any of the results of the study were based on 'data dredging', was this made clear?	Yes
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes
Were the statistical tests used to assess the main outcomes appropriate?	Yes
Was compliance with the intervention(s) reliable?	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes
Were study subjects randomised to intervention groups?	No Patients were initially randomized within the randomized controlled period; however, patients entering the open-label extension period all received ravulizumab.
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Not applicable
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes
Source: CHAMPION-MG clinical study report – 60-week addendum.[1]	

Expert consultations

A9. The EAG are unclear whether some of the evidence provided by clinical experts for this technology appraisal may be duplicative.

(a) Please clarify whether the experts participating in the expert elicitation reported in CS Appendix P were independent of those who contributed to the UK Advisory Board (Document B reference 5).

(b) Please clarify whether the experts involved in the company's expert elicitation and UK Advisory Board were independent of those experts who have made consultee submissions for this technology appraisal.

(c) For the expert elicitation reported in CS Appendix P, please clarify how many experts were invited to participate.

(a) Given the rarity of the condition, some of the experts consulted participated in both the expert elicitation presented in CS Appendix P and the UK Advisory Board. However, the purposes of these two activities were different. The expert elicitation exercise focused on participants' experience within their clinical practice to provide healthcare resource use estimates, given the lack of available evidence in the literature. The UK Advisory Board aimed to gain expert feedback on key topics of interest for the development of the submission, including:

- The natural history of gMG for patients treated within UK clinical practice
- Appropriate positioning and relevant comparators for ravulizumab within the UK gMG treatment pathway
- The clinical data available for ravulizumab
- The proposed cost-effectiveness model structure and key assumptions, particularly with respect to treatment duration and extrapolation of long-term outcomes.

Therefore, while there was some crossover in attendees participating in these processes, the likelihood of duplication within the evidence is low given their different purposes.

(b) We would like to clarify that NICE is responsible for the selection of experts consulted for consultee submissions. Therefore, we cannot confirm whether the experts involved in the expert elicitation or serving on the advisory board were independent of those who made consultee submissions for this technology appraisal.

(c) Four experts were invited to participate in the expert elicitation exercise on healthcare resource use.

Section B: Clarification on cost-effectiveness data

Model and results

We thank the EAG for undertaking a thorough review of the submitted economic materials and providing clear areas to clarify. We appreciate that there are some discrepancies between Section 3 of the company submission and the economic model and have sought to clarify them wherever possible. Alongside the response document we have also provided an amended version of the economic model, which reflects all of these changes. The deterministic and probabilistic results from this model have been included at the end of Section B.

B1. PRIORITY QUESTION: The EAG are unable to replicate the tornado diagram presented by the company (CS Figure 23) with the submitted economic model. Please explain and correct this discrepancy.

The tornado diagram presented in CS Figure 23 was incorrect. Figure presents updated results of the deterministic sensitivity analysis, which also accounts for other corrections made in response to the EAG's clarification questions.

Table 3: Updated one-way sensitivity analysis tornado diagram

B2. The 'Restore defaults' macro on the Settings page is not functional, it returns run-time error '1004', and the debugger indicates that the "UD-range_HCcost" is not defined. It also creates an error in the PSA macro by setting the 'clinev_regression' to an out of range value of 4. Please correct this function or advise us that it is not operational.

Thank you for highlighting this issue. We have repaired this functionality in the updated version of the economic model.

Modelled population

B3. PRIORITY QUESTION: Baseline characteristics for economic analysis are not defined in CS section 4 or Appendix O. The model reports baseline characteristics from the CHAMPION_MG and REGAIN trials (Clinical datastore!C5 to E17), but some of these differ from those in CS Table 8. For example, the percentage of women in the CHAMPION-MG trial is cited as 51.1% in the model, but 50.9% (86/175) in CS Table 8. Please provide a table of baseline characteristics used in the model and explain and justify any differences from the values in CS Table 8.

The patient baseline characteristics included in the model were incorrect. These values should have been in line with those presented in Table 8 of the CS. See Table 4 below for the correct values. These updated patient characteristics have

been included in the updated base case results presented at the end of this document.

Table 4: Baseline characteristics used in the cost-effectiveness model

	Pooled CHAMPION and REGAIN	CHAMPION-MG	REGAIN
Age (Years)	52.1	55.6	47.2
% Female	58.5%	53.5%	65.5%
MG-ADL Total Score	9.5	9.0	10.2
Disease duration (years)	9.9	9.9	-
% Disease duration > 2 years	0.84	0.80	0.88
Baseline EQ-5D	0.59	0.59	0.58

Clinical effects

B4. PRIORITY QUESTION: CS Table 24 reports the distribution of patients by magnitude of treatment effect in CHAMPION-MG at 18 weeks for ravulizumab and 26 weeks for standard of care (SoC). However, the reported values in Table 24 correspond to the values at the assessment point 26 weeks in the Excel model (cell Clinical Datastore!C58:D65). Please explain this.

Thank you for highlighting this discrepancy, the wrong timepoint was reported in Table 24 of Document B, this issue does not impact the results of the economic model. A corrected table is presented in Table 5.

Table 5: Distribution of patient by magnitude of treatment effect in CHAMPION-MG at 18-weeks for ravulizumab and 26 weeks for SOC

Change in total MG-ADL score	Ravulizumab (n = 86)	SoC (n = 89)
Change < 3	46.50%	65.20%
3 ≤ Change < 4	53.50%	34.80%
4 ≤ Change < 5	44.20%	25.80%
5 ≤ Change < 6	36.00%	16.90%
6 ≤ Change < 7	27.90%	7.90%
7 ≤ Change < 8	15.10%	3.40%
Change ≥ 8	7.00%	1.10%
Key: MG-ADL, Myasthenia Gravis Activities of Daily Living scale.		

B5. CS Table 25 reports the distribution of patients by magnitude of treatment effect in CHAMPION-MG at 60 weeks. Please clarify whether and how the values reported in this table inform the Excel model. Please provide clear reference to the sheet(s) and calculations within the Excel model.

The values presented in Table 25 of Document B in the CS are not used for calculations within the Excel model. The results from the CHAMPION-MG open-label extension are presented as evidence of the durability of ravulizumab's treatment effect. The 60-week MG-ADL scores are presented next to the 26-week MG-ADL scores for the ravulizumab arm of CHAMPION in Table 6. The results suggest that the modelling assumption that ravulizumab patients only move between MG-ADL substates when they discontinue treatment may be conservative.

Table 6: Distribution of patient by magnitude of treatment effect in CHAMPION-MG at 26-weeks and 60-weeks for ravulizumab

Change in total MG-ADL score (n = 86)	**26 weeks**	**60 weeks**
Change < 3	41.90%	[redacted]
3 ≤ Change < 4	58.10%	[redacted]
4 ≤ Change < 5	45.30%	[redacted]
5 ≤ Change < 6	34.90%	[redacted]
6 ≤ Change < 7	24.40%	[redacted]
7 ≤ Change < 8	14.00%	[redacted]
Change ≥ 8	9.30%	[redacted]
Key: MG-ADL, Myasthenia Gravis Activities of Daily Living scale.		

B6. PRIORITY QUESTION: CS section B.3.3.4 states that the proportion of clinical events that are crises in the model is [redacted]%, however this proportion is not consistent with the numbers of events cited, [redacted]. Please provide a

correction to CS section B.3.3.4 and confirm whether the correct value is being used in the base case model: [redacted] (Clinical datastore!F107).

The incidence rate [redacted] refers to the number of events at the 60-week timepoint, whereas the model correctly uses [redacted] events which is the 26-week data. The 60-week incidence rate has been reported in error in Section B.3.3.4. Please see corrected text below:

"The model estimates the overall number of clinical events in a given treatment cycle, which are then subdivided into exacerbations or crises. The clinical events are divided using a fixed proportion, with [redacted]% of clinical events being crises and the remaining [redacted]% being exacerbations. These proportions were based on the number of crises observed in the 26-week randomized controlled period of CHAMPION-MG and REGAIN across all arms ([redacted] clinical events were crises and [redacted] were exacerbations)."

B7. CS section B.3.3.5 cites a mortality rate of 4.42% associated with MG crises. However, the reference (Alshekhlee et al. 2009) reports a figure of 4.47%, and the model uses a value of 4.50%. Please provide a correction to CS section B.3.3.5.

Both the model and section B.3.3.5 should use the value 4.47% taken from Alshekhlee et al. (2009). The model has been updated and the corrected text is provided below:

"However, when gMG is not well controlled, patients can experience an MG crisis, which is associated with an increased rate of mortality. A study reviewing a US database on inpatient treatments reported a mortality rate of 4.47% associated with MG crises.[6] The model assumes that all MG crises that occur in each cycle are managed as an inpatient hospital stay, and the mortality rate is applied to all patients experiencing a crisis."

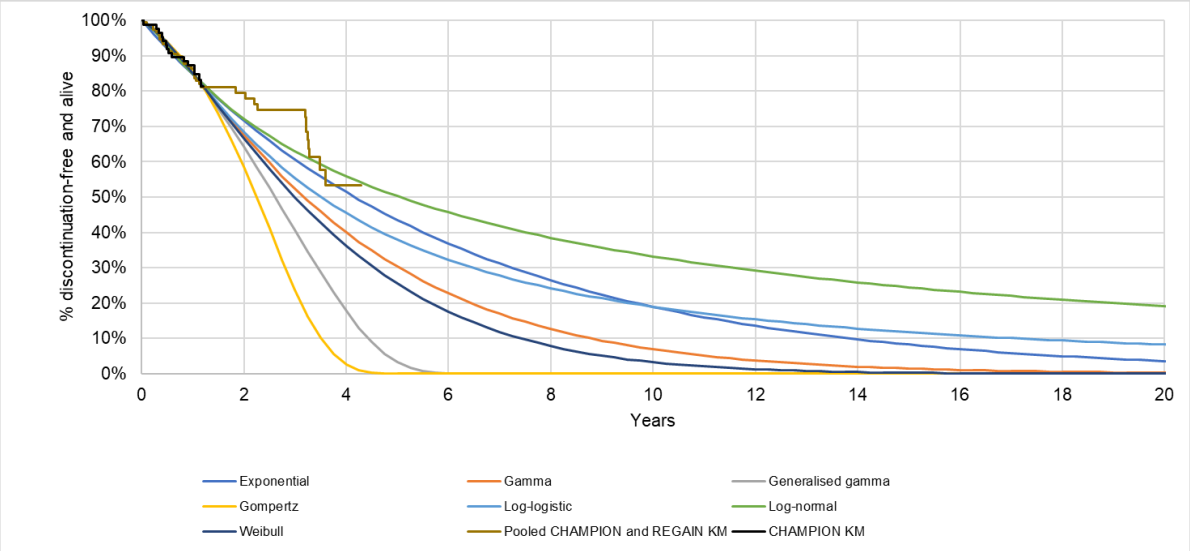
Time on treatment

B8. PRIORITY QUESTION: CS Figure 19 shows that the parametric extrapolations of time on treatment are heavily influenced by the drop off in treatment rates after year 3 in the REGAIN OLE study. It is noted in CS section

B.3.3.2 that this may have been caused by patients exiting the study when eculizumab became commercially available in their country of residence (CS section B.3.3.2). If so, this would not be reflective of long-term continuation of ravulizumab if recommended for use in the NHS. Please provide a scenario analysis with survival curves fitted to the CHAMPION-MG trial data only.

Extrapolations using only the CHAMPION-MG trial data are available in the Excel model and can be selected by using “settings_TTD_source” on the Settings sheet. Figure 9 presents these extrapolations against KM data from CHAMPION alone and the pooled KM curve for CHAMPION + REGAIN, which still provides the most robust evidence source for long-term time on treatment.

Figure 9: Time on treatment extrapolations using CHAMPION-MG trial data only



Goodness-of-fit statistics for the extrapolations using only CHAMPION-MG trial data are presented in Table 7. As with the pooled analysis, the exponential model provides the best statistical fit to the observed data. All of the models provide a good fit to the observed data but result in a wide array of long-term estimates. The exponential is considered the most appropriate curve for extrapolating time-on-treatment. It provides the best statistical fit to the data, has a plausible long-term estimate and is inherently associated with the fewest assumptions.

Table 7: Time on treatment CHAMPION-MG goodness-of-fit statistics

Model	AIC	BIC
Exponential	85.8	88.2
Gamma	86.7	91.6
Gen. Gamma	88.6	95.9
Gompertz	86.6	91.5
Log-Logistic	86.7	91.7
Log-Normal	87.6	92.5
Weibull (AFT)	86.7	91.6

Supplementing CHAMPION data with the long-term data from the REGAIN trial reduces uncertainty by providing follow-up for two additional years compared to CHAMPION-MG, therefore it is still preferred in the base case. Results using CHAMPION-MG data alone to extrapolate time-on-treatment using the best fit exponential model are presented as a scenario. The results of this scenario are presented in Table 12 and reduce the ICER by approximately £[redacted]/QALY. However the short-term follow-up compared to the expected time-on-treatment leads to significant variation in economic results dependent on the selected parametric model.

Utilities

B9. PRIORITY QUESTION: CS section B.3.4.5 states that the base case uses a simple utility regression model including only MG-ADL score and baseline EQ-5D as independent variables (CS Table 31). However, the submitted model

includes disease duration and clinical events within 3 months as additional co-variates (Utilities!D7-D11). Please explain this discrepancy and clarify which MG-ADL score utility regression model should be included in the base case analysis.

Parameter	CS Table 31	Excel model (Utilities!D7 to D12)
Intercept	[redacted]	[redacted]
MG-ADL Score	[redacted]	[redacted]
Baseline EQ-5D	[redacted]	[redacted]

The wrong regression model was selected in the model base case in error. The submitted model should have been reflected the utility regression outlined in the company submission, including only MG-ADL score and baseline EQ-5D as independent variables. The updated cost-effectiveness model reflects uses this utility regression with results reported in Table 11.

B10. Please explain and correct the following inconsistencies in the QALY decrements associated with clinical events:

(a) CS Table 32 reports a value of -0.998 for crises but the Excel model uses -0.0998 (Utilities!I21).

(b) The estimated total caregiver utility decrements for exacerbations and crises in CS Table 33 are inconsistent with the values reported in the Excel model (Utilities!D35 and I35).

(c) The EAG are unable to locate the caregiver disutilities for exacerbations and crises in the cited reference (Thomas et al. 1997). Please provide the appropriate reference.

a) -0.0998, as reported in the Excel model, is the correct value.

b) The correct utility decrements are -0.0023 for exacerbations and -0.0085 for crises as reported in the Excel model.

c) The incorrect reference was cited and should instead have been Thomas et al. 2015.[7] The value cited refers to the difference between health-related quality of life reported by non-carers (0.84) and carers for patients with gMG (0.81).

B11. CS Table 30: Adverse event disutility and duration.

(a) The Excel model uses a value of 2.4 days for duration of diarrhoea (AEs!Q16). Please explain why this is slightly different from the source, which reports 2.5 days.

(b) The EAG are unable to find the reference for the disutility of nasopharyngitis of -0.01 from the cited reference of Jit et al. Please provide the appropriate reference.

a) This is an error, the Excel model should use 2.5 days and this value is incorporated into the updated base case.

b) The reference cited[8] uses a QALY loss of -0.01 for an episode of influenza and was assumed to reflect the quality-of-life impact of nasopharyngitis. This assumption was made due to the lack of quality-of-life evidence associated with nasopharyngitis.

Resource use and costs

B12. The economic model uses a ravulizumab loading dose of 3600 mg for patients with body weight ≥100 kg (Drug costs!G17). This is inconsistent with the value reported in CS Table 22 (3000 mg). Please explain this inconsistency.

Thank you for highlighting this, the model should use a loading dose of 3000mg for patients with body weight ≥100 kg, in line with the ravulizumab SmPC. This change has been reflected in the updated base case.

B13. Please provide the CSR Tables 14.1.5.2 and 14.1.5.3, cited as the source for the distributions of SoC therapies (CS Table 23).

The wrong table within the CSR is cited as the reference in Table 23 of the company submission. The source for this information was Table 14.1.4.5.2 - MG Medications Used Prior to Study Treatment.[2] The contents of this table is presented in Table 8. The uptake of pyridostigmine reported in Table 23 of the company submission reflects the use of pyridostigmine and pyridostigmine bromide in CHAMPION-MG.

Similarly the uptake for prednisolone reflects the use of prednisolone, methylprednisolone sodium succinate and methylprednisolone in CHAMPION-MG

Table 8: Myasthenia Gravis Medications Used Prior to Study Treatment

WHO ATC Class **Generic Name**	**Placebo (N=89)** **n (%)**	**Ravulizumab (N=86)** **n (%)**	**Total (N=175)** **n (%)**
Patients with Any Prior Medication	89 (100)	86 (100)	175 (100)
Parasympathomimetics	83 (93.3)	80 (93.0)	163 (93.1)
Pyridostigmine bromide	70 (78.7)	66 (76.7)	136 (77.7)
Pyridostigmine	11 (12.4)	14 (16.3)	25 (14.3)
Ambenonium chloride	3 (3.4)	3 (3.5)	6 (3.4)
Ambenonium	0	1 (1.2)	1 (0.6)
Distigmine bromide	1 (1.1)	0	1 (0.6)
Immunosuppressants	71 (79.8)	64 (74.4)	135 (77.1)
Mycophenolate mofetil	29 (32.6)	28 (32.6)	57 (32.6)
Azathioprine	32 (36.0)	23 (26.7)	55 (31.4)
Tacrolimus	13 (14.6)	9 (10.5)	22 (12.6)
Ciclosporin	5 (5.6)	7 (8.1)	12 (6.9)
Methotrexate	1 (1.1)	2 (2.3)	3 (1.7)
Tacrolimus monohydrate	1 (1.1)	1 (1.2)	2 (1.1)
Mycophenolate sodium	0	1 (1.2)	1 (0.6)
Nipocalimab	0	1 (1.2)	1 (0.6)
Corticosteroids for systemic use, plain	72 (80.9)	62 (72.1)	134 (76.6)
Prednisone	49 (55.1)	41 (47.7)	90 (51.4)
Prednisolone	22 (24.7)	20 (23.3)	42 (24.0)
Methylprednisolone sodium succinate	4 (4.5)	5 (5.8)	9 (5.1)
Methylprednisolone	1 (1.1)	4 (4.7)	5 (2.9)
Hydrocortisone sodium succinate	0	1 (1.2)	1 (0.6)
Immunoglobulins	40 (44.9)	36 (41.9)	76 (43.4)
Immunoglobulins NOS	28 (31.5)	22 (25.6)	50 (28.6)
Immunoglobulin human normal	11 (12.4)	13 (15.1)	24 (13.7)
Immunoglobulin G human	2 (2.2)	3 (3.5)	5 (2.9)
Other antineoplastic agents	5 (5.6)	6 (7.0)	11 (6.3)
Rituximab	5 (5.6)	6 (7.0)	11 (6.3)
Alkylating agents	1 (1.1)	1 (1.2)	2 (1.1)
Cyclophosphamide	1 (1.1)	1 (1.2)	2 (1.1)

B14. CS Table 35. Unit costs for each treatment included in the model. Please explain the following inconsistencies:

(a) The CS does not report the cost of rituximab (£785.84) that is used in the Excel model.

Rituximab is not considered a relevant comparator to ravulizumab however, it was highlighted as a possible intervention for managing an adrenal crisis during a survey of clinical experts. The cost was therefore included on the drug cost sheet of the model but is only included in cost of health care resource use. The drug acquisition costs reported in table 35 correctly reflects the interventions included in the standard of care basket of therapies.

(b) EAG checks on unit costs identified the following inconsistencies:

Treatments	CS Table 35	EAG search	Source
Pyridostigmine	£45.44	£45.57	MIMS[9]
Azathioprine	£1.57	£1.95	MIMS[9]
Mycophenolate Mofetil	£6.83	£7.76	eMIT[10]
Cyclophosphamide	£52.46	£52.65	eMIT[10]

The Drugs and pharmaceutical electronic market information tool (eMIT) was updated on March 22nd 2023, between the company submission date and the EAG review. This is likely to be where the discrepancies have occurred. The new costs have been included in the updated cost-effectiveness results.

(c) The EAG could not identify the price of methotrexate. Please provide the appropriate reference.

The price of methotrexate refers to 10mg/5ml oral solution in 65 ml vials that is reported in the latest version of eMIT at £58.35.[10]

B15. CS Table 36. Please explain the inconsistencies in the price of prednisone and prednisolone for ravulizumab and SoC:

Treatments	Ravulizumab	SoC
Prednisone	£0.27	£0.37
Prednisolone	£8.57	£11.55

There was an error in the Drug costs sheet of the Excel model which was generating these incorrect values. Cells I33, L33 and M33 should be equal to cells I34, L34 and M34 respectively. This makes the costs for prednisone and prednisolone in the ravulizumab arm consistent with the SoC costs reported in the above table.

B16. CS Table 37. Please explain the following inconsistencies:

(a) The CS reports "specialist nurse" and "IVIG costs" but the Excel model does not include these costs.

(b) The cost of IVIG is reported as £2014 but the NHS Reference cost reports £1370. Please explain how you estimate this cost.

(c) The EAG note the following inconsistency in the values reported in the CS and the Excel model:

Treatments	CS Table 37	Excel model
Physiotherapist	£1.05	£1.08

a) The costs of IVIG are found in the Excel model on the Clinical Event Costs sheet in cells D55:D56. The costs of a specialist nurse are in row 11 of the Health care costs sheet.

b) The cost of IVIG in the model includes the acquisition cost (£1370) and the administration cost (£644.86) which corresponds to NHS reference cost 2020-21, HRG code SA45A (Non-elective long stay injection of RH immune globulin or other blood transfusion).

c) The value used in the Excel model is correct. The correct value and reference are:

Medical staff	Unit cost per minute	Reference
Physical therapist	£1.08	PSSRU 21[11] - Community-based Band 7 Physiotherapist, Cost per hour £65

B17. Please provide the references for CS Tables 38 and 39.

The values presented in Tables 38 and 39 are derived from the survey of UK clinicians reported in Appendix P.

B18. CS Table 40:

(a) The EAG note the following inconsistencies in the values reported in the CS and the Excel model:

Treatments	CS Table 40	Excel model
Duration of neurologist visit	22.5 minutes	27.26 minutes
Duration of specialist nurse	30 minutes	27.25 minutes

Thank you for highlighting this discrepancy. The correct values, which correspond to the mean values identified by the survey of UK clinicians with experience treating generalised myasthenia gravis are presented in Table 9. We also noted a discrepancy in the value in the model and company submission for a GP visit, this should have been [redacted] minutes rather than the [redacted] minutes reported. We have amended this too.

Table 9: The duration of each visit to a clinician during a crisis

Resource	Duration
GP visit	[redacted]
Neurologist	[redacted]
Specialist nurse	[redacted]

(b) The CS reports intravenous immunoglobulin but the Excel model does not include this cost. Please explain.

The costs of IVIG are found in the Excel model on the Clinical Event Costs sheet in cells D55:D56.

Section C: Textual clarifications and additional points

C1. In the caption for CS Table 19 please explain what footnote a refers to.

This is a mislabelling; the caption for Table 19 should not include a footnote.

C2. CS section B.3.12 states that the approach for the commercial access agreement is described further in Appendix P. However, Appendix P does not contain this information.

Alexion are unable to confirm this statement in section B.3.12 exists. We note that any discussion around commercial access agreements are between Alexion and NHS England and not part of the NICE submission package.

Updated economic model base case results

The original and updated deterministic results are reported in Table 10 and Table 11, respectively. Applying all of the changes described in the responses dossier has a minor positive impact on the ICER, reducing it by approximately £[redacted]/QALY.

Table 10: Original economic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	£87,637	18.60	10.18				
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 11: Updated economic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	£88,424	18.62	10.08				
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

The results of a scenario using the CHAMPION-MG data alone to extrapolate time-on-treatment for ravulizumab are presented in Table 12. Using this approach reduces the ICER associated with ravulizumab but is associated with more uncertainty than using the long-term data from the REGAIN open-label extension.

Table 12: Deterministic scenario extrapolating time-on-treatment for ravulizumab using only CHAMPION-MG data

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
SoC	£88,424	18.62	10.08				
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

The probabilistic results also follow a similar trend, with the ICER reducing from £[redacted]/QALY to £[redacted]/QALY. The updated cost-effectiveness plane and cost-effectiveness acceptability curve are presented in Figure 10 and Figure 11, respectively.

Figure 10: Cost-effectiveness plane

Figure 11: Cost-effectiveness acceptability curve

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Single Technology Appraisal
Ravulizumab for treating generalised myasthenia gravis [ID4019]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Muscular Dystrophy UK and Myaware
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Muscular Dystrophy UK (MDUK) is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 110,000 children and adults in the UK. We fund research, provide vital information, advice, resources and support for people with these conditions, their families and the professionals who work with them. We are also a member of NHS England's Paediatric Neurosciences Reference Group. Myaware is the only charity in the UK dedicated solely to the care and support of people affected by myasthenia gravis. Founded in 1968, we are working hard to raise awareness of myasthenia gravis, provide support for people with myasthenia gravis and their families, whilst offering advice and tips for living with the condition. There are currently around 3000 active members of myaware, all of whom have full access to a wide range of support services and events including our specialist benefits advisor and telephone or Skype counsellor. Myaware has a long history of working with patients with myasthenia. Before covid this entailed regular face to face meetings, and since Covid regular quarterly zoom meetings. Myaware also host three closed Facebook pages in which living with MG is discussed daily. We also fund the research that brings us closer to finding a cure as well as funding specialists nurses and advisors. We campaign for better medical services for people with myasthenia gravis and work to inform medical professionals. Collaboration lies at the heart of our work and as such this submission has been collated together jointly between MDUK and Myaware.
4b. Has the organisation received any funding from the company bringing the	MDUK has received the following funding from the company bringing the treatment to NICE for evaluation and from one of the comparator treatment companies in the last 12 months:

treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	• £15,000.00 from Roche for sponsorship of the 2021/22 MDUK Muscles Matter virtual seminar series (virtual patient information events) • £5,000.00 from Roche for sponsorship of the 2022 MDUK Neuromuscular Physiotherapists Conference • £5,000.00 from Alexion for sponsorship of the 15th UK Annual Neuromuscular Translational Research Conference • £7,500.00 from Alexion for sponsorship of the 2022/23 MDUK Muscles Matter virtual seminar series (virtual patient information events) Myaware have received the following from Alexion in 2016 and 2019: 1. £10,000 received on 01/08/2019 – For Young Generation face to face conference and activities in 19/20 – £8850 balance still remaining due to covid restrictions limiting ability for face-to-face support services. 2. £15, 000 received on 05/08/16 – For Young Generation face to face conference and activities in 16/17 – fully spent. Myaware has not received any such funding in the past 12 months.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No links to the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gathered information through the following avenues: - A patient survey on the impact of living with Myasthenia Gravis where we had 551 respondents. - A focus group to gather feedback on living with the condition and current treatments which was attended by 21 people living with Myasthenia Gravis. The focus group was aimed particularly at understanding what it is like to live with the condition and insight into current treatments. - Published evidence on disease burden and media case studies/published reports.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Myasthenia Gravis (MG) is an autoimmune condition that can affect anyone, old or young and of any gender. People with MG have characteristically fatigable muscles and the harder they try, the weaker they get. They are often strongest in the mornings and get weaker throughout the day. The course of the disease is extremely variable, between individuals and individual people with myasthenia can vary considerably from day to day. Some days are better than others; for no "apparent" reason. Life threatening "myasthenic crisis" can happen suddenly, requiring hospitalisation, and necessitating lifesaving treatment. Our survey revealed MG has a physical, emotional, and financial impact on individuals and their families: **<u>Physical Impact</u>** The first signs of MG often are: droopy eyelids and possibly double vision, tiredness and weakness in the neck arms and legs. It is common that people find their faces are affected, this means smiling, making facial expressions, or chewing may become difficult. The symptoms often evolve into difficulty swallowing and breathing. In addition, some peoples' speech can be difficult, especially if they have been talking for a long time, they may realise their speech has started to sound different, possibly slurred. As the day goes on, some people find they are getting weaker, and they may need a rest. Pushing yourself to do things, like walk and talk, may make this even worse. From our survey, one respondent told us: *"I am unable to do the majority of the things I used to do due to my extreme weakness, breathlessness and fatigue. I have had to reduce my working hours. I can't do much around the house or garden fatigued most of time and really weak physically."* Another told us: *"Constant double vision, poor balance, cannot drive, some bad days, poor bladder control, need to know nearest toilets. I have been refused service as restaurant owners think I am drunk and have commented on my eyes, been asked to leave."* Further, 40% of respondents were admitted to hospital within the first year of their diagnosis, of which 15% landed in intensive care mainly for close monitoring.

	Emotional impact Almost seven in ten (68%) respondents said having MG has had a negative impact on their social life, with one respondent telling us: *"Difficulty attending social events in late afternoon or evening due to fatigue, and now I no longer feel able to drive. Difficulty planning in case of fatigue. Worried about weight increase after steroids. Reaction to alcohol after starting steroids."* Another respondent told us: *"Due to fatigue and embarrassment with my slurry speech, I don't feel comfortable going out too much. I also can't walk for long durations and am unable to walk long distances which has changed me as a person with regards to feeling comfortable going out with friends and even leaving the house unless necessary."* These feelings are only further exacerbated due to the unpredictability of their symptoms which can be difficult to explain to others, with 27% of respondents finding it difficult to talk about their condition with their community. One example is: *"Because I appear well and bubbly, it feels like I'm creating a problem where none is apparent. It is difficult to explain to people how you can be all right one minute and then extremely fatigued the next. People look at me and see a "normal" person and are quite surprised when I reveal I have a disability and have never heard of or understand MG".* This emotionally impacts not only the individual, but also their families, with 50% of respondents stating that their condition has negatively impacted their family's mental health. For example, respondents told us the following: *"Being diagnosed at a young age this has been stressful for my family, especially my parents seeing me unwell and admitted to hospital numerous times and in intensive care. Caused them worry and stress which continues any time I am unwell."* *"Having your mother in hospital when doing A level exams and starting University without support is difficult."*

	"…hit my partner very hard as she saw me at the most life-threatening stages through which I passed completely unaware." Further, the impact of living with MG on mental health has been exacerbated by the pandemic. Members who have been shielding for a significant amount of time, due to the medications used to treat/manage MG, have suffered from extreme isolation. There has also been a knock-on effect in terms of consultation and face-to-face interaction with specialists. There has been an increased feeling of vulnerability in the community. For example, one attendee in our focus group told us: *"I was diagnosed 5-6 years before COVID. What I found was things take longer to compute and I had to think about things a lot more, which has an invisible effect on your mental health. It makes you more tired. With COVID you are reminded all the times of the dangers out there, which had an impact. The impact of MG on my mental health is the constant awareness of it and it is grinding you down and you have to think about the things that you do and say, and I find it tiring."* Another told us about the sense of visibility the pandemic has put on their condition: *"Shielding has led to the exposure of medical history due to work-from-home schemes. First time people found out you had a medical condition, making you stand out and encourage feelings of resentment. Having the vaccine improved my mental health by allowing more freedom from isolation and shielding. However, I was made to feel vulnerable by wearing masks at the office."* **Financial Impact** Over a third (37%) of respondents have had to stop working or change roles due to their condition. This was mainly due to fatigue, breathing challenges, vision problems, voice becoming slurred, inability to focus, unable to drive to and from work (when remote working not possible). Similarly, 37% also stated their condition had negatively impacted them financially, with many needing to change to part time working. However, some respondents told us that the hardest part was the limbo before receiving their diagnosis, where they had to take time off work due to illness resulting in loss of salary and found themselves unable to explain to employers what additional support they may need or to arrange a working pattern that suits them better.

	One respondent told us: *"Having a job paying £30,000 then having to go on benefits which only pays a pittance meant I had to cash in my private pensions and now being in a low paid job due to having to find work that fits around my MG"* For those in employment, there was a consensus in our focus group that employers are relatively understanding and generous with time and resources for employees with MG. However, MG has been seen by members as holding back their careers. For example, attendees have been wary of changing their careers or looking for better opportunities in their profession, which has limited their career progression. This is because they don't know if their new employer will be as supportive as their previous one. For example, one attendee told us: *"One of the worst things I found when I was working was (that) some days I'm good and some days I'm bad. And people will say to you 'well you don't look ill'. If you have a broken leg, it's broken until it heals. MG isn't like that."* Another attendee told us: *"I had a very encouraging employer and they helped me a lot. They supported me, I had regular reviews. They did know about MG. Even within the health service though they didn't have an in-depth understanding of it. I had regular reviews and eventually with their support I realised I had to take early retirement. Which is where my problems started as I was initially refused the ill-health pension. I went to my doctor, and he told me this was the system, people get refused and [they] don't fight back. [But] He wrote a great report with the support of my employer and managed to get me accepted for the ill-health pension."* However, despite reports of support from employers being common amongst attendees, there was also evidence of a lack of awareness and response from occupational health representatives. *"My employer (university) is incredibly generous. Occupational health not so much. They have to assess me every year even though myasthenia is not going to go away. It really has affected my career choices."* A lot of work is still required to create policies and pathways for managing myasthenia in the workplace, and these have yet to come to fruition in the occupational health sector. Another attendee commented:

	"Occupational health – the first assessment I had they basically said to me that I should meet my employer halfway and go part-time. It felt like they just dismissed me. There is a lot of identity tied to work and it is really shaken up when there is a diagnosis and extra hoops to jump through." A lack of understanding in terms of capability or the ever-evolving nature of myasthenia has left patients feeling unsupported and misunderstood, which in turn has affected career prospects and the desire to advance for fear of not receiving support universally. This has had a knock-on effect on their families, with 30% stating their condition has negatively impacted their family financially who rely on both salaries to pay for mortgage and costs of living. Additionally, having MG has led to additional costs for adaptations. For example, one respondent told us they had to purchase various electrical appliances to maintain the individual's independence such as purchasing a specific kettle as they can't lift their current kettle because they are too weak.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	People with MG are on a range of different treatments, which creates two main difficulties: (1) managing the different timings within their day-to-day activities and (2) getting the dosage right between balancing the side effects of steroids and managing MG symptoms. Overall, our focus group showed there are a lot of problems with the management of steroid intake, particularly with prednisolone. Attendees would largely like to reduce their dose but fear the impact of this on their MG. Following a stringent routine for medication intake is incredibly taxing, as the process must be consistent to achieve the most relief from MG symptoms. Ordering prescriptions has no clear sensible system either and demands a lot of time and careful coordination from patients. There is a constant feeling of being dictated by medication and 'living at the mercy of a clock'. Lots of medications must be ordered and collected at alternate times, further contributing to the burden of managing myasthenia. Access to more expensive treatments feels like it is being withheld in place of cheaper options. **<u>Scheduling treatments</u>** In our focus group, there was a lot of frustration at how an individual's treatment schedule inhibits day to day activities. For example, people with MG must consistently be aware of what food they are consuming, and at what time of the day to ensure it doesn't impact their treatments. As a result, socialising where food is involved is very challenging with their meals needing to be regulated to be in time with their medications which feels restrictive for them and the people they are eating with. Further, accessing their treatments is inconsistent with ordering all medications at the same time. One respondent told us: *"It's not just about remembering to take medication in a sort of order, but the ordering itself. Every medication has a different place it can be prescribed from, and the ordering all takes different times."* **<u>Side effects and opinion on steroids and steroid sparing agents</u>** A lot of people with MG are on steroids to reduce inflammation by reducing the production of the autoantibodies that are attacking the neuromuscular system, this is achieved by 'damping down' the activity of the body's immune system. However, getting the dose right to reduce the risk of side effects but to still manage the MG symptoms is tricky and causes a lot of stress for this community. We particularly heard: *"The medication I was put on to start with controlled my symptoms. I saw a consultant a month later who thought he found some weakness in one of my arms. The protocol was to increase prednisolone. My intuition was that it had been more down to being unable to eat for alternative reasons. The increase to steroid did not help*

	physically but stressed me mentally. I explained this to him and he was very good. It's a risky business when you want to trust your own intuition about your body even when it goes against what a consultant is recommending." Side effects from non-steroidal immunosuppressants such as Azathioprine have also been reported by respondents, with one saying: *"I did have to come off Azathioprine as it impacted my blood, liver and kidney functions."*

8. Is there an unmet need for patients with this condition?	People with MG struggle to balance their treatments with symptom management and undertaking their day-today activities such as work and socialising. As we have demonstrated this has negatively impacted their mental health as well, which clearly shows the need for new treatments to reduce this burden of care. The accessibility to new treatments is an additional problem for people with MG. Sometimes it can feel like the cost to NHS outweighs a beneficial outcome to them. As spoken by an attendee: *"I have hated prednisolone since the day they put me on it. I was convinced it was not making a difference. I was on 60 mg and have had to fight for a reduction. I'm now on 3 mg but also taking a cocktail of others. Then there is the side effects of the medication you take to reduce the side effects of prednisolone. I've found even the most empathetic of doctors find IVIG is too expensive. Rituximab really changed my life, and I would like another round of it but there is a feeling that it is being held back because of the expense. I just wonder why it feels like sometimes the doctors don't listen to you, don't fiddle with medications that do work. I knew Rituximab wouldn't be immediately effective, but after 6 months it was like magic. I was feeling so much better I felt I was in remission."* In addition, there appears to be a reluctance to deviate from treatments that work in favour of trying alternative approaches that might give an improved result. One attendee said: *"My GP will not prescribe me mycophenolate, so I have to get it prescribed by my consultant at the hospital and have to make a long car journey. GP is happy to prescribe 100 mg of prednisolone. GPs don't seem to have necessarily as much comfort with immunosuppressive agents which makes life harder sometimes."* People with myasthenia who are taking immunosuppressive drugs are at high risk of being severely affected by infections, such as Covid19. Their immune systems are "dampened down" and so cannot respond effectively to opportunist infections. Treatments that did not depend on "global" immunosuppression, would allow such patient's infection to be able to take their place in the community rather spend time under lockdown, fearing the chance

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**Advantages** Patients with myasthenia do not like taking steroids and many have problems with steroid-sparing agents such as azathioprine too. They are worried about the medical side effects of steroids including low resistance to infections, weight gain, possible onset of other disorders (diabetes, osteoporosis), and sleep and mood problems including depression. Reducing dosage brings on the fear and possibility of a loss of control of their symptoms and an increased possibility of myasthenic crisis. Ravulizumab, and other recombinant antibody treatments have been shown to be effective in clinical trials in patients with MG, and in other diseases in which the drugs are already licenced. In chronic long-term myasthenic patients, it will offer a drug that could manage the patient's symptoms without the serious and troublesome side effects of steroids. It may offer, in patients with hard to control MG who do not know from day-to-day what their condition will be like, a chance for a stable lifestyle. It could offer a possibility of resuming a normal life, an opportunity that for many has been missing after their original diagnosis In a significant minority of patients with myasthenia the symptoms are not well controlled, and these patients are seriously and chronically unwell. The new treatment Ravulizumab is a recombinant monoclonal antibody that inhibits terminal complement activation, and therefore works in a totally different way to other treatment regimes. This new treatment may certainly offer the possibility of a superior prognosis in patients in which current treatments are ineffective or partially effective. The drug is likely to be administered by intravenous injection. This is thought of by many as an advantage over multiple daily tablets which our members complain take a lot of organisation to obtain the drugs regularly from the pharmacy and to take at the correct time (and in the correct order, with or without meals). Obviously to some a trip to GP surgery/hospital may be seen as an advantage (to meet a GP, nurse, or physician). However, to some this could possibly be seen as a disadvantage as journeying to the hospital may not be a simple task.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	**Disadvantage** Myasthenia Gravis is a chronic fluctuating disease, and the severity and course of the disease varies considerably patient to patient. The drug may have a variable and possibly unpredictable response in some patients, but clinical trials have indicated a good response and tolerability of the drug The efficacy of this drug may not be effective in all forms of myasthenia gravis. According to the reported literature, 5-7% of myasthenia gravis patients who are AChR-antibody negative have antibodies to a different neuromuscular protein called MuSK (Musk-antibody positive MG). MuSK antibodies are mainly in the IgG4 subclass, which does not activate the complement pathway. Ravulizumab is a monoclonal antibody that interferes with complement activation, and so may be ineffective in this form of myasthenia. However, this can be decided by the consulting physician. Our members appreciate the cost is higher but suggest that long-term steroid usage is not cheap and leads to other medical conditions that also require treatment which have a cost to the NHS and society too.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As previously mentioned, there is a small number of myasthenia patients, which varies in different populations who present MuSK antibodies rather than AChR. This may make treatment through Ravulizumab ineffective given its mode-of-action in complement pathway interference.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Myasthenia is a very variable and fluctuating disorder. Gender-based differences in MG onset change based on age, with early onset MG being more common in women while men tend to present with MG between the ages of 40-70. With this in mind, there are some gender and ethnicity predispositions, but these are irrelevant to the treatment the patient receives. The needs of particular treatment regimes in individual patients will be administered as to their personal needs at the time, by their own physician and is independent of gender or ethnicity.

Other issues

13. Are there any other issues that you would like the committee to consider?	Nothing else to add.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Myasthenia Gravis (MG) is an autoimmune condition that can affect anyone, regardless of age or gender. It is characterised by muscle fatigue, which often worsens throughout the day. If left untreated, MG can result in swallowing and breathing difficulties. Even with treatment MG can often progress and worsen and may result in life-threatening "myasthenic crisis". The significance of associated health implications is highlighted by the fact that 40% of survey respondents were admitted to hospital within the first year of their diagnosis. • Survey data revealed that MG has a physical, emotional, and financial impact on individuals, as well as their families. • Currently, people with MG take a range of different treatments. This presents several challenges. 1) Managing a stringent and consistent routine of medication intake can negatively impact an individual's ability to carry out day-to-day activity and can feel overwhelming. There is a need for a new treatment to reduce this burden of care. 2) Lots of people with MG take steroids, such as prednisolone, to increase muscle strength. However, it can be difficult to balance getting the right dosage of steroids to help manage their symptoms against concerns about the potentially extensive and serious medical side effects of steroids. Reducing steroid dosage may lead to loss of control of symptoms and an increased possibility of myasthenic crisis. Both steroid-related side effects and loss of control of symptoms would have cost and resource implications for the NHS. • Ravulizumab, and other recombinant antibody treatments have been shown to be effective and well tolerated in clinical trials in patients with MG, and in other diseases in which the drugs are already licenced. In chronic long-term myasthenic patients, Ravulizumab could manage the patient's symptoms without the side effects of steroids. • A significant minority of patients with MG become seriously and chronically unwell due to difficulty controlling their symptoms using existing medications. As Ravulizumab works in a totally different way to other treatment regimes, it could offer the possibility of better outcomes especially in patients for whom current treatments are less effective.

Thank you for your time.

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Single Technology Appraisal

Ravulizumab for treating generalised myasthenia gravis [ID4019]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists
3. Job title or position	Consultant Neurologist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **No** Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is a registered charity funded largely by subscriptions from members
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Ravulizumab is a recombinant monoclonal antibody that inhibits the terminal complement activation at the C5 protein. The medication is currently licenced for treatment of atypical haemolytic uremic syndrome and paroxysmal nocturnal haemoglobinuria. The main aim of treatment is to reduce symptoms of generalised myasthenia in patients who have ongoing poor control on standard immunotherapy. Typically, immunotherapy would include treatment with prednisolone together with a non-steroid immunosuppressive treatment such as azathioprine or mycophenolate. In addition, patients with severe myasthenia frequently receive regular additional immunotherapy such as intravenous immunoglobulin infusion or plasma exchange.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response would be achieving a MGFA post intervention status of either minimal manifestations or pharmacological remission in patients previously resistant to standard immunotherapy. There are quite well validated patient rating scales for symptoms including MG–ADL and MG–QoL. Both these rating scales have been used in recent clinical trials of the new biological FcRn inhibitors. A greater than two point drop in the MG-ADL was felt to be clinically significant. In addition, clinicians use an objective quantitative myasthenia gravis (QMG) score, which is assessed by physicians, and a composite QMG score which includes patient assessed symptoms. A greater than three point reduction in either the QMG or composite QMG is felt to be clinically significant.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a significant unmet need for patients with treatment resistant myasthenia. Currently, these patients are often treated with either regular intravenous immunoglobulin or plasma exchange requiring treatment in hospital typically as a day case admission

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Patients with myasthenia are typically treated with pyridostigmine together with a combination of immunosuppressive treatments including prednisolone and non-steroid immunosuppressive treatments such as mycophenolate or azathioprine. Patients resistant to treatment who have positive antibodies to acetylcholine receptors are eligible for treatment with rituximab. Patients with highly resistant symptoms of myasthenia

	following satisfactory treatment with immunosuppression are usually offered either intravenous immunoglobulin or plasma exchange.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Association of British neurologists published guidelines – April 2015
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is a well-defined pathway of care for patients with myasthenia. Patients with mild to moderate myasthenia are typically treated by general neurologists with pyridostigmine, prednisolone and, if necessary, non-steroid immunosuppressive treatments.
9c. What impact would the technology have on the current pathway of care?	Biological terminal complement inhibitors such as Ravulizumab will hopefully bring about improvement in symptoms in patients with highly treatment resistant myasthenia. Evidence for its efficacy not supplied with the current documents
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently, terminal complement inhibitors including eculizumab are not commissioned for use in patients with myasthenia by the NHS.
10a. How does healthcare resource use differ between the technology and current care?	Not known- no information available for this. As an infusion therapy, it is likely not to be significantly change in resources required. If clinically effective, Ravulizumab may reduce the need for use of immunoglobulin and plasma exchange
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should only be used under supervision of a neurologist specialising in the management of patients with myasthenia

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment is needed to introduce this technology.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There is no published evidence on the efficacy of Ravulizumab in treatment of resistant generalised myasthenia gravis.
11a. Do you expect the technology to increase length of life more than current care?	Not applicable for this condition.
11b. Do you expect the technology to increase health-related quality of life more than current care?	No data available
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment will only be suitable for patients with generalised myasthenia with positive antibodies to acetylcholine receptors who have proven resistant to standard therapies including pyridostigmine, prednisolone, nonsteroid immunosuppressive treatments and rituximab. It is not clear where it would be used relative to IVIG/plasma exchange.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology will be no more difficult for use for patients and or health care professionals than current treatment as it can be administered via intravenous infusion in a day case setting. Logistically it may well be easier than plasma exchange or intravenous immunoglobulin
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It would be sensible to have clear criteria of what constitutes a positive response to treatment so that only these patients continue with treatment. In addition, it would be sensible to have annual review of therapy to decide which patients may be able to withdraw treatment. There are several reasonably well validated rating scales available for patient assessment both for eligibility criteria before starting treatment and to help develop stopping criteria for patients not responding to treatment. These include the patient-reported rating scales of MG–ADL, MG– QoL as well as physician rating scales including QMG and composite QMG.
15. Do you consider that the use of the technology will result in any	No

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Eculizumab – a biological terminal complement inhibitor – has been licenced for treatment of myasthenia gravis in the U.S. and Europe for several years now. Ravulizumab therefore is not a novel or innovative treatment for myasthenia.
16a. Is the technology a 'step-change' in the management of the condition?	Development of biological terminal complement inhibitors are an important advance in the management of patients with treatment resistant antibody positive myasthenia gravis.
16b. Does the use of the technology address any particular unmet need of the patient population?	Patients with treatment resistant myasthenia have limited options – typically either plasma exchange or intravenous immunoglobulin.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	I am unable to comment on risk of adverse effects in patients with myasthenia as there are no published randomised controlled clinical trials.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	There are no published randomised controlled clinical trials
18a. If not, how could the results be extrapolated to the UK setting?	Not applicable
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Not applicable
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not known
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not known
20. How do data on real-world experience compare with the trial data?	Not known

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No potential equality issues that need to be taken into account
21b. Consider whether these issues are different from issues with current care and why.	Not applicable

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Patients with severe myasthenia resistant to oral immunosuppressive medication and Rituximab have limited therapeutic options including plasma exchange and intravenous immunoglobulin. • There is a need to develop new therapies for severe myasthenia given the constrained supply of immunoglobulin and difficulty ensuring provision of plasma exchange in England. • Ravalizumab is a terminal complement inhibitor which prevents antibodies to acetylcholine receptors in causing damage to the muscle end-plate thereby improving symptoms • Ravalizumab is not a novel treatment for myasthenia and shares the same mechanism of action as Eculizumab which is a currently licensed but not funded treatment for myasthenia • There are no randomized controlled trials to confirm efficacy of Ravulizumab in myasthenia, no studies comparing this treatment with current standard treatments such as plasma echange and intravenous immunoglobulin and no cost-effectiveness data.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Ravulizumab for treating generalised myasthenia gravis [ID4019]
NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes or No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? **Yes** or No Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? Yes or No An expert in treating the condition for which NICE is considering this technology? Yes or No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the taxpayer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Clinical guidelines used for the treatment of this condition are: *Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults)* *NHS England Reference: 170084P* *Version 2*
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, the pathway of care is well defined for 4th or 5th line treatment for this condition. Clinicians may wish to use efgartigimod earlier in the treatment pathway if cost-effective and this would push ravulizumab to 5th line in due course. In addition to the use of ravulizumab in patients with refractory disease, our clinicians also felt it would have a beneficial role in instances where rapid disease control is required in acute gMG crisis.

8. What impact would the technology have on the current pathway of care?	Based on conversations with some of our clinical experts*, there are questions as to how well ravulizumab would work based on the evidence from the clinical trial. Clinicians felt that the evidence for efgartigimod (which is currently available under EAMS, with expected regulatory approval towards the end of 2022) was stronger, i.e. the baseline population evaluated was very similar to ravulizumab but the degree of improvement is substantially better (ADAPT study). There was consensus amongst our clinicians that this class of drug is preferred over ravulizumab. Further to this, clinicians have expressed a preference to the new class of NRAs (including efgartigimod) as these are disease modifying, rather than addressing symptom control. This would then move ravulizumab to 5th line treatment. From conversations with the manufacturer, they believe ravulizumab would be considered 3rd line in the treatment pathway, after immunotherapy but before rituximab. This was not the consensus from any of our conversations with clinicians, apart from when clinicians needed to gain immediate control of the disease. In this instance, ravulizumab would be preferred due its rapid onset of action (compared to rituximab) and therefore would have a place in the treatment pathway, but perhaps not as early as the manufacturer has suggested. Patients with poorly controlled disease can present with a myasthenia crisis, which is treated in hospital with IV immunoglobulin, or through plasma exchange therapy. *Clinical experts consulted in Nottingham, Newcastle and Manchester

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	The table below details the uptake model based on feedback from the clinical community:

	<table><tr><th></th><th>Year 1</th><th>Year 2</th><th>Year 3</th></tr><tr><td>Number of existing patients (prevalence) of refractory AChR+ gMG</td><td>605</td><td>661</td><td>717</td></tr><tr><td>Number of new patients (incidence) of refractory AChR+ gMG</td><td>56</td><td>56</td><td>56</td></tr><tr><td>Eligible population If used 3rd line (before ritux)</td><td>661</td><td>717</td><td>773</td></tr><tr><td>Eligible population if used 4th line (after ritux)</td><td>331</td><td>359</td><td>387</td></tr></table> *Refractory, AChR-positive gMG based on a population of 56M.* *Assumed an average of 50% will respond to rituximab*
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is currently not used at the moment.
10a. How does healthcare resource use differ between the technology and current care?	Ravulizumab is available through homecare providers and is funded by the manufacturer. However, NHS administrative costs should be taken into account at £600 per patient per annum. No additional resource impact expected as the service is already set up and treatment will be made available via homecare providers.
10b. In what clinical setting should the	Specialist clinics (tertiary centres)

technology be used? (For example, primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Facilities would be provided by the clinics so no extra resource implication from an estate's perspective. Training would be needed for practitioners to ensure competencies were developed and maintained.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	No additional testing would be needed except for initiation and ongoing blood monitoring
11. What is the outcome of any evaluations or audits of the use of the technology?	Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis Tuan Vu, M.D.,1 Andreas Meisel, M.D.,2 Renato Mantegazza, M.D.,3 Djillali Annane, M.D.,4 Masahisa Katsuno, M.D.,5 Rasha Aguzzi, M.S.,6 Ahmed Enayetallah, M.D., Ph.D.,6 Kathleen N. Beasley, Pharm.D.,6 Nishi Rampal, M.D.,6 James F. Howard, Jr., M.D.,7 for the CHAMPION MG Study Group* Published April 26, 2022 DOI: 10.1056/EVIDoa2100066 NEJM Evid 2022; 1 (5) RESULTS In total, 175 patients were enrolled. Ravulizumab significantly increased the magnitude of mean changes from baseline to week 26 versus placebo in MG-ADL (23.1 vs. 21.4; P,0.001) and QMG (22.8 vs. 20.8; P,0.001) total scores. Improvements in both measures occurred within 1 week of ravulizumab initiation and were sustained through week 26. QMG total scores improved by 5 points or more in a significantly greater proportion of

	ravulizumab-treated patients than of those receiving placebo (30.0% vs. 11.3%; P50.005). No notable differences in adverse events were observed. CONCLUSIONS Ravulizumab demonstrated rapid and sustained improvements in both patient and clinician reported outcomes and had a side effect and adverse-event profile that did not limit treatment in adults with anti-AChR antibody-positive gMG. (Funded by Alexion, AstraZeneca Rare Disease; ClinicalTrials.gov number, NCT03920293; EudraCT number, 2018-003243-39.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Upon diagnosis, patients are referred to a specialist consultant-led outpatient centre with six monthly reviews and 3 monthly blood tests taken within the hospital setting. Myasthenia crisis is managed in an inpatient setting, and may involve a course of immunoglobulin or plasma exchange. One of our centres estimated around five patients are admitted per year with unstable disease. Adding ravulizumab as a treatment option for refractory gMG patients may support a reduction in the number of acute admissions, and thus support a reduction in inpatient activity. Additionally, ravulizumab has a quicker mechanism of action to rituximab and may have additional benefits in getting unstable disease under control faster, thus supporting a reduction in length of stay once admitted. There are no further equality issues that should be taken into account when considering this treatment
12b. Consider whether these issues are different from issues with current care and why.	We do not consider these issues to be different from issues with current care

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Ravulizumab for treating generalised myasthenia gravis (ID4019)

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Declared competing interests of the authors and advisors

The authors, Dr Burke, and Dr Huda declare that they have no conflicts of interest.

Rider on responsibility for the report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Frampton G, Kalita N, Pickett K, Hawa, A, Lord J. Ravulizumab for treating generalised myasthenia gravis. A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2003.

Contributions of authors

Geoff Frampton critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor; Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Karen Pickett critically appraised the clinical effectiveness systematic review and drafted the report; Asyl Hawa critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Joanne Lord critically

appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report.

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CS	Company submission
CSR	Clinical study report
DSU	Decision Support Unit
EAG	External Assessment Group
FAS	Full analysis set
EPAR	European Public Assessment Report
ESS	Effective sample size
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IPW	Inverse probability weighting
ITC	Indirect treatment comparison
ITT	Intention to treat
IVIG	Intravenous immunoglobulin
KM	Kaplan Meier
LOCF	Last observation carried forward
MAIC	Matching-adjusted indirect comparison
MAR	Missing at random
MG-ADL	Myasthenia Gravis Activities of Daily Living scale
MG-QoL15r	Myasthenia Gravis Quality of Life 15 scale, revised version
MMRM	Mixed model with repeated measures
Neuro-QoL Fatigue	Quality of Life in Neurological Disorders – Fatigue subscale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QMG	Quantitative Myasthenia Gravis scale
QoL	Quality of life
RCT	Randomised controlled trial

SE	Standard error
SmPC	Summary of product characteristics
SoC	Standard of care
TA	Technology appraisal
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues identified by the EAG

ID	Summary of issue	Report sections
1	Exclusion of rituximab from the company's decision problem	2.2.3 and 2.3
2	Uncertain relevance of eculizumab	3.1.2
3	Timing of MG-ADL response assessment	4.2.3.1
4	Time on treatment extrapolations	4.2.3.2
5	Estimation of the incidence of acute clinical events	4.2.3.4

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Use baseline patient characteristics from CHAMPION-MG trial to align the model population with the main clinical data source used in the model.
- Use time on treatment data from CHAMPION-MG trial and OLE and extrapolate using exponential distribution.
- Include prior clinical events within 3 months from the incidence of clinical events
- Include coefficients for clinical event within 3 months for utilities.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Improving symptoms (MG-ADL status), associated with improved quality of life
- Reducing incidence of acute clinical events (exacerbations and crises), which are associated with disutility and a risk of mortality
- Disutility associated with adverse effects

Overall, the technology is modelled to affect costs by:

- Increased costs for drug acquisition and administration
- Reduced costs due to reduced incidence of clinical events
- Costs related to the treatment of adverse events

The modelling assumptions that have the greatest effect on the ICER are:

- Source of data and extrapolation for time on treatment
- Timing of response assessment and discontinuation due to loss of response
- Population baseline characteristics
- Mortality relative to general population

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Key issues relating to the decision problem

Report section	2.3 (also discussed in 2.2.3)
Description of issue and why the EAG have identified it as important	Rituximab is used in clinical practice as a component of standard of care but the company have excluded rituximab from their decision problem. The EAG's clinical experts agreed that rituximab is a relevant comparator and suggest that one possible positioning of ravulizumab in the treatment pathway is ravulizumab being used instead of rituximab. The EAG are uncertain whether ravulizumab effectiveness should be assessed only against standard of care (as in the pivotal CHAMPION-MG trial and implied in the NICE scope), or whether ravulizumab effectiveness should also be assessed against rituximab (and other individual therapies used within standard of care if it is expected that ravulizumab may replace specific drugs).

What alternative approach has the EAG suggested?	If placebo-controlled randomised controlled trials (RCTs) of adequate rigour are available, indirect treatment comparisons (ITCs) using the placebo arm as the common comparator could be conducted to investigate the comparative clinical effectiveness of ravulizumab against rituximab, as well as against other therapies used in standard of care for generalised MG (e.g. azathioprine, methotrexate, mycophenolate mofetil, if clinically justified).
What is the expected effect on the cost-effectiveness estimates?	Ravulizumab might be more or less cost-effective depending on the comparator therapy against which it is evaluated (i.e. overall standard of care or specific therapies within standard of care). However, this is uncertain.
What additional evidence or analyses might help to resolve this key issue?	The availability of placebo-controlled RCTs on rituximab (and other immunosuppressants used in standard MG care such as azathioprine, methotrexate, mycofenolate mofetil) could be explored to determine whether ITC analysis of ravulizumab against rituximab (and against other immunotherapies used in standard of care) would be feasible.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Key clinical effectiveness issues

Report section	3.1.2 (background), 3.3 to 3.5 (ITC critique)
Description of issue and why the EAG have identified it as important	The company include eculizumab in their submission but eculizumab is not specified as an intervention or comparator in the NICE scope. The EAG note that eculizumab was due to be appraised by NICE, but as the company did not submit an evidence submission, NICE were unable to make a recommendation for its use in the NHS. The CS states that as it is not reimbursed in the NHS, eculizumab is not used in clinical practice in the UK. The company's rationale for including eculizumab is that they believe it to have similar clinical effectiveness to ravulizumab and based on that assumption they use eculizumab outcomes in economic modelling, since longer-term outcomes are available for eculizumab than for ravulizumab. The EAG are concerned not only about the implications of including an out-of-scope technology in the appraisal, but also that there is no convincing evidence that ravulizumab and eculizumab have similar long-term clinical effectiveness. The company conducted an indirect treatment comparison (ITC) comparing ravulizumab versus eculizumab via the common comparator of placebo (CHAMPION-MG versus REGAIN RCTs), in order to demonstrate similar efficacy of the drugs. However, the ITC has major limitations (see sections 3.3 to 3.5 of this report) so its results are highly uncertain. The ITC is also limited to the short 26-week period of the RCTs. So it does not support inferences about the long-term similarity of ravulizumab and eculizumab. In previous NICE technology appraisals on haematological conditions (TA698 and TA710) the NICE Committee

	accepted similarity of ravulizumab and eculizumab; however it is unclear whether those considerations are relevant to the current technology appraisal.
What alternative approach has the EAG suggested?	The EAG have run the economic analysis limiting baseline characteristics and parameter estimates to CHAMPION-MG (ravulizumab) or adjusting the contribution of the eculizumab data.
What is the expected effect on the cost-effectiveness estimates?	Potentially depends on where eculizumab data are used in the analysis – please refer to section 6 and Key Issues 4 and 5 below.
What additional evidence or analyses might help to resolve this key issue?	NICE and expert opinion may help to clarify whether it is appropriate to include eculizumab in the economic modelling

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 3 Timing of MG-ADL response assessment

Report section	4.2.3.1
Description of issue and why the EAG have identified it as important	The main measure of treatment benefit used in the economic model is change in the total score for the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale. For their base case, the company use distributions of change from baseline MG-ADL scores from the CHAMPION-MG randomised trial: based on the 18 week assessment for the ravulizumab arm, and the 26 week assessment in the standard of care arm. The 18 week timepoint is broadly consistent with an assessment of response and consideration whether to stop ravulizumab after two maintenance doses at 16 weeks, which is clinically appropriate. However, the model does not make use of MG-ADL data between 18 and 26 weeks in the ravulizumab arm. The company argue that including these data would favour ravulizumab, so their approach is conservative. However, the EAG would like to see this demonstrated.
What alternative approach has the EAG suggested?	We consider that it would have been better to use the measure of MG-ADL change at 26 weeks for ravulizumab, as this would match the timepoint for the comparator arm and make full use of all randomised data to project long-term outcomes. The company's model includes a scenario with 26-week MG-ADL change data for both arms, but this is linked to a change in the timing of assessment for the 'stopping rule' from 16 to 26 weeks. We would have preferred an analysis retaining the 16-week assessment for lack of response, combined with estimation of the treatment effect for patients continuing ravulizumab up to 26 weeks, as for the comparator arm.
What is the expected effect on the cost-effectiveness estimates?	The company's scenario with 26-week response assessment for both arms (and stopping rule at 26 weeks) resulted in an ICER of [redacted] per QALY gained. The impact on the ICER

	of a scenario with a 16-week stopping rule for ravulizumab, and 26-week response data for both arms is not clear.
What additional evidence or analyses might help to resolve this key issue?	Additional scenario analysis by the company.

Issue 4 Time on treatment extrapolations

Report section	4.2.3.2
Description of issue and why the EAG have identified it as important	The company use pooled data from the CHAMPION-MG and REGAIN randomised trials and open label extensions to estimate the long-term duration of ravulizumab treatment. All parametric distributions have a poor fit to the pooled data, and we have concerns over the appropriateness of simple pooling of ravulizumab and eculizumab data, given the lack of evidence that they would have similar discontinuation rates. There is also a lack of clarity in how data for the transition of patients from the randomised trials into the open label extension studies was analysed. We therefore asked the company to report time on treatment extrapolations fitted to CHAMPION-MG data only, which they did.
What alternative approach has the EAG suggested?	For EAG preferred analysis, we use an exponential curve fitted to the CHAMPION-MG data. We believe that it is appropriate to exclude the REGAIN data, but this does increase uncertainty over the long-term extrapolation due to the shorter follow up from CHAMPION-MG. We agree with the company that the exponential distribution provides the best fit but note that a distribution with a declining hazard (such as the log-logistic) may be more clinically plausible.
What is the expected effect on the cost-effectiveness estimates?	Restricting the extrapolation to CHAMPION-MG data has a significant impact, reducing the company's base case ICER from [redacted] to [redacted] (with the Gompertz extrapolation) and to [redacted] (with the log-logistic).
What additional evidence or analyses might help to resolve this key issue?	Longer term data from real-world evidence sources might help in assessing the plausibility of the extrapolations. We would also welcome further clinical opinion on the appropriateness of pooling time on treatment data for ravulizumab and eculizumab, and the plausibility of alternative extrapolations.

Issue 5 Estimation of the incidence of acute clinical events

Report section	4.2.3.4
Description of issue and why the EAG have identified it as important	The company used a Poisson regression to estimate the incidence of acute clinical events, including myasthenic exacerbations and crises, for the ravulizumab and standard of care arms. They used a simple model specification, with a single independent variable 'treatment', fitted to CHAMPION-MG trial and open label extension data, pooled with data from the REGAIN trial. The EAG have several concerns about this approach. There is a lack of clarity over the methods used to fit and test the model specification and

	some discrepancies in the reporting of the data in the CS and the excel model. More importantly, we have serious concerns over the use of pooled data for ravulizumab and eculizumab to estimate a simple, unadjusted treatment effect relative to standard care. It has not been demonstrated that these therapies have similar effects on clinical event rates.
What alternative approach has the EAG suggested?	Sensitivity analysis to explore uncertainty over the data source and model specification.
What is the expected effect on the cost-effectiveness estimates?	Unknown. The EAG report a scenario using an alternative model specification provided in the model, with an additional covariate of 'prior clinical event within three months. This increased the base case ICER from [redacted] per QALY to [redacted] per QALY for ravulizumab compared to standard of care. However, this analysis does not address uncertainties over the data source and model specification.
What additional evidence or analyses might help to resolve this key issue?	Further information about the data and methods used to fit and test the Poisson regression. Sensitivity analysis excluding REGAIN data and comparing alternative model specifications.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The ICER obtained using the EAG's preferred assumption increased from [redacted] to [redacted] per QALY gained for ravulizumab compared to stsndard of care (SoC).

Table 2 Cumulative cost-effectiveness results for EAG's preferred model assumptions (discounted, PAS price for ravulizumab)

Correction	Treatment	Total cost	QALYs	ICER (£/QALY)
Company base case (clarification response)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
EAG corrections (see 5.3)	SoC	£79,993	9.967	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Baseline patient characteristics: Champion-MG trial only	SoC	£74,899	9.554	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Time on treatment: CHAMPION-MG RCT and OLE (exponential)	SoC	£74,899	9.554	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Incidence of clinical events: include prior events within 3 months	SoC	£55,974	9.585	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Utility regression: coefficients for clinical event within 3 months; and disease duration	SoC	£55,974	9.709	
	Ravulizumab	[redacted]	[redacted]	[redacted]
EAG preferred analysis	SoC	£55,974	9.709	
	Ravulizumab	[redacted]	[redacted]	[redacted]

Correction	Treatment	Total cost	QALYs	ICER (£/QALY)
Source: Produced by the EAG from the company's model submitted with their clarification response				

Modelling errors identified and corrected by the company and EAG are described in section 5.3. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.1. For a brief overview of EAG conclusions and uncertainties, see section 6.3.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Alexion on the clinical effectiveness and cost effectiveness of ravulizumab (brand name ULTOMIRIS®) for treating generalised myasthenia gravis. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 4th April 2023. A response from the company via NICE was received by the EAG on 2nd May 2023 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on generalised myasthenia gravis

2.2.1.1 Aetiology

Myasthenia gravis (MG) is an autoimmune disorder caused by the production of autoantibodies against the nicotinic acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK) or lipoprotein receptor-related protein 4 (LRP4) at the nerve-muscle (neuromuscular) junction (NMJ).[1] Most people who have MG have anti-AChR antibodies (also referred to as AChR antibody-positive disease). The licensed indication, as stated in the Summary of Product Characteristics (SmPC), is for the treatment of adult patients with generalised MG who are AChR antibody-positive. Therefore, people with MG due to anti-MuSK or anti-LRP4 antibodies are outside the scope of this report.

Normal muscle contraction requires binding of the neurotransmitter acetylcholine to AChR on the post-synaptic membrane. As shown in CS Figure 1, anti-AChR antibodies decrease post-synaptic nerve signalling both by blocking AChR at the post-synaptic membrane and by activating the complement pathway. Complement activation is a major driver of MG in AChR-positive patients and results in the formation of a membrane attack complex (MAC) where the terminal complement component (TCC) damages the post-synaptic membrane, reducing the availability of AChR for acetylcholine to bind[1] (CS section B.1.3.4).

In MG, the thymus gland plays a central role in the production of anti-AChR antibodies, associated with enlargement of the gland (hyperplasia) or a tumour (thymoma).[2]

2.2.1.2 Diagnosis

Diagnosis of MG can be difficult initially and usually starts with a review of clinical symptoms relating to muscle fatigue and weakness and a physical examination. If MG is suspected, serological blood tests are conducted to check for pathogenic antibodies, although antibodies may not be detectable early in MG and testing may be repeated if symptoms worsen. Electrodiagnostic tests to confirm muscle fatigue and anticholinesterase tests to examine a patient's response to a cholinesterase inhibitor may also be conducted (CS section B.1.3.5).

2.2.1.3 Disease severity

A characteristic feature of MG is exercise-dependent muscle weakness that improves on rest.[3] Patients with MG can be divided into those who have ocular MG - a mild form of disease in which only the eye muscles are affected (eyelid droop, double vision); and those who have generalised MG - a more generalised disease that can affect any muscle group (including the eye muscles). Generalised MG can be a serious condition if muscles responsible for swallowing or breathing are affected. Among people with ocular MG, approximately 75% to 90% develop generalised MG within two years of disease onset, meaning that most MG patients have the generalised form of the disease (CS section B.1.3.1). The current technology appraisal, as specified in the NICE scope, and hence this report, are limited to patients who have generalised MG. The extent of muscular weakness caused by MG can be divided into mild, moderate and severe, as reflected in the Myasthenia Gravis Foundation of America (MGFA) classification, which is shown in CS Table 3. One of the EAG's clinical experts said the MGFA is quick and easy to use and is often used in clinical practice, whilst the other expert gave a contrary view, suggesting they do not see the MGFA used often in clinical practice and would primarily classify MG as ocular, oculo-bulbar or generalised and then whether symptomatic or in remission.

2.2.1.4 Disease burden

Generalised MG can lead to a wide range of symptoms, as summarised in CS Figure 3, which impact on patients' health-related quality of life (HRQoL).[3-8] Fatigue and weakness are common symptoms, as well as limb weakness, walking problems, difficulty swallowing and difficulty chewing. Variations and fluctuations in symptoms are also problematic, impacting on patients' work, family, and social activities, with symptoms often persisting despite treatment[7-10] (CS section B.1.3.6.2).

Patients with suboptimal control of MG are at risk of myasthenic exacerbations and life-threatening crises. A myasthenic exacerbation is defined as a worsening of symptoms,

sometimes requiring emergency treatment.[11] A myasthenic crisis is a severe life-threatening exacerbation that requires mechanical ventilation and acute treatment with intravenous (IV) immune globulin (IVIG) or plasma exchange.[3 12 13 12 13]Approximately 15% to 20% of patients with MG experience a myasthenic crisis.[3] Healthcare resource use associated with generalised MG is summarised in CS Table 4, and is considered in more detail in section 4.2.5 of this report.

Estimates from the UK Clinical Practice Research Datalink (CPRD) of primary care records suggest that 5% to 15% of people with generalised MG are refractory to conventional treatment, with refractory patients experiencing a greater treatment burden than those who are not refractory.[9]

2.2.1.5 Epidemiology

Generalised MG can occur at any age. However, the current appraisal, as specified in the NICE scope, is limited to adults. As stated in CS section B.1.3.2, women are more likely to have early-onset generalised MG (age < 50 years) while men are more likely to have late-onset disease (age > 50 years). According to the EAG's clinical experts, generalised MG is more common in men than women and is primarily a disease of the elderly, with older adults making up most of the patient population in clinical practice. The experts estimated peak onset to be around age 80 in men but with a bimodal peak age of onset in women, some of whom are affected at a younger age, typically in their 20s, whilst others develop the disease in their 80s.

The company estimated a prevalence rate of 15 cases of MG per 100,000, based on a reference published in 2012,[14] which the CS states would equate to around 8,940 patients living with MG in the UK (CS section B.1.3.2). Assuming that 75% of MG patients have generalised MG and 90% of these are AChR-positive (based on clinical expert opinion in a company advisory board,[15]) the company estimated there are around 6,034 patients relevant to the scope of this technology appraisal in the UK (CS section B.1.3.2). These figures would appear to underestimate the current number of people in the UK with MG since a prevalence of 15 per 100,000 applied to the latest UK population estimate[16] would give larger numbers than suggested by the company in CS section B.1.3.2. Furthermore, the EAG note that a more recent UK-specific study[17] estimated the UK prevalence of MG at January 2019 from primary care records in the CPRD to be around 34 per 100,000 (i.e. more than double the company's prevalence estimate in the CS based on the 2012 reference[14]). Both the EAG's clinical experts commented that the prevalence of MG is increasing, and this more recent prevalence estimate is appropriate. Assuming the latest population estimate for England to

be 56,536,000 (2021 data),[16] and using the latest prevalence estimate and the assumptions above for the proportions with generalised and AChR antibody-positive MG, we estimate that approximately 19,222 people would be living with MG in England, of whom around 12,975 would have AChR antibody-positive generalised MG.

2.2.1.6 Prognostic factors

The CS does not mention any specific prognostic factors, either for poor outcomes, or for remission, of generalised MG, but states that patients with MG who have comorbidities have a worse prognosis (CS section B.1.3.6). The CS does not discuss which comorbidities have the greatest impact on prognosis of MG, but notes that (according to a large-scale real-world evidence study,[18]) the most frequent comorbidities in MG are cardiovascular and psychiatric/neurological conditions. One of the EAG's clinical experts highlighted that in their experience having an autoimmune disease as a comorbidity with generalised MG, or having impaired lung function (e.g. lower forced vital capacity) confers a worse MG prognosis. Both the experts also suggested that more severe MG at disease onset, and having thymic hyperplasia would be prognostic of poorer MG outcomes.

2.2.2 Background information on ravulizumab

Ravulizumab is a terminal complement inhibitor which binds to complement protein C5, inhibiting the complement cascade (CS section B.1.2). As such, ravulizumab prevents anti-AChR antibodies from damaging the post-synaptic membrane via complement activation. Ravulizumab does not influence the production of anti-AChR antibodies by the immune system, and so immunosuppressant therapies which reduce autoantibody production are also important in the treatment of generalised MG. The company's[15] and EAG's clinical experts agreed that therapy with ravulizumab does not alter the disease course but aims to control patients' symptoms which, as noted above in section 2.2.1.4, can be debilitating. Ravulizumab is administered by intravenous infusion, with the dosage determined by weight. The dosing schedule consists of an initial loading dose, followed by maintenance dosing, starting 2 weeks after the loading dose and then every 8 weeks. The loading and maintenance doses by weight class are provided in CS Table 2.

At least 2 weeks before receiving ravulizumab patients should be vaccinated against meningococcal infections, as the risk of these is increased by ravulizumab therapy. If vaccination occurs less than 2 weeks prior to receiving ravulizumab the patient is required to take appropriate prophylactic antibiotics until 2 weeks after vaccination (CS Table 2). The EAG's clinical experts commented that patients receiving immunosuppression, especially

biologic therapies, may respond less well to vaccinations and may therefore be at increased risk of certain infections. Given that patients eligible for ravulizumab are already receiving immunosuppression, the optimal treatment strategy would require careful consideration. Options could include pausing immunosuppression to enable improvement of the immune response; and measuring the immune response, before administering ravulizumab therapy.

2.2.3 The position of ravulizumab in the treatment pathway

According to the Summary of Product Characteristics (SmPC),[19] ravulizumab is indicated as an add-on to standard therapy (which the company refer to as standard of care, SoC) for the treatment of adult patients with generalised MG who are AChR antibody-positive. We briefly summarise the standard of care treatment pathway below before considering the positioning of ravulizumab in the treatment pathway.

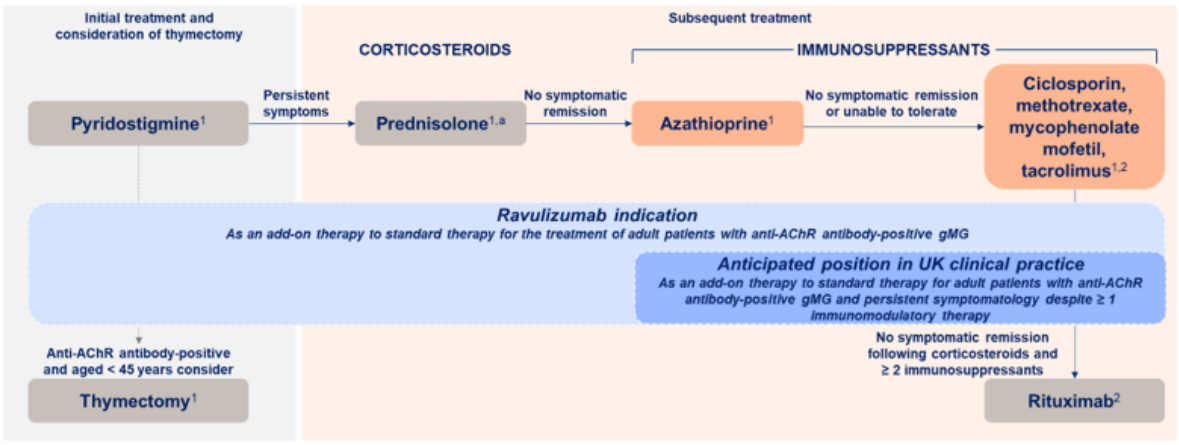
2.2.3.1 Current standard of care for generalised MG

The treatment pathway for generalised MG is shown in CS Figure 5, which we have reproduced in Figure 1 below and is based on the current (2015) Association of British Neurologists (ABN) guidelines.[20] Standard of care generally follows a sequence of therapies that aim to control patients' symptoms, with therapy escalated if patients' symptoms are not controlled on the current therapy. The overall sequence reflects differences in the drugs' time to onset of action, their effectiveness at relieving disease symptoms and in slowing the course of the disease, and their safety profiles (CS section B.1.3.7.1). The ABN guidelines suggest that pyridostigmine is used as a first-line treatment, with corticosteroids (prednisone or prednisolone) reserved as a second-line therapy if a patient on pyridostigmine continues to experience symptoms; and for severe cases of disease, immunosuppressants (ISTs) may be added to corticosteroid therapy or used as a third line of treatment. The ABN guidelines suggest that azathioprine is the first line of immunosuppressant used, although one of the EAG's clinical experts said they preferred other immunosuppressants but would use azathioprine for young female patients (since the other ISTs have teratogenic properties). Patients who experience troublesome symptoms, or side-effects, with azathioprine may receive other immunosuppressants as shown in Figure 1 (primarily mycophenolate mofetil, methotrexate or rituximab according to the EAG's clinical experts, who both agreed that tacrolimus is not used in clinical practice while ciclosporin is rarely used). However, as noted in CS section B.1.3.7.1 and agreed by the experts, the effectiveness of corticosteroids and immunosuppressants in generalised MG lacks strong evidence.

We note that the term “refractory” is often used by clinical experts to describe patients (or a population group) whose MG symptoms are not controlled despite receiving a specified therapy or line of therapies.[15] The term “refractory” is not defined in the CS or the ABN guidelines[20] and therefore in the interests of clarity any reference to “refractory” patients or populations should specify the therapy on which MG symptoms fail to be controlled. In general, “refractory MG”, unless otherwise defined, is likely to mean patients whose symptoms are not controlled despite receiving at least one immunosuppressant therapy.

The EAG agree that the treatment pathway in Figure 1 broadly reflects the pathway of standard of care, although there is variation in clinical practice in the extent to which different immunosuppressant therapies are used. Therapy decisions are made on a patient-level basis to weigh up the risks and benefits of a drug for a particular individual, as noted by the clinical experts advising the company[15] and EAG. The two EAG clinical experts estimated that different proportions of their patients with generalised MG would require later lines of therapy: one expert suggested that most of their patients had adequate symptom control with pyridostigmine alone whilst the other felt that a lower proportion of their patients would have symptom control on pyridostigmine. Both experts concurred that the proportion of patients who were refractory to at least two immunosuppressants would be relatively small.

The CS states that rituximab biosimilars may be used as a last line of therapy for patients who have failed all the other available treatment options. However, the company have excluded rituximab from consideration as they argue that rituximab can “interact with COVID-19 symptomology and the vaccine”[15] (although the specific meaning of this, e.g. whether rituximab is contraindicated in patients with COVID-19, is not explained); rituximab lacks robust trial data; and it is less effective in patients who are AChR-positive compared to those with other antibodies (CS section B.1.3.7.1). Both the EAG’s clinical experts use rituximab in their clinical practice, and they agreed that it is a relevant comparator as part of standard of care. The experts were not overly concerned about limitations placed on rituximab by COVID-19, as rituximab can be given to patients who have received COVID-19 vaccination. The NHS England Budget Impact Analysis provided for this technology appraisal[21] states that 15 centres currently provide rituximab biosimilar for treatment of myasthenia gravis in adults, which NHS England estimate equates to treatment of [redacted] patients in total.



These recommendations are based on guidance from the British Neurologists' management guideline (1) and the NHS England Clinical Commissioning Policy Statement (2) on the use of rituximab biosimilars for the treatment of generalised MG. Treatments shaded in grey indicate those that the company argue are not relevant comparators for ravulizumab.
[a]Guidelines recommend seeking expert opinion on use of plasma exchange, intravenous immunoglobulin or immunosuppression in the event of failure to respond or side effects on corticosteroids.

Figure 1 The proposed position of ravulizumab in the care pathway for generalised MG (reproduction of CS Figure 5)

2.2.3.2 Position of ravulizumab in the treatment pathway

Ravulizumab is indicated as an add-on to standard therapy (i.e. standard of care as described above) for the treatment of adult patients with generalised MG who are AChR antibody-positive.[19] The company's anticipated position of ravulizumab (Figure 1) is more specifically as a later line of therapy after patients have received at least one immunosuppressant therapy. The EAG's clinical experts commented that they would consider using ravulizumab earlier in the treatment pathway, although they acknowledged that ravulizumab would be unlikely to be used earlier in the treatment pathway due to the relatively low cost of existing therapies, so the positioning of ravulizumab by the company as a later line of therapy (Figure 1) reflects its likely use in practice. An uncertainty in the proposed treatment position of ravulizumab is whether it would be used in practice instead of immunosuppressants such as azathioprine or rituximab, and/or as a last line of therapy for patients who are refractory to all previous treatments including rituximab. The NHS England Budget Impact Analysis states that the company anticipate ravulizumab to be used third-line (after corticosteroids and immunosuppressants but before rituximab) whereas clinical experts consulted by NHS England expect to use ravulizumab after patients have failed on rituximab, i.e. as a 4th-line therapy.[21] Clinical opinion was also expressed to NHS England that ravulizumab could potentially be used

[redacted].[21] NHS England estimated that approximately 5-6% of AChR antibody-positive patients with generalised MG, around [redacted] patients, would be refractory to previous therapies including rituximab and would be eligible for other therapies such as complement inhibitors (e.g. ravulizumab).[21]

The EAG's experts said that patients requiring later lines of immunosuppressant therapy, especially those whose AChR antibodies remain detectable, would usually need to continue long-term immunosuppressant therapy as there is a high incidence of relapse if the therapy is withdrawn (noting that ravulizumab provides symptom and functional control but does not suppress antibody production). An uncertainty for the long-term use of therapies for generalised MG is how immunoscenescence (decline of immune function with age) would influence efficacy.

The EAG note that thymectomy is represented in the treatment pathway (Figure 1), but the relationship between thymectomy and the pharmacological therapies is unclear and is not discussed in the CS. After discussing the role of thymectomy with clinical experts the EAG conclude that thymectomy is unlikely to have a bearing on ravulizumab use.

EAG conclusion on the condition and treatment pathway

The CS provides an accurate overview of generalised MG although the prevalence of the disease appears to have been underestimated by the company. Ravulizumab is positioned in the treatment pathway by the company as a later line of therapy, not covering the full indication specified in the SmPC. Rituximab is a relevant comparator as part of standard of care but has been excluded by the company. The EAG's clinical experts agreed that the proposed positioning of ravulizumab reflects likely clinical practice but they disagreed with the exclusion of rituximab as a comparator and suggest that ravulizumab might be used instead of rituximab in clinical practice, along with other potential positionings.

2.3 Critique of the company's definition of the decision problem

Table 3 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this. A key issue with the company's decision problem is that they do not include rituximab as a comparator in the CS – see discussion in Table 3 below and in section 2.2.3 above.

Table 3 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	Adults with generalised MG	Adult patients with anti-AChR antibody-positive generalised MG. Ravulizumab is indicated as an add-on to standard therapy	The decision problem addressed by the company is aligned with the licensed population and clinical evidence available for ravulizumab	The company-specified population is appropriate and matches the licensed population.[19]
Intervention	Ravulizumab	As per the scope	Not applicable	The intervention is as per the NICE scope. In practice in the CS, the intervention evaluated is ravulizumab plus standard of care, which reflects the licensed indication[19] and thus is appropriate.
Comparators	Established clinical management without ravulizumab including corticosteroids and immunosuppressive therapies, with or without intravenous	As per the scope	Not applicable	The comparator is consistent with the NICE scope. However, the company do not include rituximab as a comparator in the CS, as they state it is not relevant (CS section B.1.3.7.2.2 and CS Figure 4). Expert advice to the EAG is that rituximab is used as

	immunoglobulin or plasma exchange			established clinical management in practice and is therefore a relevant comparator (see section 2.2.3).

Outcomes	The outcome measures to be considered include:
	• improvement in MG
	• hospitalisations
	• mortality
	• adverse effects of treatment
	• health-related quality of life.
		The outcome measures to be considered include:
		• Improvement in MG
		  • Change in MG-ADL score
		  • Change in QMG score
		• Mortality
		• MG exacerbations and crises
		• Number of hospitalizations
		• Adverse effects of treatment
		• Health-related quality of life
			MG exacerbations and crises are a relevant outcome for consideration in this appraisal due to their impact on patient health-related quality of life, mortality and engagement with NHS services (healthcare resource use)	All outcomes specified in the NICE scope are included. Additional outcomes included are MG exacerbations and crises. These are relevant outcomes in the context of generalised MG treatment and are included as clinical events in the company's cost-utility analysis (CS Table 43).

Economic analysis	The reference case stipulates the following requirements for cost effectiveness analyses: costs assessed as cost per quality-adjusted life year (QALY), adequate time horizon, NHS and Personal Social Services perspective, and commercial arrangements and	A cost-effectiveness model will be developed in Microsoft Excel, in line with the reference case and NICE methods for health technology evaluation. [redacted]	Not applicable	The company's cost-utility analysis adheres to the NICE reference case (see section 4.2.1). Details of a simple patient access scheme (PAS) discount for ravulizumab are included in CS Table 2) and applied in the economic evaluation (CS section B.3.9).

	managed access agreements taken into account. (NICE scope wording abridged by EAG here for brevity.)	[redacted] A managed access arrangement is not anticipated and is therefore not considered.		
Subgroups	None specified	Not applicable	Not applicable	Subgroup analyses of baseline characteristics were conducted in the pivotal trial and reported in the CS and clinical study report (CSR) but it is not stated whether they were pre-specified or post-hoc (see section 3.2.7.1.4 for further details).
Special considerations including issues related to equity or equality	The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. (NICE scope wording abridged by EAG here for brevity.)	As per the scope	Not applicable	EAG clinical experts said that generalised MG is difficult to control in Black people and that ethnic minorities are under-represented in the studies; and few centres give specialist MG treatments, which may have implications for those who have far to travel, especially if they cannot drive due to their disease activity. Cheaper biosimilars of rituximab are available now.[21] As noted above, the company have not included rituximab as a

				comparator in their decision problem.

Source: Partly reproduced from CS Table 1. MG: myasthenia gravis
AChR, acetylcholine receptor; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; PAS, patient access scheme; QALY, quality-adjusted life year; QMG, Quantitative Myasthenia Gravis scale

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's review methods

The EAG's critique of the company's approach to the evidence synthesis is summarised in Appendix 1. Overall, the EAG agree that the evidence synthesis approach was appropriate, but with the following caveats:

Searches were 1 year out of date when the CS was received by the EAG. However, the EAG believe that all relevant studies that have compared ravulizumab against placebo (standard of care) were identified (CS Appendix Table 5).

The inclusion/exclusion process for selecting studies is ambiguous (details are provided in section 3.1.1 below).

The company included studies of eculizumab in the submission, which is not stated as an intervention or comparator in the NICE scope (for explanation, see section 3.1.2 below).

3.1.1 EAG critique of the study selection process

The company's eligibility criteria (CS Appendix Table 1) are comprehensive, and wider than the NICE scope. According to CS section B.2.1 additional criteria were subsequently applied to limit the review to the NICE scope.

CS Appendix Table 5 lists 43 publications reporting on 20 unique studies that were included after screening against the broad eligibility criteria (note that CS section B.2.1 states 19 studies were included, as the REGAIN RCT and REGAIN open-label extension (OLE) studies were counted as one study; CS Appendix Table 5). Of these 20 studies, CS Appendix Table 5 implies that 16 were excluded after screening against the initial broad eligibility criteria, with reasons for exclusion provided. According to CS Appendix Table 5 the remaining four included studies were:

- CHAMPION-MG (ravulizumab versus placebo) – the pivotal ravulizumab trial, relevant to the company's decision problem
- a trial of methotrexate (which is part of standard of care)
- a trial of tacrolimus (FK506) (in Japan) (which is part of standard of care, although the EAG's clinical experts said they do not use it)
- a trial of mycophenolate mofetil (which is part of standard of care)

However, CS Document B only refers to one of these four included studies - the CHAMPION-MG RCT. Exclusion of the methotrexate, tacrolimus and mycophenolate mofetil studies is not explained anywhere in the CS or Appendices.

CS Document B includes a further three studies, without following a systematic eligibility screening process. Two of these studies had previously been excluded at the prior screening step (the REGAIN RCT and the REGAIN OLE study) whilst the third had not previously been identified among the search results (the CHAMPION-MG OLE study). As a result of this ad hoc and poorly explained process, the following four studies were included in the CS and inform the clinical effectiveness evidence base for this technology appraisal:

- CHAMPION MG RCT
- REGAIN (eculizumab versus placebo) (eculizumab is not a comparator in the NICE scope but is included in an indirect treatment comparison) (discussed below at the end of this section).
- REGAIN Open Label Extension (OLE) study (a non-randomised extension cohort of eculizumab-treated patients).
- CHAMPION-MG OLE study (a non-randomised extension cohort of ravulizumab-treated patients).

These studies are not explicitly listed as having been included in the CS, although they are summarised in CS Table 5 (the CHAMPION-MG OLE study is not obviously referred to in CS Table 5, but its presence is indicated by the “CHAMPION-MG clinical study report 60-week data addendum” cited in CS Table 5).

Importantly, although the company’s approach for the selection of studies is poorly explained and non-systematic, the EAG believe that no key studies of ravulizumab have been missed. Two of the studies included by the company (the REGAIN RCT and the REGAIN OLE study) relate to eculizumab which is not specified as an intervention or comparator in the NICE scope, and which is not licensed for the generalised MG population. For further explanation of why the company consider eculizumab in the present technology appraisal please see section 3.1.2 below.

The trials of methotrexate, tacrolimus and mycophenolate mofetil which CS Appendix Table 5 lists as included appear to have been subsequently excluded since they are not mentioned further in the CS or Appendices, although no explanation is provided. These therapies are

components of standard of care as shown in the care pathway depicted in CS Figures 4 and 5. In summary, the company excluded the following trials covering comparators that are part of standard of care, in adults with anti-AChR antibody positive generalised MG (CS Appendix Table 5):

- Rituximab (4 trials) – the company argue this comparator is not relevant (as discussed in section 2.2.3 above).
- Methotrexate (1 trial) – no rationale for exclusion is provided.
- Tacrolimus (1 trial) – no rationale for exclusion is provided (the EAG's clinical experts said tacrolimus is not used in clinical practice).
- Mycophenolate mofetil (1 trial) – no rationale for exclusion is provided.
- Plasma exchange, plasmapheresis or intravenous immunoglobulin (IVIG) (4 trials) – the company state these are not relevant comparators since they are used as acute rather than maintenance treatments in the UK (CS Appendix Table 5).

The EAG's clinical experts both agreed that whilst the overall standard of care is a relevant comparator, rituximab should have been included for consideration as a specific comparator given the similar positioning of rituximab and ravulizumab in the treatment pathway. Please see section 1 for further discussion of this, which the EAG believe is a key issue in the current technology appraisal. (Note that, depending on whether or not ravulizumab may replace other individual therapies in the treatment pathway, an argument might be made that other specific immunotherapies would also be relevant comparators against ravulizumab, but the evidence to support such comparisons is expected to be sparse and heterogeneous.)

3.1.2 Inclusion of the REGAIN trial of eculizumab

Eculizumab is not specified as an intervention or comparator in the NICE scope. However, in their submission the company have included the REGAIN trial comparing eculizumab against placebo (standard of care) in adult patients with AChR antibody-positive generalised MG. As noted in section 3.1.1 above the company have also included the OLE study for the REGAIN trial, which provides outcomes data for up to 3 years.

Eculizumab and ravulizumab have similar molecules and the company assume that these therapies have similar efficacy and safety (CS sections B.2.9 and B.3.3). The company suggest that if ravulizumab and eculizumab are similarly effective in the short-term, then eculizumab evidence can be used to inform predictions of long-term outcomes for patients treated with ravulizumab, for which shorter follow up is available than for eculizumab (CS section B.2.9.1). Outcomes from the REGAIN trial and its OLE study are used (pooled with

those from the CHAMPION-MG trial and its OLE study) to inform some aspects of the company's economic analysis (see section 4.2.3 below).

To demonstrate that eculizumab and ravulizumab have similar clinical effectiveness, the company conducted an indirect treatment comparison (ITC) of eculizumab against ravulizumab using the CHAMPION-MG and REGAIN trials, with the placebo (standard of care) arm as the common comparator. The EAG's full critique of the ITC is provided in sections 3.3 to 3.5 of this report.

The ITC was intended "for helping to predict long-term outcomes for patients treated with ravulizumab" (CS section B.2.9.1). However, the ITC is limited to the randomised phase of each trial, up to 26 weeks, so does not permit inferences about longer-term outcomes. The CS implies an unstated assumption that if ravulizumab and eculizumab have similar effectiveness over 26 weeks then they will also have similar long-term effectiveness. This is uncertain and the EAG have listed this as a key issue for consideration (section 1.1). Limitations of using eculizumab outcomes in the economic model are explored in EAG scenario analyses (see section 6 of this report).

It should be noted that eculizumab is licensed for use in patients with refractory generalised myasthenia gravis who are AChR antibody positive,[22] while ravulizumab is indicated for a wider population of people with generalised myasthenia gravis who are AchR antibody positive.[19] Thus, eculizumab is not licensed for the indication under consideration in this appraisal. The EAG note that eculizumab was due to be appraised by NICE, but as the company did not submit an evidence submission, NICE were unable to make a recommendation for its use in the NHS.[23] The CS states that as it is not reimbursed in the NHS, eculizumab is not used in clinical practice in the UK (CS section B.1.3.7).

EAG conclusion on the company's approach to evidence synthesis

The company's systematic literature review approaches were generally appropriate. The study selection process is ambiguous, but the EAG believe that all relevant studies have been included. However, the REGAIN trial and OLE study of eculizumab, which are not eligible according to the NICE scope, were also included as supporting evidence. The company argue that long-term outcomes with eculizumab can serve as a proxy for long-term outcomes with ravulizumab in their economic analysis. This assumption is uncertain and is specified by the EAG as a key issue for further consideration.

3.2 Critique of the studies included in the company's evidence synthesis

3.2.1 Study designs

The company's systematic literature review identified one study that is directly relevant to their decision problem: CHAMPION-MG (NCT03920293)[24] (CS Appendix D.1.2). CHAMPION-MG is a phase III, double-blind, international RCT that compares the efficacy and safety of ravulizumab as an add-on therapy to standard of care versus placebo plus standard of care, over a 26-week period, in people with anti-AChR antibody-positive generalised MG (CS section B.2.3.1). Data were also included from the OLE study of this trial, which assessed the efficacy and safety of ravulizumab up to two years following the end of the randomised-controlled period of the study although, as explained below, the latest data cut provides results up to 60 weeks from the time of randomisation.

The CHAMPION-MG trial was funded by the company.[25] The trial has been published as a paper in a peer-reviewed journal,[24] which was provided with the CS. The company also provided the trial clinical study report (CSR), which presents the primary analysis results from the randomised controlled part of the study for all participants who were enrolled, as well as some results from the OLE study up to 52 weeks of treatment (11th May 2021 data cut).[25] Some CSR data tables were missing from the company's original submission, and were requested in clarification question A5. All but one of these (CSR Table 14.1.5.12.2, 'Concomitant immunosuppressant therapies used during the randomised controlled period (safety set)') were provided in response to the request. The company additionally provided a CSR addendum alongside the CS, which reports efficacy and safety results from the OLE study up to Week 60 from randomisation (9th November 2021 data cut).[26] The company stated that they do not anticipate that any further data analyses of the OLE study will become available during the timescale of this technology appraisal (clarification response A7). The CS notes that the CHAMPION-MG RCT and its OLE study were conducted during the COVID-19 pandemic, which the company suggest might have influenced HRQoL outcomes (CS section B.2.3.1).

As noted in section 3.1.1 above, the CS also includes the company-sponsored REGAIN RCT of the efficacy and safety of eculizumab versus placebo in adult patients with AChR-positive refractory generalised MG,[27] and its OLE study. Eculizumab is not included in the NICE scope as a relevant comparator or intervention, but the company argue that the REGAIN trial provides data on the long-term effects of C5 inhibitor treatment in generalised MG (CS section B.2.2).

The REGAIN trial had a maximum follow-up length of 4.29 years, compared with 1.21 years for ravulizumab in the CHAMPION-MG trial (CS section B.3.3.2), although, it should be noted that in the clinical effectiveness results section of the CS (section B.2.6.2) data are provided from REGAIN up to 3 years or 130 weeks (2.5 years) of eculizumab treatment.

3.2.1.1 CHAMPION-MG RCT

The characteristics and methodology of the CHAMPION-MG RCT are described in CS Tables 5 and 7, CS Figure 6, and in CS sections B.2.2 and B.2.3.1. The key aspects of the trial are summarised in Table 4 below. Participants were symptomatic at study entry (as shown by the requirement that they had to have an MG-ADL score of ≥ *6 to be eligible for the study)* despite having previously received standard of care treatment.[28] The dosing regimens of ravulizumab (CS Table 6) were consistent with those specified in the SmPC.[19]

Table 4 CHAMPION-MG RCT study design

Study characteristics	Details
Study sites	85 sites in 13 countries, including 8 sites in Europe (no UK sites)
Population	Adult patients with anti-AChR antibody-positive generalised MG (MGFA Class II–IV) and MG-ADL score of ≥ 6, who had not previously received complement inhibitor treatment
Intervention: Ravulizumab plus standard of care treatment	A weight-based loading dose of ravulizumab was administered by IV infusion on Day 1, followed by a weight-based maintenance dose given on Day 15 and then every 8 weeks afterwards (see CS Table 6 for details of the weight-based ravulizumab dosing regimens).
Comparator: Placebo plus standard of care treatment	Placebo was administered by IV infusion, with a loading dose given on Day 1, followed by a maintenance dose given on Day 15 and then every 8 weeks afterwards.
Concomitant medication	Participants who were receiving immunosuppressant therapies at screening were allowed to stay on these during the study, but had to remain on a stable dose, with no change to medication allowed unless the study investigator deemed it necessary. Rescue medication was permitted but rituximab was disallowed (CS Table 7).
Key eligibility criteria	• Diagnosed with generalised MG at least six months prior to study screening and confirmed positive on serologic testing as having anti-AChR antibodies. • MGFA Class II-IV and MG-ADL profile ≥6 at screening. • Received vaccine for meningococcal infection. • Participants were allowed to be on stable doses of ISTs prior to screening.
Sample size	N randomised: 175 (ravulizumab: n = 86; placebo: n = 89)
Primary outcome	**Change from baseline in MG-ADL total score** at Week 26

Study characteristics	Details
Other outcomes For explanation of the outcome measures see section 3.2.5	• Change from baseline in QMG total, MG-QoL15r, and Neuro-QoL Fatigue at Week 26 • **Change in EQ-5D-5L** • Improvement of **at least 3 points in the MG-ADL total score** and of at least 5 points in the QMG total score from baseline at Week 26 • Incidence of hospitalisations/MG-related hospitalisations,[a] of **clinical deterioration/MG crisis** and of **adverse and serious adverse events**

Source: Partly reproduced from CS Tables 5, 6 and 7, CS section B.2.3.1 and CS Figure 7. Bold text in the outcomes sections of the table shows the outcomes that were used in the company's economic model.
AChR, acetylcholine receptor; IV, intravenous; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15r, MG-Quality of Life 15; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis scale; QOL, quality of life; RCT, randomised controlled trial; [a] CS Table 5 indicates that this outcome is used in the economic model, but it does not appear to have been.

As outlined in CS section B.3.3.2, generalised MG is a chronic condition that requires life-long management. A key limitation of the CHAMPION-MG RCT in this respect is its relatively short duration, of 26 weeks. Additional longer-term outcomes from patients receiving ravulizumab are available from the OLE study, described next, although all patients in the OLE received ravulizumab, with no comparator group, so the comparative evidence for ravulizumab efficacy remains limited to the 26-week RCT.

3.2.1.2 CHAMPION-MG OLE study

Patients in the CHAMPION-MG RCT were eligible to enter the OLE study from week 26 after randomisation. During the OLE study all patients received ravulizumab. The OLE study therefore comprises two cohorts: those who had previously been randomised to receive placebo in the RCT and then switched to ravulizumab in the OLE study (referred to in the CS as the PBO/RAV group); and those who had previously been randomised to receive ravulizumab in the RCT and continued to receive ravulizumab in the OLE study (referred to as the RAV/RAV group). The first dose of ravulizumab in the CHAMPION-MG OLE study was administered at Day 183 after randomisation in the CHAMPION-MG RCT (CS Figure 6). Of the 175 patients included in the RCT, 161 entered the OLE and received at least one dose of ravulizumab, with 150 remaining in the OLE at the time of the 60-week data cut. The PBO/RAV cohort at the data cut comprises 79 of the 89 patients originally randomised to the RCT placebo arm, whilst the RAV/RAV cohort comprises 71 of the 86 patients originally randomised to the ravulizumab arm (CS section B.2.6.1; Figure 1 in the 60-week CSR Addendum).

The OLE study dosing schedule is briefly described in section 3.1 of the CSR. The CSR states that at Day 183 (Week 26), in order to maintain the blind of the RCT period, all patients entering the OLE received a blinded ravulizumab dose of 900 mg (i.e. the loading dose required for the placebo group), then, starting at Week 28, all patients began open-label ravulizumab maintenance dosing q8w. Participants previously receiving standard of care treatments in the RCT could continue these during the OLE study unless there was a medical need for a change in medication.

Considering the total ravulizumab treatment during both the CHAMPION-MG RCT and OLE study (referred to by the company as the "Ravulizumab Treated Set"), the mean duration of exposure to ravulizumab was [redacted] days (equating to approximately [redacted] weeks of treatment), with a maximum duration of treatment received of [redacted] days (equating to approximately [redacted] weeks of treatment) (section 3.5.1 in the 60-week CSR Addendum).

Two key limitations of the CHAMPION-MG OLE study are that there is no comparator arm, so the study does not provide comparative efficacy outcomes for ravulizumab; and there is currently a lack of efficacy data available to assess the maintenance of the treatment effect beyond 60 weeks of therapy (the latest data cut). However, the EAG's clinical experts suggested that given the mechanism of action of ravulizumab, any comparative benefit seen at 26 weeks in the CHAMPION-MG RCT would likely be maintained into the longer-term while patients stay on the drug.

A consideration noted by one of the EAG's clinical experts is that neutralising antibodies can develop which reduce drug efficacy. Neutralising antibodies against ravulizumab were not detected during the 26 weeks of randomised therapy in CHAMPION-MG (CSR section 5.6) but it is unclear whether such antibodies would develop after prolonged ravulizumab use. Neutralising antibodies appear to have been measured during the CHAMPION-MG OLE,[26] but the EAG could not find any report of the results in either the CSR,[25] CSR Addendum,[26] CS or trial paper.[24] The expert said that in studies of eculizumab in paroxysmal nocturnal hemoglobinuria neutralising antibodies were 'transient and very infrequent with minimal impact on clinical response'. Therefore, it is possible that neutralising antibodies to complement inhibitors such as ravulizumab and eculizumab may develop with prolonged use, but this is uncertain.

3.2.1.3 REGAIN RCT

In the REGAIN RCT, 126 participants were randomised (63 to placebo and 63 to eculizumab; Figure 6 in CS Appendix M). Participants previously receiving standard of care treatments maintained these during the study unless there was a medical need for a change

in medication (CS Table 7). Thus, the study evaluated eculizumab plus standard of care versus placebo plus standard of care, with rescue medication permitted. Details about the characteristics of the REGAIN RCT are available in CS sections B.2.2 and B.2.3.2, and in CS Appendix M. For brevity, we have not summarised these here. Critical appraisal of the study design is considered in section 3.2.1.3 Characteristics of the trial population that affect generalisability of the outcomes to clinical practice are considered in section 3.2.3.

3.2.1.4 REGAIN OLE study

Participants who completed the REGAIN RCT were eligible to enter the REGAIN OLE study.[29] Of the 118 participants who completed the RCT, 117 enrolled in the OLE, comprising 56 who had received eculizumab in the RCT (referred to in the CS as the ECU/ECU group) and 61 who had received placebo (the PBO/ECU group). Interim results from the OLE period appear to be presented in the CS – this is not explicitly stated, but results are provided from a data cut dated 31st December 2017, by which point participation in the study was ongoing for 73% of the participants (CS section B.2.6.2). This data cut was described as an interim analysis in a published paper reporting the OLE study. [29]

Change in outcomes was assessed from the RCT baseline and OLE baseline.[29] The trial paper states that data were analysed in this way to enable assessment of effects from entry into the REGAIN RCT, and allowed separate evaluation of the effect in the PBO/ECU group versus those participants who had received eculizumab into the longer-term in the ECU/ECU group.[29] Safety data were reported for the safety analysis set (i.e. not broken down by the PBO/ECU and ECU/ECU groups).[29]

3.2.2 Study baseline characteristics

3.2.2.1 Baseline differences between trials

The CHAMPION-MG and REGAIN trials both included patients with AchR antibody-positive generalised MG; that is, those with MGFA Class II-IV with a MG-ADL score of ≥ 6 (CS Table 7). However, the trials differed in the following respects which the EAG's clinical experts agreed indicate that the REGAIN trial population was a more refractory group of patients while the participants in the CHAMPION-MG trial would be more reflective of a wider generalised MG population (data are from CS Table 8 unless stated otherwise):

- Differences in the trial eligibility criteria: The CHAMPION-MG trial had no requirement for prior treatment failure whereas in REGAIN patients were required to have failed treatment with at least 2 ISTs, or failed at least one IST and required chronic plasma

exchange or IVIG therapy (CS Appendix D.2). Participants eligible for the CHAMPION-MG trial were permitted to be on stable doses of ISTs prior to screening whilst in the REGAIN trial, participants had to have *"received treatment with ≥ 2 ISTs with IVIG or plasma exchange given ≥ 4 times per year, for 12 months without symptom control"* (CS Table 7).

- In CHAMPION-MG, 12% and 9% of participants in the ravulizumab and placebo arms respectively (i.e. around 10% overall) were not receiving any immunosuppressant therapy at baseline.

- A higher proportion of participants in REGAIN (98%) had received ≥2 immunosuppressant agents than in CHAMPION-MG (42% to 53%).

- A higher proportion of patients in REGAIN were receiving glucocorticoids at baseline (76%-81%) compared to those in than CHAMPION-MG (65%-73%).

- Patients in REGAIN were younger on average than those in CHAMPION-MG (around 47 years compared to 53-58 years respectively).

- There was a lower proportion of male participants in the REGAIN than CHAMPION-MG trial (around 35% compared to 49% respectively).

- Participants in REGAIN had Quantitative Myasthenia Gravis (QMG) scores that were approximately 2 points higher (indicative of more severe disease) than those in CHAMPION-MG (QMG is a measure of myasthenia gravis symptomatology; see section 3.2.5).

According to the EAG's clinical experts (section 2.2.1.6), the following baseline characteristics are likely to be indicative of poorer prognosis in generalised MG: thymic hyperplasia, co-morbid autoimmunity (presence of other autoimmune conditions), more severe disease at onset and lower forced vital capacity. We note that these prognostic factors are not reported for either the CHAMPION-MG or REGAIN trials and therefore it is unknown whether they differed between the trials or between the arms within each trial.

3.2.2.2 Baseline differences within trials

3.2.2.2.1 CHAMPION-MG RCT

Baseline characteristics of the CHAMPION-MG trial participants were generally well-balanced between the ravulizumab and placebo arms (CS Table 8), with the following exceptions:

- There was around a five-year difference between arms in age at infusion (ravulizumab: 58.0 (13.8) years, placebo: 53.3 (16.1) years (CS Table 8); the EAG assume this is presented as the mean and standard deviation, but this is not stated.

- Participants in the ravulizumab arm had slightly more severe disease by MGFA class than those in the placebo arm (MGFA class IIa or IIIa: ravulizumab 52% (n=44), placebo 65% (n=58); MGFA class IIb or IIIb: ravulizumab 42% (n=36), placebo 29% (n=26).

However, neither expert felt that the differences in age or MGFA class were clinically important given the relatively advanced age of the participants in the trial.

3.2.2.2.2 REGAIN RCT

Within the REGAIN trial, baseline characteristics were generally well-balanced between the two trial arms (CS Table 8), with the following exceptions that are reported in Table 1 of the trial publication:[27]

- Both the EAG's clinical experts noted that the placebo group had higher proportions of patients who had received previous long-term plasma exchange therapy (16% [n=10] compared to 6% [n=4] in the eculizumab group) and those who had a history of MG exacerbations (83% [n=52] compared to 74% [n=46] in the eculizumab group).

- The proportion of patients who had a previous thymectomy was higher in the eculizumab group (60%) [n=37] than the placebo group (49%) [n=31].

- The placebo group consisted of a greater proportion of Asian participants than the eculizumab group (25% [n=16] compared to 5% [n=3]).

- The EAG's clinical experts suggested that the higher proportions who had prior plasma exchange and MG exacerbations in the placebo arm could indicate that the

placebo group had more severe disease. One expert suggested that more severe disease in the placebo arm might in part be related to the lower rate of thymectomy, and the imbalance in disease severity between arms could be a potential source of bias in the comparison of eculizumab against placebo. The clinical experts do not expect the imbalance in Asian participants would have impacted the trial's results.

3.2.3 Relevance to clinical practice (external validity)

3.2.3.1 Population characteristics

As noted above (section 2.2.1.5), generalised MG is more common in men than women and is primarily a disease of the elderly, with older adults making up most of the patient population in clinical practice. The EAG's clinical experts estimated peak onset to be around age 80 in men but with a bimodal peak age of onset in women, some of whom experience disease onset in their 20s. The experts made the following observations on the relevance of the trial populations to clinical practice according to their experience:

The CHAMPION-MG and REGAIN trials both included a greater proportion of female and younger patients (CS Table 8) than the experts typically see with generalised MG in clinical practice, indicating that the trials included a more difficult to treat subset of the generalised MG population. This is a relevant group to the NHS in England but does not cover the full spectrum of patients with generalised MG.

Differences between the trials discussed above (section 3.2.2.1) indicate that REGAIN has a more refractory, i.e. more difficult to treat, population that CHAMPION-MG. One expert commented that the REGAIN population may therefore better reflect the proposed positioning of ravulizumab in the treatment pathway (although the trial was on eculizumab rather than ravulizumab). The expert also felt that the REGAIN population reflects patients who would likely receive rituximab in clinical practice. CHAMPION-MG has a more of an "all comers" population, compared to REGAIN, albeit still overall a more refractory subset of the overall generalised MG population than the experts see in clinical practice.

The experts noted that generalised MG is more difficult to control in Black people. However, one of the experts who commented further suggested that the proportion of Black people included in the study (ravulizumab 2% and placebo 6%) is representative of the patients seen in clinical practice in England.

One expert said that in their clinical practice generalised MG patients are typically overweight (often >100kg), due to the side-effects of therapies, especially corticosteroids. Being overweight makes patients more resistant to treatment. Patients in CHAMPION-MG

had a mean weight consistent with this (around 91kg). Weight is not reported for patients REGAIN but according to their reported mean body mass index (CS Table 8) the trial population would be considered overweight.

Uncertainties noted by the EAG's clinical experts

One of the EAG's clinical experts queried how some patients in CHAMPION-MG could have had generalised MG for around 10 years (CS Table 8) and not be receiving immunosuppression. Speculatively, this suggests that the CHAMPION-MG trial population was a relatively heterogeneous mix of very old patients and younger more treatment-resistant patients.

3.2.3.2 Standard of care therapy

The treatments participants were receiving at baseline, and which thus formed the permitted concomitant therapies during the trials, are shown in Table 5. Compared to CHAMPION-MG, a higher proportion of patients in REGAIN received corticosteroids, azathioprine, and ciclosporin at baseline, which is consistent with REGAIN having a more refractory and difficult to treat population, as discussed above.

Table 5 Standard of care therapy at baseline

Therapy, n (%)	CHAMPION-MG		REGAIN	
	Ravulizumab N=86	Placebo N=89	Eculizumab N=62	Placebo N=63
Corticosteroids	56 (65)	65 (73)	47 (76)	51 (81)
Azathioprine	18 (21)	22 (25)	20 (32)	21 (33)
Mycophenolate mofetil	24 (28)	24 (27)	18 (29)	16 (25)
Ciclosporin	6 (7)	4 (4)	8 (13)	9 (14)
Tacrolimus	8 (9)	12 (13)	5 (8)	6 (10)
Methotrexate	0	1 (1)	5 (8)	4 (6)
Cyclophosphamide	Not reported	Not reported	2 (3)	0
Rituximab	Not reported	Not reported	0	0
Rituximab pre-baseline [a]	6 (7) [a]	5 (6) [a]	7 (11) [b]	7 (11) [b]

Sources: From the CHAMPION-MG[24] and REGAIN[27] trial publications.
[a] In the 2 years before screening and up to baseline.
[b] Used before study enrolment (timeframe not reported)

The specific therapies used during the active phase of the CHAMPION-MG RCT are listed in CS Table 23 for the trial overall (not separately by trial arm). In CHAMPION-MG, the distribution of standard of care therapy during the trial was broadly similar to that reported at baseline, but with more frequent use of corticosteroids (prednisone and prednisolone combined 83.4%), azathioprine (31.4%) and mycophenolate mofetil (32.6%) (CS Table 23).

NB the experts commented that prednisone and prednisolone are the same drug but branded differently.

The EAG's clinical experts said that standard of care therapy in the clinical trials differs in the following respects from their experience in clinical practice:

- Tacrolimus was used by 12.6% of the trial population in CHAMPION-MG and 16% in REGAIN (CS Table 14) but according to the experts it is not used in the UK.

- Cyclosporin was used by 6.9% of patients in CHAMPION-MG and 28.0% in REGAIN (CS Table 23). The EAG's experts said ciclosporin is rarely used in the UK.

- Azathioprine was used by 31.4% of patients in CHAMPION-MG and 44.8% in REGAIN (CS Table 23). The experts estimated that around 40% of patients in clinical practice would receive azathioprine, with the REGAIN trial being more reflective of clinical practice than CHAMPION-MG in this respect.

- Pyridostigmine was used by most patients (92.0% and 95.2% in CHAMPION-MG and REGAIN respectively), but the experts would use pyridostigmine only for symptomatic patients who are not in remission, which would likely be a lower proportion.

As mentioned above (section 2.2.3), rituximab is used in clinical practice in England, but was not allowed as a part of standard of care in the CHAMPION-MG trial (Table 4 and CS Table 7). However, 11 of the trial participants (6%) were using rituximab in the two years before screening and "up to baseline" (Supplementary Appendix Table S3 in the trial publication[24]). It is unclear whether any patients received rituximab specifically at baseline, since this information is not provided (Supplementary Appendix Table S2 of the trial publication[24]). Nor is it reported at which point in the treatment pathway these 11 patients received rituximab pre-baseline.

In the REGAIN trial, rituximab was not permitted within 6 months before screening (CS Table 7) and therefore it was not used at baseline but had been used by 11% of the patients (n=14) before trial enrolment.[27] The REGAIN trial has a refractory population (section 3.2.3.1), for which, according to the EAG's clinical experts, rituximab would be used in UK clinical practice. The CS and trial publication do not state whether any patients in REGAIN received rituximab after baseline.

Overall, we conclude that the standard of care treatments received in the CHAMPION-MG and REGAIN trials may not be fully representative of those used in clinical practice in England, although we acknowledge that there is variation in clinical practice.[15] The selection of appropriate standard of care therapies for the economic analysis is explored in EAG sensitivity analyses, discussed in section 4.2.2.3 of this report.

EAG conclusion on the included studies

Key limitations of the evidence from the CHAMPION-MG RCT and OLE studies are that comparative efficacy and safety of ravulizumab was only assessed over 26 weeks, whilst longer-term non-comparative clinical effectiveness and safety data for ravulizumab are only available up to 60 weeks of treatment. These are short timescales relative to the natural history and treatment requirements of generalised MG. Results from the REGAIN OLE study of eculizumab, which the company included to provide longer-term outcomes as a proxy for ravulizumab outcomes, are also uncertain due to small sample sizes at the end of the study (reflecting the ongoing nature of the study). Standard of care in both studies differs in some respects to the standard of care used in NHS clinical practice.

3.2.4 Risk of bias assessment

The company provided risk of bias assessments for the CHAMPION-MG RCT in CS section B.2.5 and for the REGAIN RCT in CS Appendix M.1.2. We requested a critical appraisal of the CHAMPION-MG OLE study, which the company subsequently provided in Clarification Response A8. As explained below, the EAG conducted risk of bias assessments for the two RCTs and their OLE studies and compared our judgements against those of the company, except for the REGAIN OLE study which the company did not assess for risk of bias.

3.2.4.1 CHAMPION-MG RCT

The CS states that risk of bias assessment of the CHAMPION-MG trial used the Cochrane risk of bias tool[30 31] (CS Appendix D.4), although we note that the company actually used the NICE-recommended checklist for RCTs.[32] In line with the company, we used the NICE criteria. The company and EAG risk of bias assessments are shown in Table A of Appendix 2. Our risk of bias assessment differs from the company's in that we considered the trial to have:

Unclear risk of selection bias for all outcomes, since it is unclear whether all prognostic factors were balanced (prognostic factors identified by the EAG's clinical experts were not reported in the RCT).

Unclear risk of attrition bias for all outcomes due to uncertainty in the potential impact of missing data.

3.2.4.2 CHAMPION-MG OLE study

The EAG requested that the company provide a critical appraisal of the CHAMPION-MG OLE study using an instrument that meets specified criteria stated in Clarification Question A8. In response, the company provided a critical appraisal of the OLE study using the Downs and Black checklist (1998).[33] This checklist asks questions relevant to risk of bias, but does not elicit answers that yield a risk of bias judgement (merely giving yes/no responses without any further interpretation); and the company did not provide any rationale for their judgements or how they relate to risks of bias. We instead appraised the CHAMPION-MG OLE study for risk of bias using criteria suggested by NICE for non-randomised and non-controlled studies,[32] as all participants received open-label ravulizumab (although, it should be noted that efficacy results are presented separately for the RAV/RAV and PBO/RAV (explained in section 3.2.1.2 above). Full details of the EAG's critical appraisal are provided in Table B of Appendix 2.

In summary, we have no concerns about how participants were selected to enter the OLE. But we considered the OLE to have the following high or unclear risks of bias for all outcomes:

High risk of performance and detection bias: There was no blinding of the treatment received during the OLE period (by nature of, and inevitably due to, the study design where open-label ravulizumab was administered).

High risk of other sources of confounding: The CS does not discuss potential confounding factors that may have influenced the results of the OLE study (other than a general point that the COVID-19 pandemic may have impacted on HRQoL measures; CS section B.2.12.1) nor have such factors been taken into account in the data analyses. Anti-drug neutralising antibodies were measured in the OLE study but results for these have not been provided in any of the documents available to the EAG. Such antibodies, if present, could influence the effectiveness of ravulizumab.

Unclear risk of attrition bias: Follow-up was incomplete, as the OLE is ongoing, with data available at Week 60 for [redacted] of participants for the change from baseline in MG-ADL total score, in QMG total score, in MG-QoL15r score and in Neuro-QoL Fatigue score outcomes (percentages calculated by EAG). This means the results at this timepoint are subject to some uncertainty. Risk of bias is unclear since it is unknown whether the participants not followed up at the latest data cut may have differed in their characteristics from those who were analysed.

The company's critical appraisal of the OLE, using the Downs and Black (1998) checklist, did not identify any risks of bias (Clarification Response A8). As noted above the company provided no explanation for their judgements, and the EAG do not agree with the company's assessment.

3.2.4.3 REGAIN RCT

Full details of the EAG's critical appraisal of the REGAIN RCT are provided in Table A of Appendix 2. In summary, we identified the following bias risks:

High risk of selection bias for any comparisons between the trial arms: the placebo arm had more severe disease at baseline than the eculizumab arm (for explanation see section 3.2.2.2.2).

Unclear risk of attrition bias: the amount of missing data across outcomes and trial arms, and the reasons for data being missing, are unclear.

3.2.4.4 REGAIN OLE study

The EAG critically appraised the REGAIN OLE study following the same approach as for our critical appraisal of the CHAMPION-MG OLE study. Full details of the EAG's critical appraisal are provided in Table B of Appendix 2.

In summary, as with CHAMPION-MG, we have no concerns about how participants were selected to enter the OLE. But the study is subject to the following risks of bias:

High risk of performance and detection bias: Due to lack of blinding.

High risk of other sources of confounding: The CS does not discuss potential confounding factors that may have influenced the results nor take such factors into account in the data analyses.

Unclear risk of attrition bias: Follow-up was incomplete, as the OLE is ongoing, with data available at the furthest follow-up points (Weeks 104 and 130) for 41% to 44% of participants for the change from baseline in MG-ADL total score, in QMG total score, in MG-QoL15r score and in Neuro-QoL Fatigue score outcomes.

EAG conclusion on the risk of bias

Risks of selection bias and attrition bias in the CHAMPION-MG RCT were judged unclear due to uncertainty in the balance of some unreported prognostic factors for MG between trial arms, and uncertainty in the impact of missing data for all outcomes. The REGAIN RCT was judged to have a high risk of selection bias due to differences in disease severity between the trial arms and an unclear risk of attrition bias due to limited reporting of missing data. Both the CHAMPION-MG and REGAIN OLE studies were judged to have high risks of performance bias, detection bias and other sources of confounding due to the non-blinded study design and lack of consideration of potential confounding factors; as well as unclear attrition bias due to incomplete follow-up in these ongoing studies.

3.2.5 Outcomes assessment

For myasthenia gravis a key aim of treatment is to control patients' symptoms. The main clinical outcomes therefore focus on assessment of symptoms using instruments which measure disease symptoms. Responders were defined as patients who achieve specified threshold changes in scores on these instruments.

3.2.5.1 Disease symptom and severity measures

Six measures of disease symptoms and severity and HRQoL were used in the CHAMPION-MG trial and included in the CS (Table 6):

Mysathenia Gravis Activities of Daily Living (MG-ADL). The MG-ADL asks eight questions about talking, chewing, swallowing, breathing, ability to brush teeth or comb hair, ability to arise from a chair, double vision, and eyelid droop. The questions are each scored 0 to 3, with 0 representing normal ability and 3 representing maximum impairment, giving a

total score ranging from 0 to 24, with higher scores indicating greater disease severity. The MG-ADL is entirely patient-reported and relatively quick to use.[34 35]

Quantitative Myasthenia Gravis scale (QMG). The QMG has 13 items that measure endurance or fatiguability, each scored 0 to 3, giving a total score ranging from 0 to 39, with higher scores indicating greater disease severity. The QMG scale is based on a physical examination requiring a dynamometer and spirometer and can take up to 25 minutes to complete, therefore it is used mostly in research rather than clinical practice.[35]

MG Quality of Life 15 revised version (MG-QoL15r). The MG-QoL15r has 15 items relating to mobility (9 items), symptoms (3 items), and contentment and emotional wellbeing (3 items). Each item is scored 0 to 2, with total scores ranging from 0 to 30, with higher scores indicating worse quality of life. The MG-QoL15r has improved psychometric properties compared to the original version of the instrument (MG-QoL15).[35]

Quality of Life in Neurological Disorders (Neuro-QoL) Fatigue. The CS does not provide any information on this scale and the EAG's clinical experts said it is not a scale that they were very familiar with. This is a generic scale for assessing quality of life in neurological diseases, not specifically limited to MG. As far as the EAG are aware, no MG-relevant threshold for a minimum clinically important change or difference has been established for the Neuro-QoL Fatigue scale. Higher scores are indicative of worse fatigue on this scale.

EQ-5D-5L index and visual analogue scale (VAS) scores. The CS does not list EQ-5D as an outcome (CS Table 7), although EQ-5D results from the CHAMPION-MG trial are reported in CS section B.2.6.1.7.1. The company provided full tables of the EQ-5D index score and VAS score results in Clarification Response A2.

The MG-ADL and QMG are widely used outcomes for assessing patients with MG. The EAG's clinical experts agreed that the outcome measures reported in the CS are appropriate. The CS does not explicitly discuss the minimum important clinical change for each instrument; we have summarised these, where available, in Table 6. Responders are defined for the MG-ADL as patients who achieve a ≥3-point improvement (decrease) in the total score; whilst responders are defined for the QMG score as those who achieve a ≥5-point improvement (decrease) in the total score. These are conservative thresholds as they exceed the respective minimum clinically important change for each instrument (Table 6).

Table 6 Disease symptom and severity and HRQoL measures and outcomes used in the CHAMPION-MG trial

Instrument	Outcome	Minimum clinically important change	Informs economic analysis
MG-ADL total score	**Primary outcome:** Change from baseline at week 26	2 points[34 35]	Yes (changes from baseline assigned to classes: see section 4.2.3.1)
	Secondary outcome: Improvement ≥3 points from baseline at week 26		
QMG total score	**Secondary outcome:** Change from baseline at week 26	2 or 3 points [35]	No
	Secondary outcome: improvement ≥5 points from baseline at week 26		
MG-QoL15r score	**Secondary outcome:** Change from baseline at week 26	Not determined [35]	No
Neuro-QoL Fatigue score	**Secondary outcome:** Change from baseline at week 26	Not reported	No
EQ-5D-5L index score	**Exploratory outcome:** Change from baseline to week 26 (CSR Figure 12)	Not reported	Yes (mapped to EQ-5D-3L: see section 4.2.4.2)
EQ-5D-5L VAS score	**Exploratory outcome:** Change from baseline to week 26 (CSR Figure 11)	Not reported	No

HRQoL: health-related quality of life; MG-ADL: Mysathenia Gravis Activities of Daily Living; MG-QoL15r: MG Quality of Life 15 revised version; Neuro-QoL: Quality of Life in Neurological Disorders; QMG: Quantitative Myasthenia Gravis scale; VAS: visual analogue scale.

3.2.5.2 Other clinical effectiveness outcomes

The other clinical effectiveness outcomes reported in the CS from the 26-week randomised phase of CHAMPION-MG are:

- **Clinical deterioration outcomes:** The total number of patients reporting clinical deterioration, and the number of clinical deterioration events, as well as the constituent events making up these totals, classified as MG crisis, significant symptomatic worsening, and rescue therapy required for health in jeopardy (CS Table 13).

- **Rescue therapy outcomes:** The total number of patients requiring rescue therapy, and the constituent numbers requiring high-dose corticosteroids, plasma exchange, and intravenous immunoglobulin (CS Table 13).

- **Clinical deterioration events requiring rescue therapy:** The total number of deterioration events requiring rescue therapy, and the constituent numbers requiring high-dose corticosteroids, plasma exchange, and intravenous immunoglobulin (CS Table 13).

- **Hospitalisations:** The number of patients hospitalised, the number of patients with an MG-related hospitalisation, total all-cause hospitalisations, total MG-related hospitalisations, duration of all-cause hospitalisations, and duration of MG-related hospitalisations (CS Table 14).

3.2.5.3 Safety outcomes

The CS reports numbers and frequencies of all adverse events by each Grade (1 to 5), serious adverse events, treatment-related adverse events, and those leading to treatment discontinuation, both for the 26-week randomised phase of CHAMPION-MG (CS Table 17) and up to week 60 in the open-label extension study (CS Table 18). The CS also reports the total number and frequencies of the adverse events experienced by >10% of patients receiving eculizumab up to 3 years in the REGAIN trial (CS Table 19). The EAG agree that the information provided on adverse events is sufficiently detailed.

3.2.5.4 Outcomes in the REGAIN trial

The REGAIN trial had the same primary, secondary and exploratory outcomes as the CHAMPION-MG trial, although incidence of hospitalisations, exacerbations, clinical deteriorations, and MG crises (exploratory outcomes) were reported in more detail for CHAMPION-MG (CS Tables 13 and 14) than for REGAIN (trial publication[27]). Clinical event outcomes (exacerbations, crises) as well as changes in MG-ADL score, discontinuations due to lack of treatment effect, and time on treatment from REGAIN are used to inform the economic analysis (section 4.2.3). MG-ADL, QMG, Neuro-QoL Fatigue, EQ-5d index, and EQ-5D VAS scores from the CHAMPION-MG and REGAIN trials are used in the company's indirect treatment comparison of ravulizumab against eculizumab (CS section B.2.9.2.3).

EAG conclusion on the company's outcome selection

The CS does not report full details of the HRQoL outcome instruments but the outcomes reported by the company are appropriate and adequately comprehensive for the appraisal of therapies for treating generalised MG.

3.2.6 Statistical methods of the included studies

The EAG's critique of the statistical analysis methods employed in the CHAMPION-MG RCT (and also the REGAIN RCT) is provided in detail Appendix 3 of this report. In summary, the EAG's main comments on the statistical methods of the CHAMPION-MG RCT are as follows:

Analysis populations. The full analysis set (FAS) appears to have included the majority of the randomised patients in their originally randomised groups so is likely to be equivalent to an intention to treat (ITT) analysis. The safety set appears to be appropriately defined, i.e. all randomised patients who received at least one dose of ravulizumab or placebo.

Sample size calculation. This appears to be appropriate. The number of patients randomised exceeded that required to achieve the specified 90% power to reject the null hypothesis of no treatment effect for the MG-ADL change from baseline.

Methods to account for multiplicity. The CHAMPION-MG RCT used hierarchical testing for secondary outcomes to account for multiple comparisons, but no rationale is provided for the specific approach used or for the sequence of the secondary outcomes in the hierarchy. The EAG note that sensitivity and subgroup analyses were not adjusted for multiple testing.

Analysis of outcomes. The overall approach to statistical analysis of the outcomes appears appropriate, except that the selection of covariates for inclusion in the analyses is not explained and appears inadequate. Of the demographic baseline characteristics available, only region was adjusted for (in addition to the treatment, outcome and visit covariates) (CS Table 9), although no effect of region on outcomes was seen in subgroup analyses (CS Section B.2.7). No explanation is provided why other factors such as patient age and MGFA class – which differed between the ravulizumab and placebo groups at baseline (section 3.2.2.2.1) – or other key variables, such as rescue therapy or prior immunosuppression, were not considered as potential covariates in the analyses. The EAG are uncertain whether analysis models including different covariates would have yielded different results, and therefore whether the current analysis approach is unbiased. Sensitivity analyses could have been conducted to explore the impact of adjusting for different baseline variables.

Handling of missing data. Missing data were not imputed for any outcomes. However, the company conducted two sensitivity analyses ("placebo based" and tipping point analysis) to test the robustness of the primary outcome analysis to missing data. These sensitivity analyses are described very superficially in the CS, CSR,[25] and trial publication,[24] and the

EAG are uncertain whether they were conducted appropriately. No sensitivity analyses on missing data assumptions were conducted for secondary or exploratory outcomes.

Sensitivity and other post hoc analyses. As noted above, pre-specified sensitivity analyses were conducted to test the robustness of the primary analysis to missing data. The company also conducted sensitivity analyses to explore the effect of a range of baseline characteristics on the primary and key secondary outcomes (see section 3.2.7.1.4 below). The EAG's main concerns around the subgroup analyses are that it is unclear whether they were pre-specified or post hoc; no adjustments were made for the multiple comparisons involved; and for some of the subgroups sample sizes were small, so the analyses would likely have insufficient statistical power to detect differences in treatment effects between groups.

EAG conclusion on study statistical methods

The company's overall approach to statistical analysis appears broadly appropriate. However, limited baseline variables were adjusted for in the analyses, without explanation. The EAG are therefore uncertain whether analysis results may have been biased by the choice of covariates.

3.2.7 Efficacy results of the intervention studies

The company report results from the CHAMPION-MG RCT and OLE study (CS section B.2.6.1), the REGAIN RCT (CS Appendix M.2) and the REGAIN OLE study (CS section B.2.6.2). Results from the CHAMPION-MG RCT and OLE study are summarised in section 3.2.7.1 below.

The REGAIN RCT and OLE are outside the scope of this technology appraisal. However, the company do use outcomes from the REGAIN OLE study (but not the RCT) to inform their economic model, based on an assumption that ravulizumab and eculizumab have similar efficacy. We therefore briefly summarise results from the REGAIN OLE study in section 3.2.7.2 below. Results of the REGAIN RCT are not considered here but are discussed in relation to the company's ITC in section 3.5 of this report.

3.2.7.1 CHAMPION-MG RCT and OLE study results

Below we summarise results for the primary outcome (change from baseline in MG-ADL total score) (section 3.2.7.1.1), the secondary outcome measures of disease symptoms, severity and HRQoL (section 3.2.7.1.2), clinical events and hospitalisations (section 3.2.7.1.3), and subgroup analyses (section 3.2.7.1.4).

As reported below, for the primary and all secondary outcomes that assessed disease symptoms and severity and HRQoL (except the EQ-5D) there was an improvement from baseline to Week 26 in the placebo arm of the RCT, despite stable background therapy. The company suggest that this placebo effect could represent a natural fluctuation in outcomes and would not persist in the long term, but this is speculative and based solely on limited expert opinion (CS section B.2.12.1). Implications of the placebo effect for the health economic analysis are considered and explored in a sensitivity analysis (see sections 4.2.3.1 and 5.4 of this report).

3.2.7.1.1 Primary outcome: Change from baseline in the MG-ADL total score

RCT: The change from baseline in MG-ADL total score at Week 26 showed an improvement (decrease) in both the ravulizumab and placebo arms, with the improvement being statistically significantly larger for the ravulizumab arm compared to the placebo arm (Table 7). The improvement in the ravulizumab (but not the placebo) arm exceeds 2 points which is regarded as the minimum clinically important difference for the MG-ADL (Table 6). Missing data (9.3% and 7.9% in the ravulizumab and placebo arms respectively) were not imputed for this analysis (trial publication Table S6). We judged this outcome to have an unclear risk of selection and attrition biases (section 3.2.4.1).

OLE study: The group of patients previously randomised to ravulizumab (RAV/RAV group) and those previously randomised to placebo (PBO/RAV group) both experienced sustained improvements in MG-ADL score throughout the OLE study relative to baseline in the RCT (CS Figure 8) although the reference baseline for estimating the least squares mean change for the PBO/RAV group is unclear (Table 7). Note that all outcomes in the OLE study were judged to be at high risk of bias and confounding (3.2.4.2)

Table 7 Disease symptom, severity and HRQoL measures in the CHAMPION-MG RCT

Outcome	Ravulizumab	Placebo	Difference
LS Ravulizumab mean change from baseline in MG-ADL total score (95% CI)	-3.1 (not reported)	-1.4 (not reported)	-1.6 (-2.6 to -0.7) p<0.001
LS mean change from baseline in QMG total score (95% CI)	-2.8 (-3.7 to -1.9)	-0.8 (-1.7 to 0.1)	p<0.001
LS mean change from baseline in MG-QoL15r total score (95% CI)	-3.3 (not reported)	-1.6 (not reported)	p=0.0636 (p=0.0424 in a sensitivity analysis) [a]

Outcome	Ravulizumab	Placebo	Difference
LS mean change from baseline in Neuro-QoL Fatigue score (95% CI)	-7.0 (not reported)	-4.8 (not reported)	p=0.3734
Proportion with ≥3 point improvement in MG-ADL (95% CI)	Unadjusted 60.3% (not reported) Adjusted [b] 56.7% (44.3 to 68.3)	Unadjusted 36.6% (not reported) Adjusted [b] 34.1% (23.8 to 46.1)	Unadjusted 23.7% [c] p-value not reported Adjusted [b] 22.6% [c] p-value not reported
Proportion with ≥5 point improvement in QMG (95% CI)	Unadjusted 35.5% (not reported) Adjusted [d] 30.0% (19.2 to 43.5)	Unadjusted 12.8% (not reported) Adjusted [d] 11.3% (5.6 to 21.5)	Unadjusted 22.7% [c] p-value not reported Adjusted [d] 18.7% [c] p=0.0052
LS mean (SE) change from baseline in EQ-5D health state index	[redacted]	[redacted]	[redacted]

Source: CS sections 2.6.1.1 to 2.6.1.6
LS: least squares; MG-ADL, QMG, MG-QoL15r, Neuro-QoL: for explanation of these instrument names and for further details of the instruments please see section 3.2.5.
[a] A sensitivity analysis excluded 10 patients (ravulizumab n=6, placebo n=4) who had been significantly impacted by COVID-19 (CS section B.2.6.1.4).
[b] Adjusted based on a generalized linear mixed model that included treatment arm stratification factor, region, and outcome score at baseline, at trial visit and at trial visit multiplied by treatment arm interaction.
[c] Difference calculated by EAG.
[d] Not reported in the CS or CSR whether the same adjustment factors were used as in the analysis of the proportion with ≥3 point improvement in MG-ADL

Table 8 Disease symptom and severity measures in the CHAMPION-MG OLE study

Outcome	RAV/RAV Week 26 to Week 60 [a]	PBO/RAV Up to Week 60 [a]
LS Ravulizumab mean change in MG-ADL total score (95% CI)	[redacted]	[redacted]
LS mean change in QMG total score (95% CI)	[redacted]	[redacted]
LS mean change in MG-QoL15r total score (95% CI)	[redacted]	[redacted]
LS mean change in Neuro-QoL Fatigue score (95% CI)	[redacted]	[redacted]
Proportion with ≥3 point improvement in MG-ADL	67.9% at week 60	

Outcome	RAV/RAV Week 26 to Week 60 [a]	PBO/RAV Up to Week 60 [a]
Proportion with ≥5 point improvement in QMG (95% CI)	Not reported	
Source: CS sections 2.6.1.1 to 2.6.1.6 LS: least squares; MG-ADL, QMG, MG-QoL15r, Neuro-QoL: for explanation of these instrument names and for further details of the instruments please see section 3.2.5. [a] Week 26 is the OLE baseline for the RAV/RAV group. The baseline for the PBO/RAV group is unclear due to ambiguous reporting in the CS and CSR.		

3.2.7.1.2 Other disease symptom measures (secondary outcomes)

Note that all the secondary outcomes reported here from the CHAMPION-MG RCT were judged to have unclear risks of bias (section 3.2.4.1) whilst all those reported from the OLE study were judged to have high risks of bias and confounding (section 3.2.4.2). The outcomes, particularly from the OLE study, may therefore be more uncertain than is suggested by their confidence intervals or standard errors.

Change from baseline in the QMG total score

RCT: At Week 26 in the CHAMPION-MG RCT, an improvement (decrease) in the QMG total score was achieved in both trial arms and was statistically significantly greater in the ravulizumab arm than the placebo arm (Table 7). The change from baseline in the ravulizumab (but not placebo) arm is appears to be clinically significant (the minimum clinically important difference for the QMG total score is "2 or 3"; Table 6). Missing data (11.6% and 12.4% in the ravulizumab and placebo arms respectively) were not imputed for this analysis (trial publication Table S6).

OLE study: Improvements were sustained at Week 60 of the OLE study in the RAV/RAV group, with similar improvement also evident in the PBO/RAV group (CS Figure 9), although the reference baseline for estimating the least squares mean change for this group is unclear (Table 8).

Change from baseline in the MG-QoL15r total score

RCT: At Week 26 the MG-QoL15r score had improved (decreased) in both trial arms, with a larger improvement in the ravulizumab arm than in the placebo arm (Table 7). This difference was not statistically significant; however, it did reach marginal statistical significance in a sensitivity analysis that excluded patients who had been significantly impacted by COVID-19 (Table 7). Missing data (9.3% and 7.9% in the ravulizumab and placebo arms respectively) were not imputed for this analysis (trial publication Table S6).

OLE study: Both the RAV/RAV and PBO/RAV groups showed a sustained improvement in the MG-QoL15r score, to a similar extent at Week 60 (CS Figure 10). However, as for the previously discussed outcomes, the reference baseline for estimating the least squares mean change in the PBO/RAV group is unclear (Table 8).

Change from baseline in MG-QoL Fatigue score

RCT: At Week 26 the Neuro-QoL Fatigue score had improved (decreased) in both trial arms, with a larger improvement in the ravulizumab arm than in the placebo arm (Table 11). This difference was not statistically significant. Missing data (10.5% and 7.9% in the ravulizumab and placebo arms respectively) were not imputed for this analysis (trial publication Table S6).

OLE study: The improvement in Neuro-QoL Fatigue scores was sustained to Week 60 (CS Figure 11). The improvement was larger in the PBO/RAV group than in the RAV/RAV group although it is unclear what the reference baseline is for estimating the least squares mean change in the PBO/RAV group (Table 8).

Proportion of patients with a ≥ 3-point improvement in MG-ADL

RCT: An improvement of ≥ 3 points on this measure, which exceeds the minimum clinically important difference, was achieved by 60.3% of patients in the ravulizumab arm and 36.6% in the placebo arm at Week 26 (Table 7). These percentages remained similar after adjustment for covariates (treatment arm, stratification factor, region and endpoint score at baseline, at trial visit and at trial visit multiplied by treatment arm interaction; CS section B.2.6.1.6). Missing data were not imputed but the number of data missing is not reported.

OLE study: Overall, 67.9% of the participants in the CHAMPION-MG study achieved an improvement of ≥ 3-points in the MG-ADL total score by the end of the OLE period at Week 60. Unlike the other outcomes, this measure was not reported for the RAV/RAV and PBO/RAV groups (Table 8).

Proportion of patients with ≥ 5-point improvement in QMG

- **RCT:** Proportionally more participants randomised to ravulizumab achieved a ≥ 5-point improvement in this outcome, which exceeds the minimum clinically important difference, at Week 26 than those receiving placebo (35.5% versus 12.8%) (Table 7). After adjustment for unspecified covariates (not reported whether these were the same as used for the preceding outcome) these percentages were 30.0% and 11.3% respectively (Table 7). Missing data were not imputed but the number of data missing is not reported.

- **OLE study:** Results for this outcome at Week 60 are not reported in the CS.

EQ-5D

EQ-5D-5L data collected during the CHAMPION-MG RCT inform the company's economic model, along with those collected in REGAIN (see section 4.2.4 of this report). The CS reports a statistically significant greater improvement in the Health State Index score of this measure at Week 26 in the ravulizumab compared with the placebo arm of the CHAMPION-MG RCT at Week 26 (Table 8). There was no statistically significant difference between arms in the change from baseline at Week 26 in the visual analogue scale of the EQ-5D ([redacted]; CS Table 12).

3.2.7.1.3 MG exacerbations and crises (clinical events) and hospitalisations

Exacerbations and crises

During the CHAMPION-MG RCT more participants in the placebo arm than the ravulizumab arm experienced clinical deterioration (exacerbations) (17% versus 9%) and required rescue therapy for health in jeopardy ([redacted] versus [redacted]) (CS Table 13).

Only one patient, in the placebo arm, experienced an MG crisis during the 26-week RCT. Overall numbers of clinical deteriorations, general use of rescue therapy and the total numbers of clinical deterioration events requiring rescue therapy were numerically higher in the placebo arm. As rescue therapy for exacerbations, IVIG was used more frequently than either plasma exchange or high-dose corticosteroids: the proportions of patients who received rescue IVIG was [redacted] in the placebo arm and [redacted] in the ravulizumab arm, compared to [redacted] and [redacted] respectively for plasma exchange and [redacted] and [redacted] respectively for high-dose corticosteroids (CS Table 13).

During the CHAMPION-MG OLE study, a higher proportion of participants in the RAV/RAV group ([redacted]) than in the PBO/RAV group ([redacted]) experienced a clinical deterioration that met protocol criteria (CS section B.2.6.1.7.2) although it is unclear from the wording in the CS whether the reported percentages refer to all clinical deteriorations or specifically those that required rescue therapy. These results suggest that patients who had longer-term receipt of ravulizumab [redacted]; however, only [redacted] patients experienced clinical deteriorations up to week 60 in the OLE study which limits confidence in this interpretation.

Hospitalisations

Proportionally fewer participants in the ravulizumab arm than placebo arm were hospitalised during the 26 weeks of the CHAMPION-MG RCT, although the difference is small (19%, n = 16, versus 21%, n = 19). Hospitalisation rates are not reported in the CS for the OLE study.

3.2.7.1.4 Subgroup analyses

No patient subgroups were specified to be of interest in either the NICE scope or the company's decision problem. CS section B.2.7 states that subgroup analyses of the primary outcome (change from baseline in MG-ADL total score) and key secondary outcomes in CHAMPION-MG were conducted, but the CS and CSR do not mention whether the subgroup analyses were pre-specified or post-hoc. The following patient characteristics were used for the subgroup analyses: age, race, sex, geographic region, baseline IST use, years from diagnosis to informed consent, MGFA clinical classification at baseline and body weight at baseline. Results are reported narratively in the CS with no supporting numerical data or graphical representation of the results provided, but forest plots showing the results are available in the trial CSR (CSR Figures 20 to 25).[25] The CS states that no subgroup effects were identified for the outcomes of MG-ADL total score, QMG total score, QMG 5-point response, MG-QoL15r or MG-ADL 3-point response. The CS reports that on the Neuro-QoL Fatigue measure, point estimates for most groups favoured ravulizumab, but results for participants within the Asia-Pacific and body weight category of ≥ 40 kg to < 60 kg favoured placebo. The EAG checked the forest plots in the CSR and agree with the company's interpretation of the results, except that the Neuro-QoL Fatigue score subgroup differences referred to by the company in CS section B.2.7 are not statistically significant (95% confidence intervals overlap zero) (CSR Figure 24).[25]

3.2.7.2 Long-term results from the REGAIN OLE study

The company provide results from the REGAIN OLE in CS section B.2.6.2. Note that eculizumab is not specified as an intervention or comparator in the NICE scope. However, we briefly summarise changes in MG-ADL scores, and clinical event and rates from the REGAIN OLE as they are used to inform the economic model, based on a company assumption that eculizumab and ravulizumab would have similar clinical effectiveness. MG-ADL scores among participants who were randomised to eculizumab and who received eculizumab during the OLE (ECU/ECU) did not statistically significantly change between the OLE baseline and any of the following assessment points up to Week 130 (CS section B.2.6.2.1 and CS Figure 12).

Improvements in QMG total score and MG-QoL15 total score from baseline were also maintained in the ECU/ECU cohort up to Week 130 (CS Figures 13 and 14).

During the REGAIN OLE, there were statistically significant reductions in exacerbations, rescue therapy use and hospitalisation rates compared to either and/or pre-trial or those observed in the placebo arm only (Table 9).

Table 9 Exacerbation, rescue therapy and MG-related hospitalisation rates in the REGAIN trial

Event	Pre-trial, per 100 patient-years	OLE, per 100 patient-years	Rate observed in placebo arm only of RCT, per 100 patient-years
Exacerbation rate (number of exacerbations)	102.4	25.4	73.5
Rescue therapy use rates (number of events)	Not reported	23.1	67.5
MG-related hospitalisations (number of hospitalisations)	81.3	13.7	48.4

As shown in Table 9, rates of exacerbations, rescue therapy use and MG-related hospitalisations were lower during the OLE study that either before the start of the REGAIN RCT or in the placebo arm of the REGAIN RCT. The company report statistical comparisons between these different time periods (C section B.2.6.2.4) but we have not reproduced them here as the OLE study was judged to have a high risk of bias so results should not be over-interpreted in terms of their accuracy.

EAG conclusion on the clinical effectiveness results

All measures of MG disease symptoms, severity and HRQoL improved during the 26-week CHAMPION-MG RCT, with a greater improvement in the ravulizumab arm which was statistically and clinically significant for the MG-ADL and QMG total scores. A placebo effect was evident for all outcomes. The improvements in outcomes were maintained to 60 weeks in the OLE study. As noted in previous sections of this report, these results should be interpreted in the context of uncertainty in the statistical analysis methods of the RCT and high risk of bias in the OLE study.

3.2.8 Safety outcomes

Safety results from the CHAMPION-MG trial are reported in CS section B.2.10. The company also provide longer-term safety results for eculizumab in CS section B.2.10.2. We briefly summarise the safety findings for both ravulizumab and eculizumab below. We note from the ravulizumab EPAR[28] that meningococcal infection is a risk of ravulizumab IV treatment and has also been observed from long-term experience with eculizumab. Clinical expert advice to the EAG is that patients need a meningococcal vaccination before ravulizumab use. We report the incidence of meningococcal infections during both the ravulizumab and eculizumab studies below.

3.2.8.1.1 Adverse events in CHAMPION-MG

During the RCT, 91% of participants in the ravulizumab arm and 87% in the placebo arm experienced at least one adverse event (CS Table 17). The proportions of participants in each trial arm assessed as having experienced an adverse event related to the study drug (as determined by the study investigator) were the same in both trial arms (34%). The most common adverse events, reported in ≥ 10% of patients were headache (ravulizumab 19% versus placebo 26%), diarrhoea (ravulizumab 15% and placebo 12%) and nausea (10% in both arms).

Including the OLE study, up to Week 60, among all 169 participants treated with ravulizumab (i.e. those receiving RAV/RAV and PBO/RAV), [redacted] of participants had had at least one treatment emergent adverse event, with [redacted] experiencing one related to the study drug (as assessed by the study investigator) (CS Table 18). Again, the most common AEs (reported in ≥ 10% of patients) were headache and diarrhoea ([redacted] and [redacted], respectively).

3.2.8.1.2 Serious adverse events in CHAMPION-MG

During the CHAMPION-MG RCT, serious adverse events occurred in 23% of the ravulizumab arm compared with 16% of the placebo arm (CS Table 17). In the ravulizumab arm, 2% of participants assigned to ravulizumab experienced a serious adverse event determined by the study investigator to be related to the study drug, compared with 4% in the placebo arm. One MG crisis that was classed as a serious adverse event occurred in the ravulizumab arm, while no MG crises were classed as such in the placebo arm. Two deaths occurred in the ravulizumab arm, due to COVID-19 and cerebral haemorrhage (CS section B.2.10.1.2), while there were none in the placebo arm.

Including the OLE study, up to Week 60, among all 169 participants treated with ravulizumab (i.e. those receiving RAV/RAV and PBO/RAV), 24.3% of participants experienced a serious

adverse event, with 3.0% experiencing a serious adverse event thought to be related to the study drug by the investigator (CS Table 18). In total, [redacted] deaths occurred (two during the RCT and [redacted] during the OLE study).

The CS reports that no meningococcal infections were reported during the OLE study up to Week 60 (CS section B.2.10.1.3). We note from the EPAR[28] that after the 52-week data cut-off, one placebo patient who switched to ravulizumab during the OLE had meningitis (classed as a serious adverse event) and this was thought by the study investigator to be related to ravulizumab. The participant had had meningococcal vaccination before entering the study. The EPAR reports that the patient continued on ravulizumab treatment.

3.2.8.1.3 Adverse events associated with eculizumab

In addition to safety data for ravulizumab, the company also report the adverse events associated with eculizumab treatment up to three years of treatment in the REGAIN OLE study (CS section B.2.10.2). At least one adverse event was experienced by 96.6% of patients. The most common were headache (37.6%), nasopharyngitis (31.6%), diarrhoea (23.1%) and upper respiratory tract infection (23.1%). At least one serious adverse event occurred in 44.4% of the participants. The most common serious adverse event was worsening of MG (n = 15, 12.8% of patients). There were three MG crises classed as serious adverse events and three deaths. As of the interim analysis cut-off, no meningococcal infections were reported, but the company note that one occurred after this cut-off and was resolved with antibiotic treatment (CS section B.2.10.2).

EAG conclusion on safety

The safety results for ravulizumab, and eculizumab for which longer-term data are available, do not identify any major concerns other than the risk of meningococcal infections, experienced by one patient receiving ravulizumab, as reported in the ravulizumab EPAR and one patient receiving eculizumab in the REGAIN OLE study. However, a serious limitation of the safety data is the short duration of the available evidence relative to the anticipated long-term use of ravulizumab in clinical practice. The EPAR highlights the need for post-authorisation monitoring for meningococcal infections.

3.2.9 Pairwise meta-analysis of intervention studies

No pairwise meta-analysis of intervention studies is reported in the CS. As only one RCT is available for this indication (i.e. the CHAMPION-MG trial) no pairwise meta-analysis is necessary.

3.3 Critique of studies included in the indirect treatment comparison

3.3.1 Rationale for the ITC

The company argue that ravulizumab is likely to have similar effectiveness and safety to eculizumab, as the former therapy was developed from the latter and so both drugs have similar molecules (over 99% homology) (CS section B.2.9.1). Eculizumab is not specified as a relevant intervention or comparator in the NICE scope and is not currently recommended by NICE as a therapy for generalised MG in the UK. However, the company point out in CS section B.2.9.1 that previous NICE appraisals in other indications considered eculizumab to have similar effectiveness as ravulizumab (TA698: paroxysmal nocturnal haemoglobinuria; and TA 710: atypical haemolytic uremic syndrome). The EAG's clinical experts considered these appraisals to have uncertain relevance to generalised MG and commented that the company's assumption of similar efficacy of eculizumab compared to ravulizumab appears plausible but is speculative.

The company assume that if the short-term effectiveness of ravulizumab and eculizumab can be demonstrated to be similar in generalised MG, then the REGAIN study could be a useful source of evidence for helping to predict long-term outcomes for patients treated with ravulizumab (CS section B.2.9.1). This is relevant since longer-term outcomes are available for eculizumab than for ravulizumab and the company use eculizumab outcomes as a proxy for long-term ravulizumab outcomes in their economic analysis (see section 4.2.3). To explore whether ravulizumab and eculizumab have similar effectiveness in generalised MG the company conducted an ITC comparing the CHAMPION-MG (ravulizumab versus placebo) and REGAIN (eculizumab versus placebo) trials, using the placebo arm as the common comparator.

In summary, there are two assumptions being made by the company: that eculizumab and ravulizumab have comparable clinical effectiveness in the short term; and that short-term comparable clinical effectiveness of these therapies can predict long-term clinical effectiveness of ravulizumab. It is important to stress that the company's ITC only tests the first of these assumptions.

3.3.2 Identification, selection and feasibility assessment of studies for the ITC

The CHAMPION-MG and REGAIN trials were identified in the company's systematic literature review (CS Appendix Table 5). No study selection or feasibility assessment process for the ITC is reported. However, the EAG are not aware of any other trials that would be relevant for the company's ITC.

3.3.3 Clinical heterogeneity assessment

Baseline characteristics of the trials considered as covariates for inclusion in the adjusted ITC analyses are listed in CS Appendix Table 6 (CS section D.1.6). However, six baseline characteristics that were available for both the CHAMPION-MG and REGAIN trials (CS Table 8) were not considered (see Table 10 below). No explanation is provided in the CS or in CS Appendix D.1.6 for the selection of baseline characteristics for inclusion in the ITC analysis and it is unclear whether the variables that were "considered" as listed in CS Appendix Table 6 were all finally included in the analysis as covariates. The CS does not discuss which of the baseline characteristics listed in CS Table 8 are prognostically important.

Table 10 Baseline covariates for ITC analysis

Baseline characteristics reported in both trials (CS Table 8)	
Considered as covariates for the ITC analysis (CS Appendix Table 6)	Not considered as covariates for the ITC analysis (CS Appendix Table 6)
Age at infusion	Race
Gender	Age at diagnosis
MGFA class	Any prior ventilation support since diagnosis
Disease duration	Number of patients with a MG crisis since diagnosis
MG-ADL score	Number of patients receiving glucocorticoids at baseline
QMG score	Number of patients receiving ≥2 immunosuppressant agents at baseline
Prednisone dose	
Nonsteroidal immunosuppressant therapy class:	
1 (cyclosporine, tacrolimus);	

2 (azathioprine, methotrexate, mycophenolate mofetil); 3 (cyclophosphamide, rituximab)	
Source: EAG summary of selected data in CS Table 8 and CS Appendix Table 6.	

Heterogeneity in the subset of the trial baseline characteristics considered for the ITC is discussed in CS Appendix N.1.1. The company state that patients in CHAMPION-MG tended to be older, had lower MG-ADL and QMG scores and were more likely to be female (sic*) than those in REGAIN, with these differences being statistically significant (*CS Appendix Table 31 shows CHAMPION-MG had a lower proportion of female participants). CS Appendix N.1.1 also states that there were statistically significant differences in nonsteroidal IST use group 2 (azathioprine, methotrexate, mycophenolate mofetil) between the trials. No details of the levels of significance or the statistical test employed are reported. Among those baseline criteria that were not considered as covariates for the ITC analysis, we note that the proportion receiving glucocorticoids at baseline was higher in CHAMPION-MG whilst the proportion receiving ≥2 IST agents at baseline was higher in REGAIN (CS Table 8).

CS Appendix D.2 highlights a difference between the trials' inclusion criteria. CHAMPION-MG had no requirement for participants to have had prior treatment failure whilst REGAIN specified that participants had to have failed treatment with at least two prior ISTs or at least one IST and required chronic plasma exchange or intravenous immunoglobulin therapy (although "chronic" is not defined in this context).

Overall, the key differences in baseline characteristics between the CHAMPION-MG RCT and REGAIN RCT noted by the company are consistent with those identified by the EAG (section 3.2.2.1)

3.3.4 Risk of bias assessment for studies included in the ITC

The EAG's risk of bias assessments for the CHAMPION-MG and REGAIN RCTs are discussed in section 3.2.4 of this report and presented in detail in Table A of Appendix 2. In REGAIN, patients in the placebo arm had more severe disease (section 3.2.2.2.2) which we judged as conferring a high risk of bias for any outcome comparisons between the eculizumab and placebo arms (section 3.2.4.3). In CHAMPION-MG, patients in the ravulizumab arm were older and had slightly more severe disease on the MGFA classification than those in the placebo arm; however, the EAG's clinical experts did not

regard these differences as clinically important (section 3.2.2.2.1) and we judged there to be a low risk of bias for any outcome comparisons between the ravulizumab and placebo arms. CHAMPION-MG was also judged to have an unclear risk of selection bias since not all prognostic factors identified by the EAG's clinical experts (section 2.2.1.6) were reported and so it is unknown whether they were balanced between the trial arms. Both RCTs were additionally considered to have an unclear risk of attrition bias due to uncertainties around the reasons for and handling of missing data (section 3.2.4).

EAG conclusion on the studies included in the ITC

The trials included in the ITC are relevant placebo-controlled trials of ravulizumab and eculizumab, but they differed in several key characteristics, including the extent to which their populations were refractory to prior therapy; it is unclear how well these differences could be adjusted for by the ITC matching methods. The company have not discussed heterogeneity in the trials' baseline characteristics. Six baseline characteristics that are reported for both the trials were not considered as potential covariates in the adjusted ITC analysis, with no explanation given. It is unclear whether all the covariates "considered" for the ITC analysis were finally included in the analysis.

3.4 Critique of the indirect comparison

3.4.1 Data inputs to the ITC

The outcomes analysed were changes from baseline in MG-ADL and QMG as the "primary objective" and changes from baseline in MG-ADL sub-domains, Neuro-QoL Fatigue, EQ-5D, and EQ-5D VAS scores as a "secondary objective" (CS Appendix D.2.2). The company also conducted "responder analyses" for MG-ADL score and for QMG score, with responders defined as those participants who had a change, without rescue therapy, from a baseline score of 2 to 9 for MG-ADL and a change from baseline score of 3 to 10 for QMG (CS Appendix D.2.3). The meaning of this definition is not fully clear as it differs from how responders are defined for the outcome analyses within the CHAMPION-MG RCT (CS Table 7). Missing data were imputed using last observation carried forward (LOCF) (CS Appendix section D.2.3).

Change from baseline was analysed in two ways: the average change at week 26, and the average change over 26 weeks calculated as the area under the curve (AUC), that is, the area between the outcome curve and x-axis (CS Appendix D.2.2).

3.4.2 Statistical methods for the ITC

The company conducted three types of ITC of ravulizumab against eculizumab:
An **unadjusted analysis** which the company say was anchored on the placebo arms, as calculated using the Bucher method[36] (CS Appendix D.2.1.1). This unadjusted approach does not take account of the heterogeneity between studies discussed in section 3.3.3 above.

A **matching-adjusted indirect comparison (MAIC)** was conducted following methods recommended by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) on population-adjusted indirect comparisons[37] (CS Appendix D.2.4.1). The MAIC used IPD from CHAMPION-MG and aggregate data from REGAIN, and matched the intervention and placebo arms of the RCTs separately to account for within-trial differences between arms. The company state that the population of CHAMPION was matched to that of REGAIN rather than the reverse, as CHAMPION-MG is "composed of a broader population", although the company do not explain this interpretation and do not discuss which of the trials best reflects the population likely to be encountered in NHS clinical practice. CS section B.2.9.2.2 and CS Appendix D.2.4.1 state that the subset of baseline characteristics available for both populations that were identified as either prognostic of survival or a treatment-effect modifier were selected for adjustment, but do not list which baseline characteristics these were (it is unclear if these are the same baseline characteristics referred to in CS Appendix Table 6, as summarised in Table 10 above). CS Appendix Table 42 shows that the baseline characteristics that were included in the MAIC were well-matched from CHAMPION-MG to REGAIN but at the expense of a low effective sample size (ESS 19.7 and 36.2 for the ravulizumab and placebo arms of CHAMPION-MG respectively). The frequency distribution of rescaled weights shows a number of patients with high weights (>5.0) for the ravulizumab arm of CHAMPION-MG, which due to their relatively high contribution could potentially bias the results (CS Appendix Figure 17).

An **adjusted analysis using inverse probability weighting (IPW)** was conducted using propensity scores to balance observable characteristics between the trials, following recommendations of the NICE DSU TSD on analysis of observational data.[38] (CS Appendix D.2.4.2). The intervention and placebo arms of the RCTs were matched separately to account for within-trial differences between arms, with separate regression models conducted on the paired active arms and the paired placebo arms. CS Appendix Table 53 shows that the adjusted baseline characteristics of the CHAMPION and REGAIN trials were more homogeneous than the unadjusted baseline characteristics but less homogeneous

than the matching achieved in the MAIC; however, effective sample sizes achieved in the IPW analysis are larger than those in the MAIC (lowest ESS were for the REGAIN ravulizumab and placebo arms: ESS 31.6 and 41.5 respectively). Furthermore, the IPW analysis achieved a relatively low frequency of high weights (CS Appendix Figure 25) which is appropriate.

The EAG consider the IPW to be the strongest analysis due to the best use of available data (TSD17[38]). The unadjusted comparison is the weakest as it fails to control for differences in baseline characteristics between studies, whilst the MAIC could be open to bias given the large reduction in ESS and relatively high weights attributed to few individuals. Nevertheless, confidence in the results is undermined by missing prognostic factors and lack of sensitivity analysis.

3.4.3 Summary of the EAG's critique of the ITC

- The ITC analyses are necessarily limited to the randomised comparison phase of each trial which has a relatively short duration (26 weeks).
- Six participant baseline characteristics reported in both the CHAMPION-MG and REGAIN trials were not considered for inclusion as covariates in the ITC, without explanation.
- No sensitivity analyses were provided to test the robustness of the analyses to the inclusion of different covariates.
- The trials' eligibility criteria and baseline characteristics differed in several respects, including that patients in REGAIN required to have failed treatment but patients in CHAMPION-MG not required to have failed treatment.
- LOCF, used in the responder analysis, is a weak imputation method that might lead to overestimation of the duration of transient clinical effects. A multiple imputation approach would be more robust. The numbers of missing data in each trial arm in the responder analysis are not reported.
- The MAIC analysis used individual participant data (IPD) from the CHAMPION-MG trial whilst the IPW analysis used IPD from both trials (CS Appendix D.2). The IPD and statistical code were not provided with the CS, so the EAG are unable to check the input data and whether the ITC analyses were executed appropriately.

- The IPW analysis is the approach best aligned with NICE guidance given the availability of IPD from both studies. However, inclusion of a comprehensive set of covariates remains a concern.

3.5 Results from the indirect comparison

Results of the ITC analyses are summarised for each outcome and analysis method (i.e. unadjusted analysis, MAIC analysis, IPW analysis) in CS Table 15 with further details provided in CS Appendix N.

Overall, the ITC results lack statistical significance which the company interpret as indicating that ravulizumab and eculizumab have similar treatment benefit after matching the trial population characteristics (CS section B.2.9.2.3). Only one outcome from an adjusted ITC analysis showed a statistically significant effect. That is, the change in EQ-5D VAS (but not the EQ-5D index score) when analysed using the MAIC approach favoured eculizumab (CS Table 15). Change from baseline in the Neuro-QoL Fatigue score was statistically significant in the unadjusted analysis, also favouring eculizumab, but only significant for the change to week 26, not the AUC to week 26. Heterogeneity is evident among the ITC results, with the magnitude of change from baseline in MG-ADL and in QMG varying with the outcome assessment method (change at week 26 versus AUC to week 26) and between the ITC adjustment methods (MAIC versus IPW) (CS Table 15). Due to the limitations summarised above, including incomplete matching of trial populations and lack of clarity around the analysis methods (section 3.4.3) it is not possible to draw any firm conclusions from the ITC analyses.

3.6 Conclusions on the clinical effectiveness evidence

The EAG's conclusions on the clinical evidence are summarised in Table 11. Two areas considered to be important with high uncertainty have been raised as key issues and are discussed in section 1 of this report.

Table 11 Summary of the EAG's clinical evidence conclusions

Conclusion	Explanation	Where discussed
KEY ISSUE (1) Rituximab is a relevant comparator but has been excluded by the company.	Rituximab is a late line of therapy for generalised MG, i.e. a component of standard of care. The company claim rituximab is not a relevant comparator and have excluded it from	Background Section 2.2.3.1

This is regarded as a key uncertainty by the EAG.	their decision problem. Both the EAG's clinical experts use rituximab and agreed that it is a relevant comparator.	Decision problem Section 2.3
KEY ISSUE (2) Eculizumab is included in the technology appraisal but it is unclear whether this is appropriate. Eculizumab is assumed to have similar clinical effectiveness to ravulizumab, but there is no convincing evidence to support this assumption. This is regarded as a key uncertainty by the EAG.	Eculizumab outcomes have been included as longer-term proxy outcomes for ravulizumab in the economic analysis but eculizumab is not specified in the NICE scope and is not used in the NHS. The company assume eculizumab has similar efficacy to ravulizumab and tested this by conducting an ITC of the CHAMPION-MG RCT versus the REGAIN RCT. Due to methodological limitations of the ITC, results are highly uncertain and do not provide convincing evidence of similar clinical effectiveness of these therapies.	Background Section 3.1.2 ITC critique Sections 3.3 to 3.5
The likely position of ravulizumab in clinical practice is uncertain	Clinical experts had differing opinions on where ravulizumab would be used in the treatment pathway. It is unclear whether the clinical effectiveness (and hence potentially the cost effectiveness) of ravulizumab would differ according to whether it is compared against the overall "basket" of standard care, or specific relevant comparators within standard of care.	Section 2.2.3.2
Short-term clinical effectiveness improvements in disease severity, symptom and HRQoL measures in the CHAMPION-MG RCT are positive but subject to uncertainty	The primary outcome and all six other disease severity, symptom and HRQoL outcomes showed improvement at Week 26 in the CHAMPION-MG RCT relative to baseline which was clinically significant and larger in the ravulizumab than the placebo group (difference statistically significant for for the MG-ADL total score [primary outcome], QMG total score and EQ-5D [secondary outcomes]). However, statistical analysis results are uncertain due to potentially selective and limited adjustment for covariates.	Statistical considerations Section 3.2.6 Results Section 3.2.7.1
Long-term clinical effectiveness findings in the	Six disease severity, symptoms and HRQoL outcomes which were measured up to Week	Risk of bias Section 3.2.4

OLE studies are positive but subject to high uncertainty	60 showed that the improved scores at the end of the RCT remained stable up to the end of the available data (Week 60) in the CHAMPION-MG OLE study. However, the OLE study outcomes are subject to high risk of bias due to the open-label design with lack of adjustment for confounding variables.	Efficacy results Section 3.2.7.1
All disease severity, symptom and HRQoL outcomes except EQ-5D experienced a placebo effect in the CHAMPION-MG RCT	The placebo effect has potential to distort the long-term clinical effectiveness of ravulizumab and has implications for economic modelling (see section 4.2.3.1).	Section 3.2.7.1
The main safety concerns relating to ravulizumab are risk of meningococcal infections and lack of long-term safety data	The CHAMPION-MG and REGAIN RCTs and OLE studies do not raise safety concerns for ravulizumab or (assuming it is relevant) eculizumab, other than the risk of meningococcal infection. However, the safety data are of short duration relative to the natural history of generalised MG and the long-term requirement for therapy.	Section 3.2.8

4 COST EFFECTIVENESS

4.1 EAG comment on the company's review of cost-effectiveness evidence

The company report their economic search strategy in CS B.3.1 and Appendix G. They conducted a single search to identify economic studies (cost-effectiveness, cost/resource use and HRQoL) relating to ravulizumab, eculizumab or comparators for people with generalised MG. Three cost-effectiveness studies were identified that reported results for patients with anti-AChR antibodies (CS Table 20 and Appendix G Tables 9 and 10). These included two studies that used a Markov model to compare eculizumab with conventional therapy (CADTH 2020 and Tice et al. 2022), and a study based on retrospective data on the use of rituximab in a Portuguese population (Peres et al. 2017).[39-41]

EAG conclusion on cost-effectiveness searches

The searches were conducted on 28 March 2022. No grey literature was searched, and search strings are not reported in the CS. The cost-effectiveness studies identified in the company's search are not pertinent to the current appraisal.

4.2 Summary and critique of the company's submitted economic evaluation

4.2.1 NICE reference case checklist

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment. Company model meets reference case criteria?
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes. Direct patient effects included. Although carer disutilities are reported, they are not included in the company's analysis (see section 4.2.4.4).
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes (lifetime)
Synthesis of evidence on health effects	Based on systematic review	Yes

Element of health technology assessment	Reference case	EAG comment. Company model meets reference case criteria?
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes (severity modifier does not apply, CS B.3.6)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
Source: EAG assessment based on the company submission		

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company describes the structure and key features of their model in CS Section B.3.2.2. They summarise the model assumptions in CS Tables 43, the parameters in CS sections B.3.3 to 3.5 and CS Table 24 to Table 42. The model is a three-state cohort state-transition model, developed in Microsoft Excel®: see Figure 2. The Markov has a cycle length of 3 months and a 48-year time horizon (effectively lifetime from a starting baseline age of 52.19 years). Costs and QALYs are discounted at an annual rate of 3.5% and the analyses conducted from the perspective of NHS and PSS. The clinical effectiveness data were informed by two RCTs: CHAMPION-MG and REGAIN, discussed earlier in section 3. Briefly, the company model consisted of two alive health states differentiated by treatment status ('on ravulizumab' and 'on usual care'), and a death state. Patients in the ravulizumab arm who discontinue treatment transfer to usual care and remain there until death. Patients in the usual care (SoC) arm, remain on standard treatment with no discontinuation until death. MG-ADL scores, a patient-reported outcome measure to assess MG related

symptoms and functional activities in daily activities, are used to assess the improvement in patient outcomes.

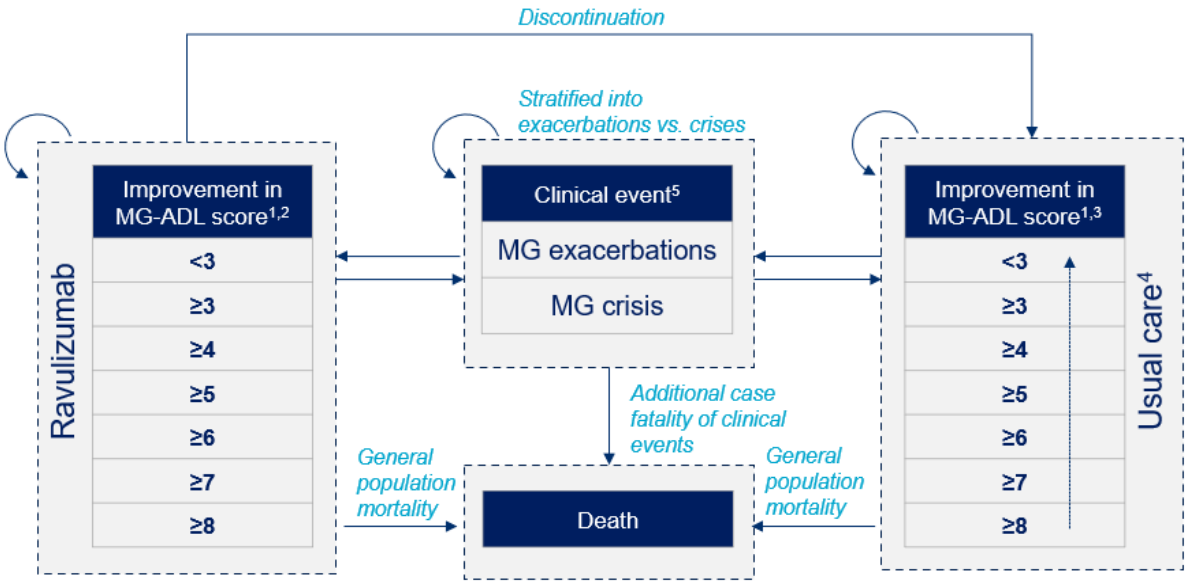


Figure 2 Company's model structure

Source: CS Figure 17

The ravulizumab and usual care health states are sub-divided into seven substates defined by change in MG-ADL score from baseline in the CHAMPION-MG RCT (<3, 3-4, 4-5, 5-6, 6-7, 7-8, ≥8), to reflect the differing levels of patient benefit in each treatment arm. Except for patients who discontinue treatment with ravulizumab, the model assumes no transition between the substates: patients stay in the same substate following their initial MG-ADL score change in the randomised trial period.

The model also includes two MG associated clinical events: exacerbations and crises. A Poisson regression analysis, using the pooled data from the CHAMPION-MG and REGAIN trials, was conducted to estimate the average number of clinical events in each cycle. Detailed discussion of the clinical parameters is in section 4.2.3. To estimate utilities, the company used EQ-5D-5L data obtained from the CHAMPION-MG and REGAIN trials and mapped to EQ-5D-3L. Costs were sourced from standard UK databases. For further discussion on utilities and costs, see sections 4.2.4 and 4.2.5, respectively.

EAG conclusion on the model structure

The overall model structure is reasonable, although the use of substates defined by change from baseline MG-ADL, as observed in the CHAMPION-MG trial, does make it difficult to understand. The company assume that patients do not transition

between the change in MG-ADL substates after the initial trial period, except where patients in the ravulizumab arm discontinue treatment. We view this as a reasonable simplification based on clinical expert opinion that although the MG-ADL score can fluctuate over time for individuals, it is not expected to change systematically as the patients age. A half-cycle correction is not implemented within the company's model, which will cause some inaccuracy in the calculation of the cost-effectiveness results.

4.2.2.2 Population

The company do not clearly specify the target population for ravulizumab. They note the licensed indication and cite clinical opinion that ravulizumab is likely to be used in UK practice as a later-line treatment option, 'particularly' for patients who remain symptomatic despite active treatment (CS B.3.2.1). The company state that this population is 'broadly aligned' to the population in the CHAMPION-MG trial, with a mean time from diagnosis of 10 years. The company use pooled baseline characteristics from the CHAMPION-MG and REGAIN trial populations in their base case model. In response to clarification question B3, they state that the baseline characteristics in the original submitted model were incorrect and should have been aligned with those reported in CS Table 8. However, we note that the percentage of females in CHAMPION-MG in the revised model after clarification questions (53.5%) does not match that in CS Table 8 or Table 9 of the CSR (89/175, 50.9%). Based on the latter, the pooled percentage of females across both trials is 57.0%, see Table 13 below.

Table 13 Baseline characteristics reported in CS Table 8

	CHAMPION-MG RCT			**REGAIN RCT**			**Pooled mean across trials**
	Ravulizumab (n=86)	Placebo (n=89)	Overall (n=175)	Eculizumab (n=62)	Placebo (n=63)	Overall (n=125)	
Age, years	58.0	53.3	55.6	47.5	46.9	47.2	52.1
Female, % (n)	51.2% (44)	50.6% (45)	50.9% (89)	66.1% (41)	65.1% (41)	65.6% (82)	57%
MG-ADL Total score	9.1	8.9	9.0	10.5	9.9	10.2	9.5
Disease duration, years	9.8	10.0	9.9	-	-	-	-
Source: CS Table 8, means calculated by EAG							

EAG conclusion on the population

Patient characteristics in the company's model, based on the pooled CHAMPION-MG and REGAIN trial populations, are broadly reflective of UK clinical practice.

Although, it is clinically observed that the incidence of generalised MG is bimodal, there is insufficient data to estimate results for subgroups based on age of onset. We noted an error in the percentage of females in the CHAMPION-MG trial population in the model, which we correct in EAG analyses (see section 5.3.2). Furthermore, as there is a lack of clarity on the target positioning for ravulizumab (discussed earlier section 2.2.3), and the relevance of the REGAIN study is not clear, we prefer to use baseline characteristics of the CHAMPION-MG RCT trial population alone to align the model population with the main clinical data source used in the model (see section 6).

4.2.2.3 Interventions and comparators

The economic model evaluates the intervention (ravulizumab) against a standard of care (SoC) comparator. The company describe the intervention in CS section B.1.2 and we discuss the intervention and its intended use in practice earlier in Section 2.2 of this report. The dosing regimen for ravulizumab (see CS Table 22) is consistent with that used in the CHAMPION-MG trial and the SmPC. In response to clarification question B12, the company acknowledged an error in the loading dose for ravulizumab in the economic model, which was corrected in the revised model submitted with the company's clarification response. The comparator arm, SoC, consists of a basket of steroids and non-steroidal ISTs (see Table 14). The distribution of drugs in this basket only affects costs: the impact on clinical outcomes cannot be captured in the current model structure. The company assume that the same basket of drugs is used while patients are on ravulizumab, after discontinuation of ravulizumab, and in the SoC treatment arm. Therefore, the cost of SoC largely cancels out, although there is a small impact on the ICER due to modelled survival differences between the arms.

It is stated in CS B.3.2.3.2 that the distribution of therapies is based on those administered in both arms of the CHAMPION-MG trial, adjusted to exclude cyclosporin and tacrolimus based on consultation with UK clinicians (CS Table 23). In response to clarification question B13, the company revised the citation to the source for the CHAMPION-MG trial data (CSR Table 14.1.4.5.2, reproduced in the Table 8 of the clarification response). This table reports medications used prior to study treatment. In practice, due to a coding error, the company's base case model uses pooled data from the CHAMPION-MG and REGAIN trials, and cyclosporin and tacrolimus are not excluded (see section 5.3.1 below).

Table 14 Standard of care therapy distribution

Therapy	CHAMPION-MG RCT (n = 175)	REGAIN RCT (n=125)	Pooled CHAMPION & REGAIN (n=300) [a]	UK clinical practice
Pyridostigmine	92.0%	95.2%	93.3%	92.0%
Azathioprine	31.4%	75.2%	49.7%	31.4%
Mycophenolate mofetil	32.6%	44.8%	37.7%	32.6%
Cyclosporin	6.9%	28.0%	15.7%	0.0%
Tacrolimus	12.6%	16.0%	14.0%	0.0%
Methotrexate	1.7%	11.2%	5.7%	21.2%
Cyclophosphamide	1.1%	4.8%	2.7%	1.1%
Prednisone	51.4%	54.4%	52.7%	51.4%
Prednisolone	32.0%	50.4%	39.7%	32.0%

Source: CS Table 23, with REGAIN and pooled results from the economic mode
[a] Estimates in this column are used in the company's base case.

EAG conclusion on the intervention and comparators

The intervention and pooled SoC comparator in the economic model are broadly consistent with the NICE scope. The model does not include rituximab as a comparator and there remains uncertainty whether this is an appropriate reflection of clinical practice in relation to the positioning of ravulizumab in the care pathway. It also is not clear that the basket of drugs included for costing SoC is reflective of current established clinical management in England, as discussed in section 2.2.3. In particular the model does not include rituximab, IVIG or plasma exchange, except in the context of an acute MG crisis. The model structure does not support the addition of rituximab as a comparator or estimation of the clinical effect of changes to the components of SoC on clinical outcomes. The impact of changing the basket of SoC drugs on costs can be explored, but this has a limited impact on the ICER because it is assumed that ravulizumab is added to SoC, so the costs largely cancel out. For EAG analysis, we follow the company's 'UK clinical practice' scenario, with SoC therapy based on usage at baseline in the CHAMPION-MG trial, excluding cyclosporin and tacrolimus, which the experts consulted by the EAG considered to be reasonable (section 6.2).

4.2.2.4 Perspective, time horizon and discounting

The company appropriately uses a lifetime horizon to reflect the condition of MG. Their analyses take the perspective of the NHS and PSS in England, which aligns with the NICE

manual for health technology evaluations. Costs and outcomes (life years and QALYs) are discounted at 3.5%.

4.2.3 Clinical parameters

The sets of key clinical parameter sets and sources used in the company's economic analysis are presented in Table 15 below.

Table 15 Key clinical parameter sources for economic model

Parameter	Sources
Allocation to MG-ADL change substates	CHAMPION-MG trial
Mean change in MG-ADL score by substate	Pooled CHAMPION-MG and REGAIN trials
Discontinuation due to non-response	CHAMPION-MG trial
Time on treatment extrapolations	Pooled CHAMPION-MG and REGAIN RCT and OLE data
Incidence of clinical events (exacerbations and crises)	CS B.3.3.4 reports pooled CHAMPION-MG RCT and OLE and REGAIN trial data, but the number of participants and events in the trial period reported in the company's model does not match the numbers reported in the CS.
Proportions of exacerbations: crises	Pooled CHAMPION-MG and REGAIN trials
Mortality	UK Life Tables; Alsgekhlee et al. 2009[42]
Adverse event rates	CHAMPION-MG trial
Source: Produced by the EAG	

4.2.3.1 MG-ADL change

The model estimates treatment effect in terms of improvement in the MG-ADL total score. A cohort of patients enters the model with a mean MG-ADL score of 9.5, which is the weighted mean score at baseline across the CHAMPION-MG and REGAIN trial populations (see Table 13 above).

To reflect the treatment benefit, the cohort is allocated to seven substates based on change from baseline MG-ADL scores in the CHAMPION-MG RCT. The company use change from baseline to 18 weeks in the ravulizumab arm and change from baseline to 26 weeks in the SoC arm (clarification response Table 5). They state that this difference in time-points was due to the difference in the 'speed of onset' for effects (CS page 90). This broadly reflects the MG-ADL results in CS Figure 8, which shows a mean reduction (improvement) in the MG-ADL total score by week 18 in the ravulizumab arm which is sustained to the end of the randomised period at week 26 (and through the open label extension up to 60 weeks).

However, it is difficult to compare the distributions of MG-ADL change at different timepoints, as the company reports these results using cumulative categories (≥3, ≥4 etc.), see Table 16. We report the same results with discrete MG-ADL change substates in Table 17, which shows that the direction of change from 18 to 26 weeks is not consistent.

The reduction in MG-ADL that the patients experience is dependent on the substate they are in. Table 18 shows estimates from the model of the mean change in total MG-ADL scores for the seven substates by treatment arm and timepoint. The company assume a midpoint reduction for the one-unit categories and estimate reductions for the two unbounded substates (<3 units and ≥8 units) from the mean reduction in MG-ADL of patients in these bands in CHAMPION-MG and REGAIN (CS section B.3.3.1.1). The base case uses the mean reductions at 18 weeks, based on timing of the assessment of response for the stopping rule (16 weeks).

Table 16 MG-ADL change from baseline in CHAMPION-MG with cumulative categories

MG-ADL reduction	Ravulizumab			SoC	
	18 weeks (n=86)	26 weeks (n=86)	60 weeks (n=78)	18 weeks (n=89)	26 weeks (n=89)
< 3 points	46.5%	41.9%	[redacted]	60.7%	65.2%
≥ 3 points	53.5%	58.1%	[redacted]	39.3%	34.8%
≥ 4 points	44.2%	45.3%	[redacted]	28.1%	25.8%
≥ 5 points	36.0%	34.9%	[redacted]	20.2%	16.9%
≥ 6 points	27.9%	24.4%	[redacted]	10.1%	7.9%
≥ 7 points	15.1%	14.0%	[redacted]	7.9%	3.4%
≥ 8 points	7.0%	9.3%	[redacted]	3.4%	1.1%
Source: Clarification response Table 5 and 6, with additional data from the company model					

Table 17 MG-ADL change from baseline in CHAMPION-MG with discrete categories

MG-ADL reduction	Ravulizumab			SoC	
	18 weeks	26 weeks	60 weeks	18 weeks	26 weeks
< 3 points	46.5%	41.9%	[redacted]	60.7%	65.2%
3-4 points	9.3%	12.8%	[redacted]	11.2%	9.0%
4-5 points	8.2%	10.4%	[redacted]	7.9%	8.9%
5-6 points	8.1%	10.5%	[redacted]	10.1%	9.0%
6-7 points	12.8%	10.4%	[redacted]	2.2%	4.5%
7-8 points	8.1%	4.7%	[redacted]	4.5%	2.3%
≥ 8 points	7.0%	9.3%	[redacted]	3.4%	1.1%
Total	100%	100%	100%	100%	100%
Source: Calculated by the EAG from data in the economic model (Clinical datastore sheet)					

Table 18 Distribution and mean MG-ADL change by substate

MG-ADL reduction	Ravulizumab		SoC	
	18 weeks	26 weeks	18 weeks	26 weeks
< 3 points	-0.40	-0.028	0.02	-0.263
3-4 points	-3.50	-3.500	-3.50	-3.50
4-5 points	-4.50	-4.500	-4.50	-4.50
5-6 points	-5.50	-5.500	-5.50	-5.50
6-7 points	-6.50	-6.500	-6.50	-6.50
7-8 points	-7.50	-7.500	-7.50	-7.50
≥ 8 points	-9.17	-9.000	-8.33	-8.00
Source: CS Table 26, and economic model (Clinical datastore sheet)				

After changes in MG-ADL based on 18-week data, patients in the ravulizumab arm are assumed to remain in the same MG-ADL substate for the remaining duration of treatment. To validate this assumption, the company report the distribution of patients by treatment effect from the OLE of CHAMPION-MG for the ravulizumab arm at week 60 (clarification response B5). On treatment discontinuation, patients are assumed to transition to usual care, with the same costs and distribution and MG-ADL status as in the SoC arm. The company assumed no retained benefit of ravulizumab after discontinuation, although the model includes a function to include a percentage of the treatment benefit for up to four model cycles (one year in total).

The SoC arm is based on data from the placebo arm of the CHAMPION-MG trial, and there is evidence of a substantial placebo effect in the trial (CS Figure 20). The company argue that maintaining this effect in the long-term would underestimate the effectiveness of ravulizumab. The base case assumes that the placebo effect is for the first year, but then patients are assumed to return to baseline the MG-ADL of 9.5. The model includes an option to retain the placebo effect, which has a large impact on the ICER.

EAG conclusion on the clinical parameters

In the company's base case, patients in the ravulizumab arm with <3-unit reduction in MG-ADL score were assumed to discontinue at 16 weeks. The clinical experts advising the EAG considered this to be reasonable, as they anticipated that a response should be apparent once patients had received a loading dose and two maintenance doses, at 8 and 16 weeks. The use of 18-week data measured in the trial is a reasonable proxy for the effect at 16 weeks.

For the main treatment effect, we consider that it would have been better to use the measure of MG-ADL change at 26 weeks for ravulizumab, as this would match the timepoint for the comparator arm and make full use of all randomised data to project long-term outcomes. The company's model includes a scenario with 26-week MG-ADL change data for both arms, but this is linked to a change in the timing of response assessment for application of the stopping rule from 16 to 26 weeks. We would have preferred an analysis retaining the 16-week assessment for lack of response to ravulizumab, combined with 26-week data for estimation of the treatment effect for patients continuing ravulizumab and for the comparator arm.

The company assumed no retained benefit of ravulizumab after discontinuation. This is clinically plausible, as clinical experts advising the EAG consider that effects will wane quickly, say over 8 weeks after discontinuation. We report scenarios with gradual waning of the treatment effect over 3 and 6 months after discontinuation.

The company assume the duration of the placebo effect to be one year, after which the MG-ADL scores of the patients in the SoC return to the baseline values. There is uncertainty over this assumption, which we explore in EAG scenario analysis (section 6.1).

4.2.3.2 Time on treatment

The company modelled time on treatment (ToT) by pooling Kaplan Meier (KM) data from the CHAMPION-MG and REGAIN RCT and OLE studies (Figure 4). In favour of their approach, they argued that: i) the pooled dataset is larger; and ii) the discontinuation of ravulizumab and eculizumab showed a similar trend up to the maximum follow up point in the CHAMPION-MG study.

Parametric survival curves were fitted to the pooled KM data, see Figure 3. While all the parametric models had good fit to the pooled data up to 2 years, none of them fitted the plateau and the subsequent spike in treatment discontinuation between Year 3 and 4. The CS reported that the plateaus were due to less frequent patient assessments in the OLE than in the randomized control period up to 26 weeks.

Based on AIC/BIC statistics and long-term outcomes, the company used the exponential distribution in their base case, with scenarios for Gompertz and log-logistic distributions (see section 5.2.3). The parametric extrapolations fitted to the pooled KM data are heavily influenced by the plateau and the drop off in treatment rates after year 3 in the REGAIN OLE

study. It is noted in CS section B.3.3.2 that this may have been caused by patients exiting the study when eculizumab became commercially available in their country of residence. If so, this would not be reflective of long-term continuation of ravulizumab if recommended for use in the NHS.

In their response to EAG clarification question B8, the company provided time on treatment extrapolations based on CHAMPION-MG data only, reproduced below in Figure 5. Again, the company selected the exponential distribution, based on the goodness of fit statistics, to extrapolate the long-term outcomes for this scenario. This assumption had a significant impact on the overall ICER, reducing the overall ICER by circa [redacted] per QALY from the base case results.

Figure 3 Kaplan Meier data from CHAMPION-MG and REGAIN for time on treatment

Source: CS Figure 18

Figure 4 Parametric models fitted to pooled CHAMPION-MG and REGAIN ToT data

Source: CS Figure 19

Figure 5 Time on treatment extrapolations using CHAMPION-MG trial data only

Source: Figure 9 in company's clarification response

Table 19 below reports the percentage of patients predicted to be still on ravulizumab treatment at defined time-points, with selected distributions that have a similar fit to the KM data for the pooled and CHAMPION-MG only datasets.

Table 19 Percentage of patients on treatment: pooled CHAMPION-MG and REGAIN

Distribution	1-year	3-year	5-year	10-year	20-year
Pooled CHAMPION-MG and REGAIN RCT and OLE data					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHAMPION-MG RCT and OLE data only					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: Produced by the EAG using results from the company's model (TTD sheet)					

EAG conclusion on treatment discontinuations and extrapolations

The company's methods for modelling the treatment discontinuation rates from the pooled CHAMPION-MG and REGAIN data are appropriate, but the fit of all extrapolations to the long-term KM data is poor. We have serious reservations about using the pooled data due to the uncertainties associated with the REGAIN OLE, as summarised in section 3.6 above. To reflect the pivotal trial and avoid the assumption of equivalence for eculizumab, we prefer to base the EAG analysis on KM data from the CHAMPION-MG RCT and OLE only.

Regarding the choice of distribution for the extrapolation, while we agree with the company that the exponential distribution provides the best fit to the data, we explore the impact of other distributions in EAG additional analyses, see section 6.1 below. Clinical experts advising the EAG suggested that a discontinuation rate of 3.7% per month (as with the company's base case exponential distribution) may be high. They thought that the rate of discontinuation is likely to decline over time, as patients get accustomed to the long-term dosing interval (in general, most dropouts occur early on when a new medicine is administered). This suggests that a log-logistic distribution may better reflect the long-term trend.

4.2.3.3 Discontinuation due to non-response

Patients in the ravulizumab arm of the CHAMPION-MG trial who did not achieve a reduction of at least 3 points in MG-ADL score at 16 weeks were treated as non-responders and assumed to stop treatment. These patients continue on SoC alone. In the economic model, the proportion of non-responders to ravulizumab is estimated from the 18-week assessment in the CHAMPION-MG trial ([redacted]). The CS stated that while all patients who experienced an MG-ADL score reduction of <3 were assumed to discontinue, some may have discontinued due to other reasons than a lack of response.

4.2.3.4 Clinical event rates

The economic model includes two types of acute myasthenic clinical events:

- **Exacerbation**: worsening of symptoms, sometimes requiring emergency treatment;
- **Crisis**: severe life-threatening exacerbation that requires mechanical ventilation and acute treatment with IVIG or plasma exchange (see section 2.2.1.4).

A Poisson regression model was used to estimate the number of clinical events in each treatment cycle, which are sub-divided into exacerbations or crises. The model assigned [redacted]

of clinical events as crises and [redacted] as exacerbations (see company clarification response B6). These proportions were based on the number of crises observed at week 26 in the CHAMPION-MG and REGAIN trials, across all the arms.

The CS states that the regression to estimate the incidence of clinical events was conducted with pooled data from the CHAMPION-MG RCT and OLE supplemented by data from the REGAIN RCT, with non-responders in the treatment arms (reduction from baseline of MG-ADL < 3) at 18 weeks removed from the dataset (CS B.3.3.4). The company chose a simple model specification, with the treatment arm used as the only independent variable (CS Table 28). They justified this as a parsimonious approach, which gave a good fit to the observed data. Results for a specification with an additional covariate for prior clinical event within 3 months are also reported in the model (see Table 20).

We note that the results presented in CS Table 28 correspond to the regression with non-responders at 26 weeks removed as reported in the Excel model. The company's base case model actually uses the regression with a treatment coefficient of -[redacted], which predicts [redacted] and [redacted] clinical events per patient year in the ravulizumab and SoC arms, respectively.

Table 20 Poisson regression models for clinical events

Covariates	Simple model: non responders removed at 26 weeks [a]	Simple model: non responders removed at 16 weeks[b]	Prior event co-variate: non-responders removed at 16 weeks[b]
Intercept	[redacted]	[redacted]	[redacted]
Treatment	[redacted]	[redacted]	[redacted]
Prior event within 3 months	-	-	[redacted]

Source: Obtained by the EAG from the company's economic model submitted with CQ response
[a] Reported in CS Table 28 as the simple model with 18 week non-responders removed
[b] 18-week trial assessment as proxy for 16-week stopping rule for ravulizumab

EAG conclusion on clinical event modelling

We have several concerns with the company's approach to estimating the incidence of clinical events. The methods used for fitting and testing the specification of the Poisson regression model are not well described. There appear to be discrepancies in the reporting of the sample and event numbers from the dataset and the timing of censoring for non-response in the CS and Excel model. More importantly, we are

concerned about the use of pooled data from the CHAMPION-MG and REGAIN trials. As discussed in section 3.6, the population in these studies differed. Furthermore, the use of a single 'treatment' variable, grouping the effects of ravulizumab and eculizumab on the incidence of clinical events is not appropriate. We would have preferred an analysis based on CHAMPION-MG RCT and OLE studies alone, but this has not been reported. Of the available analyses, we prefer the model with non-responders removed at 16 weeks (to reflect the proposed stopping rule for ravulizumab), and with adjustment for prior clinical events within 3 months, on the basis that previous clinical events are usually predictive of a further event.

4.2.3.5 Mortality

Age-adjusted general population mortality, obtained from the UK Life Tables (2017-19), was used to inform mortality associated with generalised MG. No excess mortality was associated with the condition, except for patients experiencing crises. A fatality rate of 4.47%, obtained from the study by Alshekhlee et al. 2009, was applied in the economic model for patients experiencing an MG crisis.[42] We noted a minor inconsistency in the mortality rate associated with a crisis, which the company clarified in their response to EAG clarification question B8, and an error in coding general population mortality (see correction in section 5.3.2 below).

EAG conclusion on mortality

Literature on the mortality associated with generalised MG is limited. Due to lack of data, it may be reasonable to use UK general population mortality as background mortality rates. However, advice from experts indicate that there is likely to be excess mortality associated with generalised MG related to therapies. For example, use of corticosteroids is associated with higher hip fractures which are in turn associated with increased mortality. Similarly, use of azathioprine, steroids and other ISTs increase the risk of malignancy which may impact mortality, along with age. Considering this, we conduct a scenario analysis with an increased mortality rate associated with generalised MG, based on a proxy condition – rheumatoid arthritis (all-cause mortality rate ratio compared with general population 1.4).[43] Further details are in Section 6.

4.2.3.6 Adverse event rates

The economic model included all grades of adverse events that occurred in at least 2% of patients in either arm of the CHAMPION-MG trial. Only four adverse events are presented: headache, diarrhoea, nasopharyngitis, and upper respiratory tract infection, see CS Table 29. The average duration and one-off disutility applied for each AE are presented in CS Table 30. These estimates are multiplied to obtain QALY loss due to AEs, which is applied to patients in the first cycle of the model. Further discussion is in section 4.2.4.4.

4.2.4 Health related quality of life

4.2.4.1 Systematic literature review for utilities

The company conducted a systematic literature review of existing HRQoL studies in generalised MG, and detail the search and findings in CS Appendix H. 57 studies were found in the search that met the population, intervention, comparator, and study design inclusion criteria. Of these, 20 used SF-36 scores and seven studies reported EQ-5D scores. In general, the Mental Component Summary scores were higher than the Physical Component Summary scores, indicating that the patients experienced a greater impact on their physical health due to the disease than their mental health.

4.2.4.2 Study-based health related quality of life

HRQoL data from the CHAMPION-MG and REGAIN RCTs were used to estimate utilities and disutilities in the model. EQ-5D-5L data were collected at baseline and at 4, 12, 18, and 26 weeks in the CHAMPION-MG trial, and at baseline, 4, 12, 16, and 26 weeks in the REGAIN trial. The EQ-5D-5L data from both trials were mapped onto EQ-5D-3L using the method designed by Hernandez-Alava et al. (2017).[44]

4.2.4.3 Health related quality of life data related to MG-ADL score

The company pooled HRQoL data for eculizumab, ravulizumab and placebo arms from the CHAMPION-MG and REGAIN trials. Utility values based on EQ-5D-5L scores were used in regression models fitted for all patients in the population. The company's base case utility regression included MG-ADL scores and baseline EQ-5D as independent variables, as shown in Table 21 below.

The Excel model also includes results from alternative regression specifications, including additional covariates of baseline disease duration and exacerbation or crisis within 3 months. The company confirmed in a response to EAG clarification question B9 that the incorrect utility regression (including disease duration and clinical event within 3 months) was used in

the original model provided. This was rectified in the updated company model submitted with the clarification response.

Table 21 MG-ADL score utility regression model used in company base case

Parameter	Estimate	Standard error	p-value
Intercept	[redacted]	0.0280	0.0000
MG-ADL Score	[redacted]	0.0018	0.0000
Baseline EQ-5D	[redacted]	0.0355	0.0000
Source Reproduced from CS Table 31			

4.2.4.4 Disutilities for adverse events and clinical events

The economic model included all grades of adverse events that occurred in at least 2% of patients in either arm of the CHAMPION-MG trial. Only four adverse events are presented: headache, diarrhoea, nasopharyngitis, and upper respiratory tract infection. The total QALYs lost due to the adverse events are calculated and applied to patients in the first cycle of the model. Due to a lack of quality of life evidence for nasopharyngitis, the company assumed a QALY loss of 0.01 for an episode of influenza (Jit et al. 2011).[45] However, in the company's model this QALY loss was treated as a utility loss lasting for 5 days - the duration for nasopharyngitis provided in CS Table 30 - which underestimates the total QALY loss (0.01*5/365.25 = 0.00014). The EAG have therefore included a correction (see section 5.3.2). Table 22 summarises the disutilities for adverse events.

The company obtained disutilities for clinical events using pooled CHAMPION-MG and REGAIN trial data. The disutilities are multiplied by the duration of the clinical event to produce a decrement which is applied as a one-off in the model to the proportion of patients experiencing a clinical event per cycle. In response to EAG clarification question B10a, the company reports that the disutility for a myasthenic crisis provided in CS Table 32 is incorrect; the correct value is [redacted], which matches the disutility in the economic model. Further, it was noted in response to EAG clarification question B10c that the caregiver disutility for a myasthenic crisis reported in CS Table 33 is also incorrect and should match the disutility for a myasthenic exacerbation, however the company do not include caregiver disutilities in their base case. Table 22 reports the disutilities for adverse events, clinical events, and caregivers during a clinical event with the company's updated values.

Table 22 Disutilities for adverse events, clinical events, and caregivers

Event	Disutility	Duration (days)	Total Decrement
Adverse Events			
Headache	-0.027	2.0	-0.0540
Diarrhoea	-0.047	2.5	-0.1175
Nasopharyngitis	-0.010	5.0	-0.0500
Upper respiratory tract infection	-0.014	14.0	-0.1960
Clinical Events			
Exacerbation	[redacted]	[redacted]	-0.0022
Crisis	[redacted]	[redacted]	-0.0085
Caregivers			
Exacerbation	-0.03	11.8	-0.3540
Crisis	-0.03	31.1	-0.9330
Reproduced from CS Table 30, CS Table 32, CS Table 33, and CQ B10.			

The economic model applies an appropriate age adjustment to the overall utility, including MG-ADL based utility and disutilities associated with MG crises and exacerbations, and adverse events. The age adjustment is based on the Ara and Brazier formula.[46]

EAG conclusion on utility modelling

The company do not justify the choice of regression model for the utility values. No regression statistics were provided in either the company submission or the company base case model to show whether adding or removing alternative covariates improves the fit of the regression model. Furthermore, the company submission states that pooled CHAMPION-MG and REGAIN HRQoL trial data were used to inform the regression; although the company Excel model only reports coefficients using CHAMPION-MG 26-week trial data. The EAG have conducted scenarios including disease duration and prior clinical events (within three months) as additional covariates, along with MG-ADL score and baseline EQ-5D. This regression model is used in the EAG preferred analysis (section 6.2).

Pooled CHAMPION-MG and REGAIN HRQoL data are used for disutilities of clinical events. In this case, the company assume that the effect of clinical events on utility is the same for patients being treated with eculizumab and ravulizumab are equivalent. The EAG have conducted scenario analyses using separate CHAMPION-MG and REGAIN HRQoL data to show the impact of differences in trial populations (section 6.1).

The company assumed a disutility of -0.01 for nasopharyngitis, using influenza as a proxy, and multiply it by the 5-day duration to obtain a QALY loss. However, according to the source, this disutility is actually the overall QALY loss per episode, and the company's calculation underestimates the QALY loss.[45] The EAG have performed a correction where a QALY loss of 0.01 per episode is used (see section 5.3.2).

4.2.5 Resources and costs

4.2.5.1 Drug acquisition

Patients in the ravulizumab arm are prescribed one loading dose at the start of the model, followed by a maintenance dose every 8 weeks starting from day 15. The dosing of ravulizumab is dependent upon patients' weights, based upon weight distributions of the patient population in CHAMPION-MG (see CS Table 34). The cost reported in the company model for one loading dose and two maintenance doses of ravulizumab is £144,020 at list price ([redacted] with the PAS discount), which is administered to all patients in the ravulizumab arm at the start of treatment. Note that the company submission states the cost for ravulizumab for the first model cycle as £146,491, a slight variation of the cost provided in the base case model. The company note that one or two maintenance doses are administered in subsequent cycles: an average cost of £82,574 is stated in CS Table 36 based upon approximately 1.625 doses per 3 month cycle.

Ravulizumab costs pertain to all patients on treatment in the ravulizumab arm of the model. As patients on ravulizumab are assumed to also be receiving SoC therapies, the cost of SoC drugs are applied to all patients in both arms of the model. The unit costs and per-cycle costs of ravulizumab and SoC are reported in CS Table 35 and CS Table 36. The EAG discusses the distribution of therapies in the SoC arm of the model above in section 4.2.2.3 above.

4.2.5.2 Drug administration

The company assume that SoC therapies do not incur administration costs. The cost of administering ravulizumab by intravenous infusion is assumed to be £281.11, equivalent to the cost of administering chemotherapy as an outpatient, obtained from the NHS Reference Cost 2020-2021. This cost is only pertinent to the loading dose and the first maintenance dose, as patients are assumed to receive a homecare infusion service funded by the company for subsequent doses.

4.2.5.3 Resource use

4.2.5.3.1 Routine care

The company surveyed UK clinicians with generalised MG experience to obtain routine care costs for the model (CS Appendix P). CS Table 37 and CS Table 38 report the unit costs and frequencies of resource use, with PSSRU 2021 and NHS Reference Costs 2020-2021 used as sources for unit costs. The total cost for routine care is £78.62 per 3-month cycle. The EAG notes that the cost for a specialist nurse during routine care in CS Table 37 is reported as £90.27 from NHS Reference Costs 2020-2021, which does not match the cost reported in the company model, £12.75, taken from PSSRU 21. The EAG do not have any changes to make to the estimates, based on expert input. The costs and durations for routine resource use is given below in Table 23.

Table 23 Routine care resource use and costs

Resource	Unit cost	Annual Frequency	Duration
GP visit	£19.61	[redacted]	[redacted]
Neurologist for MG	£46.13	[redacted]	[redacted]
General neurologist	£30.75	[redacted]	[redacted]
Specialist nurse	£12.75	[redacted]	[redacted]
Physical therapist	£13.13	[redacted]	[redacted]
Blood test	£3.63	[redacted]	[redacted]
Urinalysis	£3.61	[redacted]	[redacted]
Serum creatinine test	£3.63	[redacted]	[redacted]
Source: Reproduced from the company base case model			

4.2.5.3.2 Clinical events

Exacerbations and crises are also assumed to incur costs. The company assumes that all crises are associated with an inpatient stay, which is appropriate for the definition of crisis used in the model. For patients experiencing myasthenic exacerbations, clinicians estimated that [redacted] are treated as inpatients, with the remaining [redacted] treated as outpatients. Clinical event costs are applied as a one-off cost in the model cycle in which the event occurs. CS Table 39 and CS Table 40 provide the resource use for exacerbations and crises, respectively. In response to EAG clarification question B18, the company have amended the duration of a GP visit, neurologist, and specialist nurse stated in CS Table 40 for myasthenic crises, and have changed the relevant values in the clarification response base case model. Furthermore, the company also remark in clarification B16 that the cost of IVIG comprises the acquisition cost, £1370, and the administration cost, £644.86, corresponding to the NHS

reference cost for a non-elective long stay injection of RH immune globulin or other blood transfusion.

The company model reports the use of rescue therapy for both exacerbations and crises, which was not reported in tables in the company submission. Rescue therapy comprises a basket of standard of care therapies, costing [redacted] and [redacted] per exacerbation and per crises, respectively. The estimated therapies present in rescue therapy were obtained through a survey completed by UK clinical experts, and include rituximab for patients experiencing crises. In addition, Table 40 of the company submission indicates that [redacted] of patients experiencing a crisis receive IVIG; the company model reports only [redacted] of these patients are given IVIG, with the remaining [redacted] receiving plasma exchange.
The EAG note that the company base case model reports an expected cost per exacerbation of [redacted], and an expected cost per crises of [redacted]. These values differ from the costs stated in the company submission of [redacted] and [redacted] for exacerbations and crises, respectively.

The EAG agree with the company's estimates and no scenario analyses are conducted. Table 24 and
Table 25 below report the updated resource use for clinical events.

Table 24 Resource use during myasthenic exacerbation

Resource	Proportion of patients	Frequency per event	Duration
GP visit	[redacted]	[redacted]	[redacted]
General neurologist	[redacted]	[redacted]	[redacted]
Specialist nurse	[redacted]	[redacted]	[redacted]
Blood test	[redacted]	[redacted]	[redacted]
Urinalysis	[redacted]	[redacted]	[redacted]
Serum creatinine	[redacted]	[redacted]	[redacted]
Inpatient stay	[redacted]	[redacted]	[redacted]
Intubation	[redacted]	[redacted]	[redacted]
Rescue therapy	[redacted]	[redacted]	[redacted]
Source: Reproduced from company base case model			

Table 25 Resource use during myasthenic crisis

Resource	Proportion of patients	Frequency per event	Duration
GP visit	[redacted]	[redacted]	[redacted]
General neurologist	[redacted]	[redacted]	[redacted]
Specialist nurse	[redacted]	[redacted]	[redacted]
Inpatient stay	[redacted]	[redacted]	[redacted]

Intubation	[redacted]	[redacted]	[redacted]
ICU stay	[redacted]	[redacted]	[redacted]
IVIG	[redacted]	[redacted]	[redacted]
Plasma exchange	[redacted]	[redacted]	[redacted]
Rescue therapy	[redacted]	[redacted]	[redacted]
Source: Reproduced from company base case model			

4.2.5.3.3 Adverse events

As with utilities, the economic model included costs associated with adverse events that occurred in at least 2% of patients, regardless of grade. The company assumed that headache and nasopharyngitis did not incur any costs, with costs for diarrhoea and upper respiratory tract infection obtained from NHS Reference Costs 2020-2021. The management costs for adverse events are applied as a one-off cost in the first cycle of the model. Table 26 below reports the adverse event costs.

Table 26 Adverse event costs used in the model

Adverse event	Cost
Headache	-
Diarrhoea	£686.81
Nasopharyngitis	-
Upper respiratory tract infection	£292.00
Source: Reproduced from CS Table 41	

4.2.5.3.4 Vaccinations

As the administration of ravulizumab may increase the likelihood of meningococcal infection, all patients must be vaccinated at least two weeks prior to starting treatment, according to the SmPC for ravulizumab, provided the risk of delaying treatment does not outweigh the risks of contracting a meningococcal infection. The company obtain the cost and dosing of two vaccines, MenACWY and MenB, from Hampstead Health Pharmacy (ref) (see CS Table 42). A booster is also given for both vaccines every five years for all patients on complement-inhibitor treatment, which is implemented in the model. The total cost of vaccines implemented in the first cycle of the model is £275. Table 27 reports the costs and frequencies of the vaccines.

Table 27 Meningococcal vaccine costs for patients on ravulizumab

Vaccine	Number of doses	Cost per dose	Booster frequency
MenACWY	1	£70	5 years
MenB	2	£135	5 years (single dose)
Source: Reproduced from CS Table 42			

EAG conclusion on resources and costs

In the company's base case, the cost of rituximab is only included in the rescue therapy treatment of myasthenic crises, however the impact of rituximab is not considered. The clinical experts advising the EAG agree that rituximab should be used as a comparator to ravulizumab.

The company assume that patients receive a homecare infusion service funded by the company, with the NHS only funding the administration costs for the loading dose and first maintenance dose. The company do not indicate whether the patients are trained to self-administer the medication, or whether they pay for nurses to conduct home visits. In the case of elderly or disabled patients, additional assistance may be required. Given a cost of £281.11 on the NHS per outpatient infusion, costs may increase significantly for patients unable to use the homecare infusion service. We suggest that the implementation of the homecare infusion service may underestimate the true cost of ravulizumab administration for the NHS.

There is a large difference in the costs of treating clinical events reported in the company submission ([redacted] and [redacted] for exacerbations and crises, respectively), compared with the costs included in the economic model ([redacted] and [redacted]). The reason for this large difference is not clear.

The company use different sources for the cost of a specialist nurse in the company submission and the company base case model, with the submission citing a cost of £90.27 from the NHS Reference costs 2020-2021, and the model reporting a cost of £12.75 from PSSRU 21. The EAG consider the cost used in the model from PSSRU 21 to be more appropriate when taking into account the corresponding costs for the specialist and general neurologists, and have used the latter cost in the preferred analyses.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company reported their original deterministic base case results in CS Table 44, with an ICER of [redacted] per QALY gained (Table 28). This and all other cost-effectiveness results in this report are conducted with a confidential patient access scheme (PAS) price discount for ravulizumab and all other drugs at published prices (from eMIT or MIMS). Sensitivity analysis results for the original base case are reported in CS section B.3.10.

The company made corrections to their model in response to clarification questions, see Appendix 4 for a list of the changes. Revised deterministic base case results are reported in clarification response Table 11, with an ICER of [redacted] per QALY gained (Table 28).

Table 28 Cost-effectiveness results: company base case (deterministic)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Original company submission							
SoC	£87,637	18.60	10.18				
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised in response to clarification questions							
SoC	£88,424	18.62	10.08				
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: CS Table 44 and Clarification response Table 11							

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

The company reported a probabilistic ICER for their original base case of [redacted] per QALY gained (CS B.3.10.1), which is very close to the deterministic estimate. The cost-effectiveness scatterplot and cost-effectiveness acceptability curve (CEAC), CS Figures 21 and 22 respectively, show a very narrow range of variation around the deterministic results. Similarly, the probabilistic ICER for the revised base case, [redacted] per QALY (Table 29) and cost-effectiveness scatterplot and CEAC reported for the revised base case (clarification response Figures 10 and 11) indicate very little uncertainty in the ICER. The EAG are concerned that the probabilistic results do not accurately reflect uncertainty because the PSA omits some key parameters: see section 5.3.1 below.

Table 29 Revised cost-effectiveness results: company base case (probabilistic)

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
SoC	£88,646	18.62	10.09				
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: Company revised economic model submitted with the clarification response							

5.2.2 Deterministic sensitivity analyses

The company report deterministic, one-way sensitivity analysis results in the form of a Tornado diagram, showing the top 10 parameters associated with the largest impact on the ICER. In response to clarification question B1, the company note that the tornado diagram in CS Figure 23 was incorrect. They provide a diagram for the revised base case analysis in Table 3 of their clarification response, reproduced in Figure 6 with ICER values added at the upper and lower limits for each parameter. We note that the DSA does not include all parameters that are subject to uncertainty (see section 5.3.1).

Figure 6 One way sensitivity tornado diagram: ICER with revised company base case

Source: Produced by the EAG from the company's revised model

The results for the 'MG-ADL Total Score' parameter appear counter-intuitive. This parameter is the mean baseline MG-ADL score for the population, 9.5 in the base case. The ICERs at both the lower limit (7.6) and upper limit (11.4) lie above the base case ICER. This u-shaped relationship is caused by interaction between the discrete and unbounded limits of the

change in MG-ADL substates (Table 17), the fixed mean reduction in each category (Table 18), and the boundaries of the MG-ADL Total score (from 0 to 24).

5.2.3 Scenario analysis

The company reported deterministic scenario analyses in CS Table 47. Updated results for these scenarios were not reported in the clarification response, but this did include results for an additional scenario with time on treatment for ravulizumab extrapolated from CHAMPION-MG data only (the base case uses pooled data from CHAMPION-MG and REGAIN). We show results for the company's scenarios produced by the EAG from the revised model submitted with the clarification response in Table 30.

Table 30 Scenario analysis results, revised base case model (deterministic)

Model assumption	Base case	Scenario	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)
Base case			[redacted]	[redacted]	[redacted]
Time horizon	48 years	40 years	[redacted]	[redacted]	[redacted]
Discounting	3.5% for cost and health outcomes	1.5%	[redacted]	[redacted]	[redacted]
		5.0%	[redacted]	[redacted]	[redacted]
Time on treatment extrapolation	Exponential	Gompertz	[redacted]	[redacted]	[redacted]
		Log-logistic	[redacted]	[redacted]	[redacted]
Time on treatment data source [a]	CHAMPION-MG and REGAIN	CHAMPION-MG only	[redacted]	[redacted]	[redacted]
EQ-5D model	With baseline EQ-5D	Without baseline EQ-5D	[redacted]	[redacted]	[redacted]
Non-response assessment timepoint for ravulizumab	16 weeks (18 week CHAMPION-MG data)	26 weeks	[redacted]	[redacted]	[redacted]

Source: Based on CS Table 47 with revised results produced by the EAG from the company's revised model in response to clarification questions. [a] Clarification Response Table 12

5.3 Model validation and face validity check

5.3.1 EAG validation and model check

We conducted a range of checks on the submitted model using an EAG QA checklist:

- Input checks: comparison of all parameter values in the model against the values stated in the CS and the cited sources.
- Output checks: replication of CS reported results using the submitted model.
- 'White box' checks: manual checking of formulae working from the Markov trace sheets. This included reviewing the calculations across each trace and working backwards to trace links to input parameters and forwards to the results.
- 'Black box' checks: working through a list of tests to assess whether changes to key model inputs or assumptions have the expected on the model results.
- Initial checks were used to inform clarification questions to the company. In response, the company made several corrections to their model and provided results for a revised base case and an additional scenario with time to discontinuation extrapolations for ravulizumab based on CHAMPION-MG trial data only. The EAG conducted further checks on the revised model that was submitted with the company's response to clarification questions. We identified some additional errors, which we discuss in section 5.3.2.

We also consider that the company's sensitivity analyses do not adequately reflect the uncertainty of the results. The DSA and PSA excluded some key parameters that are subject to uncertainty, including:

- The mean MG-ADL change by substate
- The incidence of clinical events (coefficients of the Poisson regression are sampled on the 'Clinical datastore' tab, but the sensitivity control is not linked to the PSA)
- The proportion of clinical events that are crises
- The proportion of crises that are fatal
- Healthcare resource use for crises and exacerbations

5.3.2 EAG corrections to the company model

The company made several corrections to their original model in response to clarification questions: see 0 for a list of these changes. We identified additional errors in the revised version of the model submitted with the company's response to clarification questions (Table 31).

Table 31 EAG corrections to the company model

Parameter	Location in model	Company model	EAG correction	Comments
% female in CHAMPION-MG trial population	Clinical datastore! C6-D6	53.5%	50.9% (89/175): CS Table 8 and CSR Table 9	Overall estimate with pooled trial data 57.0%
SoC use of drug treatments	Parameters! K102-K110	Pooled trial data (from Drug costs! E25-33)	Parameters linked to 'Current selection' column on Drug costs sheet	Correction uses CHAMPION-MG data, UK practice assumptions (as in CS Table 23)
Disutility of nasopharyngitis	AEs! J17	Disutility 0.01 for 5 days per episode	Disutility 0.731 for 5 days: QALY loss of 0.01	Jit et al. estimate QALY loss per episode of 0.01 [45]
Survival estimates	Mortality! K11-111	Per cycle mortality calculated from qx for previous age from life table	General survival column in trace sheets linked to original life table qx	The error over-estimated survival in both arms

Source: Table created by the EAG based on the company's clarification response model
qx: the mortality rate between age x and (x +1), that is the probability that a person aged x exact will die before reaching age (x +1)

The cumulative impact of these corrections is shown in Table 32. The first three corrections have a minimal impact on the ICER. The correction to the method of calculation of survival estimates has a moderate impact, increasing the ICER by about [redacted] per QALY gained. The EAG-corrected estimate of the company's base case is [redacted] per QALY gained.

Table 32 Cumulative impact of EAG corrections to company base case (deterministic)

Correction	Treatment	Total cost	QALYs	ICER (£/QALY)
Company base case (clarification response)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
% female in CHAMPION-MG trial population	SoC	£88,345	10.075	
	Ravulizumab	[redacted]	[redacted]	[redacted]
SoC use of drug treatments	SoC	£80,961	10.075	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Disutility of nasopharyngitis	SoC	£80,961	10.074	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Survival estimates	SoC	£79,993	9.967	
	Ravulizumab	[redacted]	[redacted]	[redacted]

Source: Table created by the EAG using the company's model submitted with their CQ response

5.4 EAG additional scenarios and sensitivity analyses

The company presented a small number of scenario analyses in CS Table 47. The EAG tested the impact of a wider range of uncertainties in additional scenario analysis. Table 33 summarises the scenarios and our reasons for conducting them. The results are reported in the following section.

Table 33 Additional EAG scenarios

Parameter	Company's base case analysis	EAG scenarios	Reason for analysis
Baseline patient characteristics source	Pooled CHAMPION-MG and REGAIN RCTs	CHAMPION-MG RCT only	To reflect the population in the pivotal trial for ravulizumab
Time on treatment data source	Pooled CHAMPION-MG and REGAIN data	CHAMPION-MG only	To reflect pivotal trial and avoid assumption of equivalence for eculizumab
Time on treatment extrapolation distribution	Exponential	Distributions with a similar fit to KM data (Gompertz, Weibull, gamma, log-logistic).	To reflect uncertainty over long-term treatment duration for ravulizumab
Timing of MG-ADL change response assessment	Ravulizumab 16-week assessment and stopping rule SoC 26 weeks	26-week assessment for both arms, with 26 week stopping rule for ravulizumab	To illustrate the effect of a later stopping rule

Parameter	Company's base case analysis	EAG scenarios	Reason for analysis
Retained treatment benefit	No retained benefit of ravulizumab after discontinuation	Waning of treatment effect over 3 and 6 months after discontinuation	To illustrate effect, although expert opinion is that effects will wane quickly
Loss of placebo effect in SoC arm	MG-ADL assumed to return to baseline value (9.5) at one year	Return to baseline at 6 and 9 months. No loss of placebo effect.	To illustrate the effect of a faster, or no loss of the 'placebo effect'
Incidence of clinical events	Pooled CHAMPION-MG and REGAIN data Poisson regression without adjustment for prior events with 3 months	Poisson regression with adjustment for prior events within 3 months	The incidence of clinical events is likely to be higher for those with a recent event
Proportion of clinical events that are crises	Pooled CHAMPION-MG and REGAIN RCT data (26 week)	CHAMPION 60 week and REGAIN 26 week	To show the effect of including longer OLE follow up for CHAMPION-MG
Mortality risk for generalised MG population	Rate ratio 1.0 compared with general population mortality	Rate ratio 1.4 illustrative example, rheumatoid arthritis (Widdifield et al. 2018)[43]	To explore the impact of higher background mortality
Utility regression model (choice of co-variates)	Adjustment for MG-ADL score and baseline EQ-5D; separate disutilities for clinical events	Include coefficients for clinical event within 3 months; and disease duration	To test sensitivity of results to alternative model specification
Source for disutilities of clinical events	Pooled CHAMPION-MG and REGAIN data	CHAMPION-MG only	To illustrate the impact of differences in trial populations
Cost of treatment for exacerbation and crisis	Exacerbation [redacted] Crisis [redacted] (base case model)	Exacerbation [redacted] Crisis [redacted] (CS B.3.5.2)	To test the impact of alternative estimates reported in the CS
Source: Table created by the EAG			

6 EAG'S ADDITIONAL ANALYSES

6.1 Impact on the ICER of additional analyses undertaken by the EAG

Results from EAG scenario analyses conducted on the company's base case analysis are shown in Table 34. The ICER remains well above the conventional NICE thresholds in all scenarios.

Table 34 EAG additional scenarios applied to the company's base case (deterministic)

Scenario	Treatment	Total Cost (£)	Total QALYs	ICER (£/QALY)
Company's base case (at clarification response)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Population				
Baseline patient characteristics: CHAMPION-MG only	SoC	£82,990	9.688	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Time on treatment				
CHAMPION-MG trial (exponential)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
CHAMPION-MG trial (Gompertz)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
CHAMPION-MG trial (Weibull)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
CHAMPION-MG trial (gamma)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
CHAMPION-MG trial (log-logistic)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Treatment effect: change in MG-ADL				
Response assessment at 26-weeks for both arms (and stopping rule at 26 weeks)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Retained treatment benefit (waning over 3 months)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Retained treatment benefit (waning over 6 months)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Loss of placebo effect in SoC arm: return to baseline MG-ADL				
Return to baseline at 6 months	SoC	£88,424	10.061	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Return to baseline at 9 months	SoC	£88,424	10.072	
	Ravulizumab	[redacted]	[redacted]	[redacted]
No loss of placebo effect	SoC	£88,424	10.824	
	Ravulizumab	[redacted]	[redacted]	[redacted]

Scenario	Treatment	Total Cost (£)	Total QALYs	ICER (£/QALY)
Clinical events				
Incidence of clinical events: prior events within 3 months covariate	SoC	£68,006	10.119	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Exacerbation: crisis split (CHAMPION 60 week and REGAIN 26 week)	SoC	£108,124	9.982	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Mortality				
Fatality rate for crises 2%	SoC	£88,914	10.136	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Fatality rate for crises 10%	SoC	£87,340	9.965	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Mortality risk ratio 1.4 versus general population	SoC	£83,581	9.582	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Utilities				
Utility regression: include clinical events within 3 months and disease duration	SoC	£88,424	10.204	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Disutilities for clinical events from CHAMPION-MG only	SoC	£88,424	10.116	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Cost of clinical events				
Higher costs cited in CS (B.3.5.2): exacerbation [redacted] and crisis[redacted]	SoC	£171,947	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]

Source: EAG produced from the company's revised model in response to clarification questions

6.2 EAG's preferred assumptions

Table 35 EAG's preferred assumptions

Parameter	EAG preferred	Reason for inclusion
Baseline patient characteristics	CHAMPION-MG	To align with the principal source of clinical evidence
Time on treatment	CHAMPION-MG only, exponential distribution	To reflect pivotal trial and avoid assumption of equivalence for eculizumab
Incidence of clinical events	Poisson regression with adjustment for prior events within 3 months	The incidence of having a clinical event is likely to be higher for those with a recent event
Utility regression model	Include coefficients for clinical event within 3 months; and disease duration	
Source: Table created by the EAG		

Table 36 Cumulative EAG preferred assumptions (deterministic)

Correction	Treatment	Total cost	QALYs	ICER (£/QALY)
Company base case (clarification response)	SoC	£88,424	10.083	
	Ravulizumab	[redacted]	[redacted]	[redacted]
EAG corrections, (see Table 32)	SoC	£79,993	9.967	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Baseline patient characteristics: Champion-MG trial only	SoC	£74,899	9.554	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Time on treatment: CHAMPION-MG RCT and OLE (exponential)	SoC	£74,899	9.554	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Incidence of clinical events: include prior events within 3 months	SoC	£55,974	9.585	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Utility regression: coefficients for clinical event within 3 months; and disease duration	SoC	£55,974	9.709	
	Ravulizumab	[redacted]	[redacted]	[redacted]
EAG preferred analysis	SoC	£55,974	9.709	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Source: Table created by the EAG using the company's model submitted with their CQ response				

6.3 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost effectiveness of ravulizumab compared to SoC. The EAG consider the overall model structure to be appropriate. The

model uses clinical effectiveness data from the CHAMPION-MG and REGAIN trials and open label extension studies. The company base case produced a revised ICER of [redacted] per QALY gained for ravulizumab compared to SoC (after corrections made by the company in response to clarification questions). This ICER was obtained by applying a confidential PAS discount for ravulizumab.

We identified additional errors on further checking the revised model and addressed these in additional EAG scenario analyses. The ICER obtained in the EAG corrected company's revised base case was [redacted] per QALY gained for ravulizumab compared to SoC.

The EAG disagrees with several of the assumptions in the company's model. Our preferred assumptions include:

- Using baseline patient characteristics from CHAMPION-MG trial to align the model population with the main clinical data source used in the model
- Using time on treatment data from CHAMPION-MG trial and OLE, again to align with the clinical data for ravulizumab
- Inclusion of prior clinical events within 3 months for the incidence of clinical events
- Inclusion of coefficients for clinical event within 3 months for utilities

The EAG preferred assumptions increase the ICER to [redacted] per QALY gained for ravulizumab compared to SoC. In addition to the above issues addressed by the EAG, there are other key uncertainties in the company's assumptions. These include:

- The company use 16-week MG-ADL response data from the CHAMPION-MG trial for the ravulizumab arm, but 26-week data for the comparator. This approach does not make full use of all randomised data to inform the long-term projections of the effect of ravulizumab on MG-ADL status. The model includes a scenario with 26-week MG-ADL response data used for both arms, but this is linked to the timing of the stopping rule (also set at 26 weeks). Clinical experts advising the EAG agreed that stopping ravulizumab for patients with an inadequate response after a loading dose and two cycles of maintenance treatment at 16 weeks would be appropriate. We suggest that an analysis combining a 16-week stopping rule for ravulizumab with use of 26-week trial data to estimate the long-term effect on MG-ADL status would be more appropriate.

- The model does not include a half-cycle correction. Given the 3-month model cycle length, this may introduce some error in the calculation of QALYs and costs.

- We have concerns whether the basket of drugs included for costing SoC is reflective of current established clinical management in England. The model excludes rituximab as a comparator and there remains uncertainty whether this is an appropriate reflection of clinical practice. The model structure does not support the addition of rituximab as a comparator or estimation of the clinical effect of changes to the basket of SoC treatments on clinical outcomes. We note that the model is not sensitive to the cost of SoC or routine health care, as these costs are applied to both arms of the model and largely cancel out.

- The company's approach to modelling clinical events using Poisson regression has limitations with respect to the data source used, inconsistency in the estimates reported in the CS and used in the excel model, poor quality of reporting for the fitting of the regression equation, use of limited covariates implying a potential risk of bias for the treatment effect due to lack of adjustments for baseline differences between the trials. We consider that the use of REGAIN data in the clinical event regression is a source of uncertainty, and potentially bias, and would have preferred to see an analysis based on CHAMPION-MG data alone.

- There are also limitations in the reporting of the regression equation used to estimate the relationship between MG-ADL score and EQ-5D utility. Again, we would have preferred to see this analysis conducted without REGAIN data.

We note that the company's probabilistic sensitivity analysis does not reflect parametric uncertainty in a meaningful way, because several important parameters are omitted. There are also flaws in the deterministic sensitivity analysis, as several included parameters did not result in any variation in the ICER and were therefore excluded from the Tornado diagram.

7 DECISION MODIFIERS

The company state that generalised MG is not eligible for any severity modifiers based on proportional or absolute QALY shortfall measures (CS Table 21). We show the absolute and proportional QALY shortfalls for the company's base case analyses and EAG preferred assumptions in Table 37 below. The criteria for severity weighting are not met in either analysis.

Table 37 QALY shortfall analysis

Model	Mean age	Female	Expected total QALYs [a]		QALY shortfall	
			General population [b]	Model	Absolute	Proportional
Company base case	52 years	59%	15.33	10.08	5.25	34.26%
EAG preferred	56 years	54%	14.05	9.71	4.34	30.91%

Source: Produced by the EAG
[a] QALYs discounted at 3.5% over the model time horizon (48 years from staring age)
[b] From QALY Shortfall Calculator reference case (https://shiny.york.ac.uk/shortfall)

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9 APPENDICES

Appendix 1 EAG critique of the company's approach to the evidence synthesis

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The PICO structure of the question is clearly specified in the company's Decision Problem (CS Table 1).
Were appropriate sources of literature searched?	Partly	MEDLINE, MEDLINE In-Process, Embase, CENTRAL, CDSR and DARE were searched. But the CS does not state which conferences were included or how they were searched. No other grey literature sources are listed.
What time period did the searches span and was this appropriate?	Partly - searches were one year out of date on receipt of the CS by the EAG	Bibliographic databases: 2000 to 3rd February 2022. Conferences: "2019 to present".
Were appropriate search terms used and combined correctly?	Partly	The search syntax (CS Appendix Tables 2 to 4) is appropriate. MEDLINE and Embase searches used an RCT filter, so searches may have missed relevant non-randomised studies.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Specified: yes Appropriate: partly	Eligibility criteria (CS Appendix Table 1) are comprehensive. We note they are wider than the NICE scope. CS section B.2.1 states that additional criteria were subsequently applied to limit the review to the NICE scope. A PRISMA flow diagram is provided (CS Appendix Figure 2) but refers only to screening against the initial broad eligibility criteria. Studies of eculizumab were initially excluded (CS Appendix Table 5) but then included in the CS (CS section B.2.2) although eculizumab is not in the NICE scope or company Decision Problem summarised in CS Table 1. Some studies of comparators are excluded without explanation (see section 3.1). A list of excluded studies corresponding to the PRISMA diagram was provided in Clarification Response A1.
Were study selection criteria applied by two or more reviewers independently?	Yes	Stated in CS Appendix D.1.2.

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was data extraction performed by two or more reviewers independently?	Unclear	Not reported in the CS or Appendices.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Pivotal trial: Yes. OLE study for the pivotal trial: No (provided in clarification response).	Reported for the pivotal trial (CHAMPION-MG) using NICE criteria for RCTs32 in CS Table 10 and CS Appendix Table 7. Critical appraisal of the CHAMPION-MG OLE study was provided in Clarification Response A8 using the Downs and Black checklist. 33 The company also provided a critical appraisal of the REGAIN RCT of eculizumab in CS Appendix Table 28, but not of its OLE study.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Unclear	Not reported in the CS, Appendices or Clarification Response A8. However, the rationale for each critical appraisal judgement is stated in CS Appendix Tables 7 and 28 and Clarification Response A8.
Is sufficient detail on the individual studies presented?	Yes	The CSR and trial publications were provided in addition to the CS and Appendices. All but one of the data tables missing from the CSR were provided as separate documents in response to Clarification Question A5.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes. The statistical methods of ITC analysis appear appropriate.	The company conducted an ITC comparing ravulizumab against eculizumab which the company argue have similar effectiveness and safety. The ITC was intended “for helping to predict long-term outcomes for patients treated with ravulizumab” (CS section B.2.9.1). However, the ITC is limited to the randomised phase of each trial, up to 26 weeks, so does not permit inferences about longer-term outcomes. The CS implies an unstated assumption that if ravulizumab and eculizumab have similar effectiveness over 26 weeks then they will also have similar long-term effectiveness.

Appendix 2 Details of the risk of bias assessments

The company and EAG risk of bias assessments are provided below for the CHAMPION-MG and REGAIN RCTs in Table A and for the respective OLE studies in Table B. We used the NICE-recommended checklist for critically appraising the RCTs.[32] To critically appraise the OLE studies, we used the criteria suggested by NICE for non-randomised and non-controlled studies.[32]

Appendix 2: TABLE A

Company and EAG risk of bias assessments for the CHAMPION-MG and REGAIN RCTs

		CHAMPION-MG	REGAIN
1. Was randomization carried out appropriately?	Company	Yes	Yes
	EAG	Yes (low risk of bias)	Yes (low risk of bias)
EAG comment: **CHAMPION-MG:** Randomisation was carried out using a central interactive response technology to assign participants to treatment arms. **REGAIN:** Randomisation was carried out using a central interactive voice or web response system.[27]			
2. Was the concealment of treatment allocation adequate?	Company	Yes	Yes
	EAG	Yes (low risk of bias)	Yes (low risk of bias)
EAG comment: **CHAMPION-MG:** Central allocation was used. **REGAIN:** Central allocation was used and this was run by an independent company.[27]			
3. Were the groups similar at the outset of the study in terms of prognostic factors?	Company	Yes	Yes
	EAG	Unclear (unclear risk of bias)	No (high risk of bias)
EAG comment: **CHAMPION-MG:** Baseline characteristics reported in the CS were generally well-balanced between treatment arms, apart from imbalances for the age at infusion and MGFA severity class, which the EAG's clinical experts did not regard as clinically important (section 3.2.2.2.1 in this report). However, the CS does not present baseline characteristics for all the factors that the EAG's clinical experts considered to be prognostic in generalised MG (section 3.2.2.2.1) and therefore the balance of these factors between the trial arms is uncertain. **REGAIN:** There were differences between arms in race, rates of thymectomy, previous long-term plasma exchange and history of MG exacerbations (section 3.2.2.2.2). The EAG's clinical experts said that the higher proportions of people who had long-term plasma exchange and history of MG exacerbations in the placebo arm suggest that this arm had more severe MG disease, which could introduce bias in the comparison of eculizumab against placebo (section 3.2.2.2.2).			
4. Were the care providers, participants and	Company	Yes	Stated "No", but EAG assume this is a typographical error [a]

		CHAMPION-MG	REGAIN
outcome assessors blind to treatment allocation?	EAG	Yes (low risk of bias)	Yes (low risk of bias)
EAG comment: **CHAMPION-MG:** The study was double-blinded during the randomised controlled period. The Supplementary Appendix of the trial paper states that patients, study site staff and the sponsor were blind to treatment group assignments.[24] The Supplementary Appendix also states that the ravulizumab and placebo drugs used were identical in appearance. The drugs were administered following the same schedule (CS section B.2.3.1). **REGAIN:** This was a double-blind study. Patients, personnel, investigators and the trial sponsor were blinded to treatment allocation during the study. Placebo matched eculizumab in appearance and was administered to patients following the same schedule as used for eculizumab.[27]			
5. Were there any unexpected imbalances in drop-outs between groups?	Company	No	No
	EAG	No (low risk of bias)	No (low risk of bias)
EAG comment: **CHAMPION-MG:** the proportion of participants discontinuing the trial was similar between the trial arms (ravulizumab 8%, placebo 7%). There appear to be no important differences between the arms in reasons for discontinuation that would suggest a risk of bias (CS Figure 7). **REGAIN:** As for CHAMPION-MG above, the proportions of participants who discontinued treatment did not differ substantially between treatment arms (eculizumab 8%, placebo 3%; percentages calculated by the EAG). The reasons given for discontinuation in each arm do not suggest a risk of bias (CS Appendix Figure 6).			
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Company	No	No
	EAG	Yes (but low risk of bias)	No (low risk of bias)
EAG comment: **CHAMPION-MG:** The EPAR[28] reports that all assay results for antidrug neutralizing antibodies were negative. These findings are not reported in any of the company documents including the CSR,[25] CSR Addendum,[26] CS or trial paper.[24] The CSR Addendum lists Table 14.3.4.4.2 as showing the results, but this table was not included in the copy of the CSR Addendum provided to the EAG. Presence of anti-drug neutralizing antibodies would be a potentially important outcome that could have implications for the efficacy of ravulizumab. However, as such antibodies were not detected during the trial the efficacy of ravulizumab would not be compromised during the RCT so we consider the risk of bias to be low. **REGAIN:** The study protocol and CSR were not available to the EAG but based on the trial paper and its supplementary Appendix[27] we have not identified any outcomes that the company intended to measure but for which they have not reported results.			
7. a) Did the analysis include an intention-to-treat analysis? b) If so, was this appropriate and were appropriate methods used to account for missing data?	Company	Yes	Yes
	EAG	a) No, the analysis did not include all randomised patients.	Unclear (unclear risk of bias)

		CHAMPION-MG	REGAIN
		b) Unclear whether sensitivity analyses on missing data assumptions for the primary outcome were conducted appropriately. No imputation or sensitivity analyses for missing data were conducted for other outcomes. Unclear risk of bias for all outcomes.	

EAG comment:

CHAMPION-MG: The CS defines the full analysis set population as all randomised participants with at least one dose of trial agent grouped by randomised treatment group (CS section B.2.4); CS Figure 7 confirms that all patients did receive at least one dose of either ravulizumab or placebo (N=175). However, in the primary efficacy analysis of change from baseline in MG-ADL total score at Week 26, missing data were not imputed (CS Table 9) so a true intention-to-treat analysis does not appear to have been used. The number and proportion of participants missing data on this outcome at 26 weeks were similar between the trial arms (n = 8 [9.3%] in the ravulizumab arm, n = 7 [7.9%] in the placebo arm; trial paper, Supplementary Appendix, Table S6). Reasons for missing data were not provided. Two sensitivity analyses were undertaken of the primary outcome to explore the impact of different missing data imputation assumptions (see CS Table 9); the assumptions used appear appropriate. However, the EAG are unclear whether these analyses were conducted appropriately (section 3.2.4.1) so we consider the risk of bias due to missing data unclear for this outcome. Table S6 in the trial publication shows that there were missing data for other outcomes analysed (change from baseline in QMG total score, in MG-QOL15r and Neuro-QoL Fatigue at 26 weeks). The percentage of participants with missing data ranged from 7.9% to 12.4% and was well-balanced between trial arms. However, as sensitivity analyses were not conducted to test missing data assumptions for these outcomes and reasons for missingness were not reported, we consider these outcomes to also be at an unclear risk of bias.

REGAIN: The full analysis set was used to analyse efficacy outcomes and was defined as "all randomly assigned patients who received at least one dose of study drug, had a valid baseline assessment available, and at least one post-baseline assessment".[27] If the defined 'full analysis set' is the same as the 'modified intention-to-treat analysis' population referred to in CS Appendix Figure 6, then it appears that all but one of the randomised participants were included in the full analysis set, and thus an intention-to-treat analysis appears to have been used. In the repeated measures analyses (which assessed changes over time from baseline at each assessment visit) of MG-ADL, QMG, MGC and MG-QoL15, missing data were not imputed. There is no information in the study publication about the extent of missing data and reasons for missingness across the outcomes, so it is unclear if the amount of missing data may potentially bias the results.

Source: CS Appendix D.4, CS Appendix M.1.2, REGAIN and CHAMPION-MG trial publications, and CHAMPION-MG CSR

ANCOVA, analysis of covariance; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living

[a] The company's "No" answer in CS Appendix Table 28 is inconsistent with their textual description which would suggest a "Yes" answer was intended, so we believe "No" is a typographical error.

APPENDIX 2: TABLE B

Company and EAG risk of bias assessments for the CHAMPION-MG and REGAIN OLE studies

Study name	CHAMPION-MG (yes/no/not clear/N/A)	REGAIN (yes/no/not clear/N/A)
Was the cohort recruited in an acceptable way?	Yes (low risk of bias)	Yes (low risk of bias)
EAG comment: **CHAMPION-MG:** [redacted] (60-week CSR Addendum Figure 1). Similar and minimal numbers of participants between the trial arms had discontinued from the RCT, for similar reasons (CS Table 7), raising no concerns for us about the possibility of selection bias regarding the participants entering the OLE. **REGAIN:** Of the 118 participants who completed the REGAIN RCT, 117 entered the OLE and 116 were included in the efficacy analyses (one participant not included as permission was not granted by their national health authority).[29] The EAG therefore have no concerns about any differences in drop-outs between the trial arms in the RCT (CS Appendix Figure 6) that may then have potentially impacted the selection of participants for the OLE.		
Was the exposure accurately measured to minimise bias?	Yes (low risk of bias)	Yes (low risk of bias)
EAG comment: **CHAMPION-MG:** Exposure to ravulizumab appears to have been accurately measured. **REGAIN:** Exposure to eculizumab appears to have been accurately measured.		
Was the outcome accurately measured to minimise bias?	No (high risk of bias)	No (high risk of bias)
EAG comment: **CHAMPION-MG:** Appropriate measures of generalised MG symptoms and HRQoL were used (see section 3.2.5), but by nature of the open-label extension design, there was no blinding to the treatment being received; that is, all participants were receiving open-label ravulizumab during this period. Knowledge of this could potentially bias ratings on some of the more subjective measures used, such as the MG-ADL, during the OLE period. (Participants and investigators would not have been aware during the OLE, though, of the treatment received during the randomised controlled period of the study, as the start of the OLE period drug dosing was blinded so that this could not be worked out, which helps to reduce subsequent bias in the OLE from knowledge about the treatment initially received; CS section B.2.3.1.) **REGAIN:** The REGAIN OLE followed a similar design to the CHAMPION-MG OLE.[29] Therefore the same considerations apply as stated above for the CHAMPION-MG OLE. Appropriate measures of MG symptoms and HRQoL were used.		
Have the authors identified all important confounding factors?	No (high risk of bias)	No (high risk of bias)
EAG comment:		

Study name	CHAMPION-MG (yes/no/not clear/N/A)	REGAIN (yes/no/not clear/N/A)
CHAMPION-MG: The CS does not discuss potential confounding factors other than to comment that the COVID-19 pandemic may have been a confounding factor that impacted on the HRQoL measures (CS section B.2.12.1). The EAG suggest that potential confounding factors during the OLE period may include use of rescue therapy and changes in background therapy (we note from the EPAR[28] that changes in background therapy were permitted during the OLE). We note that anti-drug neutralising antibodies were measured in the OLE study[26] but results were not provided to the EAG in the study publication[29] or any of the CS documents (the CSR Addendum[26] lists Table 14.3.4.4.2 as showing the results, but this table was not included in the copy of the CSR Addendum provided to the EAG). Such antibodies, if present, could confound the efficacy of ravulizumab. **REGAIN:** The study authors do not discuss any confounding factors.[29]		
Have the authors taken account of the confounding factors in the design and/or analysis?	No (high risk of bias)	No (high risk of bias)
EAG comment: **CHAMPION-MG:** OLE data were summarised descriptively (CS Table 9) and analyses do not appear to take into account potential confounding factors. **REGAIN:** No confounding factors have been taken into account in the statistical analyses.[29]		
Was the follow-up of patients complete?	No (unclear risk of bias)	No (unclear risk of bias)
EAG comment: **CHAMPION-MG:** The OLE is ongoing and data were provided in the CS for [redacted] of the [redacted] participants who entered the OLE for the outcomes of change from baseline in MG-ADL total score, change from baseline in QMG total score, change from baseline in MG-QoL15r score and change from baseline in Neuro-QoL Fatigue score at Week 60 (calculated by the EAG from the information available in CS Figures 8, 9, 10 and 11). This equates to data being presented for these outcomes for [redacted] of the OLE participants (percentages calculated by the EAG). It is unclear whether the patients not followed up at the latest data cut would have had different outcomes to those remaining in the study (potentially a type of selection bias). **REGAIN:** As of 31st December 2017, five participants had completed the study, 27 had discontinued and 85 were still continuing the study.[29] We note that at the furthest follow-up points of 104 weeks and 130 weeks, efficacy results for the change in MG-ADL total score, change in QMG total score and change in MG-QoL15 total score are available for between 47 and 51 participants at 104 weeks (41-44% of the 116 patients who were included in the OLE analysis) and for 28 participants at 130 weeks (24% of those who were included in the OLE analysis) (calculated by the EAG, using data in CS Figures 12, 13 and 14). As with the CHAMPION-MG OLE the risk of bias due to incomplete follow up is unclear.		
How precise (for example, in terms of confidence interval and p values) are the results?	Yes – confidence intervals appear moderately precise	No – most confidence intervals appear relatively precise, except for those at Week 130
EAG comment:		

Study name	CHAMPION-MG (yes/no/not clear/N/A)	REGAIN (yes/no/not clear/N/A)
CHAMPION-MG: The presented confidence intervals in CS section B.2.6 appear moderately precise (i.e. they are neither very narrow nor very wide). **REGAIN:** Week 130 confidence intervals appear wide to the EAG, reflecting uncertainty in the precision of the results, and this is probably due to the low numbers of participants with follow-up data at this timepoint (see above). The EAG note that the confidence intervals reflect the degree of precision (random error) but would not include any bias (systematic error) that may be present (e.g. due to the non-blinded nature of the studies as discussed above).		

Appendix 3 EAG critique of statistical methods in the CHAMPION-MG RCT

Analysis populations	
Brief description	**Full analysis set (FAS):** All randomised patients who received ≥1 dose of study drug grouped by randomised treatment arm. **Safety analysis set:** All patients who received ≥1 dose of study drug grouped by treatment actually received for the full randomised comparison period. All patients who received ≥1 dose of ravulizumab after week 26 were included in the OLE study safety analysis set (CS section B.2.4).
EAG comment: CS Figure 7 indicates that all patients received at least one dose of ravulizumab or placebo. However, as missing data were not imputed for outcomes (other than sensitivity analyses using different assumptions about the nature of the missing data being conducted for the primary outcome), the EAG argue that a true intention-to-treat analysis was not used (see detailed risk of bias assessment in Appendix 2). Other than this, the analysis populations appear appropriate.	
Sample size calculations	
Brief description	Total N=160 gives 90% power to reject the null hypothesis of no treatment effect for the MG-ADL change from baseline at 26 weeks.[28]
EAG comment: The sample size calculation appears appropriate. The EPAR for ravulizumab[28] does not identify any concerns regarding the sample size calculation for CHAMPION-MG. The sample size after dropouts exceeded that required for the stated statistical power.	
Methods to account for multiplicity	
Brief description	Multiplicity was addressed by hierarchical testing of secondary outcomes (CS Table 9). The trial publication[24] states that ~~a~~ two-sided type I error rate (alpha 0.05) was used and that “no inferences should be drawn from results after the failure of statistical significance in the hierarchy”.
EAG comment: Hierarchical testing is a commonly-used approach to account for multiple testing but no rationale is provided for the specific approach used or for the order of the secondary outcomes in the hierarchy. Note that sensitivity and subgroup analyses were not adjusted for multiple testing.	
Analysis of outcomes	
Brief description	Mixed model repeated measures (MMRM) analysis was used for the primary outcome and all continuous secondary and exploratory outcomes using all available longitudinal data regardless of whether patients received a rescue therapy. Covariates were the outcome baseline value, treatment arm, visit date, and region. The MG-ADL 3-point and QMG 5-point responder analyses followed a broadly similar approach[24] (CS Table 9).
EAG comment: The overall analysis approach appears appropriate. However, of the demographic baseline characteristics available, only region was included as a covariate (in addition to treatment, outcome and visit covariates) (CS Table 9). No rationale is provided for why region was included as a covariate, given that region did not influence outcomes according to subgroup analyses (CS section B.2.7). And no explanation is given in the CS, CSR or trial publication why other baseline variables were not adjusted for, such as patient age and MGFA disease class - which differed between the trial arms (section 3.2.2.2.1) - or other key variables such as rescue medication or prior immunosuppressant therapy. The EAG are therefore uncertain whether analysis results may have been influenced by the choice of variables adjusted for. Sensitivity analyses to explore the impact of different baseline covariates could have been conducted but are not among the sensitivity analyses listed in CS Table 9.	
Handling of missing data	

Brief description	Missing data were not imputed for the primary analysis (CS Table 9) and data were assumed to be missing at random (MAR).[24] Pre-specified sensitivity analyses tested plausibility of the MAR assumption (see "sensitivity analyses" below in this table).
EAG comment: Missing data were not imputed. The company conducted sensitivity analyses to test the robustness of the MAR assumption underpinning the primary analysis (see next section below) which appear appropriate in principle but were described very superficially (see next section).	
Sensitivity & post-hoc analyses	
Brief description	Two sensitivity analyses which were pre-specified[24] are mentioned in the CS (CS Table 9), both of which tested the robustness of the MMRM analysis to missing data: a "placebo-based" analysis using data missing not at random, and a tipping-point analysis. The shift parameter in the tipping point analysis was 6.5 points but the company do not explain how they interpreted this. Due to superficial reporting the EAG are unclear whether these sensitivity analyses were conducted appropriately. Further pre-specified sensitivity analyses were conducted which: excluded the randomisation stratification factor; included rescue therapy; used a per-protocol analysis; and used a modified FAS analysis population excluding patients who were significantly affected by the COVID-19 pandemic.[24] The CS does not explain why results of the COVID-19 sensitivity analysis are only reported for one, secondary, trial outcome (the MG-QoL15r total score) (CS section B.2.6.1.4). We assume this was because it was the only outcome for which the sensitivity analysis influenced the result, changing a non-significant effect of ravulizumab on the MG-QoL15r total score to a statistically significant one when patients affected by COVID-19 were excluded.[24]
EAG comment: Sensitivity analyses to test robustness of the primary analysis MAR assumption for missing data in CHAMPION-MG are, in the opinion of the EAG, described superficially in the CS, CSR and trial publication, making the interpretation unclear.	

Appendix 4 Company corrections to model at clarification response

Table 38 Company corrections to the model in the clarification response

Question	Sheet	Cell	Previous value	Update
CQ B8	TTD Data	G65:I75	N/A	Added goodness of fit statistics for CHAMPION-only TTD extrapolations
	Settings	G56	Yes	Changed to No in order to reflect the base case utility regression
	AEs	Q16	2.4	Changed to 2.5 to align with the cited source
	Drug costs	G17	3600	Corrected to 3000
	Drug costs	I18:I20		Updated to EAG's identified costs
	Drug costs	I33, L33 and M33		Set equal to I34, L34 and M34
	Clinical event costs	N13:N15		Updated to mean values identified in HCRU survey
CQ B7	Clinical	D55	4.5	4.47 corrected to match value in source (Alshekhlee 2009)
	Clinicl datastore	C128		Updated formula to remove #N/A errors
	Parameters	N163:O164	blank	Added upper and lower bounds
	Parameters	Column E		Corrected the DSA index
	Parameters	N193:O194		Corrected upper and lower bounds
	Traces	Column EC	IF(perspective_code_live=2,#REF!,0)	Removed the societal cost addition as these are no longer available in the model
	Traces	Column DY	CHOOSE(HSU_cost_code_live,cost_health_care_per3m_micro,cost_health_care_per3m_mean	Changed to only microcosting as we no longer have an aggregate available
CQ B3	Clinical datastore	C5-E10	Various	Baseline characteristics changed to match CQ Table 4. Note % female for CHAMPION-MG differs from CS Table 8 (and CSR Table 9)

Single Technology Appraisal

Ravulizumab for treating generalised myasthenia gravis [ID4019]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 12 June 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Minor clarifications – clinical section

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report that approximately 15% to 20% of patients with MG experience a myasthenic crisis based on one study; however, the company submission identified a number of studies, which suggested that this estimate ranged from 15% to 30% of patients with MG. [Page 10 of the EAG report] The EAG describe estimates of patients with gMG who are refractory to treatment as being from a UK Clinical Practice Research Datalink study of primary care records (Harris et al. 2022). The estimate provided suggests 5% to 15% of patients with gMG are refractory to conventional	Update this statement to: Approximately 15% to 30% of patients with MG experience a myasthenic crisis[12, 59, 61, 62, 68-77] Update reference to reflect primary sources, which were studies conducted in the US, India and Japan: • Boscoe AN, et al. Impact of refractory myasthenia gravis on health-related quality of life. J Clin Neuromuscul Dis. 2019;20(4):173-81. • Engel-Nitz NM, et al. Burden of illness in patients with treatment refractory myasthenia gravis.	Minor issue. The statement could be amended to provide a more thorough estimate of the proportion of patients with MG who experience myasthenic crisis. While this is a minor amend, it is important to reference the primary sources for this estimate range.	Not a factual inaccuracy. The EAG report cites the recent BMJ Best Practice reference which is also cited by the CS (ref 61) and should be more relevant to this appraisal than the 13 other non-UK studies cited in the CS. The EAG's clinical experts did not raise any concerns about the accuracy or generalisability of these data. In any case, only one of the 14 studies cited by the CS (ref 74) gives a rate of 20% to 30% (the other studies, where reported, all give a rate of 15% to 20%). No source of the 20% to 30% rate of MG crises is specified in ref 74 (yet that paper also gives a MG crisis rate of 15% to 20%, citing two prior papers). Therefore, the EAG disagree with the company's response here that "*the company submission identified a number of studies, which suggested that this estimate*

treatment, and the way this sentence is written suggests that these estimates come from a UK population. [Page 10 of the EAG report]	Muscle Nerve. 2018;58(1):99-105. • Murai H, et al. Clinical burden and healthcare resource utilization associated with myasthenia gravis: Assessments from a Japanese claims database. Clin Exp Neuroimmunol. 2019;21:1-8. • Sudulagunta SR, et al. Refractory myasthenia gravis – clinical profile, comorbidities, and response to rituximab. Ger Med Sci. 2016;14:Doc 12. • Suh J, et al. Clinical characteristics of myasthenia gravis patients. Yale J Biol Med. 2013;86(2):255-60. The Harris et al. 2022 CPRD study included 66 patients with refractory gMG and 1,083 patients with non-refractory gMG. Therefore you could feasibly suggest that ~6% is a more reasonable estimate of the refractory gMG population in the UK.	Minor clarification.	*ranged from 15% to 30% of patients with MG*". The EAG could not locate the MG crisis rate data in CS refs 12, 62, and 69. The EAG are unclear why the company are providing references in the bullet list here relating to Indian, Japanese and US populations given that more recent and relevant UK data are available. Regarding the CPRD data, 6% refractory as suggested by the company is consistent with the 5% to 15% range stated on EAG report page 10, so no change is necessary. No changes made.
In Table 7 of the EAG report (page 44), the p value for the proportion of patients with ≥ 5 point	Remove 'p-value not reported'		Thank you for highlighting this discrepancy. We have removed the text in EAG Report Table 7 as suggested.

improvement in QMG is reported for the adjusted analysis and subsequently described as not reported.			

Issue 2 Minor clarifications – economic section

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report: Ravulizumab for treating generalised myasthenia gravis (ID4019). Section 4.2.3.1	The EAG note that patients enter the model with a mean MG-ADL score of 9.5. This should be 9.53.		Not a factual inaccuracy. The EAG note that the company model used an estimate of 9.498 for the baseline MG-ADL score, which was rounded to 9.5 in our report. The suggested estimate of 9.53 in the FAC is incorrect. No changes made.
A publication by Alshekhlee is in incorrectly referenced as Alsgekhlee in Section 4.2.3.5	Correct spelling		Thank you for highlighting this. The spelling has been corrected on page 75.

Issue 3 Exclusion of rituximab as a relevant comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG raised the exclusion of rituximab as a relevant comparator as a key uncertainty in Table 11. We would recommend including some further clarification as to why we do not believe rituximab to be a relevant comparator.	The company claim rituximab is not a relevant comparator and have excluded it from their decision problem for several reasons: • Rituximab does not have marketing authorisation in gMG • According to international guidelines, rituximab is recommended for use in anti-MuSK-antibody-positive gMG, and the efficacy in anti-AChR-antibody-positive gMG is uncertain • The company conducted an ITC feasibility assessment, which found that only 1 Phase II study, BeatMG, was eligible, and would require too much reweighting of baseline characteristics and a reduced sample size BeatMG investigators concluded rituximab would show low probability of clinical effect in Phase III trials	The table does not reflect the clarifications previously provided by the company.	Not a factual inaccuracy. EAG Report Table 11 provides concise statements of the key conclusions; it is not intended as a repetition of the detail provided in earlier sections. The key point is that both the EAG's clinical experts use rituximab and agreed that it is a relevant comparator. We also note that whilst rituximab is more effective in MuSK antibody-positive patients, NHS England do not exclude the use of rituximab for AChR antibody-positive patients in their clinical commissioning guidelines for rituximab biosimilars (CS ref 109). The company's ITC feasibility assessment is not mentioned in the CS, appendices, or clarification responses so the EAG have no information about this to consider. No changes made.

Issue 4 Inclusion of eculizumab in the technology appraisal

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Additional context missing from the Table 11 summary of the EAG's clinical evidence conclusions regarding the inclusion of eculizumab	A matched-adjusted indirect comparison (MAIC) was conducted comparing the change from baseline in MG-ADL between ravulizumab and eculizumab, which found no statistically significant difference between the two therapies. The similarity of ravulizumab and eculizumab has previously been demonstrated and accepted in NICE TA698 and TA710.	Table 11 omits a key piece of evidence around this issue	Not a factual inaccuracy. EAG Report Table 11 states that an ITC was conducted by the company. The table also states that "*Due to methodological limitations of the ITC, results are highly uncertain and do not provide convincing evidence of similar clinical effectiveness of these therapies"*. We disagree that TA698 and TA710 "demonstrate" similarity of ravulizumab and eculizumab since these NICE committee opinions acknowledge uncertainty in whether the drugs have similar efficacy. Furthermore, these appraisals were not on neurological disorders so their generalisability to MG is uncertain. No changes made.

Issue 5 Estimation of the incidence of acute clinical events

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
When describing Key Issue 5 (section 1.5) the EAG notes "It has not been demonstrated that these therapies *[ravulizumab and eculizumab]* have similar effects".	As described in Issue 3, a matched-adjusted indirect comparison (MAIC) was conducted comparing the change from baseline in MG-ADL between ravulizumab and eculizumab, which found no statistically significant difference between the two therapies.	The note should be amended to reflect that statistical analysis exploring this relationship has been conducted and provided supportive results.	Not a factual inaccuracy. The EAG's rationale for concluding that the MAIC results are uncertain and therefore do not provide convincing evidence that ravulizumab and eculizumab have similar clinical efficacy is clearly stated in EAG Report sections 3.3 to 3.5 and summarised in Key Issue 1. The wording of Key Issue 5 is consistent with this. No changes made.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ravulizumab for treating refractory antibody positive generalised myasthenia gravis [ID4019]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Thursday 20 July**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Alexion Pharma UK Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	I am an employee of Alexion Pharma UK
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	none

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Alexion recognises that, with the available evidence and the current level of discount, ravulizumab would not be considered cost-effective according to NICE willingness-to-pay thresholds. Increasing the simple PAS discount to the level where ravulizumab meets the NICE willingness-to-pay threshold is not financially viable. To provide patients with gMG access to ravulizumab, Alexion is currently in discussions with NHS England to develop a commercial access agreement that accounts for the benefit ravulizumab already provides for patients with aHUS [TA710] and PNH [TA698]. This agreement is expected to result in a discount of [redacted]% on ravulizumab list price across the gMG indication.

This level of discount results in the company base case ICER being reduced from [redacted]/QALY to [redacted]QALY. The discount reduces the EAG ICER from [redacted]/QALY to [redacted]. The results presented from this point forward are presented using this revised discount, which would be cost effective at a willingness-to-pay threshold of £30,000/QALY, and are subject to approval of Alexion's commercial offer by NHS England

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Exclusion of rituximab from the company's decision problem	No	Ravulizumab is indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-AChR antibody-positive. There is little robust

		trial data that supports the use of rituximab in anti-AChR antibody-positive patients; most evidence is available in anti-muscle-specific kinase (MuSK) antibody-positive populations. Current understanding, based on available data and clinical input, demonstrates that rituximab is not as effective in patients who are anti-AChR antibody-positive compared with patients who are anti-MuSK antibody positive. Therefore, rituximab is used primarily for patients with anti-MuSK antibody-positive gMG, and for this reason, clinical input received by the company indicated that rituximab would not be considered a relevant comparator to ravulizumab within its licensed indication. According to the NHS England Clinical Commissioning Policy statement published in 2018 on the use of rituximab biosimilars for the treatment of gMG, rituximab is also used in later lines of therapy "*as a last resort for patients who have received all other treatment options"*. In addition, as stated in the company submission, studies supporting the effectiveness of rituximab in refractory gMG are mostly in the form of case reports, open-label studies and retrospective analyses involving small numbers of patients. Therefore, even were rituximab to be considered a relevant comparator, there are no appropriate data available for comparison to ravulizumab in the population of interest for this appraisal.
Uncertain relevance of eculizumab	No	For clarification, the company are not positioning eculizumab as a relevant comparator for this appraisal, noting that this has not been approved by NICE, is not used in clinical practice in the UK, and was not included in the scope for this appraisal. However, the company are aware of the uncertainty surrounding long-term outcomes with ravulizumab, based on the data that are currently available. In order to reduce some of this uncertainty, long-term data for eculizumab have been used as a proxy to represent long-term outcomes with ravulizumab. As eculizumab and ravulizumab have the same mechanism of action and over 99% homology, it is expected that ravulizumab would have at least similar long-term effects – this has been confirmed in discussions with clinical experts. In fact, as ravulizumab was engineered from eculizumab to have a longer half-life and has benefits in terms of its dosing schedule providing greater complement inhibition, long-term outcomes with ravulizumab would be expected to be improved. Therefore, the use

<table>
<tr><td></td><td></td><td>of long-term eculizumab data in place of long-term ravulizumab data would be considered a conservative approach.</td></tr>
<tr><td>Timing of Myasthenia Gravis Activities of Daily Living scale (MG-ADL) response assessment</td><td>No</td><td>The company has updated the functionality of the cost-effectiveness model so that non-response at 16-weeks in ravulizumab patients can be assessed using MG-ADL data from CHAMPION at 18-weeks or 26-weeks. This functionality is independent to the controls related to the time when patients discontinue ravulizumab.
The distribution of ravulizumab patients by change in MG-ADL score from baseline at 18- and 26-weeks in CHAMPION is summarised in the table below.

<table>
<tr><th>Change in total MG-ADL score</th><th>Distribution of ravulizumab patients at 18-weeks</th><th>Distribution of ravulizumab patients at 26-weeks</th></tr>
<tr><td>Change < 3</td><td>46.50%</td><td>41.90%</td></tr>
<tr><td>3 ≤ Change < 4</td><td>53.50%</td><td>58.10%</td></tr>
<tr><td>4 ≤ Change < 5</td><td>44.20%</td><td>45.30%</td></tr>
<tr><td>5 ≤ Change < 6</td><td>36.00%</td><td>34.90%</td></tr>
<tr><td>6 ≤ Change < 7</td><td>27.90%</td><td>24.40%</td></tr>
<tr><td>7 ≤ Change < 8</td><td>15.10%</td><td>14.00%</td></tr>
<tr><td>Change ≥ 8</td><td>7.00%</td><td>9.30%</td></tr>
<tr><td colspan="3">Key: MG-ADL, Myasthenia Gravis Activities of Daily Living scale.</td></tr>
</table>

The timing of the MG-ADL readout from CHAMPION and REGAIN controls the dataset that is used for the clinical event regressions, with patients who did not achieve a 3-point MG-ADL response at the selected timepoint removed from the dataset. This control is independent of when the stopping rule is implemented in the model. This means that the model can implement assessments at 16-weeks using the 26-week data collection from CHAMPION, if required. Employing this</td></tr>
</table>

		scenario, with the 26-week data used to assess patients for a 16-week stopping rule, results in the ICER shifting from [redacted]/QALY to [redacted]/QALY. The company recognises that only using data up to 16-weeks means that some of the randomized follow-up period from CHAMPION is not used. However, we believe this is the best reflection of the data that would be available to a physician in clinical practice.
Time on treatment extrapolations	No	The company acknowledges that there is uncertainty regarding long-term time on treatment extrapolations for ravulizumab used in the cost-effectiveness model. However, the time on treatment data from CHAMPION and from CHAMPION pooled with REGAIN provided in this submission constitutes the best available evidence for this indication. The EAG agreed that the exponential model provided the best fit to the data from CHAMPION but Clinical advice they received suggested that time on treatment may have decreasing hazards over time. The company accepts there is uncertainty around the long-term hazard profile. We believe that the selection of the exponential model, and therefore assuming a constant hazard of discontinuation, is well supported by the fact that the exponential model provides the best fit to the CHAMPION-MG data and the pooled CHAMPION-MG and REGAIN analysis. We do not believe any further analyses can be provided to alleviate this uncertainty, therefore the company maintains its preferred position of modelling time on treatment with an exponential model fitted to pooled CHAMPION and REGAIN data. This is despite the selection providing a slightly more-conservative ICER than CHAMPION alone, as preferred by the EAG ([redacted]/QALY and [redacted]/QALY).
Estimation of the incidence of acute clinical events	No	When developing the clinical event Poisson regressions we were conscious of the small number of event that the regression model could leverage. We were also cautious about over-fitting the model. As a result we focused our analyses on a handful of key variables: • MG-ADL score

- Treatment
- Experiencing a clinical event within 3-months

The fit of each model was primarily assessed on the broadest data set, pooled 60-week CHAMPION and 26-week regain data. Once the preferred method was selected the model's fit to data sets with only patients who had a change in MG-ADL > 3 beyond 16 or 26 weeks was assessed.

We initially tested models that used either treatment or MG-ADL along with a covariate for a prior clinical event within 3 months. All covariates were statistically significant in either model, but the approach using treatment was preferred based on a better statistical fit. A clear placebo effect was also observed in the SoC arm of CHAMPION and we believe using MG-ADL to model crises would exacerbate this effect's impact on model results, creating more uncertainty.

Clinical events Poisson regression on treatment arm and prior clinical event within 3 months, Pooled CHAMPION 60-week and REGAIN 26-week data

Parameter	Coefficient	SE	P
(Intercept)	-1.2858	0.1911	< 0.001
C5 inhibitor vs. PBO	-0.6633	0.2207	0.002
Prior clinical event within 3 months	2.6578	0.2195	< 0.001
Model summary			
n events	85		
Person-years	246.2806		
AIC	25.5857		

Clinical events Poisson regression on MG-ADL and prior clinical event within 3 months, Pooled CHAMPION 60-week and REGAIN 26-week data

Parameter	Coefficient	SE	P
(Intercept)	-2.7144	0.2522	< 0.001
MG-ADL	0.1411	0.0228	< 0.001

Prior clinical event within 3 months	2.3270	0.2266	< 0.001
Model summary			
n events	85		
Person-years	246.2806		
AIC	131.9886		

After selecting treatment as the primary driver for analysing clinical events, we assessed whether to include the prior clinical events in the Poisson regression model. We assessed this on datasets with patients who did not achieve a 3-point MG-ADL response at 16-weeks, or at 26-weeks, removed.

Clinical events Poisson regression on treatment arm and prior clinical events within 3 months, pooled CHAMPION 60-week and REGAIN 26-week data (excluding patients in the C5-inhibitor arm who do not achieve a 3-point MG-ADL response at week 18 in CHAMPION or week 16 in REGAIN)

Parameter	Coefficient	SE	P
(Intercept)	-1.2521	0.2119	< 0.001
C5 inhibitor vs. PBO	-1.4341	0.4179	< 0.001
Prior clinical event within 3 months	2.5971	0.2807	< 0.001
Model summary			
n events	54		
Person-years	166.5079		
AIC	21.7350		

Clinical events Poisson regression on treatment arm, pooled CHAMPION 60-week and REGAIN 26-week data (excluding patients in the C5-inhibitor arm who do not achieve a 3-point MG-ADL response at week 18 in CHAMPION or week 16 in REGAIN)

Parameter	Coefficient	SE	P
(Intercept)	-0.5458	0.1459	< 0.001
C5 inhibitor vs. PBO	-1.9554	0.4051	< 0.001
Model summary			
n events	54		
Person-years	166.5079		
AIC	13.4992		

Clinical events Poisson regression on treatment arm and prior clinical events within 3 months, pooled CHAMPION 60-week and REGAIN 26-week data (excluding patients in the C5-inhibitor arm who do not achieve a 3-point MG-ADL response at week 26)

Parameter	Coefficient	SE	P
(Intercept)	-1.2971	0.2163	< 0.001
C5 inhibitor vs. PBO	-1.4128	0.4187	< 0.001
Prior clinical event within 3 months	2.6778	0.2815	< 0.001
Model summary			
n events	54		
Person-years	167.5428		
AIC	22.4847		

Clinical events Poisson regression on arm, pooled CHAMPION 60-week and REGAIN 26-week data (excluding patients in the C5-inhibitor arm who do not achieve a 3-point MG-ADL response at week 26)

Parameter	Coefficient	SE	P
(Intercept)	-0.5458	0.1459	< 0.001
C5 inhibitor vs. PBO	-1.9674	0.4051	< 0.001
Model summary			
n events	54		
Person-years	167.5428		
AIC	13.4992		

Assessing on either dataset, with non-responders removed at either 16 or 26 weeks, the simple model provides an improved statistical fit compared to the model that also includes the prior event within 3-months covariate, showing a significant improvement in the AIC statistic. However, assessing a best-fitting model is subjective and the regression models including the prior events covariate could be considered appropriate given the covariate has a statistically significant p-value. Therefore, the company has incorporated this model into its revised base case.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Half-cycle correction	Section 4.2.2.1 Page 73	No	The company agrees with the EAG that half-cycle correction may be beneficial given the 3-month cycle length. The model structure is not ideally suited to having a half-cycle correction incorporated, but the company has implemented the methodology in the hope of reducing uncertainty resulting from the cycle-length.
Additional issue 2: EAG corrections	Section 5.3	No	The company accepts the following technical corrections implemented by the EAG and has incorporated them into the updated base case: • Percentage females in CHAMPION • SOC drugs in UK clinical practice • Implementation of disutility for nasopharyngitis • Correction to survival estimates

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Company base case results	**Incremental QALYs:** [redacted] **Incremental costs:** [redacted] **ICER:** [redacted]/QALY		
Additional issue 2: EAG corrections		Included the technical corrections outlined in section 2. Incremental QALYs: [redacted] Incremental costs: [redacted]	Revised ICER: [redacted]/QALY Change from base-case ICER: [redacted]/QALY
Key Issue 5: Estimation of the incidence of acute clinical events	Modelled the incidence of clinical events using a Poisson regression using treatment as the sole covariate	Included a covariate for prior clinical events in the Poisson regression Incremental QALYs: [redacted] Incremental costs: [redacted]	Revised ICER: [redacted]/QALY Change from base-case ICER: [redacted]/QALY
Additional issue 1: Half-cycle correction	No half-cycle correction	Half-cycle correction incorporated	Revised ICER: [redacted]/QALY

		Incremental QALYs: [redacted] Incremental costs: [redacted]	Change from base-case ICER: [redacted]/QALY
Company's base case following technical engagement (or revised base case)		Incremental QALYs: [redacted] Incremental costs: [redacted]	Revised ICER: [redacted]/QALY

Sensitivity analyses around revised base case

Table 5 Probabilistic sensitivity analysis of company's base case following technical engagement

	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Usual care	[redacted]	[redacted]	[redacted]				
Ultomiris	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1: Cost-effectiveness plane - company's base case following technical engagement

Figure 2: Tornado diagram of the 10 most impactful parameters on the ICER

Alexion response to additional information request: Myasthenia gravis (generalised) - ravulizumab [ID4019] received 17 August 2023

Follow-up question	Does this response contain new evidence, data or analyses?	Response
The company base-case currently incorporates a 16-week response assessment for ravulizumab, using 18-week data, with 18-week data also used to extrapolate long-term outcomes. At technical engagement, the EAG requested a scenario analysis retaining the 16-week assessment (based on 18-week data), combined with 26-week data for estimating long-term treatment effect (and utility) for patients continuing ravulizumab. It appears there was a misunderstanding between the EAG and the company, with the company then providing an option within the model to estimate the proportion of patients discontinuing at a 16-week response assessment using either 18-week or 26-week data. Please would you be able to provide the scenario requested by the EAG, to allow committee to assess the impact of this change on the cost-effectiveness?	No	We apologies for the misunderstanding and have conducted the analysis requested. We would also like to clarify how the data is utilised in the model as the question gives the impression that data beyond 18-weeks is not used in the ravulizumab arm. In the company base case, it is only the data of patients who fail to achieve a 3-point change in MG-ADL from baseline that are removed from the dataset used to fit the Poisson regression model. The model includes all of the data for patients who achieved the 3-point change in MG-ADL from baseline. This is so that the patient outcomes of those receiving ravulizumab in our dataset are aligned with the modelled costs. The utility regressions are fitted to all of the data from the CHAMPION 26-week follow-up (and REGAIN in the company base case). We do not remove patients from this analysis as the regression is primarily driven by MG-ADL and the data of patients who failed to respond to treatment are still relevant to the analysis, simply providing examples of higher MG-ADL scores. In the ravulizumab arm patients are then assigned to the MG-ADL substates based on their MG-ADL score at 16-weeks, when they would be assessed in clinical practice. The midpoint MG-ADL score of each substate is then used in the aforementioned regression model to estimate a patient's utility in each cycle. We have provided two scenarios, with the base case results presented in Table 1 for context. In both scenarios a patient's response is measured at 16 weeks (using 18-week data from CHAMPION and 16-week data from REGAIN) and patients are assigned to the MG-ADL substates accordingly. The utility regression are fitted to all of the data from 26-week data from CHAMPION and REGAIN. The difference in each scenario is the data available for fitting the Poisson regression model for estimating the number of clinical events. In the first scenario (Table 2) the data of patients who did not achieve the 3-point reduction in MG-ADL at 26-weeks are

removed from the dataset that the Poisson regression model is fitted to. In the second scenario (Table 3) all of the data from the 60-week follow-up of CHAMPION and the 26-week follow-up of REGAIN.

Table 1: Base-case deterministic results removing patients who do not achieve the ravulizumab stopping rule at 18-weeks

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	£60,207	18.57	10.08				
Ravulizumab	[redacted]	18.55	10.98	[redacted]	-0.02	0.90	[redacted]

Key: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALYs, quality-adjusted life years.

Table 2: Deterministic results removing patients who do not achieve the ravulizumab stopping rule at 26-weeks

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	£58,594	18.58	10.08				
Ravulizumab	[redacted]	18.56	10.98	[redacted]	-0.02	0.90	[redacted]

Key: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALYs, quality-adjusted life years.

Table 3: Deterministic results with all patients included

		<table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Inc. costs (£)</th><th>Inc. LYG</th><th>Inc. QALYs</th><th>ICER (£/QALY)</th></tr><tr><td>SoC</td><td>£60,613</td><td>18.57</td><td>10.08</td><td></td><td></td><td></td><td></td></tr><tr><td>Ravulizumab</td><td>[redacted]</td><td>18.54</td><td>10.97</td><td>[redacted]</td><td>-0.03</td><td>0.90</td><td>[redacted]</td></tr><tr><td colspan="8">Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.</td></tr></table> We believe that both of these scenarios are methodologically inferior to the base case. In the base case approach, the data used to estimate the long-term frequency of clinical event reflects the patients who will be expected to receive ravulizumab long-term in clinical practice As a result, the analysis is not skewed by patients who, in clinical practice, would have been taken off treatment after only two cycles.
The company base-case currently uses a Poisson regression (with 'treatment' and 'prior clinical event' as covariates) fitted to pooled data from the CHAMPION-MG and REGAIN trials to estimate the incidence of acute clinical events. Please would you be able to provide a scenario analysis using a Poisson regression (with 'treatment' and 'prior clinical event' as covariates) fitted to CHAMPION-MG trial data only to calculate the incidence of acute clinical events? As before, this will allow the committee to assess the impact of this change on the cost-effectiveness.	Yes	Regression models using CHAMPION 60-week data only are presented in Table 4 and **Table *5***. We have provided the company base case assumption, with the data of patients who did not respond to ravulizumab at 18-weeks removed from the dataset. We have also include the model fitted to the dataset without patients who did not respond at 26-weeks, in line with the EAG's prior request. <table><tr><th>Parameter</th><th>Coefficient</th><th>SE</th><th>P</th></tr><tr><td>(Intercept)</td><td>-1.3528</td><td>0.2859</td><td>< 0.01</td></tr><tr><td>C5 inhibitor vs. PBO</td><td>-1.4012</td><td>0.5130</td><td>< 0.01</td></tr><tr><td>Prior clinical event within 3 months</td><td>2.5650</td><td>0.3776</td><td>< 0.01</td></tr><tr><td colspan="4">Model summary</td></tr><tr><td>n events</td><td colspan="3">31</td></tr><tr><td>Person-years</td><td colspan="3">118.1875</td></tr><tr><td>AIC</td><td colspan="3">20.2711</td></tr></table>

Table 4: Clinical events Poisson regression fitted to CHAMPION 60-week data only, excluding patients in the ravulizumab arm who did not achieve a 3-point MG-ADL response at week 18

Parameter	Coefficient	SE	P
(Intercept)	-1.3217	0.2789	< 0.01
C5 inhibitor vs. PBO	-1.2675	0.4724	< 0.01
Prior clinical event within 3 months	2.5078	0.3695	< 0.01
Model summary			
n events	32		
Person-years	116.5804		
AIC	20.3085		

Table 5: Clinical events Poisson regression fitted to CHAMPION 60-week data only, excluding patients in the ravulizumab arm who did not achieve a 3-point MG-ADL response at week 26

Parameter	Coefficient	SE	P
(Intercept)	-1.3528	0.2859	< 0.01
C5 inhibitor vs. PBO	-1.4012	0.5130	< 0.01
Prior clinical event within 3 months	2.5650	0.3776	< 0.01
Model summary			
n events	31		
Person-years	118.1875		
AIC	20.2711		

The deterministic results using these two scenarios are presented in Table 6 and Table 7.

Table 6: Deterministic results - Clinical events Poisson regression fitted to CHAMPION 60-week data only, excluding patients in the ravulizumab arm who did not achieve a 3-point MG-ADL response at week 18

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	£57,059	18.58	10.08				
Ravulizumab	[redacted]	18.56	10.98	[redacted]	-0.02	0.90	[redacted]

Key: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALYs, quality-adjusted life years.

Table 7: Deterministic results - Clinical events Poisson regression fitted to CHAMPION 60-week data only, excluding patients in the ravulizumab arm who did not achieve a 3-point MG-ADL response at week 26

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	£56,064	18.58	10.09				
Ravulizumab	[redacted]	18.56	10.99	[redacted]	-0.02	0.90	[redacted]

Key: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALYs, quality-adjusted life years.

<table>
<tr><th>Follow-up question</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td>Based on the description of these scenarios, it appears that the 18-week MG-ADL data is still used to estimate the proportion of responders at a 16-week assessment, and to assign patients to the 6-month MG-ADL substates. The EAG wanted the latter (assignment of patients to the 6-month MG-ADL substates) to be based on the distribution of MG-ADL change at 26-weeks for the subset of 16-week responders.</td><td>Yes</td><td>We have completed the patient level data analysis and compiled the results in the model. The distribution of change in MG-ADL scores at 26-weeks for those with a change MG-ADL score of ≥ 3 at 18-weeks in CHAMPION is reported in Table 1.

Table 1: MG-ADL score at 26-weeks of patients who responded at 18-weeks
<table><tr><th>Change in total MG-ADL score</th><th>CHAMPION at 26-weeks for those who responded at 18-weeks</th></tr><tr><td>Change < 3</td><td>[redacted]</td></tr><tr><td>3 ≤ Change < 4</td><td>[redacted]</td></tr><tr><td>4 ≤ Change < 5</td><td>[redacted]</td></tr><tr><td>5 ≤ Change < 6</td><td>[redacted]</td></tr><tr><td>6 ≤ Change < 7</td><td>[redacted]</td></tr><tr><td>7 ≤ Change < 8</td><td>[redacted]</td></tr><tr><td>Change ≥ 8</td><td>[redacted]</td></tr><tr><td colspan="2">Key: MG-ADL, Myasthenia Gravis Activities of Daily Living scale.</td></tr></table>
These values were compiled in the model using the approach described in the previous document. Patients in the < 3 MG-ADL score sub-state are now assumed to remain in this state for the duration of the model time horizon.
The results of this scenario are reflected in Table 2.</td></tr>
</table>

Table 2: Scenario deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
SoC	£60,207	18.57	10.08				
Ravulizumab	£[redacted]	18.55	10.73	£[redacted]	-0.02	0.65	[redacted]

Key: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALYs, quality-adjusted life years.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ravulizumab for treating refractory antibody positive generalised myasthenia gravis [ID4019]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Thursday 20 July**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating generalised myasthenia gravis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Jennifer Spillane
2. Name of organisation	National Hospital for Neurology and Neurosurgery, Queen Square UCLH NHS Foundation Trust and Guys and St Thomas' NHS Foundation Trust
3. Job title or position	Consultant Neurologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with generalised myasthenia gravis? ☐ A specialist in the clinical evidence base for generalised myasthenia gravis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for generalised myasthenia gravis?	The main aim is to (1) induce remission or (2) if this is not possible to achieve a state of minimal manifestations where the symptoms of the disease or controlled to a degree that they are not impacting on a patient's activity of daily living or

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	quality of life whilst (3) keeping the burden of treatment /side effects to a minimum
9. What do you consider a clinically significant treatment response? (For example, a reduction in disease activity by a certain amount)	1)In terms of outcome measures, a clinically significant response would be an improvement in MG ADL score of 2 or more or an improvement in QMG of 3 or more 2) Areduction in burden of treatment is clinically significant – eg reduction in prednisolone dose of 30% of total dose or getting the total dose below 15mg is clinically significant as would the ability to stop regular IVIg or regular PLEX. 3)A reduction or cessation in the need for emergency rescue treatments such as IVIg or PLEX or unplanned admissions would be a clinically significant response. 4) From the patient point of view there are various patient specific factors – eg being able to go out for a meal, return to work, read a bed time story to their children that are specific to them. There is often a specific activity that patients can't do when unwell and can do when well – I try to find this out and use it as a marker of effective treatment.
10. In your view, is there an unmet need for patients and healthcare professionals in generalised myasthenia gravis?	The unmet needs are 1) There are a proportion of patients who have refractory disease and don't respond to current tx so have an unacceptable symptom burden with impact on QOL – 15% of patients have super refractory disease 2) Burden of treatment - patients disease may be controlled but they are on high dose steroids with unacceptable side effects 3) Time to improvement – the current treatments often take a long time to take effect meaning that patients have unacceptable symptoms for a long time.
11. How is generalised myasthenia gravis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	The ABN guidelines provide a template for treatment of gMG – they are often used more by general neurologists than by experts. There are broad recommendations that most MG experts would follow

across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	1) Pyridostigmine provides symptomatic relief in some patients and is first line treatment for most patients with MG -however it is rarely sufficient as a sole treatment for those with gMG 2) Thymectomy is indicated for all patients with a thymoma (unless unfit for surgery) and in younger onset (<50yrs – maybe up to 65yr) patients with AchRab positive generalised MG 3) Prednisolone is required when generalised disease is not manageable using pyridostigmine alone - the dose is started low at 5mg and then increased according to symptoms. We always aim for the lowest dose possible to manage symptoms. There is a debate about alternate day vs daily steroids 4) Steroid sparing agents are used if ongoing steroid tx is indicated – some start this when prednisolone is commenced -others wait to see if symptoms relapse after steroids are weaned. – Most patients with gMG will require a steroid sparing agent at some time. Azathioprine is generally 1st line esp in young females, mycophenolate and methotrexate are occasionally used. Ciclosporin, tacrolimus and cyclophosphamide are rarely used 5) Rituximab is indicated for refractory MG, explosive onset MG, MG with frequent relapses and there is a lower threshold for its use in MuSK MG. The effect of Rituximab in AchR MG has been disappointing with a <50% response rate in my opinion especially if it is not used at disease onset. 6) IVIg and PLEX are generally reserved for acute exacerbations though there are a cohort of patients (between 5-10% of total MG population) who require regular IVIG or PLEX as they do not respond to., or are intolerant of other treatments. There are some differences of opinion amongst professionals eg – use of daily vs alternate day steroids etc but overall amongst MG specialists the above pathway is accepted

	There is however a lack of equity across the country - in some areas there is a lack of MG specialist clinic so patients are not seen by an MG expert The impact of Ravulizumab would mean that there is a new option for patients with refractory AchR gMG - patients who have failed currently available treatments would have the option to try a drug with a new mecANSISM of action Also as it is quick acting there would be an option to use it whilst waiting for more traditional oral agents (such as aza, mmf etc) to take effect thus reducing the need for high dose long term steroids, hopefully reducing need for unplanned admissions It would have a potential IVIg /PLEX sparing effect for those currently dep on IVIg and PLEX In summary RAviluzumab could be used in refractory patients and those with severe explosive onset disease or those with an unacceptable burden of treatment.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It should be used in centres with expertise in treating refractory MG and treatment should be initiated by an MG specialist. Ideally centres would have an MG specialist nurse to help coordinate care and do outcome measures but this should not be a pre requisite

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes – it is a different mechanism of action. Trial results are very encouraging and the drug works faster than current drugs – this means that the effect can be ascertained quickly and the drug can be withdrawn if not effective. It is used in Europe – for example in Germany, experience there has suggested that it provides clinically meaningful benefit (based on personal conversations with colleagues there) The mortality of MG is about 3-5% - mainly from crisis. If the risk of myasthenic crisis can be reduced this drug could reduce risk of death I would expect it to improve health related QOL – QOL measures in studies have been encouraging and if it improves symptoms and reduces steroid use//IVIG dependence I would expect HR-QOL to improve
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It would not be effective in MUSK MG given mech of action . It should be effective in AchR positive generalised MG Those with refractory or explosive onset disease have most to gain. Further real world experience is required to see if there are subgroups of patients with AchR gMG who are more likely to respond or if there are any factors that may predict response.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It is an 8 weekly IV infusion so will require health care professional administration (rather than taking an oral tablet) Meningococal vaccination is required before treatment starts

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I would suggest pre and post treatment ADL scores, as well as recording steroid use and use of IVIG and PLEX. AchR ab status should be confirmed before treaetment but all pts with MG would have this done anyway so additional testing is not required.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The burden of treatment related to steroids and steroid related side effects eg bone health, skin integrity, weight gain etc may not be captured. This is important as I'd expect Raviluzumab to have a steroid sparing effect in responders. Unplanned admissions should hopefully be reduced and that data should be captured IVIg use – both regular and emergency should be reduced. There are potential knock on effects for being able to get back to work (up to 50% of MG patients are unemployed)
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes – it is innovative and is a step change. It is directly targeting the complement pathway which is one of the ways that AchR antibodies expert pathogenic effect. This is more specific than the general immunosuppression that current therapies employ.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The risks may include infection (already a problem with agents we use), burden of IV administration (some of these patient will be dependent on IVIG anyway) and the risk of meningococcal infection (patients will need to have meningococcal vaccine before starting treatment)

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The CHAMPION trial and the open label extension can be extrapolated to UK practice – it was a multi centre study amongst 85 centres in 13 countries with 175 pts. The patient population is similar to what we see in UK clinical practice The primary outcome measure was the MG ADL score which is what we tend to use in clinical practice. The OLE study show that efficacy and safety are maintained up to 60 weeks. Vu T, Meisel A, Mantegazza R, Annane D, Katsuno M, Aguzzi R, Enayetallah A, Beasley KN, Rampal N, Howard JF Jr. Summary of Research: Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. Neurol Ther. 2023 Jun 23. doi: 10.1007/s40120-023-00514-4. Epub ahead of print. PMID: 37351816. Meisel A, Annane D, Vu T, Mantegazza R, Katsuno M, Aguzzi R, Frick G, Gault L, Howard JF Jr; CHAMPION MG Study Group. Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension. J Neurol. 2023 Aug;270(8):3862-3875. doi: 10.1007/s00415-023-11699-x. Epub 2023 Apr 27. PMID: 37103755; PMCID: PMC10134722.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No- other than conversations with European colleagues that have had good experience with this rug
22. How do data on real-world experience compare with the trial data?	Im not aware of long team real world data that has been published but from my conversations with European colleagues they say that the results that they seen in clinical practice reflect what was reported in the clinical trials.

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	The main equality issue is equity of access to specialist centres The other issue may be groups of patients may not wish to receive meningococcal vaccine which is a pre requisite to starting treatment.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Exclusion of rituximab from the company's decision problem *The company does not include rituximab as a possible comparator or alternative to ravulizumab*	We would also welcome further clinical opinion on the appropriateness of excluding rituximab. The effect of Rituxiamb in refractory gMG is variable. A Phase II study failed to show a steroid sparing effect of Rituximab in gMG with AchR ab. Nowak RJ, Coffey CS, Goldstein JM, Dimachkie MM, Benatar M, Kissel JT, Wolfe GI, Burns TM, Freimer ML, Nations S, Granit V, Smith AG, Richman DP, Ciafaloni E, Al-Lozi MT, Sams LA, Quan D, Ubogu E, Pearson B, Sharma A, Yankey JW, Uribe L, Shy M, Amato AA, Conwit R, O'Connor KC, Hafler DA, Cudkowicz ME, Barohn RJ; NeuroNEXT NN103 BeatMG Study Team. Phase 2 Trial of Rituximab in Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis: The BeatMG Study. Neurology. 2021 Dec 2;98(4):e376–89. doi: 10.1212/WNL.0000000000013121. Epub ahead of print. PMID: 34857535; PMCID: PMC8793103.

	I think Rituximab is more likely to be effective if used earlier in the disease course as was suggested ty the RINOMAX study- Piehl F, Eriksson-Dufva A, Budzianowska A, Feresiadou A, Hansson W, Hietala MA, Håkansson I, Johansson R, Jons D, Kmezic I, Lindberg C, Lindh J, Lundin F, Nygren I, Punga AR, Press R, Samuelsson K, Sundström P, Wickberg O, Brauner S, Frisell T. Efficacy and Safety of Rituximab for New-Onset Generalized Myasthenia Gravis: The RINOMAX Randomized Clinical Trial. JAMA Neurol. 2022 Nov 1;79(11):1105-1112. doi: 10.1001/jamaneurol.2022.2887. PMID: 36121672; PMCID: PMC9486640. However there is a maximum of 16 week follow up here so long term data are lacing. The effect of Rituximab takes longer to take effect than complement inhibition. Rituximab is more likely to be effective in MusK MG and we know that complement is not implicated in pathogenesis of MusK MG – hence Raviziumab would not be effective here. My personal experience has shown that Rituximab rarely has an IVIg sparing effect in refractory MG and given the length of time it takes to work I do not think that Rituximab and Ravilzumab should be directly compared
Uncertain relevance of eculizumab *The company considers that eculizumab, which has been studied in clinical trials but does not have a recommendation for use in generalised myasthenia gravis, is likely have similar effectiveness to*	I think this is reasonable. Eculizumab and Ravilizumab have the same mechanism of action but Ravilizumab requires 8 weekly rather than 2 weekly dosing. There are no reasons in my mind whey Ravilizumab should be less effective than Eculizumab for gMG.

ravulizumab and uses longer term data on eculizumab where longer term data on ravulizumab are not available	
Timing of Myasthenia Gravis Activities of Daily Living scale (MG-ADL) response assessment *The company uses MG-ADL data from different timepoints for the ravulizumab arm compared with the standard care arm*	I would suggest measuring ADL at baseline and at 4 – 8 weekly intervals. A response should certainly be seen by 16 weeks – if not I would say that Ravilizuamb is not effective (apologies if I'm not answering this question in full – I'm happy to provide more information if needed)
Time on treatment extrapolations *The EAG has concerns about the way the company has modelled (predicted) how many people stay on treatment in the long-term, and whether data on ravulizumab and eculizumab be pooled*	We would also welcome further clinical opinion on the appropriateness of pooling time on treatment data for ravulizumab and eculizumab, and the plausibility of alternative extrapolations. I think that data from Raviliuzmab and Eculaizumab could be pooled given the mechanism of action With regard to how many patients stay on treatment long term; I think that depends on what group you look at. If one is using Ravilizumab in patient previously dependent on IVIG in whom all other treatments have been ineffective it is likely that long term treatment would be needed.

	However if one is using it at the beginning of explosive onset disease or in an acute severe exacerbation as an 'induction' treatment it is likely that treatment could be stopped once the disease stabilises or other treatments (eg traditional immunosuppressant agents take effect) I would suggest that all patients should have a drug pause after 12 months approx. to assess disease severity and to see whether Raviluzimab is still needed – weekly ADLs could be done to assess disease severity – once ADLs begin to increase the drug should be resumed. If a patient fails two drug pauses it is likely that they will require ongoing treatment There may be a subset of patients with extremely brittle disease in whom a drug holiday is not appropriate but that number is likely to be small
Estimation of the incidence of acute clinical events *The EAG has concerns about the way the company has estimated the occurrence of 'exacerbation' and 'crisis' clinical events and that data on ravulizumab and eculizumab is pooled*	MG crisis and MG exacerbation remain frequent clinical events that have an impact on IVIG/PLEX use, steroid use, unplanned admissions etc. These remain clinical problems for patients with MG. Let me know if further data regarding this are required.
Other issues identified by the NICE technical team (not included in the EAR):	

Is intravenous immunoglobulin used as maintenance treatment for those with gMG or is its use restricted to exacerbations or crises?	The majority of MG patients receiving IVIG get it for short term use for acute exacerbations. There is however a small subset of patients who are refractory to all other treatments or who are intolerant of them and this group require regular maintenance IVIg – this group comprises between 5-10% of the total MG population but this is the group in whom we are most likely to consider using Ravilizumab given the known problems with IVIg (cost, availability, need for hospital administration, risk of thromboembolic events etc)
Ravulizumab is given by weekly intravenous infusion (or subcutaneous infusion). Could people with gMG receive ravulizumab at home?	Potentially – we have experience of IV infusions being delivered at home (eg with efgarigimod home care early access scheme)
Are there any important issues that have been missed in EAR?	I think it's important to state that there is the option for drug holidays ie it is not necessarily a long term treatment in all patients.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This is an innovative treatment for patients with gMG (AchR ab positive) that directly targets the effect of the pathogenic antibodies
It has the potential to improve symptoms in those with refractory MG for whom there are limited options
It has the potential to be used as an induction agent in those with severe new onset disease whilst awaiting the onset of action of other traditional immunosuppressant agents
It has the potential to have a steroid sparing and IVIG sparing effect
It seems to work faster than other agents we currently use with effect being seen within weeks – thus the drug can be stopped if not effective

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ravulizumab for treating refractory antibody positive generalised myasthenia gravis [ID4019]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

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A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

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Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

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The deadline for your response is **5pm** on **Thursday 20 July**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with generalised myasthenia gravis

Table 1 About you, generalised myasthenia gravis, current treatments and equality

1. Your name	Amanda Hayes
2. Are you (please tick all that apply)	☒ A patient with generalised myasthenia gravis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with generalised myasthenia gravis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the

	expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with generalised myasthenia gravis? **If you are a carer (for someone with generalised myasthenia gravis) please share your experience of caring for them**	Initially I think you need to know my beginning I was living and working in London when I was diagnosed. I felt unwell and finding it hard to swallow and chew food. I went to my GP and was diagnosed with a virus. Within weeks I had symptoms we now know was MG. I was already under a neurologist. He quickly diagnosed me. I have lived with MG for 31 years. In 1992 the treatments were not as readily available. This meant the first option was Pyridostigmine then Azathioprine. Lastly due to poor control prednisolone. The whole process took over a year. This due primarily due t getting the dosage right. Plasma exchange and IViG were only ever given when you had a crisis or preoperative. Due to poor control of my MG I was medically retired. I was a trainee accountant on my final year of study. It was devastating and to add to this my husband found it hard to cope so we separated and later divorced. Within a year my whole life had changed.

	Living with MG is extremely difficult for me due to the unpredictability of the condition itself. It is a struggle to plan, and you find it physically and mentally challenging. On a good day I could go shopping, housework, meet friends, general socializing. All of this on a good day! On a bad day none of these are possible. It has over the years meant that I let people down time and again. One of the hardest things for me was not being able to pick up my nieces when they were born and being able to play ball games with them. Luckily, over the years I have made 'coping mechanisms' and find these work very well. An example being I still see friends but we have dinner at home. Whether that be ours or theirs. Rather than cooking we always have take out. This means no-one is out of pocket. Eating – My swallow is my main area of weakness and with my speech therapists help I have again devised a 'coping mechanisms'. If cooking, I rest for approximately two hours prior to dinner preparation. Then once dinner is cooked, I find I can manage slightly easier.

	You may say I am lucky as I am retired and can manage the luxury of being able to rest. It is bittersweet. I loved my job but due to the medication in 1992 my MG was badly controlled. Luckily with the support now for those in the workplace, the treatments and support mean that being medically retired would not be their way forward. This brings me on to financially. It is always difficult especially in today's economic crisis and it is a worry. As previously said I was medically retired so am in receipt of a pension. I also receive Employment and Support Allowance. As well as Disability Living Allowance. Along with this I receive the lowest rate of Carers Allowance. This was awarded as I cannot always care for myself. Having to apply for benefits has been difficult over the years. Personal care has also been difficult. At times you cannot lift your hands above your head so washing your hair is impossible. I cannot get into a bath. I cannot sit in one or get into one to use an overhead shower. My second husband and I decided to have a second bathroom installed. We have a walk-in shower so I could see to my personal needs.

	It is demoralizing and mentally challenging to accept help with personal care. It has such a big impact on your general wellbeing. Something often not considered. Someone who one minute is living an independent, high flying lifestyle is then challenged with a condition that is so unpredictable In conclusion: I think I have shown how over the years Myasthenia Gravis has had an impact on my quality of life. That being personal, financial, social and sadly friendships. Lastly and most importantly family. My husband left me quite suddenly so I also understand lack of support is extremely difficult.
7a. What do you think of the current treatments and care available for generalised myasthenia gravis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	As we know the first point of attacking MG is pyridostigmine. A good all-round start to helping to lessen the symptoms of MG. For some it may be all they need. So many go onto the second stage: immunosuppression and steroids. Extremely effective for many of the remaining patients. These do in the long term have quite toxic side effects. I am however under no illusion that biologics do not have side effects.

	The introduction of biologics and plasma exchange has been life changing for so many. Bringing their symptoms under control. Letting them work and have quite normal lives. I say for the majority. I know many who have these biologics and plasma exchanges on regular cycles and their symptoms hold strong. Thus making it possible to work, remain mobile and generally lead as normal life as they can. I know of one patient who has gone on to have two children. Mainly through good control of her symptoms. This is with regular plasma exchange and biologics. 7A & 7B So, it brings me onto the immunoglobulins, the Eculicumab, Rituximab, Efgartigimod etc. With (I believe) the exception of IViG which can be given subcutaneously all of them are infusions. I have a friend who found subcutaneous IViG less effective and is now back onto monthly infusions of IViG. I myself am currently taking Pyridostigmine, Azathioprine, steroids, three plasma exchanges every four weeks. I do have weekly infusions of HyQvia. This however is for the Immunodeficiency disease I have acquired due to the immunosuppression.

	These new treatments can be life changing for so many. Unfortunately they are still not reaching everyone as a regular treatment. Whether cost plays a part in this I am unsure. It may be due to clinician decisions, possible lack of specialist neurologists in that area. I am purely speculating. I conclude by saying these new treatments are indeed life changing but the administering of them can have an impact on quality of life. (See section 8)
8. If there are disadvantages for patients of current NHS treatments for generalised myasthenia gravis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	As I say in 7A & 7B new effective treatments currently appearing on the MG stage are affective and quick to act. Helping some as a prophylactic treatment and importantly those in crisis. Except for IViG (I believe) they all must be given as an infusion. This needs a clinician to administer them. Whether this be in the home or hospital (as an inpatient for some) or on a day care unit. With these treatments needing to be given regularly it can affect your quality of life. The possibility of days off work affecting your income. The knock-on effect could be stress which then can affect your condition and general wellbeing. Childcare issues if you have

	children. These are just two examples of problems that arise from the administration of infusions. One side effect that is not directly due to the medication itself but the administering of it is venous access. I and others who I know have the same problem because of long term infusions. Over time the veins can become fragile and scarred. it makes it difficult to put cannulas in. Especially with plasma exchange where larger cannulas are needed. I have a portacath for this. Even a normal cannula is difficult to access. Long term use of any infusion will, I believe cause venous issues.
9a. If there are advantages of generalised myasthenia gravis over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ravulizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9A Quite simply it is the onset of relief from symptoms. As we know traditional treatment for MG takes time and will potentially take many months to get right. As I have said previously MG is unpredictable and as such making day to day plans difficult. The length of time finding treatment can impact quality of life can be challenging as well as time consuming. Within that time patients will need the support from both family,

	employers and friends. Whether this be to help in the home, take you to hospital visits etc., cook meals or personal care. Employers, the understanding of being unable to fulfil the duties you are there to do and time off for hospital visits and ill health. So in conclusion anything that speeds up the stability of MG must be beneficial. 9B Advantages of the new treatments coming through are the onset of relief of symptoms. These can be quite dramatic and can begin the journey of returning to as normal life as possible. Especially when you live with a neuromuscular disease such as MG. Looking at my own experience of IViG and plasma exchange has meant the reduction of immunosuppression. This is a journey I welcome. I am already experiencing side effects of the steroids and Azathioprine. Both of which have after 30 years caused some other serious problems. I can see the potential for the current treatments coming through.

	9C I assume that the question relates to comparable treatments. The one possible improvement I can see from the literature I have read is the time in which it is shown to control or improve symptoms. Other than that, I (as a lay person) cannot differentiate between then.
10. If there are disadvantages of ravulizumab over current treatments on the NHS please describe these. For example, are there any risks with ravulizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I cannot see that Ravulizumab shows any more or different side effects already attributed to other biologics.
11. Are there any groups of patients who might benefit more from ravulizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I can only comment as a lay person but I am sure this group of treatments can be used for other autoimmune conditions. For example, I am taking immunoglobulins for my Acquired Immunodeficiency Disease. A further example is that of my brother. He currently resides in the United States and is having IViG for his Chronic Inflammatory Demyelinating Polyneuropathy. He has spoken with his neurologist and other Biologics as further treatment are being discussed but as yet in the early stages of discussion.

	I know of others with rheumatoid arthritis who are trying themas an alternative to steroids or the ability to reduce their steroid dose.
12. Are there any potential equality issues that should be taken into account when considering generalised myasthenia gravis and ravulizumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I cannot answer this due to lack of knowledge
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Exclusion of rituximab from the company's decision problem *The company does not include rituximab as a possible comparator or alternative to ravulizumab*	We consider patient perspectives may particularly help to address this issue. *I am confused by the companys need to exclude Rituximab. It is a known effective treatment for MG. it is an infusion. The regimen given in a day unit but sometimes overnight as an inpatient. I just cannot understand why it has not been included. It is a puzzle to me, and I would like to know the reasoning behind it. I know people who are on Rituximab and are happily leading very productive and stable lives.*
Uncertain relevance of eculizumab *The company considers that eculizumab, which*	

has been studied in clinical trials but does not have a recommendation for use in generalised myasthenia gravis, is likely have similar effectiveness to ravulizumab and uses longer term data on eculizumab where longer term data on ravulizumab are not available	
Timing of Myasthenia Gravis Activities of Daily Living scale (MG-ADL) response assessment *The company uses MG-ADL data from different timepoints for the ravulizumab arm compared with the standard care arm*	
Time on treatment extrapolations *The EAG has concerns about the way the company has modelled (predicted) how many people stay on treatment in the long-*	

term, and whether data on ravulizumab and eculizumab be pooled	
Estimation of the incidence of acute clinical events *The EAG has concerns about the way the company has estimated the occurrence of 'exacerbation' and 'crisis' clinical events and that data on ravulizumab and eculizumab is pooled*	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- HAVING LIVED WITH MG FOR OVER 30 YEARS I HAVE SEEN THE QUALITY OF LIFE IMPROVING.
- THIS IS PRIMARILY DUE TO THE NEW TREATMENTS AND READINESS OF CLINICIANS PUTTING PATIENTS ONTO THEM.
- AS THERAPEUTIC MEDICATION MEANS THAT THE GENERAL WELL-BEING OF PATIENTS HAS IMPROVED.
- THERE ARE DOWNSIDES, I BELIEVE THE BIGGEST OF THESE ARE THAT INFUSIONS CAN ONLY BE GIVEN BY CLINICIANS VIA VENOUS ACCESS.
- QUALITY OF LIFE IS IMPACTED DUE TO THIS WAY OF ADMINISTERING THESE TREATMENTS.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ravulizumab for treating refractory antibody positive generalised myasthenia gravis [ID4019]

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Part 1: Living with this condition or caring for a patient with generalised myasthenia gravis

Table 1 About you, generalised myasthenia gravis, current treatments and equality

1. Your name	Tracey Maitland
2. Are you (please tick all that apply)	☒ A patient with generalised myasthenia gravis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with generalised myasthenia gravis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	myaware
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the

	expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with generalised myasthenia gravis? **If you are a carer (for someone with generalised myasthenia gravis) please share your experience of caring for them**	I have lived with myasthenia gravis for 20 years. Over the years the treatments I have been on are pyridostigmine, steroids, Azathioprine, Mycophenolate and Methotrexate & IVIG.
7a. What do you think of the current treatments and care available for generalised myasthenia gravis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a/ There can be many side effects with some of the tablet form of treatments many of them I still suffer from today, yet I haven't taken that medication in 17+ years. I think some of the newer treatments offer less harmful side effects, which lower the risk of developing other conditions and suffering from their long-term side effects, which is a welcomed consequence. The care available for those with MG on the NHS depends on who you see and if you can get an appointment before a crisis becomes inevitable. If the GPs or A&E were more aware of the condition when presenting with problems, diagnosis and treatment would be accessed sooner and hopefully less medication would be needed leading to less side effects, it is very much a postcode lottery in my opinion. b/ I believe my opinions are echoed very strongly amongst those with MG or those living alongside those with MG.
8. If there are disadvantages for patients of current NHS treatments for generalised myasthenia gravis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The disadvantages of the current more common medications (tablets forms) are the number of tablets you must take daily. The number of tablets you take to counteract the side effects of those tablets, and additional tablets for other conditions acquired because of taking the initial medications for MG. Then if after 18-24 months (as in my case) it is decided they are not working, you then start weaning off them and starting again with another option, which includes all the new possible side effects that come with these tablets – you are continually adding to the list. The side effects I personally have been affected by are: arthritis, bone density issues, breathlessness, carbuncles/furuncles, cataracts (both eyes twice), chewing issues, C-PAP machine, Cushing syndrome, diabetes (steroid induced), depression,

	diarrhoea, hair growth, hair loss, high blood pressure, high cholesterol, incontinence (bowel & bladder), migraines, muscle weakness, nail problems, osteoporosis, slurred speech, septic meningitis, sickness, skin thinning/tearing, stretch marks, sweating (excessive), swollen feet/ankles, teeth & gum issues, thrush (oral/vaginal), vomiting and weight gain to name a few – I still live with many of these issues today. I was unable to follow the career path planned. I was unable to have children because of the medication I was taking, their side effects and ongoing issues and how my condition was at the time. I was unable to care for myself for many years, my parents bathed and showered me and took over personal care. I was able to work in a reduced capacity for some time but had to give up when it became too much.
9a. If there are advantages of generalised myasthenia gravis over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ravulizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	a/ If Ravulizumab were able to reduce side effects gained from taking steroids and other immunosuppressants, if it could reduce symptoms of MG, reduce the amount of tablets you have to take and give you more freedom to live, resulting in a better quality of life, I would see that as advantageous. Some would find weekly/bi-weekly or monthly IV treatments extremely beneficial. b/ I would consider the quality of life the most important. c/ I do not know the answer to this currently.
10. If there are disadvantages of ravulizumab over current treatments on the NHS please describe these. For example, are there any risks with ravulizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	a/ If Ravulizumab did not reduce the side effects gained from taking steroids and other immunosuppressants, if it did not reduce symptoms of MG, if it did not improve the quality of life for the patient, I would see that as disadvantageous. Some may not find IV treatments suited to their lifestyle. I do not know enough about the potential side effects to comment.

11. Are there any groups of patients who might benefit more from ravulizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I'm sure medically there would be many arguments for this.
12. Are there any potential equality issues that should be taken into account when considering generalised myasthenia gravis and ravulizumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Only that if someone wishes to have children, they should perhaps be considered separately.
13. Are there any other issues that you would like the committee to consider?	At my highest, I was on 125mg per day of steroids, which caused 8 st weight gain in 3 months, meaning maximum doses of immunosuppressants because of my size. I had terrible side effects and still have additional illnesses I live with today - this because of my condition being wrongly managed. Because of incorrect treatments and side effects my life has been irreparably damaged. I was unable to follow the career path planned. I was unable to have children because of the medication I was taking and the side effects at the time and there long-lasting effects. I was unable to care for myself for many years, my parents bathed and showered me and took over personal care from the age of 28

	years old. I was able to work in a reduced capacity for some time but had to give up when it became too much. Knowledge of the condition and better treatments along with better care would have given me a life I'd dreamed of. Current treatments and lack of care caused the problems I had, and those I still live with today. There must be better options out there.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Exclusion of rituximab from the company's decision problem *The company does not include rituximab as a possible comparator or alternative to ravulizumab*	I would be interested to know why Rituxmab was excluded.
Uncertain relevance of eculizumab *The company considers that eculizumab, which has been studied in clinical trials but does not have a*	

recommendation for use in generalised myasthenia gravis, is likely have similar effectiveness to ravulizumab and uses longer term data on eculizumab where longer term data on ravulizumab are not available	
Timing of Myasthenia Gravis Activities of Daily Living scale (MG-ADL) response assessment *The company uses MG-ADL data from different timepoints for the ravulizumab arm compared with the standard care arm*	
Time on treatment extrapolations *The EAG has concerns about the way the company has modelled (predicted) how many people stay on treatment in the long-term, and whether data on ravulizumab and eculizumab be pooled*	

Estimation of the incidence of acute clinical events *The EAG has concerns about the way the company has estimated the occurrence of 'exacerbation' and 'crisis' clinical events and that data on ravulizumab and eculizumab is pooled*	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The person's treatment should be based on what is best for them which includes their quality of life, not what is the cheapest option for the NHS at the time.
- Treatments should be given with knowledge and consultation, not what just what "worked" for the last patient.
- Treatments should only be given with a clear plan and managed correctly if further medical conditions develop as a negative consequence.
- The side effects and additional conditions acquired because of current medications are and can often be harder to live with and manage then the MG itself.
- We didn't ask for this, please see "us" as a complete person and not "something rare" from a lecture in your past.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

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Single Technology Appraisal

Ravulizumab for treating refractory antibody positive generalised myasthenia gravis [ID4019]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Thursday 20 July**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Myaware & MDUK
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	MDUK has received the following: • £15,000.00 from Roche for sponsorship of the 2021/22 MDUK Muscles Matter virtual seminar series (virtual patient information events) • £5,000.00 from Roche for sponsorship of the 2022 MDUK Neuromuscular Physiotherapists Conference • £5,000.00 from Alexion for sponsorship of the 15th UK Annual Neuromuscular Translational Research Conference • £7,500.00 from Alexion for sponsorship of the 2022/23 MDUK Muscles Matter virtual seminar series (virtual patient information events) Myaware has received no such funding in the past 12 months.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	No links for either respondent.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Exclusion of rituximab from the company's decision problem	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Uncertain relevance of eculizumab	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Timing of Myasthenia Gravis Activities of Daily Living scale (MG-ADL) response assessment	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Time on treatment extrapolations	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Estimation of the incidence of acute clinical events	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1:[None]	Please indicate the section(s) of the EAR that discuss this issue	Yes/**No**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
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Single Technology Appraisal

Ravulizumab for treating refractory antibody positive generalised myasthenia gravis [ID4019]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Neuromuscular Advisory Group (Association of British Neurologists)
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	**nil**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**nil**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Exclusion of rituximab from the company's decision problem	No	• We agree entirely that rituximab should be included in the analysis to reflect real life clinical practice in the UK. Ravulizumab may be used as next step if AZA/MTX is not sufficiently effective (2nd line) but given likely cost difference between this new drug and generic rituximab it is unlikely this will be the pattern of the therapeutic algorithm for most NHS clinicians (therefore 3rd or 4th line more likely). • **We note that this model does not acknowledge the small but clinically and financially significant cohort of refractory MG patients maintained on regular IVIg or plasma exchange.** • We feel this is something worth considering in the cost analysis, as well as other novel therapies (efgartigimod -available to NHS MG patients via the early access scheme) – rendering ravulizumab potentially 5th line (as mentioned).
Uncertain relevance of eculizumab	No	• We do not think you can take eculizumab evidence as a proxy for ravulizumab for all the reasons mentioned in the report. • Importantly, the financial modelling based on eculizumab is open to meaningful inaccuracy because of multiple assumptions of similarity with ravulizumab which are not definitively established, as well as the well described differences in study populations, study design and analysis.

Timing of Myasthenia Gravis Activities of Daily Living scale (MG-ADL) response assessment	No	• Although there is risk of bias and confounding with the MG-ADL score but it is an MG outcome measure which is broadly acceptable and widely used in UK clinical neurology. It is one of the recommended clinical outcome measures in the NHSE IVIg commissioning guidelines. • In a trial setting we believe the timing of assessment is reasonable - baseline and week 26. In clinical practice, we would expect expect earlier evidence of response if ravulizumab was effective in an individual (given the mechanism of action of C5 inhibition and the pathogenesis of MG). **We would recommend assessing for evidence of response at 4 and 8 weeks.** • We would recommend the use of published and validated MCID as meaningful evidence of change. • The clinometrics of this score suggest it is not a perfect biomarker for MG disease activity but it is practical, patient focused and easy to apply in clinical practice. We think this is a sensible choice in this scenario.
Time on treatment extrapolations	No	• We do not think it is appropriate or informative to combine the data from the three trials to extrapolate or model. Longer term post-marketing studies will be needed to truly understand drop-out rates but we suspect 3.7% per month is an overestimate. Rate is lower for treatments with more frequent infusions and higher side effects such as IVIG/PLEX when these interventions are used in the refractory MG cohort. • **We would also like to consider the likelihood of ravulizumab use as an immunomodulatory therapy for MG in real life clinical practice. If we consider it in comparison to alternatives already used in this cohort (regular plasma exchange or IVIG or rituximab) there are no real practical benefits to the individual as infusions are frequent and are performed in the hospital setting. Yet this drug will (at least at introduction) be more expensive than rituximab and possibly equally expensive as plasma exchange or IVIg. However, compared to another novel (probably comparable drug cost): efgartigamod, this drug can**

		be self-delivered over seconds in the home environment and may therefore be preferential to ravulizumab in long-term refractory patients.
Estimation of the incidence of acute clinical events	No	• We agree that this is a less useful measure of responsiveness, prone to bias and feel primary outcome measures of MCID change in MGADL and QMG are more helpful. Other measurable metrics could include need for NGT feeding, NIV and ITU admission/ need for ventilation. • For the reasons already stated, we do not think it is appropriate to pool ravulizumab and eculizumab analysis**.**

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
The model does not consider the use of regular IVIg or PLEX in the management of refractory MG patients.	Page 14, Figure 1	Yes	Algorithm does not fully reflect patients who are refractory with frequent relapses requiring IVIG/PLEX often or as regular maintenance management. Cost of treatment is high and quality of life is affected by treatment side effects and the inconvenience of hospital admission. Novel therapeutics such as ravulizumab are likely to present an impactful alternative therapy in this cohort
Comparison of raviluzimab, efgartigimod, eculizumab efficacy and tolerance.		Yes	These three therapies have comparable roles in 'next step' or adjunctive therapy. It is important for NICE to consider these drugs (whether currently available or potentially soon to be available) in any financial modelling in MG.
Accurate UK based epidemiology		Yes	Note is made of the probable underestimation of frequency of MG in the UK. We would like to bring your attention to a published UK-based population based study in MG which may be helpful in this model: • AS Carr. Actual world epidemiology of Myasthenia Gravis (Chapter 2). In Mineo TC, editor. Novel Challenges in Myasthenia Gravis. Nova Science Publishers, Inc.: 2015;

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Summary of changes to the company's cost-effectiveness estimate(s)

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

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Evidence Review Group Report commissioned by the
NIHR Evidence Synthesis Programme on behalf of NICE

Ravulizumab for treating generalised myasthenia gravis (ID4019)

Evidence Review Group's summary and critique of the company's response to technical engagement

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Date completed	2nd August 2023

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LIST OF ABBREVIATIONS

AIC	Akaike information criterion
EAG	External Assessment Group
ICER	Incremental cost effectiveness ratio
KM	Kaplan-Meier
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living scale
OLE	Open-label extension
PAS	Patient access scheme
QALY	Quality-adjusted life year
RCT	Randomised controlled trial(s)
SoC	Standard of care
TE	Technical engagement

1. Introduction

This document is the External Assessment Group (EAG)'s summary and critique of the response by the company, Alexion, to the key issues for technical engagement (TE) proposed in the EAG report for this appraisal (submitted to NICE on 1st June 2023). The EAG received the company's response on 21st July 2023.

The company's TE response form contains the following information:

- A written response to each of the five key issues, (see Table 1). Although the company indicate that none of these responses include new evidence or analyses, they have revised the model and report an additional analysis related to key issue 3.
- A brief summary of two additional issues noted by the company, with an amendment to the model for the first of these issues (see Table 1).
- A set of updated cost-effectiveness results, incorporating:
    - An updated confidential Patient Access Scheme (PAS) price discount of [redacted] on the ravulizumab list price for the generalised MG indication, which the company expect to result from ongoing discussions on a commercial access agreement with NHS England.
    - A revised company base case and sensitivity analyses (TE response Tables 4 and 5 and Figures 1 and 2).
- An updated version of the company's economic model accompanies the response form.

In this report we present the following:

- Our critique of the company's response to each of the five key issues for technical engagement and the two additional issues noted by the company (Section 2).
- A validation of the results of the company's updated cost-effectiveness analysis, and the results of an updated EAG base case and scenario analyses (Section 3).

The cost-effectiveness results in this report are calculated using the updated PAS discount estimate for ravulizumab and publicly available list prices for all other medications. Results using confidential price discounts for other medications are reported in a confidential addendum.

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	Exclusion of rituximab from the company's decision problem	No
2	Uncertain relevance of eculizumab	No
3	Timing of MG-ADL response assessment	Yes
4	Time on treatment extrapolations	No
5	Estimation of the incidence of acute clinical events	No (but additional clarification provided)
Additional issues noted by the company		
1	Half-cycle correction	Yes
2	EAG corrections	No

2. Critique of the company's response to the key issues for technical engagement

2.1 Issue 1 – Exclusion of rituximab from the company's decision problem

The company's response reiterates arguments presented in their CS, without providing any new information. In summary:

- The company state that rituximab is used less in AChR antibody-positive MG patients than in MuSK antibody-positive MG patients and therefore would not be considered a relevant comparator in the current appraisal. **EAG response:** As noted in EAG report section 2.2.3, two clinical experts who advised the EAG both said they use rituximab for their patients with AChR antibody-positive generalised MG and they considered rituximab to be a part of standard of care.

  In addition to the company's response, three consultees who responded to TE discussed rituximab use, with mixed opinions:

  - The Association of British Neurologists (ABN) response concurs with the opinion of the EAG's clinical experts, stating that "rituximab should be included in the analysis to reflect real life clinical practice in the UK".

- An MG patient stated that they are aware that rituximab is used in clinical practice and can be effective. However, it is unclear whether the consultee is referring to patients with AChR antibody-positive and/or MuSK antibody-positive disease.
- A consultant neurologist (nominated by the company) stated that they do not believe rituximab should be a comparator for ravulizumab. Their rationale is based on the limited use and efficacy of rituximab in AChR antibody-positive patients and an argument that rituximab would take longer to work than ravulizumab. The consultee appears to be referring particularly to steroid sparing, although this is not an outcome specified in the NICE scope or CS.

- The company argue that rituximab is used in later lines of therapy "*as a last resort for patients who have received all other treatment options"* (citing the NHS England Clinical Commissioning Policy statement on rituximab biosimilars) and would not be a relevant comparator for ravulizumab. **EAG response:** These refractory patients are a relevant patient group within the licensed indication. The company do not state whether they believe ravulizumab would be used before, instead of, or after, rituximab therapy.
- The company argue that there is a lack of robust studies on rituximab in refractory generalised MG so there would be no appropriate data available for a comparison of ravulizumab against rituximab. **EAG response:** The CS and company TE response do not present any evaluation of the availability and rigour of evidence for potentially comparing rituximab against ravulizumab in an indirect treatment comparison. CS Appendix Table 5 lists one placebo-controlled RCT and three single-cohort studies of rituximab in non-UK patients with refractory generalised AChR antibody-positive MG but the company do not discuss these studies and no specific search for non-randomised studies was conducted to check whether others exist. The EAG and our clinical experts were not aware of any further robust studies. We note that a health technology assessment conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) [1] had identified a further eight potentially relevant single-cohort studies of rituximab in addition to those listed in CS Appendix Table 5, but these had limitations, notably small sample size, with the largest having only 39 patients.

In summary, rituximab appears to be a relevant comparator for ravulizumab but it seems unlikely that there is adequately robust clinical efficacy evidence to enable an indirect treatment comparison of ravulizumab against rituximab.

2.2 Issue 2 – Uncertain relevance of eculizumab

The company's response reiterates arguments presented in their CS, without providing new information. The company state that ravulizumab has greater complement inhibition than eculizumab but they do not provide any data to support this assertion in CS section B.2.2 or their TE response. As noted in EAG Report section 3.5, the company's ITC comparing ravulizumab against eculizumab was limited to a short-term comparison whose results are uncertain.

In addition to the company's response, two consultees who responded to TE commented on the suitability of eculizumab as a proxy for ravulizumab, providing differing opinions:

- The ABN representative stated that they did not think eculizumab can be taken as a proxy for ravulizumab, "for all the reasons mentioned in the report" which we presume refers to the information summarised in EAG Report section 1.4.
- A consultant neurologist (nominated by the company) was supportive of long-term eculizumab clinical efficacy outcomes being used as a proxy for long-term ravulizumab outcomes, stating that they were not aware of any reasons why ravulizumab should be less effective than eculizumab for generalised MG.

2.3 Issue 3 – Timing of MG-ADL response assessment

The company state that use of 18-week data provides the best reflection of the data that would be available for a response assessment at 16 weeks in clinical practice, although this does not make use of all available data for the randomized follow-up period for ravulizumab. The revised model submitted with the company's TE response includes an option to estimate the proportion of patients who would discontinue ravulizumab at a 16-week response assessment based on either 18-week or 26-week data from the CHAMPION-MG trial. The company also report cost-effectiveness results for a scenario with a 16-week stopping rule using 26-week ravulizumab data. **EAG Response:** We have reproduced the company's scenario with a 16-week response assessment based on 26-week data, in addition to an EAG scenario with a 26-week stopping rule and 26-week data for comparison (see Table 2 below).

However, the company's scenario misinterprets the EAG's request for additional analysis on this issue. As stated in the EAG Report, we consider that assessment of response after two maintenance doses of ravulizumab at 16 weeks is clinically appropriate, and that the 18-week trial data is broadly consistent with this assessment. Our concern is that the model does not then make use of the randomised data between weeks 18 and 26 to model any

further change in MG-ADL for patients who pass the response assessment and continue to take ravulizumab. This means that 18-week trial data are used to extrapolate the long-term change in MG-ADL, which impacts on estimates of utility. We would have preferred a scenario analysis retaining the 16-week assessment for lack of response to ravulizumab (based on 18-week trial data), combined with 26-week data for estimation of the long-term treatment effect (and utility) for patients continuing ravulizumab, as for the comparator arm.

Table 2 Scenarios for timing of response assessment (revised PAS)

Treatment	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	(£/QALY)
Base case pre-TE: 16-week stopping rule based on 18-week data for ravulizumab					
SoC	£88,424	10.083			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company scenario: 16-week stopping rule based on 26-week data for ravulizumab					
SoC	£88,424	10.083			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario: 26-week stopping rule and 26-week data for ravulizumab					
SoC	£88,424	10.083			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: produced by the EAG from the company's model submitted with their TE response					

2.4 Issue 4 – Time on treatment extrapolations

The company maintain their preference for use of pooled CHAMPION-MG and REGAIN data, and an exponential distribution for extrapolation of time on treatment for ravulizumab. They note that use of CHAMPION-MG data alone, as preferred by the EAG, results in a lower ICER estimate.

EAG response: We have summarised the company's scenario analyses with their revised PAS estimate in Table 3. We maintain our preference for analysis based on CHAMPION-MG data only, due to uncertainties associated with use of the REGAIN OLE study data, and the very poor fit of all fitted extrapolations to the long-term data from this trial (see EAG Report Figure 4). We agree with the company's use of an exponential extrapolation for their base case, but we also report scenarios with a log-logistic distribution, as this has a similar fit to the KM data and a declining hazard over time, which clinical experts advising the EAG thought might be more realistic.

Table 3 Scenarios for time on treatment extrapolation (revised PAS)

Treatment	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	(£/QALY)
Base case pre-TE: pooled CHAMPION and REGAIN data, exponential extrapolation					
SoC	£88,424	10.083			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company scenario: CHAMPION data only, exponential extrapolation					
SoC	£88,424	10.083			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario: pooled CHAMPION and REGAIN data, log-logistic extrapolation					
SoC	£88,424	10.083			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario: CHAMPION data only, log-logistic extrapolation					
SoC	£88,424	10.083			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: produced by the EAG from the company's model submitted with their TE response

2.5 Issue 5 – Estimation of the incidence of acute clinical events

As requested, the company have provided further information about the process used to fit the Poisson regression model for incidence of acute clinical events. They compared models based on a pooled dataset of 60-week CHAMPION-MG data (RCT and OLE study) and 26-week REGAIN data (RCT only).

- First, the company compared the fit of models according to two independent variables, prior clinical event within 3 months and data source (treatment group or MG-ADL score), for the total pooled population ([redacted] events observed over [redacted] person-years of follow up). Based on this comparison, they chose treatment arm rather than MG-ADL score as the 'primary driver' of clinical events.
- The next step was to assess whether inclusion of the prior clinical event covariate improved the fit of the regression when the dataset was limited to patients in the ravulizumab arm with a response (≥ 3-point reduction in MG-ADL score) at either 16 or 26 weeks ([redacted] events observed over [redacted] person-years, respectively). The company concluded that the prior clinical event variable did not improve the fit in either restricted dataset.

However, the company concluded that although the simple model with a single independent variable (treatment arm) provides the best fit, it would be appropriate to include the prior

event covariate in their revised base case, as the coefficient was statistically significant. They also adjust the regression for the stopping rule (removing non-responders to ravulizumab at 18 and 16 weeks from the CHAMPION-MG and REGAIN trials respectively).

EAG response: We consider that the process used to fit the clinical event model is reasonable and agree with the decision to include prior clinical events, as the AIC statistics are similar for the models with or without this covariate; the coefficient is highly statistically significant; and *a priori* one would expect the recent incidence of an event to be predictive of another event. We also agree with adjusting the regression by removing non-responders to reflect a 16-week stopping rule, which we understand would be applied in clinical practice. We show the effect on the ICER of including the prior event covariate in Table 4 below. However, the company have not addressed the EAG's serious concerns about the pooling of data from the CHAMPION-MG and REGAIN trials, as it has not been demonstrated that ravulizumab and eculizumab have similar effects on clinical event rates. They have not reported a sensitivity analysis excluding data from REGAIN from the Poisson regressions.

Table 4 Scenarios for clinical event regression model (revised PAS)

Treatment	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Base case pre-TE: no prior event covariate					
SoC	£88,424	10.083			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case: prior event covariate included					
SoC	£68,006	10.119			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: produced by the EAG from the company's model submitted with their TE response					

2.7 Additional issues

The company have addressed two further issues based on comments in the EAG Report:

1. They have added a half-cycle correction to the model to adjust estimates of change in MG-ADL score and treatment discontinuation mid-way within the three-month model cycles.
2. They state that they agree with four technical corrections made by the EAG: proportion of women in the CHAMPION-MG trial; assumptions about use of standard care treatments; the disutility for nasopharyngitis; and survival estimates (see EAG Report Table 31).

EAG response: We agree with these changes and believe that they have been correctly implemented.

3. Updated cost-effectiveness results - EAG summary and critique

3.1 Company's revised base case results

The company report the changes to their base case in Table 4 of their TE response. We have replicated these results using the revised TE response version of the model; and verified where possible that the results are consistent with the previous version of the model. Changes to the company's base case increase the ICER from [redacted] to [redacted] per QALY gained with the current PAS discount price for ravulizumab. With the estimated revised PAS discount, the ICER increases from [redacted] to [redacted] per QALY gained. We show the cumulative impact of the changes with the revised PAS discount estimate in Table 5 below. These and other analyses results in this report use the revised PAS discount estimate for ravulizumab and the list price for all other concomitant and comparator medications. Where applicable, we report results with the confidential discounts for comparators in a confidential addendum to this report.

Table 5 Cumulative change in company base case (revised PAS)

Treatment	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Base case before technical engagement					
SoC	£88,424	10.083			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Additional issue 2: EAG corrections					
SoC	£79,993	9.967			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Key Issue 5: Incidence of acute events, prior clinical events covariate					
SoC	£59,804	10.002			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Additional issue 1: Half cycle correction					
SoC	£60,207	10.078			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised base case following technical engagement					
SoC	£60,207	10.078			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: Produced by the EAG from the company's model submitted with TE response					

We note that Table 4 in the company's TE response document includes errors in the reporting of the incremental cost ([redacted] rather than [redacted]) and incremental QALYs ([redacted] rather than [redacted]) for the previous base case, although the ICER reported is consistent with our results ([redacted] per QALY gained).

The company report results from their probabilistic sensitivity analysis in Table 5 and Figure 1 of their TE response document, and results of deterministic one-way sensitivity analyses in Figure 2 of that document. The EAG believe that these analyses do not adequately reflect uncertainty in the results, due to the omission of some key parameters (see section 5.3.1 of the EAG Report).

3.2 EAG's revised preferred assumptions

The EAG agree with the changes that the company have made in their revised base case. We retain our preference for additional changes, as stated in the EAG's preferred analyses in section 6.2 of the EAG Report. We prefer to use CHAMPION-MG data only (not including data from REGAIN) to define the baseline patient characteristics and the time on treatment extrapolation. This aligns with the pivotal clinical data and avoids the assumption of equivalence for ravulizumab and eculizumab. We also prefer the version of the company's utility regression model that includes prior clinical events within three months as a covariate, in addition to MG-ADL score and baseline EQ-5D. Table 6 shows the cumulative change from the company's revised base case analysis to the EAG preferred analysis, including the company's revised PAS discount estimate for ravulizumab (all other medications costed at list price). The additional EAG assumptions are associated with a small increase in the ICER from [redacted] to [redacted] per QALY gained.

Table 6 Cumulative change in EAG preferred analysis (revised PAS)

Treatment	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Company revised base case					
SoC	£60,207	10.078			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Baseline patient characteristics: Champion-MG trial only					
SoC	£56,376	9.662			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Time on treatment: CHAMPION-MG RCT and OLE only (exponential)					
SoC	£56,376	9.662			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Utility regression: including covariate for clinical event within 3 months					
SoC	£56,376	9.786			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised analysis with EAG preferred assumptions					
SoC	£56,376	9.786			
Ravulizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG from the company's model submitted with TE response

3.4 Scenario analyses conducted on the EAG's revised preferred analysis

Table 7 shows results for a selected range of scenarios applied with the EAG's preferred assumptions. The model is sensitive to the duration of ravulizumab treatment, as estimated with extrapolations fitted to CHAMPION-MG data (EAG preference) or pooled CHAMPION-MG and REGAIN data (company base case). The choice of distribution has a large effect; extrapolations with higher rates of long-term treatment (log-normal and log-logistic) have higher ICERs (see comments on Issue 4 above). As noted in the discussion on Issue 3, the company's scenarios for use of 26-week trial data to model the response and ongoing effect of ravulizumab give higher ICERs, but we do not believe that these scenarios make appropriate use of the trial data. As might be expected, assuming no loss of the observed placebo effect over time results in a very large increase in the ICER.

Table 7 Additional scenarios applied to the EAG's preferred analysis (revised PAS)

ERG preferred assumption	Scenario	Treat-ment	Total Cost (£)	Total QALYs	ICER (£/QALY)
EAG's preferred analysis post TE		SoC Rav	£56,376 [redacted]	9.786 [redacted]	[redacted]
Population characteristics at baseline					
CHAMPION-MG population	Pooled CHAMPION-MG and REGAIN	SoC Rav	£60,207 [redacted]	10.217 [redacted]	[redacted]
Time on treatment extrapolation for ravulizumab					
		SoC	£56,376	9.786	

ERG preferred assumption	Scenario	Treat-ment	Total Cost (£)	Total QALYs	ICER (£/QALY)
CHAMPION-MG (exponential)	CHAMPION-MG and REGAIN (exponential)	Rav	[redacted]	[redacted]	[redacted]
	CHAMPION-MG (log-normal)	SoC	£56,376	9.786	
		Rav	[redacted]	[redacted]	[redacted]
	CHAMPION-MG (log-logistic)	SoC	£56,376	9.786	
		Rav	[redacted]	[redacted]	[redacted]
	CHAMPION-MG (gamma)	SoC	£56,376	9.786	
		Rav	[redacted]	[redacted]	[redacted]
	CHAMPION-MG (Weibull)	SoC	£56,376	9.786	
		Rav	[redacted]	[redacted]	[redacted]
	CHAMPION-MG (Gompertz)	SoC	£56,376	9.786	
		Rav	[redacted]	[redacted]	[redacted]
Ravulizumab treatment effect (change in MG-ADL score)					
16-week stopping rule based on 16-week trial data. No retained benefit after stopping ravulizumab	16-week stopping rule using 26-week data	SoC	£54,864	9.790	
		Rav	[redacted]	[redacted]	[redacted]
	26-week stopping rule using 26-week data	SoC	£54,864	9.790	
		Rav	[redacted]	[redacted]	[redacted]
	Retained benefit (waning over 3 months)	SoC	£56,376	9.786	
		Rav	[redacted]	[redacted]	[redacted]
	Retained benefit (waning over 6 months)	SoC	£56,376	9.786	
		Rav	[redacted]	[redacted]	[redacted]
Placebo effect					
Placebo effect removed at 12 months (return to baseline MG-ADL)	Return to baseline at 6 months	SoC	£56,376	9.765	
		Rav	[redacted]	[redacted]	[redacted]
	Return to baseline at 9 months	SoC	£56,376	9.776	
		Rav	[redacted]	[redacted]	[redacted]
	No loss of placebo effect	SoC	£56,376	10.440	
		Rav	[redacted]	[redacted]	[redacted]
Clinical event incidence (Poisson regression)					
Treatment and prior event covariates	No prior events covariate	SoC	£75,434	9.737	
		Rav	[redacted]	[redacted]	[redacted]
Mortality					
No increase in general mortality risk. Fatality rate for crises 4.47% (Alshekhlee 2009)	Mortality risk ratio 1.4 for gMG versus general population	SoC	£52,799	9.219	
		Rav	[redacted]	[redacted]	[redacted]
	Fatality rate for crises 2%	SoC	£56,554	9.816	
		Rav	[redacted]	[redacted]	[redacted]
	Fatality rate for crises 10%	SoC	£55,980	9.721	
		Rav	[redacted]	[redacted]	[redacted]
Utilities: EQ-5D regression					
MG-ADL, prior event and baseline EQ-5D covariates	Exclude prior clinical event covariate	SoC	£56,376	9.662	
		Rav	[redacted]	[redacted]	[redacted]
Cost of clinical events					
As in company model: [redacted] for exacerbation; [redacted] for crisis	Costs cited in CS (section B.3.5.2): exacerbation [redacted] and crisis[redacted]	SoC	£104,871	9.786	
		Rav	[redacted]	[redacted]	[redacted]

ERG preferred assumption	Scenario	Treat-ment	Total Cost (£)	Total QALYs	ICER (£/QALY)
Source: Produced by the EAG using the company's TE response model Abbreviations: Rav ravulizumab; SoC standard of care					

3.5 Remaining uncertainties

There are uncertainties that we have not been able to reflect in scenario analysis. We have not attempted to model rituximab as a comparator, treatment sequencing, or changing the composition of the standard care comparator or assumed use of treatments for acute exacerbations and crises. There is uncertainty over how well the assumptions in the company's model reflect current UK practice and how this might change if ravulizumab were to be recommended. In particular, we note uncertainty over the availability and routine use of IVIg, plasma exchange and rituximab in UK practice.

References

1. Young C, McGill SC. Rituximab for the treatment of myasthenia gravis: a 2021 update. CADTH Health Technology Review. Canadian Journal of Health Technologies 2021; 1 (4): 1-58.

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Evidence Assessment Group report commissioned by the
NIHR Evidence Synthesis Programme on behalf of NICE

Ravulizumab for treating generalised myasthenia gravis (ID4019)

Additional EAG scenarios

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Date completed	17 August 2023

[redacted]

[redacted]

Following discussions at the pre-meeting briefing on 16 August, the EAG was asked by NICE to conduct some additional scenario analyses. We applied these scenarios to the revised EAG preferred analysis after technical engagement (TE). Results are shown in Table 1 below, using the confidential revised PAS price discount for ravulizumab proposed by the company in their TE response, and with all other drugs at list prices.

The first set of scenarios relate to questions about the company's approach to estimating the hospital cost for acute clinical events (exacerbations and crises):

1. The rationale is not clear for the company's assumption that in addition to an ICU admission for intubation in the event of a myasthenic crisis, [redacted] of patients will also have an extended ICU stay. However, the effect on the ICER of removing the additional ICU stay is small, because crises are rare events.
2. The second scenario uses a cost for intubation of £4,219, which is a weighted average for the non-elective long stay HRG categories DZ27M to U (respiratory failure of different levels of complexity). It has been suggested that this may be an overestimate, and we have tested the effect of using the cost for a non-elective short stay for this HRG (£870). This causes a moderate increase in the ICER.
3. The third scenario corrects what we consider to be an error in the company's model. They have multiplied the HRG costs for each type of hospital care (intubation, ICU stay and inpatient care) by an assumed length of stay. We do not consider this to be appropriate, as the HRG costs already cover an average length of stay per finished consultant episode (FCE) in each category. Removing the length of stay multipliers, and assuming a maximum of one of each category of FCE per clinical event has a large impact on the ICER.
4. The fourth scenario combines above scenarios and gives an ICER that is similar to that for scenario 3.

The second set of scenarios in Table 1 relate to assumptions about the use of rituximab. The company have argued that rituximab would only be used in the population of interest for treatment in an acute crisis. However, there is some disagreement on this point between clinical experts. We test the impact of assuming that a proportion of patients (5-15%) are treated with rituximab as part of the SoC comparator, and after discontinuation of ravulizumab in the intervention arm. We have based the cost of rituximab in these scenarios on the NHS England Clinical Commissioning Policy Statement (170084P), which recommends rituximab (or biosimilar) for a number of indications, including refractory myasthenia gravis. We assume a course of two intravenous doses of 1,000 mg with outpatient administration (HRG code SB13Z) over a period of six months: £3,143 for drug

acquisition and £514 for administration. Scenarios 5 to 7 show that although the cost of the ravulizumab arm is predicted to increase with the use of rituximab after discontinuation, this is offset by a larger increase in the cost of SoC, so the ICER declines. We note that these scenarios do not account for the clinical effects of rituximab, and so may not provide a realistic estimate of the impact of rituximab use as part of standard care.

Finally, scenario 8 combines the clinical event cost scenarios with 5% use of rituximab in standard care and after ravulizumab.

Table 1 Additional scenarios applied to the EAG's preferred analysis (revised PAS)

Scenario	Treatment	Total Cost (£)	Total QALYs	ICER (£/QALY)
EAG's preferred analysis post TE	SoC	£56,376	9.786	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Methods for costing clinical events				
1. No HRG cost for ICU stay in addition to in HRG cost for intubation	SoC	£55,620	9.786	
	Ravulizumab	[redacted]	[redacted]	[redacted]
2. HRG cost for intubation £870 (DZ27 non-elective short stay)	SoC	£47,625	9.786	
	Ravulizumab	[redacted]	[redacted]	[redacted]
3. No more than one FCE per clinical event (intubation, ICU and inpatient)	SoC	£30,889	9.786	
	Ravulizumab	[redacted]	[redacted]	[redacted]
4. Scenarios 1 to 3 combined	SoC	£29,957	9.786	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Routine use of rituximab as part of standard care				
5. 5% of patients in SoC arm and after discontinuation of ravulizumab	SoC	£62,735	9.786	
	Ravulizumab	[redacted]	[redacted]	[redacted]
6. 10% of patients in SoC arm and after discontinuation of ravulizumab	SoC	£69,095	9.786	
	Ravulizumab	[redacted]	[redacted]	[redacted]
7. 15% of patients in SoC arm and after discontinuation of ravulizumab	SoC	£75,454	9.786	
	Ravulizumab	[redacted]	[redacted]	[redacted]
Combined scenarios for clinical event costs and 5% rituximab in SoC				
8. Scenarios 4 and 5 combined	SoC	£36,316	9.786	
	Ravulizumab	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG using the company's TE response model

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Evidence Assessment Group report commissioned by the
NIHR Evidence Synthesis Programme on behalf of NICE

Ravulizumab for treating generalised myasthenia gravis (ID4019)

EAG critique of additional scenarios from company responses dated 24/08/23, 30/08/23 and 31/08/23

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Date completed	6 September 2023

[redacted]

[redacted]

Introduction

Following discussions with the committee chair and lead team, NICE sent a letter to the company dated 17 August 2023 requesting additional analyses to explore two remaining areas of uncertainty raised by the EAG in technical engagement. The company provided responses to this request on 24, 30 and 31, and additional versions of their model dated 30 and 31 August.

We provide EAG critique of the company's responses below. All results in this document use the confidential revised PAS discount proposed by the company at technical engagement, and publicly available list prices concurrent and comparator drugs. We report the results with confidential discounts for other drugs in a separate document.

Issue 1: Use of available MG-ADL data

The company base case uses 18-week MG-ADL data from the ravulizumab arm of the CHAMPION trial to estimate both the proportion of 'non-responders' (MG-ADL change < 3), who are assumed to stop ravulizumab at a 16-week assessment; and the 26-week MG-ADL distribution for the 'responders' who continue ravulizumab after 16 weeks.

NICE has requested a scenario using 26-week trial data for the subgroup of patients with a response at 18-weeks, to model outcomes with the 16-week response assessment. We consider that this is a better use of the trial data, as it retains information about change in MG-ADL between 18 and 26 weeks for the ravulizumab arm and is consistent with the use of 26-week data in the usual care arm (EAG report key issue 3 and section 4.2.3.1). This is potentially important as the model assumes that the distribution of MG-ADL at 26 weeks persist over time, and MG-ADL is a covariate in the utility regression equation.

There was a misunderstanding over the requested scenario in the company's response of 24 August, which was corrected in additional responses on 30 and 31 August. Table 1 below shows the conditional distribution of 26-week MG-ADL change for the 18-week responders, alongside previously reported results from the CHAMPION RCT and open label extension (company responses 30/08/23 and 31/08/23). We note that the 26-week distribution for 18-week responders is similar to the open label extension results at 60 weeks.

The company conducted the requested scenario by applying the 26-week distribution of MG-ADL change to 18-week responders in the ravulizumab arm of the model after the second 3-month model cycle, with an assumption that patients with MG-ADL change <3 would remain in this state for the rest of the time horizon. The company calculated the 26-week MG-ADL change distribution for ravulizumab allowing for the 46.5% of 18-week non-responders (

Table 2). However, we consider that the [redacted] (46.5% + [redacted]) estimate for the overall proportion in the <3 category is incorrect, as the [redacted] 26-week non-response only applies to the 53.5% of the original cohort with MG-ADL change ≥ 3 at 18 weeks. Thus, we consider that the correct estimate for the < 3 category is [redacted] (46.5% + 53.5% * [redacted]). Similarly, the expected proportion in the 3-4 category is [redacted] (53.5% * [redacted]), and so on.

Table 1 Distribution of MG-ADL change from baseline: CHAMPION ravulizumab arm

Change in total MG-ADL score	Ravulizumab arm at 18 weeks	Ravulizumab arm at 26 weeks	Ravulizumab Open label extension study 60 weeks	26 weeks for those who responded at 18 weeks
N	86	86	78	[redacted]
Change < 3	46.5%	41.9%	32.1%	[redacted]
3 ≤ Change < 4	9.3%	12.8%	10.2%	[redacted]
4 ≤ Change < 5	8.2%	10.4%	12.8%	[redacted]
5 ≤ Change < 6	8.1%	10.5%	14.1%	[redacted]
6 ≤ Change < 7	12.8%	10.4%	10.3%	[redacted]
7 ≤ Change < 8	8.1%	4.7%	7.7%	[redacted]
Change ≥ 8	7.0%	9.3%	12.8%	[redacted]
Source: Adapted by the EAG from Table 1 in the company's response of 30/08/23 and Table 1 of the company's response of 31/08/23. Sample sizes from company model dated 31/08/23.				

Table 2 MG-ADL change estimated with 26-week data for 18 week responders

Change in total MG-ADL score	Distribution applied to ravulizumab arm beyond cycle 2	
	Company's analysis	EAG's analysis
Change < 3	[redacted]	[redacted]
3 ≤ Change < 4	[redacted]	[redacted]
4 ≤ Change < 5	[redacted]	[redacted]
5 ≤ Change < 6	[redacted]	[redacted]
6 ≤ Change < 7	[redacted]	[redacted]
7 ≤ Change < 8	[redacted]	[redacted]
Change ≥ 8	[redacted]	[redacted]
Total	100.00%	100.00%
Source: produced by the EAG from the company's TE model version 3.0, dated 30/08/23		

The company reported an ICER for the MG-ADL responder scenario of [redacted] per QALY gained (Table 2, company response 31/08/23), compared with [redacted] in their base case analysis. The EAG obtained a slightly different result from the company's model (version 3.0

31/08/23): [redacted] per QALY (see Table 3 below). Applying our estimates of the 26-week MG-ADL change distribution for this scenario (as in

Table 2 above) to the company's TE base case, we estimate an ICER of [redacted] per QALY gained. This reflects our higher estimates of retained MG-ADL response ≥3 at 26 weeks in the ravulizumab arm.

Issue 2: Estimation of incidence of clinical events

The company use a Poisson regression to estimate the incidence of acute clinical events in their model. The regression was fitted to pooled data from the CHAMPION and REGAIN studies. We requested a scenario analysis using CHAMPION data only for the clinical event regression due to concerns about naive pooling of data from the different trial populations, and the assumption of equal treatment effects for eculizumab and ravulizumab (EAG report 4.2.3.4 and key issue 5 discussed at technical engagement).

The company provided two scenario analyses with the event regression fitted to CHAMPION data only in their response of 24/08/23. These scenarios both included the treatment arm and prior clinical event within 3 months as covariates, as in the company TE base case and EAG preferred analysis. They differed in the timing of removal of non-responders from the dataset: at 18 or 26 weeks. As stated in the EAG report, we prefer the analysis with non-responders removed at 18 weeks, as this more closely reflects the 16-week stopping rule. Results from the two scenarios are similar, with ICERs a little higher than the company base case and EAG preferred analysis (Table 3 and Table 4).

Table 3 Additional scenarios applied to the company's base case (revised PAS)

Scenario	Treatment	Total Cost (£)	Total QALYs	ICER (£/QALY)
Company revised base case post TE	SoC Ravulizumab	£60,207 [redacted]	10.078 [redacted]	[redacted]
1. MG-ADL scenarios: use 26-week MG-ADL data for 18-week ravulizumab responders				
Company's analysis	SoC Ravulizumab	£60,207 [redacted]	10.078 [redacted]	[redacted]
EAG's analysis	SoC Ravulizumab	£60,207 [redacted]	10.078 [redacted]	[redacted]
2. Clinical event regression scenarios: use CHAMPION trial data only				
Excluding patients 18-week non-responders in ravulizumab arm	SoC Ravulizumab	£57,059 [redacted]	10.083 [redacted]	[redacted]
Excluding patients 26-week non-responders in ravulizumab arm	SoC Ravulizumab	£56,064 [redacted]	10.085 [redacted]	[redacted]
Source: Produced by the EAG using version 3.0 of the company's model, dated 31/08/23				

Table 4 Additional scenarios applied to the EAG's preferred analysis (revised PAS)

Scenario	Treatment	Total Cost (£)	Total QALYs	ICER (£/QALY)
EAG's preferred analysis post TE	SoC Ravulizumab	£56,376 [redacted]	9.786 [redacted]	[redacted]
1. MG-ADL scenarios: use 26-week MG-ADL data for 18-week ravulizumab responders				
Company's analysis	SoC Ravulizumab	£56,376 [redacted]	9.786 [redacted]	[redacted]
EAG's analysis	SoC Ravulizumab	£56,376 [redacted]	9.786 [redacted]	[redacted]
2. Clinical event regression scenarios: use CHAMPION trial data only				
Excluding patients 18-week non-responders in ravulizumab arm	SoC Ravulizumab	£53,427 [redacted]	9.794 [redacted]	[redacted]
Excluding patients 26-week non-responders in ravulizumab arm	SoC Ravulizumab	£52,495 [redacted]	9.797 [redacted]	[redacted]
Source: Produced by the EAG using version 3.0 of the company's model, dated 31/08/23				