Single Technology Appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Contents:

The following documents are made available to stakeholders:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Argenx
2. **Company summary of information for patients (SIP)** from Argenx
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. Myaware & Muscular Dystrophy UK joint submission
5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre
6. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

7. **Technical engagement response from company:**
   a. Main response
   b. Additional evidence
   c. Burden of caregivers study report
   d. Letter on maintenance IVIg usage
8. **Technical engagement responses and statements from experts:**
   a. Frances Copeland – patient expert, nominated by Muscular Dystrophy UK
   b. Penelope Henrion – patient expert, nominated by Myaware
   c. Fiona Norwood, Consultant Neurologist – clinical expert, nominated by Myaware
   d. Channa Hewamadduma, Consultant Neuromuscular Neurologist and Honorary Senior Lecturer – clinical expert, nominated by Argenx
9. **Technical engagement responses from stakeholders:**

a. Myaware & Muscular Dystrophy UK joint response

10. External Assessment Group critique of company response to technical engagement prepared by Southampton Health Technology Assessments Centre

11. Expert response to NICE technical team questions from Sanjeev Patel, clinical lead for NHS England Innovative Medicines Fund (IMF)

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

Efgartigimod alfa (VYVGART™) for treating generalised myasthenia gravis [ID 4003]

Document B

Company evidence submission

14 February 2023

File name	Version	Contains confidential information	Date
ID4003_Vyvgart_gMG_Document B_v2.0_[redacted]	2.0	No	28 February 2023

Contents

List of Figures

List of Tables

Abbreviations

AANEM	American Association of Neuromuscular & Electrodiagnosis Medicine
ABN	Association of British Neurologists
AChEis	Acetylcholinesterase inhibitors
AChR	Acetylcholine receptor
AChR-Ab+/−	Acetylcholine receptor antibody positive/negative
AE	Adverse events
AESI	AEs of special interest
AIC	Akaike information criterion
AUC	Area under the curve
AUEC	Area under the effect curve
AWTTC	All Wales Therapeutics and Toxicology Centre
BIC	Bayesian information criterion
CI	Confidence interval
CMI	Clinically meaningful improvement
CRD	Centre for Reviews and Dissemination
EAMS	Early Access to Medicines Scheme
ECG	Electrocardiogram
ECM	Established clinical management
EFG	Efgartigimod
EMA	European Medicines Agency
EU	European Union
gMG	Generalised myasthenia gravis
HBV	Hepatitis B virus
HCRU	Healthcare resource utilisation
HCV	Hepatitis C virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IQR	Interquartile range
ITT	Intention-to-treat
IV	Intravenous
IVIg	Intravenous immunoglobulin
KM	Kaplan-Meier
LMSD	Least squares mean difference
LS	Least squares
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living Scale
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MG-QOL15	Myasthenia Gravis Quality of Life 15
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention-to-treat
MMRM	Mixed model for repeated measures
MSE	Minimal Symptom Expression
MuSK	Muscle-specific tyrosine kinase
NA	Not applicable
NDC	New Drugs Committee
NMJ	Neuromuscular junction
NSIST	Nonsteroidal immunosuppressive therapy
OR	Odds ratio
PAR	Public Assessment Report
PAS	Patient access scheme
PBO	Placebo
PD	Pharmacodynamics
PIM	Promising innovative medicine
PK	Pharmacokinetics
PLEX	Plasma exchange
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
QMG	Quantitative Myasthenia Gravis
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse events
SC	Subcutaneous
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
ToT	Time on treatment
TPE	Therapeutic plasma exchange
VAS	Visual analogue scale
VAT	Value added tax

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

B.1.1 Decision problem

A summary of the decision problem is shown in Table 1.

The submission covers the full marketing authorisation for efgartigimod alfa (efgartigimod) as an add on to standard therapy for the treatment of adult patients with generalised Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive (Ab+).

The company submission is consistent with the final NICE scope and the NICE reference case. However, there is a lack of data describing the use of plasma exchange (PLEX) outside the management of acute episodes (exacerbations or myasthenic crisis). Therefore, the company does not consider that PLEX should be included as a comparator to efgartigimod in the base case, and the inclusion of PLEX in established clinical management has been explored in a scenario analysis.

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 who are AChR-Ab+	As per scope, the company submission is in adults with gMG who are AChR-Ab+	NA
Intervention	Efgartigimod	Efgartigimod	NA
Comparator(s)	Established clinical management without efgartigimod including corticosteroids and immunosuppressive therapies, with or without intravenous immunoglobulin (IVIg) or plasma exchange (PLEX)	Similar to the NICE scope the company submission compares established clinical management without efgartigimod including corticosteroids and immunosuppressive therapies, with or without IVIg vs. efgartigimod added to established clinical management including corticosteroids and immunosuppressive therapies, with or without IVIg. PLEX is not included as a comparator.	The company does not consider that PLEX should be included as a comparator for management of gMG for this decision problem as a result of the lack of clinical data that describes its use outside the management of acute episodes (exacerbations or myasthenic crisis).
Outcomes	The outcome measures to be considered include: • Improvement in myasthenia gravis • Time to clinically meaningful improvement • Mortality • Hospitalisations • Adverse effects of treatment • Health-related quality of life	As per scope, the company submission considers the following outcomes: • Improvement in myasthenia gravis (MG-ADL responder) • Time to clinically meaningful improvement • Mortality • Hospitalisations • Adverse effects of treatment • Health-related quality of life	NA

Abbreviations: AChR-Ab+, acetylcholinesterase inhibitor antibody positive; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living score; NA, not applicable; PLEX, plasma exchange

SUMMARY

- gMG is a rare, chronic, neuromuscular autoimmune disease. gMG is mediated by pathogenic IgG autoantibodies which cause debilitating and potentially life-threatening muscle weakness, disrupting the ability to perform normal daily activities and profoundly impairing health-related quality of life (HRQoL).[1–9] The most common IgG autoantibody targets AChRs.[4,10]
- The muscle weakness experienced by gMG patients severely impacts their day-to-day functioning, which can lead to difficulties with swallowing, vision, speech, breathing, and mobility, as well as extreme fatigue.[11]
- Up to 20% of gMG patients experience a myasthenic crisis at least once in their lives; each crisis affects the muscles that control breathing and can result in life-threatening respiratory impairment.[3,12]
- As a chronic debilitating disease, gMG has a serious impact on healthcare resource utilisation (HCRU), direct healthcare costs, and productivity.[13–15] The high economic burden associated with MG is largely driven by hospitalisation costs for mechanical ventilation, intravenous Ig (IVIg), and plasmapheresis or PLEX as well as the costs of managing the side effects of corticosteroids and nonsteroidal immunosuppressive therapy (NSISTs).[16,17]
- The goals for treatment of gMG are for patients to experience normal or near-normal function with little weakness or fatigue due to gMG (i.e., remission), and no or only mild side effects from medication. This is generally referred to as Minimal Symptom Expression (MSE) and equates to a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 0 or 1.[18]
- Currently, there is no curative treatment for gMG. Most treatments are used off-label, lack robust clinical data for use in gMG, and rely mainly on broad suppression of the immune system (Section B.1.3.3.4).[19–29]
- Established clinical management for gMG in England and Wales comprises initial symptomatic treatment with acetylcholinesterase inhibitors (AChEis), followed by corticosteroids and/or NSISTs. IVIg and plasmapheresis or PLEX are typically used to treat acute exacerbations or crisis. IVIg may also be used on an ongoing basis in patients with more active disease.[19,30]
- Rituximab is not approved for treatment of gMG but has been commissioned by NHS England and the All Wales Therapeutics and Toxicology Centre (AWTTC), for defined patient groups including those whose disease is refractory to standard therapy, following referral and assessment by a myasthenia clinic within a specialised neuroscience centre.[31,32]
- Despite the use of current treatments, many patients continue to suffer substantial disease burden, including debilitating symptoms that affect their quality of life and impair their productivity.[11,33–37]
- Side effects can be severe and include long-term severe weight gain, skin disorders, malignant cancers, bone loss, and increased risk of infection and/or infection-related complications including COVID-19.[35,38–40]
- Only 25% of MG patients are able to achieve pharmacological remission (e.g., no symptoms on treatment), and only 8% achieve clinical remission (no symptoms off-treatment for more than a year).[41]
- For these reasons, there is an urgent unmet need for an effective, well tolerated therapy that can be used to treat gMG patients whose symptoms remain uncontrolled despite established clinical management. Specifically, patients need options that: (1) have proven efficacy supported by randomised controlled trials (RCTs); (2) provide better symptom control and tolerability than corticosteroids and NSISTs, (3) allow the reduced use of

corticosteroids and (4) target the underlying disease pathophysiology rather than broadly suppressing the immune system.

- Efgartigimod is a first-in-class human IgG1 antibody Fc-fragment that blocks the neonatal Fc receptor (FcRn), leading to targeted reduction of IgG, including disease-causing IgG autoantibodies.[42] In contrast to many therapies in routine use for the treatment of gMG, blocking of FcRn does not result in widespread immunosuppression.[43,44]
- Phase 3 studies have demonstrated that efgartigimod is efficacious and well tolerated in AChR-Ab+ gMG patients whose symptoms remain significantly uncontrolled despite conventional therapy.[42,45,46]
- In recognition of its promising efficacy and acceptable safety profile (observed from clinical trials and prior to marketing authorisation) for a population of patients with high unmet clinical need, efgartigimod was granted promising innovative medicine (PIM) status in November 2021 and a positive scientific opinion by the MHRA under the Early Access to Medicines Scheme (EAMS) in May 2022.[47,48] As of 2 Feb 2023, [redacted] patient requests for efgartigimod were approved from [redacted] specialist centres across England.

B.1.2 Description of the technology being evaluated

A description of efgartigimod is presented in Table 2. The Summary of Product Characteristics (SmPC) and UK Public Assessment Report (PAR) are provided in Appendix C.

Table 2: Technology being evaluated

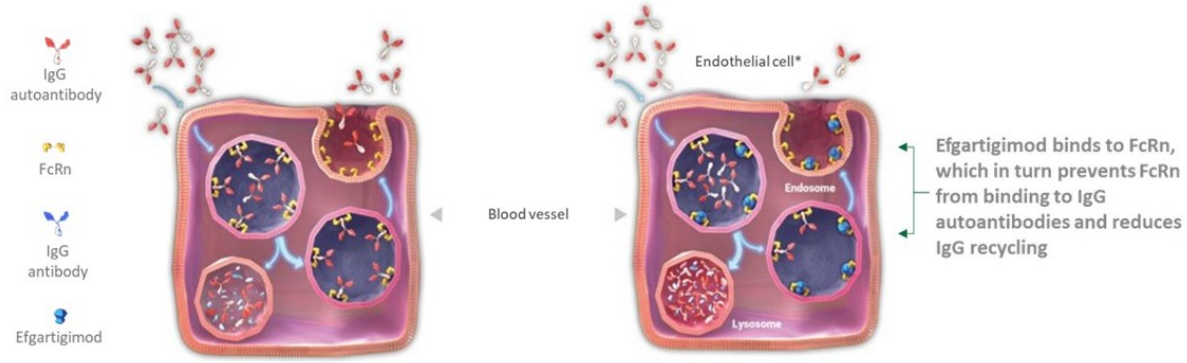
UK approved name and brand name	Efgartigimod (Vyvgart)
Mechanism of action	Efgartigimod is a human IgG1 antibody fragment engineered for increased affinity to the neonatal Fc Receptor (FcRn). Efgartigimod binds to FcRn, resulting in a reduction in the levels of circulating IgG including pathogenic IgG autoantibodies, by preventing recycling and promoting degradation of IgG. FcRn has a specific role in IgG homeostasis, namely recycling IgG and rescuing it from lysosomal degradation.[49] Recycling by FcRn is why IgGs, including pathogenic IgG autoantibodies, have a longer half-life and higher concentration than other immunoglobulins that are not recycled by FcRn.[43,49] By blocking FcRn, treatment with efgartigimod leads to the degradation of circulating disease-causing pathogenic IgG autoantibodies without impacting other immunoglobulins that are not recycled by FcRn.[43,44,49] Therefore, FcRn blocking does not result in widespread immunosuppression, in contrast to many other therapies in routine clinical use for the treatment of gMG (discussed in Section B.1.3.3.4).[43,44] Efgartigimod is a natural ligand of FcRn and binds with high affinity to FcRn in a pH dependent way, reducing all IgG subtypes and allowing the treatment of a broad gMG patient population (Figure 1)[42,44,50,51] Efgartigimod does not affect the levels of other immunoglobulins (IgA, IgD, IgE or IgM), or reduce albumin.[50] IgG autoantibodies are the underlying cause of the pathogenesis of gMG. They impair neuromuscular transmission by binding to AChRs, muscle-specific tyrosine kinase (MuSK) or low density lipoprotein receptor-related protein 4 (LRP4) resulting in debilitating and life-threatening muscle weakness.[50] By selectively reducing IgGs, including pathogenic IgG autoantibodies, efgartigimod specifically targets gMG's underlying disease mechanism and represents a rational and innovative therapeutic approach for the treatment of gMG.

Marketing authorisation/CE mark status	The European commission issued a marketing authorisation for efgartigimod throughout the European Union (EU) on [redacted].[52] Efgartigimod is currently under review by the Medicines and Healthcare products Regulatory Agency (MHRA), and marketing authorisation is expected in Q1 2023 following the Decision Reliance procedure. A decision by the EMA on the application for marketing authorisation of a subcutaneous (SC) formulation of efgartigimod is expected in [redacted]. Following the Decision Reliance procedure, the application for UK Marketing Authorisation will be submitted to the MHRA at the time of CHMP positive opinion ([redacted]) with an anticipated approval in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Efgartigimod is indicated in the EU as an add on to standard therapy for the treatment of adult patients with generalised myasthenia gravis (gMG) who are AChR-Ab+.[50] The anticipated indication for efgartigimod in the UK is aligned with the EU indication.
Method of administration and dosage	Efgartigimod is provided as a sterile concentrate for intravenous (IV) infusion. The recommended dose is 10 mg/kg as a 1-hour IV infusion to be administered in cycles of once weekly infusions for 4 weeks. Administer subsequent treatment cycles according to clinical evaluation. The frequency of treatment cycles may vary by patient.[50] The SC formulation will be given at a dose of 1000mg per week for 4 weeks per cycle. Cycles will be repeated according to clinical evaluation.
Additional tests or investigations	No additional tests or investigations are required to determine eligibility for efgartigimod in this indication beyond those routinely conducted in NHS clinical practice.
List price and average cost of a course of treatment	List price: £6,569.73 per 400 mg vial Cost per treatment cycle (once weekly infusion for 4 weeks): [redacted]† (All costs exclude VAT)
Patient access scheme (if applicable)	A simple discount patient access scheme (PAS) for efgartigimod in the form of a fixed discount of [redacted] has been submitted to NHS England for approval. The Patient Access Scheme Liaison Unit (PASLU) have communicated that they expect to be able to issue advice on or before 20 February 2023. PAS price: [redacted] per 400 mg vial Cost per treatment cycle (once weekly infusion for 4 weeks): [redacted]† (All costs exclude VAT)

†Dose is dependent on patient weight, RDI and wastage. The cost per cycle calculation is explained in Section B.3.5.1

Abbreviations: AChR, acetylcholine receptors; EU, European Union; FcRn, neonatal Fc Receptor; gMG, generalised myasthenia gravis; Ig, immunoglobulin; IV, intravenous; MHRA, Medicines and Healthcare Regulatory Agency; NHS, National Health Service; PAS, patient access scheme; SC. subcutaneous; UK, United Kingdom; VAT, value added tax.

Figure 1: Mechanism of action of efgartigimod



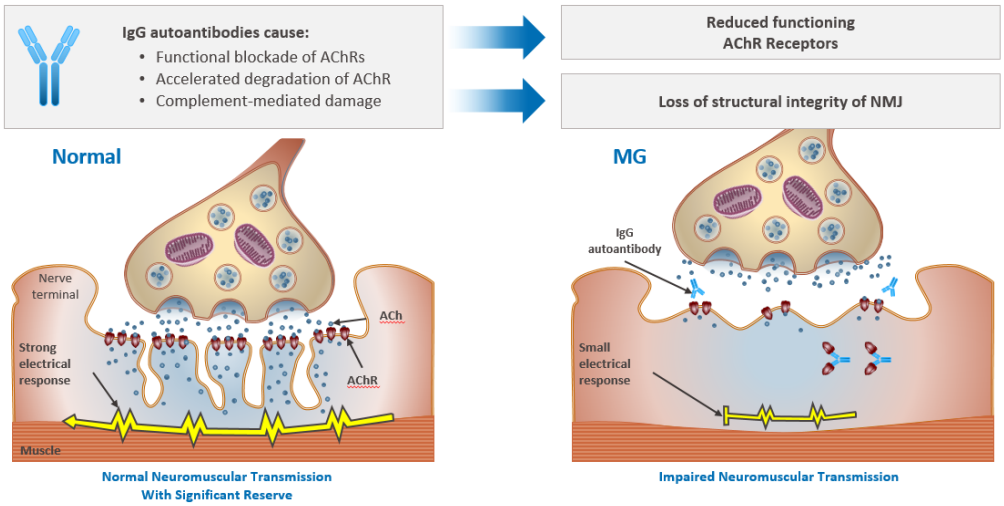
The figure illustrates endothelial cells that line the interior surface of blood vessels.
Abbreviations: FcRn, neonatal Fc Receptor Ig, immunoglobulin.
Adapted from Habib A. Neurol Rev 2020;suppl: 34-36.[53]

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

B.1.3.1 Disease overview

gMG is a rare, chronic, complex neuromuscular disease caused by IgG autoantibodies targeting AChRs and other components of the neuromuscular junction (NMJ), impairing neuromuscular transmission, and leading to the characteristic debilitating muscle weakness and fatigue.[7–9] The NMJ is the site of transmission between nerve endings and skeletal muscle fibres that controls muscle contractions via the neurotransmitter acetylcholine (ACh).[54] The most common IgG autoantibody targets AChR and is detected in 80% of gMG patients.[4,10] Pathogenic actions of IgG autoantibodies include the functional blockade of AChRs, accelerated internalisation and degradation of AChRs, and activation of the complement system, which together results in a reduced density of functional AChR and damage to the neuromuscular junction, leading to failure of neuromuscular transmission (Figure 2).[1,4,7,8,55–59]

Figure 2: Pathophysiology of MG



Abbreviations: ACh, acetylcholine; AChR, acetylcholine receptor; IgG, immunoglobulin G; MG, myasthenia gravis; NMJ, neuromuscular junction
Figure adapted from Kasper DL, Fauci AS, Hauser SL et al. Harrisons Principles of Internal Medicine, 19th Edition. www.accessmedicine.com, McGraw-Hill Education.

IgG antibodies, including pathogenic autoantibodies are regulated by FcRn. FcRn is present throughout life (the term neonatal refers to its discovery in neonatal rodents) and expressed predominantly in endothelial cells and cells of myeloid lineage. FcRn has a specific role in IgG homeostasis and recycles all IgG subtypes (IgG1, IgG2, IgG3, IgG4), rescuing them from lysosomal degradation. This FcRn-mediated recycling accounts for the longer half-life and higher plasma concentrations of IgGs compared to other immunoglobulins that are not recycled by FcRn (half-life is approximately 21 days for IgGs compared to approximately 5–6 days for IgM, IgE, IgA, and IgD).[60,61] In addition, FcRn also promotes transcytosis of IgG into tissues and recycles albumin, which binds at a site that is distinct from the IgG binding site. IgG is taken up by cells and binds to FcRn at the relatively acidic conditions in the early endosome. Bound IgG does not enter the lysosome, in contrast to other unbound immunoglobulins, and is therefore rescued from lysosomal degradation. FcRn returns IgG to the cell surface where at more neutral conditions it is released back to the circulation or transcytosed to other tissues. Therefore in IgG-mediated autoimmune diseases, such as MG, FcRn perpetuates the availability of disease-causing autoantibodies. Blocking FcRn recycling of IgG to selectively reduce IgG levels, including pathogenic IgG autoantibodies, represents a rational and innovative therapeutic approach for IgG-mediated autoimmune diseases, including gMG.

The reason for development of autoantibodies in MG cannot be identified in most patients, but – consistent with its autoimmune nature – a genetic susceptibility combined with environmental factors such as stressful life events, pregnancy, metabolic derangements, viral infections and various drugs (e.g., penicillamine) or toxins have been postulated to precipitate its development.[62,63] It can also be caused by thymoma or thymic dysplasia.[9]

Although there is heterogeneity in the distribution of muscles affected, the characteristic feature of gMG is a fluctuating fatigable muscle weakness. While many patients first present with symptoms affecting eye muscles only (ocular MG), approximately 80% will go on to

develop generalised weakness affecting the neck, trunk, limbs, bulbar and respiratory muscles (gMG).[4,10,19,64]

Patients may experience ptosis (drooping upper eyelid); diplopia (double vision); difficulty making facial expressions; problems chewing and dysphagia (swallowing difficulties); dysarthria (speaking difficulties); weak arms, legs, or neck; and dyspnoea (breathing difficulties).[65] Additionally, central fatigue – defined as a lack of energy physically or mentally – is also common, occurring in 72% of gMG patients.[65,66] Together, these symptoms have a substantial and chronic impact for patients (see Sections B.1.3.2.1 and B.1.3.2.2 for further details).

While symptoms vary over the course of the day, the debilitating muscle weakness caused by gMG can also progress over weeks or months during periods of exacerbation.[67] Muscle weakness is worsened by prolonged physical activity, exposure to heat, and infection. In addition to the chronic debilitating muscle weakness that disrupts the ability to perform normal daily activities and profoundly impairs HRQoL, up to 20% of gMG patients will experience a myasthenic crisis, which occurs when respiratory muscles become too weak to function. Myasthenic crisis often results in respiratory failure, a medical emergency that requires mechanical ventilation.[3,12]

B.1.3.1.1 Diagnosis and classification

Physical and neurological examination are the initial steps for people presenting with symptoms of gMG.[68] The main diagnostic test for gMG is serum anti-AChR antibody testing, as most gMG patients will have abnormally elevated levels of AChR antibodies.[19,68] Serum anti-MuSK antibody testing is performed for all people strongly suspected of having gMG but whose test results are negative for AChR antibodies. Neurophysiology tests may also help to establish the diagnosis in seronegative patients with suspected gMG. In patients with negative serology and neurophysiology, an MRI brain scan may be required to exclude other diseases. All patients with suspected MG, irrespective of type (ocular/generalised) or serology (seropositive/negative), should undergo thymus imaging with CT or MRI to detect thymoma. MG is often associated with thymic abnormalities; thymic lymphoid hyperplasia and thymoma can be found in up to 65% and 15% of patients, respectively.[69]

The Myasthenia Gravis Foundation of America (MGFA) clinical classification is used to categorise MG patients based on clinical features and/or disease severity (Table 3).[10] The classification ranges from Class I (i.e., ocular weakness only) to Class V (i.e., myasthenic crisis).

Table 3: MGFA clinical classification

Class	Characteristics
I	Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
II	Mild weakness affecting muscles 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 muscles 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 muscles 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.
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.

Abbreviations; MGFA, Myasthenia Gravis Foundation of America
Source: Jaretzki et al, 2000[70]

B.1.3.1.2 Patient-reported outcomes to assess disease activity and severity

Patient-reported outcome (PRO) instruments are critical for monitoring changes in gMG symptom severity in clinical trials and clinical practice. This is because the signs and symptoms: (1) fluctuate over time, (2) may worsen later in the day, and (3) are often more evident to the patient than to the physician (e.g., dysphagia and chewing fatigue).[71,72]

The MG-ADL questionnaire is a reliable and validated PRO instrument comprising eight items assessing the frequency and severity of symptoms relevant to gMG patients and their effects on daily activities.[72] These symptoms relate to ocular function, speech, chewing, swallowing, respiratory function, and strength of proximal upper and lower extremities. A higher score indicates more severe symptoms. As shown in Section B.1.3.2.2, worsening MG-ADL scores are associated with declining EQ-5D-5L utilities.[73] UK clinicians report that the MG-ADL is simple and quick to administer in clinical settings and will routinely complete the questionnaire at most appointments.[30] Most published and ongoing Phase 3 trials use the MG-ADL as their primary endpoint.[74]

The MG-ADL may be supported with other PRO and clinician-reported disease-specific clinical scales which have been validated to assess the severity of muscular weakness and response to treatments for gMG; these scales include the MG quality of life 15 (MG-QOL15) quantitative MG (QMG) scale and the MG composite (MGC) scale (Table 4).[74] These scales are also commonly used in clinical trials of treatments for MG to assess responses to treatment.[72]

Table 4: Description of key validated disease specific HRQoL and disease assessment scales for gMG

Instrument	Reporter	Description	MCID
MG-ADL	Patient	An eight-item scale developed to assess MG symptoms and their effects on daily activities. Responses for each item are given on a 4-point scale, representing normal (0) to severe (3), and the total score ranges from 0 to 24, with higher scores indicating more severe MG symptoms.	≥2 point reduction

MG-QOL15	Patient	A validated HRQoL questionnaire that evaluates four domains: mobility (nine items), MG symptoms (three items), general contentment (one item), and emotional well-being (two items). Responses for each item are given on a 5-point scale: not at all (0), a little bit (1) somewhat (2), quite a bit (3), and very much (4), and the total score ranges from 0 to 60, with higher scores indicating more severe MG.	Dependent on disease severity
QMG	Physician	The QMG objectively assesses muscle strength and fatigability using objective measures of double vision, ptosis, facial muscles, dysphagia, dysarthria, proximal limb, hand muscles, neck muscles and respiratory function. Each item is given a score of 0–3, resulting in an unweighted total score of 0–39. A higher score corresponds to more severe disease.	≥3 point reduction
MGC	Physician and patient	Evaluates a patient's ocular, neck and proximal limb muscles using quantitative tests and spirometry. Furthermore, four patient-reported items assess speech, chewing, swallowing and respiratory function. Total score spans from 0 to 50; a higher score indicating more severe disease.	≥3 point reduction

Abbreviations: MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QOL15, Myasthenia Gravis Quality of Life scale 15-item; MGC, myasthenia gravis composite; QMG, quantitative myasthenia gravis scale.
Source: Barnett et al, 2018[75]

B.1.3.1.3 Epidemiology

MG is a rare disease that affects about 15 in every 100,000 people, equivalent to 7,050 patients in England.[33] MG affects people of any age, sex, race and ethnic background although is slightly more prevalent in people of African ancestry.[2,9,62,76,77] Incidence rates have a bimodal distribution in women, with peaks around age 30 and 50 years. In men, the incidence increases steadily with age with the highest rates between age 60 and 89 years. Women are more commonly affected before age 40, with a female: male ratio of 3:1. In their 40s, women and men are equally affected, while men have a higher proportion after age 50, with a male:female ratio of 3:2. In Europe and North America, childhood MG is uncommon; only around 10% of cases are diagnosed in children before age 18.[9]

An estimated 80% of prevalent MG patients will develop gMG, of whom 77.2% will have AChR-Ab+ disease.[42,54] Treatment goals are for gMG patients to experience normal or near-normal function with little weakness or fatigue due to gMG (i.e., remission), and no or only mild side effects from medication.[19] Despite treatment with current standard of care many patients continue to experience substantial disease burden and debilitating symptoms that profoundly impact their quality of life. Although a number of treatments are used for gMG – described in Section B.1.3.3.2 – most are unlicensed for this condition, the evidence for their efficacy is variable and they have side-effects that are either incompatible with co-morbidities that are common in people with gMG or which deter patients from wanting to use them.[11,34,36,78] This combination of limited efficacy and treatment burden means that many patients continue to experience substantial disease burden and debilitating symptoms even with treatment. One published estimate is that between 10% and 30% of gMG patients have disease that is uncontrolled as a result of such difficulties.[54] UK clinical opinion confirms 20% for the proportion of gMG patients who are uncontrolled despite current treatments as being a reasonable mid-point estimate.[30]

B.1.3.2 Burden of generalised myasthenia gravis

gMG is a rare, chronic, neuromuscular autoimmune disease mediated by pathogenic IgG autoantibodies that cause debilitating and potentially life-threatening muscle weakness, disrupting the ability to perform normal daily activities and profoundly impairing HRQoL.[1–9] The muscle weakness experienced by gMG patients severely impacts their day-to-day functioning, which can lead to difficulties with swallowing, vision, speech, breathing, and mobility, as well as extreme fatigue. The symptoms can be further worsened by infection, changes in gMG treatments, use of aggravating medications, or emotional stress.[11,65] Additionally, up to 20% of gMG patients experience a myasthenic crisis, affecting the muscles that control breathing and resulting in life-threatening respiratory impairment, at least once in their lives.[3,12] Overall, the negative impact arising from the symptoms of gMG includes work and lifestyle planning limitations, productivity losses, and need for caregivers.[79,80]

Despite standard therapy, many patients continue to experience substantial disease burden and debilitating symptoms that profoundly impact their quality of life.[11,34,36,78] Just 25% of MG patients are able to achieve pharmacological remission (e.g., symptom control with existing treatment), and only 8% achieve clinical remission (no symptoms off-treatment for more than a year.[41] Furthermore, existing therapies are burdensome for patients demonstrated by 48% of patients experiencing treatment-related side effects and 37% reporting having discontinued therapy in the past (56% of those patients discontinued due to side effects).[41]

B.1.3.2.1 Clinical burden

Physical burden

A German HRQoL study in 1,518 gMG patients with an average disease duration of 10.2 years found that most patients (82%) considered their disease stable. However, despite this stability, 75% still experienced limited mobility due to muscle weakness after physical strain, 71% had weakness in their upper limbs, and 70% had walking problems (Table 5).[34] Problems with swallowing, chewing, defecation, and vision were also common. Overall, these data highlight that many patients with stable disease have a significant symptom burden and multiple sources confirm high rates of patient dissatisfaction with their symptom state despite treatment.[78,81]

Table 5: Proportion of patients experiencing MG-related impairment, based on German survey (N=1,518)

Impairment	Patients (%)
Muscle weakness after physical strain	75.4
Weakness of upper limbs	71.3
Walking problems	69.6
Dysphagia	43.9
Chewing problems	39.1
Defecation problems	38.5
Ptosis	37.8
Diplopia	37.8
Neck weakness	31.6
Speech disorders	28.9
Facial expression disorders	25.9
Urination problems	24.9
Sexual disorders	18.7
Muscle weakness at rest	16.9

Abbreviations; MG, myasthenia gravis. Multiple answers possible.
Source: Twork et al, 2010[34]

Mental burden

Mood disorders are common in gMG patients. A review of studies describing affective disorders in patients with MG included 6,060 patients from 32 studies worldwide between 1971 to 2020. The review identified that approximately one-third of MG patients exhibit depression, and nearly half exhibit an anxiety disorder.[82] Depression has been found to be a statistically significant prognostic indicator of poor HRQoL in MG patients and is associated with decreased motivation for self-care and significant limitations in physical abilities along with increased mortality rates.[82] Likewise, depression also correlates with increased somatic complaints, ambulatory visits, and healthcare costs, all of which may contribute to poor HRQoL in MG patients.[82] Whereas, experts from leading studies have postulated that the higher rates of anxiety disorders, including generalised anxiety, panic disorder, and agoraphobia, can be attributed to the unpredictable, fluctuating nature of respiratory dysfunction, which can be exacerbated by physical or emotional stress.[82] Higher rates of anxiety in MG patients with respiratory distress are thus an element of anticipatory anxiety, given the presence of erratic, potentially life-threatening episodes of significant respiratory distress and apprehension about treatment with mechanical ventilation.[82]

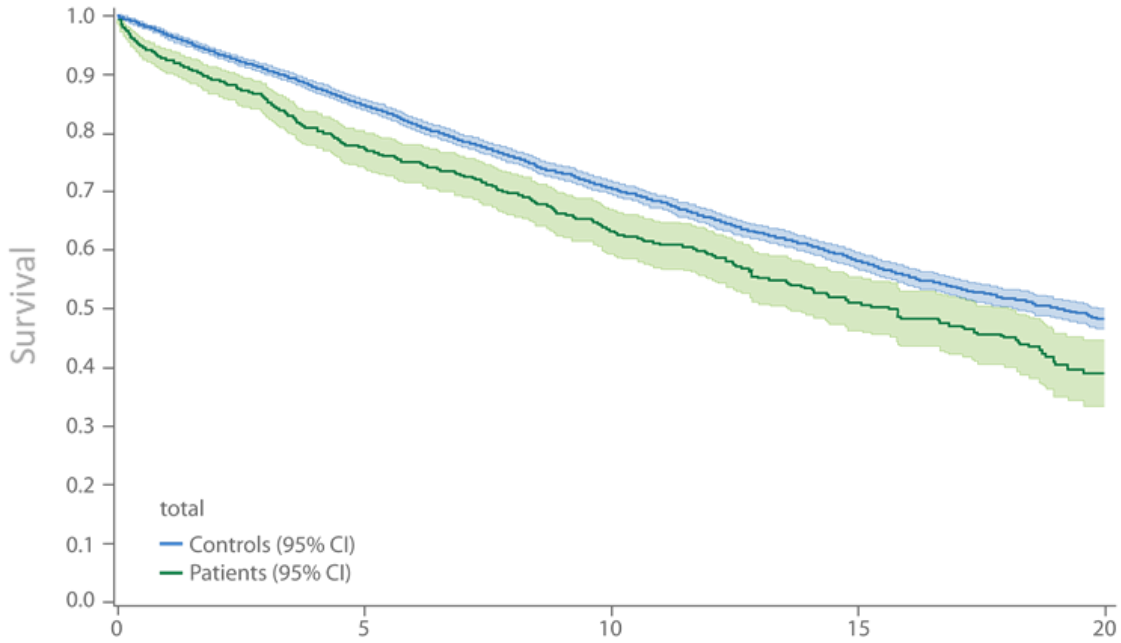
Although data has been conflicting, there may be an association between gMG and cognitive decline. A meta-analysis of eight cross-sectional studies containing 381 patients and 220 healthy controls identified that gMG patients have poorer global cognitive function than the healthy controls.[83] In this study, the domains of language, visuospatial function, information processing, verbal immediate and delayed recall memory, visual immediate recall memory and response fluency were affected in gMG patients.[83] On its own, lower cognitive function and cognitive decline increase the risk of mortality, disability and poor quality of life, and thereby add to the negative outcomes experienced by gMG patients as a result of their disease.[84]

Mortality

For some patients, gMG can be life-threatening, when weakness of diaphragm and intercostal muscles leads to myasthenic crisis due to respiratory failure or when impairment of swallowing and coughing ability results in pulmonary aspiration and pneumonia.[64] Management of myasthenic crisis requires extended intensive care support including invasive or non-invasive ventilation, with an average duration of intubation of 5 days.[63,85] Complications of myasthenic crisis include fever, respiratory infections, atelectasis, arrhythmias, heart failure, and hypotension.[17] Dysarthria, dyspnoea, and weakness of tongue, larynx, vocal cords or throat muscles may occur. Altogether, these symptoms impair patients' ability to get help during a myasthenic crisis, even when hospitalised.[64]

There is variation between studies in the estimates of mortality in gMG patients. While survival has improved over time, a nationwide population-based study of all patients diagnosed with MG between 1985 and 2005 in Denmark found overall mortality remained significantly higher in MG patients than in the general population (mortality rate ratio [MRR]: 1.41 [95% confidence interval (CI) 1.24, 1.60]), particularly within the first 5 years of diagnosis (MRR: 1.67 [95% CI 1.41, 1.98]) (Figure 3).[86] A similar nationwide retrospective database analysis of four Swedish National Board of Health and Welfare registers (2006–2016), could not confirm a higher mortality rate compared to the general population but found that the estimated time from MG diagnosis to death was 8.9 ± 6.8 years. MG was the third most common ultimate cause of death in these patients (cancer: 19.5%; ischaemic heart disease: 13.3%; MG: 11.3%).[87] Estimates of mortality in myasthenic crisis are also heterogeneous, and this proportion changes across studies, usually ranging from 5%–22%.[85]

Figure 3: Kaplan–Meier survival curves with 95% CIs for AChR-Ab+ MG patients compared with controls



Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; CI, confidence interval, MG, myasthenia gravis
Source: Hansen et al, 2016[86]

Chronic use of corticosteroids is associated with an increased risk of mortality. Data from a retrospective, record-linkage, open-cohort study spanning primary and secondary care in England between 1998 and 2017 reported a two-fold risk of death in patients chronically exposed to corticosteroids for the treatment of inflammatory diseases compared to the general UK population. The increased risk of adrenal adverse events and death was observed in patients taking the equivalent of 5 mg of prednisolone per day and above.[88]

Treatment burden

The side effects of treatments for gMG symptoms further add to the clinical burden of gMG.[89] Prolonged corticosteroid use can cause osteoporosis, weight gain, cardiac conditions, gastrointestinal conditions, hypertension, glucose intolerance, and diabetes.[17] As stated in international consensus guidance, it is usually necessary to maintain immunosuppression for many years, sometimes for life, which predisposes patients to opportunistic infections.[21,22,90,91] A Canadian study of 3,823 MG patients followed over 5 years found MG was associated with a 39% increased infection risk compared with matched controls.[92] Respiratory infections, including bacterial pneumonia, septicaemia, and skin/soft tissue infections were the most common infections reported in the study. The unmet need for current therapies is described further in Section B.1.3.3.4.

B.1.3.2.2 Patient burden

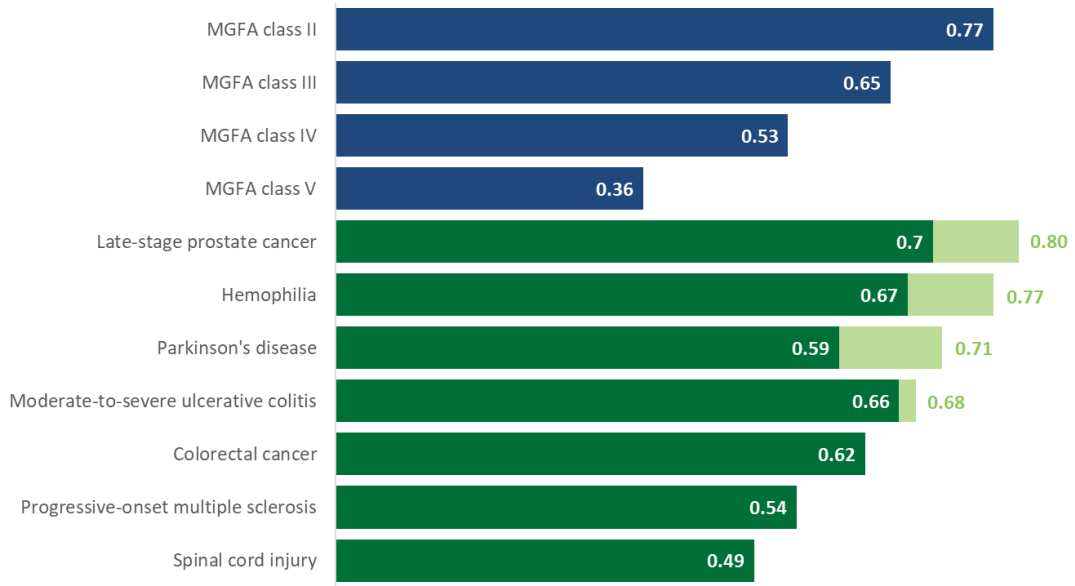
Multiple studies have found that the overall HRQoL for MG patients is reduced compared with healthy control populations.[33,34,41] The profound negative impact on MG patients' HRQoL is due to:

- debilitating physical impairments caused by muscle weakness[33,34,36]
- poor psychological well-being, including significant fatigue, depression, and anxiety[11,33,82,93]
- treatment-related side effects, mainly due to the long-term use of immunosuppressive therapies[33,37]
- comorbid autoimmune conditions[34,94]

HRQoL reduction is often greater in female MG patients compared with men, possibly due to a longer duration of disease.[13] Older age, older age at onset of disease, obesity, lack of employment, low educational attainment, and low physical activity have also been shown to negatively affect HRQoL in MG.[37,93] A 10-year longitudinal study in 78 MG patients found that even in remission, patients' HRQoL was reduced.[93]

The MyRealWorld MG study is a prospective, observational, longitudinal study aiming to capture the impact of MG from the patient perspective. Based on an interim analysis of responses from 610 patients (70% female, mean age 47 years) from the UK, Canada, Germany, Italy, Japan, Spain, and the US who completed the EQ-5D-5L at baseline, gMG patients have lower EQ-5D-5L utility values than the general population of the same age and gender (mean utility: 0.69 vs 0.86).[95] The study also demonstrated that utility was significantly associated with disease severity as defined by MGFA class; utility values significantly declined with higher MGFA class ($p<0.0001$), indicating worsening HRQoL with greater disease severity. These values are similar to, or worse than, those associated with several debilitating diseases (Figure 4).[71,95,96]

Figure 4: Mean EQ-5D-5L utility scores from the MyRealWorld MG study based on MGFA classification, with comparison across other diseases



Abbreviations: MGFA, Myasthenia Gravis Foundation of America; EQ-5D-5L, EuroQoL 5 dimension 5-level HRQoL instrument
High- and low-end values for other diseases are based on utilities provided in relevant publications identified in a systematic review by Zhou et al.
Sources: Dewilde et al, 2021[73,95]; Zhou et al, 2021[96]

Utility decreases were also significantly associated with worsening in scores on the Myasthenia Gravis Activities of Daily Living (MG-ADL) and Myasthenia Gravis 15-item Quality of Life (MG-QOL15) scales, depression, anxiety, need for caregiver help, and additional comorbidities (Table 6). This indicates that reduced ability to perform activities of daily living, impairment of physical and mental health, and the necessity for a caregiver all significantly diminish the HRQoL of gMG patients.[73]

Table 6: HRQoL utility decrements in gMG patients

Event	Utility decrement	p value
Worsening in MG-ADL total score (1-point decline)*	0.0375	<0.0001
Worsening in MG-QOL15 total score (1-point decline)	0.0207	<0.0001
Depression Mild Moderate Severe	 0.121 0.230 0.408	<0.0001
Anxiety Mild Moderate Severe	 0.078 0.147 0.252	<0.0001
Needing caregiver help	0.236	NR
Comorbidities	0.105	<0.0001

NR, not reported; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MG-QOL15, Myasthenia Gravis 15-item Quality of Life scale
*The MG-ADL is an eight-item patient-reported scale developed to assess MG symptoms and their effects on daily activities.[97] Responses for each item are given on a 4-point scale, representing normal (0) to severe (3), and the total score ranges from 0 to 24, with higher scores indicating more severe MG symptoms.
Source: Dewilde 2021[73]

The everyday burden of gMG for patients is substantial. The fluctuating and unpredictable nature of symptoms affects the ability to plan for the short-, medium- and long-term and diminishes all aspects of a patient's life.[89] Patients describe how the muscle weakness and fatiguability that they experience with gMG means they have to make continuous adaptations and trade-offs when working or taking care of themselves or their family, leading to a sense of loss due to restrictions in activity and limitations in life choices.[89] They rely on coping mechanisms such as long-term planning, frequent breaks, reducing the amount or type of work they do, proactively cancelling plans if necessary and adapting the ways in which they conduct activities of daily living such as eating or personal hygiene.[89] It has been estimated that about one-third of patients require regular care from their partner. Beyond this, many patients also report central fatigue, experienced as a lack of physical and/or mental energy, which is associated with reduced quality of life. In spite of this exhaustion, gMG patients frequently experience disrupted sleep.[89]

A study capturing the perspectives of 48 gMG patients and six caregivers from around the world, including from the UK, provides insights into the reality of living with gMG (Table 7).[89] Insights were consolidated from qualitative research, a Patient Council of patient advocates, and a literature review.

Table 7: Statements describing the lived experience of gMG by key domains[89]

Domain	Patient quotes
Physical	'Every patient will have muscle weakness, but the difficulty to live with is that it is so unstable…the fluctuation is even worse to live with than the muscle weakness itself'
	'You feel it from the moment you wake up and you have to adjust your routines and expectations; I live day by day. Those bad days you need to prioritise the most important activities, or the most basic, and try to work with your medication'
Psychological	'You don't know how you will feel from one day to the next or what the future holds'
Social	'Soon I couldn't breathe or speak well enough to chat with friends on the phone, much less meet for a social gathering. My world grew smaller and my close friends less numerous. I aimed my loneliness at books—both the reading and writing of them. But when my eyes couldn't work well enough to read a page, and when my muscles were too wobbly to allow me to write for more than a few moments at a time, I retreated even further into the solitude of my mind'
Family	'I was really willing to look after my children, but that made me get worse. It was too difficult to fulfil a mother's responsibility with MG. I did not bring up my children by myself, I feel regret for losing intimacy with them. Meanwhile because of my disease, I was abandoned by my husband'
Flare-ups	'Whenever I think about joining in on strenuous activities with friends…I'm never sure how far I'll make it'
Treatment burden	'Living with the idea that these medicines have bad side effects, you want to get by on the lowest meds you can even if you know you could be stronger on 20 mg instead of 5 mg, people are living with that trade

Domain	Patient quotes
	off and that's why we need better treatments and not after everything else has failed you'
	'There is a disconnect sometimes. One of the leading doctors in MG was quoted in a magazine saying 80% of his patients are in remission. Patients say "He may think I'm in remission, but I'm taking 20–30 mg prednisone, I have all these side effects. It's not adequate control"'
Uncontrolled MG	'It is particularly frustrating [for people with refractory disease] to read that most people with MG are well managed on treatment, or have "normal" lives, when their experiences are quite the opposite'

Abbreviations: CV, curriculum vitae; MG, myasthenia gravis

Currently, a high proportion of gMG patients feel their disease could be controlled better. Many are living with trade-offs between feeling better and having side effects from their treatments that diminish their quality of life. Some are willing to accept a greater treatment burden, for example, although IVIg can have a positive impact on reducing gMG symptoms, it requires a significant time commitment and some people experience intolerable side effects.[89] Ultimately, patients would like a cure for gMG, but in the absence of that, treatments offering better long-term efficacy and tolerability would be an improvement on the existing treatment paradigm. The psychological consequences of exacerbations are severe, and patients fear experiencing a myasthenic crisis. Previous traumatic experiences such as being intubated can leave people with psychological distress and a reluctance to return to hospital in future.[89]

The ability to work and contribute financially to their households can present challenges for gMG patients. Eye fatigue, neck pain, the ability to smile or speak, or problems staying alert make both desk based and manual jobs difficult and may prevent patients undertaking a full-time role. The impact of gMG on patient's ability to drive can also be a barrier to employment and negatively impacts independence.

Beyond the aptitude to complete work tasks, gMG patients are also often concerned about the emotional stresses of gMG manifesting in the workplace, or, conversely, the stress of work negatively impacting their disease.[89] Employer attitudes vary considerably, and can even affect the treatments gMG patients are able to commit to; for example, they may not feel able to take time away from work to receive infused treatments.[89] As a result of all of these factors, unemployment rates are high, with an estimated 55% of gMG patients unable to work at all.[15] Even in those who were still employed, MG patients were 9 times more likely to take long-term sick leave than the general population.[98] Many of these issues are also relevant to the ability of both children and adults with gMG to pursue educational activities.[89]

B.1.3.2.3 Economic and societal burden

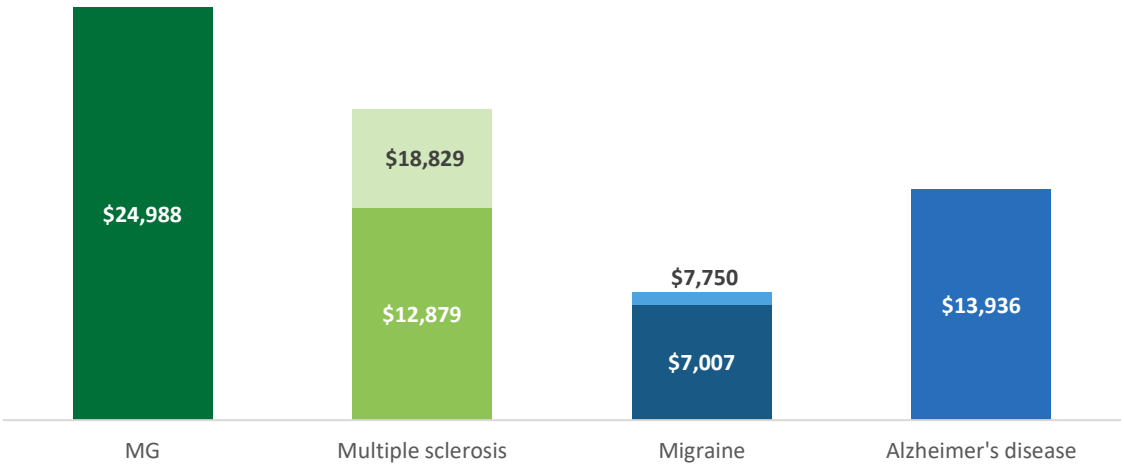
As a chronic debilitating disease, gMG has a serious impact on healthcare resource utilisation (HCRU), direct healthcare costs, and productivity.[13–15]

B.1.3.2.3.1 Direct costs

Data describing direct costs of gMG in the UK are sparse and have been supplemented here with international comparisons. Most studies describing the direct cost of MG focus on costs

for hospital admission for IVIg or PLEX treatment, or for myasthenic crisis, although pharmacy costs are also reported in some studies. Based on a study by Guptill et al. in 1,288 patients diagnosed with MG from a nationwide medical and pharmacy claims database, the annual per-patient costs for MG management in the US are $24,988. This is considerably higher than estimated costs for many other chronic neurological diseases (Figure 5).[14]

Figure 5: Mean annual costs of chronic neurological diseases (US)



Abbreviations: MG, myasthenia gravis
Costs for MG based on insured US patients, 2008–2010. Dark and light bars represent estimated cost range for multiple sclerosis and migraine.
Source: Guptill at al, 2011[14]

Evidence suggests that the high economic burden in terms of direct costs of illness associated with gMG is largely driven by hospitalisation costs for mechanical ventilation, IVIg, and plasmapheresis or PLEX.[16,99] Costs appear to also be driven by very high healthcare utilisation in some patient groups. For example, Guptill et al. reported that the subset of US patients who received more than 20 infusions of IVIG in the 2-year study period (determined from the health plan payments) accounted for 62% of all MG-related pharmacy costs.[14]

Contact with health services is frequent. A German survey of 1,518 MG patients and an average disease duration of 10.2 years found that 68% of patients consulted a doctor >6 times per year, and 34.1% >12 times per year. Patients also reported having further treatment by physiotherapists (11.1%) or consulting a healer or non-medical practitioner (4.2%).[34] In the UK, a retrospective, longitudinal cohort study of patients in England aged ≥ 18 years with gMG, using data recorded during 1997–2016 in the Clinical Practice Research Datalink and the Hospital Episode Statistics databases was completed.[17] The study identified that of a total of 1,149 patients, 38.6% experienced MG-related hospitalisations.[17] Most of the events occurred within the first 2–3 years after diagnosis. The study did not provide information on the average duration of admission, however evidence from other countries describes that the length of stay for hospitalised gMG patients ranges from 4 to 10 days. Patients who needed mechanical ventilation experienced longer average admissions of 17 to 22 days.[16,100–104]

A systematic review including estimates of costs of MG from eight countries across Europe, North America, South America and Asia estimated the mean per-patient cost per hospitalisation, all based on claims data, ranged between $2,550 and $164,730 (in 2018 US dollars).[99] The lowest estimate was derived from a sample of 936 Thai patients hospitalised for MG, and the highest for 994 US patients hospitalised for MG requiring continuous mechanical ventilation.[102,105] In relation to all US hospital admission that calendar year, Omorodion et al. estimated the mean per-patient added cost per hospitalisation for MG exacerbation in the US in 2013 at $59,340 ($98,800 vs. $39,460).[104]

The mean per-patient cost of IVIG as a treatment for myasthenic crisis/exacerbation was estimated at $6,620 in Canada (including hospital costs, costs of blood products, and physician fees) and $90,760 in the US (including cost of therapy, cost of hospitalisation, and cost of secondary complications).[99,106,107] Corresponding estimates for PLEX were $4,990 and $116,470, respectively.[106,107] In addition, Mandawat et al. estimated the median per-patient hospital cost (reflecting total hospital charges) of IVIG and PLEX in the US at $28,080 and $35,450 in MG patients, and $45,100 and $71,520 in those with myasthenic crisis.[103]

B.1.3.2.3.2 Indirect costs

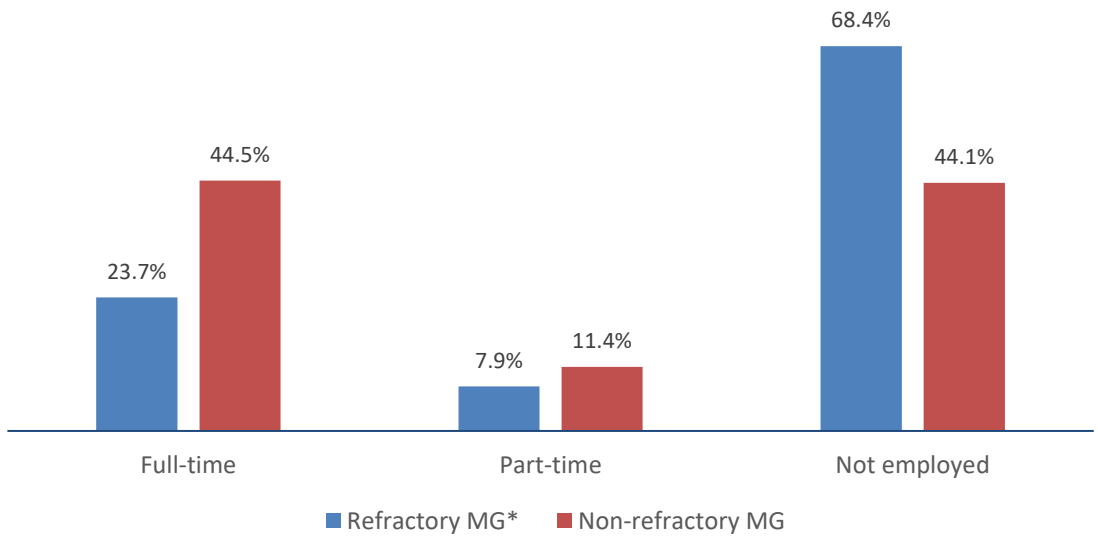
The indirect burden due to disability and impaired HRQoL in MG patients is high, adversely affecting personal finances due to absence from the labour market.[25,90]

MG is typically diagnosed in women at the peak of their working age (30–50 years old). A meta-analysis covering 3,600 working-age MG patients, with an average age of 48 years (range 35–60), estimated that only around 50% of MG patients were employed.[15] This is higher than the employment rate reported in a survey of 1,518 German MG patients, in which approximately 30% of patients reported being employed.[34] A community-based survey of 165 Australian patients found 40.6% were working at the time of the survey and of these, almost half had required sick leave due to MG in the past 12 months.[94] A further 39.4% had stopped work due to MG and 19.4% had to change occupation.

In the previously discussed German study, 58% of respondents had a disability pass, with an average degree of disability recorded in their passes as 68%. This aligns with disability-related retirement being a main reason for unemployment.[34] German patients also reported that: MG influenced their job choice (8.1%); they changed job due to their MG (8.5%); they experienced hardships in their job (21%); and they were forced to retire early due to MG (28.3%). Nearly 77% of respondents reported out-of-pocket spending at €25–500 per month for assistance with housekeeping, transportation and for prescription charges due to their MG.[34]

A US study examined the impact of MG on employment. The study compared patients with refractory and non-refractory MG enrolled in the MGFA registry from 2013 to 2018 and found in both groups, >50% of patients worked part-time hours or were unemployed (Figure 6).

Figure 6: Proportion of patients with refractory MG* and non-refractory MG in employment, based on a US registry study (N=825)



Abbreviations: MG, myasthenia gravis
*Participants were considered to have refractory MG if their past treatments included ≥2 immunosuppressant therapies (azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate, prednisone, rituximab, and/or tacrolimus) for ≥6 months each, or ≥1 of the immunosuppressant therapies for any duration plus repeated use of IVIg or plasmapheresis (≥4 rounds in the previous year). Participants with refractory disease were also required to have reported the following at enrolment: current use of ≥1 immunosuppressant therapies, IVIg, or plasmapheresis; and a total score for the MG-ADL scale of ≥6. Participants who did not meet the criteria for refractory MG were considered non-refractory, regardless of their MG-ADL scale score.
Source: Harris et al, 2019[108]

B.1.3.3 Current treatment pathway

B.1.3.3.1 Goals of treatment

gMG is a chronic disease, and the majority of patients need long-term and often lifelong treatment. Approximately 90% of gMG patients cannot maintain normal muscle strength without medication.[3,20] The goals for treatment are for patients to experience normal or near-normal function with little weakness or fatigue due to gMG (i.e., remission), and no or only mild side effects from medication.[19] Despite this, as discussed in detail in Section B.1.3.3.4, current treatments are associated with substantial tolerability and safety concerns due to broad suppression of the immune system.

B.1.3.3.2 UK HTA recommendations and national commissioning policies

A summary of the UK HTA recommendations and national commissioning policies for treatments for gMG are provided in Table 8. To date, there are no published positive reimbursement recommendations for treatments for gMG in England, Scotland or Wales. HTA assessments are in progress for ravulizumab (NICE) and efgartigimod (SMC and NICE) and are expected to be published in 2023.[109,110]

NHS England and the AWTTC have published commissioning statements recommending the use of the biosimilar rituximab in a group of patients whose disease is refractory to standard therapy, following referral and assessment by a myasthenia clinic within a

specialised neuroscience centre.[31] Additionally, NHS England have published commissioning guidance for the use of IVIg in immunology, haematology, neurology and infectious diseases. This guidance recommends the use of IVIg to patients requiring urgent treatment for gMG or as maintenance therapy for chronic gMG when a patient has failed all standard therapy (including steroids and immunosuppression) under the recommendation of a specialist neuromuscular service.[111]

Table 8: HTA or national commissioning policy recommendations for gMG

HTA or Commissioning body	Type	Recommendation
NICE	Guideline	NG127: Suspected neurological conditions: recognition and referral[112]
	Quality Standard	QS198: Suspected neurological conditions: recognition and referral[113]
	Single technology appraisal (*terminated)*	Eculizumab. Assessment terminated, no recommendation for AChR-Ab+ patients with refractory gMG[114]
	Single technology appraisal *(in progress)*	Ravulizumab for generalised myasthenia gravis [ID4019]. **Expected publication 26 July 2023**[109]
NHS England	Commissioning policy	Rituximab biosimilar for the treatment of myasthenia gravis (adults)[31]
	Commissioning guidance	The use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England[111]
SMC	*Non submission*	Eculizumab. Assessment terminated. Not recommended for use within NHS Scotland for AChR-Ab+ patients with refractory gMG[115]
	Full *(in progress)*	Efgartigimod as an add on to standard therapy for the treatment of adult patients with gMG who are AChR-Ab+. The NDC meeting date is scheduled for [redacted] [110]
AWTTC	One Wales interim decision	OW12: Rituximab for the fourth-line or later treatment of refractory MG in adults*[32]

*the One Wales interim decision provides the same access to rituximab in refractory MG as the NHS England commissioning policy for rituximab biosimilar for the treatment of MG.
Abbreviations: AChR-Ab+, anti-acetylcholine receptor antibody positive; AWTTC, All Wales Therapeutics and Toxicology Centre; gMG, generalised myasthenia gravis; NDC, New Drugs Committee; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium

B.1.3.3.3 Current treatment guidelines

Available clinical practice guidelines and international consensus statements for the management of gMG broadly describe a similar treatment pathway. As a result of a historically limited evidence base – including use of medicines that did not meet the primary endpoint in clinical studies – and the extensive use of off-label treatments – recommendations are largely based on anecdotal clinical experience.[20,21,40] There is no single, universally accepted treatment algorithm for gMG.[116] Table 9 lists the guidelines and consensus documents referenced in the subsections of Section B.1.3.3.

Table 9: Clinical practice guidelines and consensus statements describing the treatment of patient with gMG

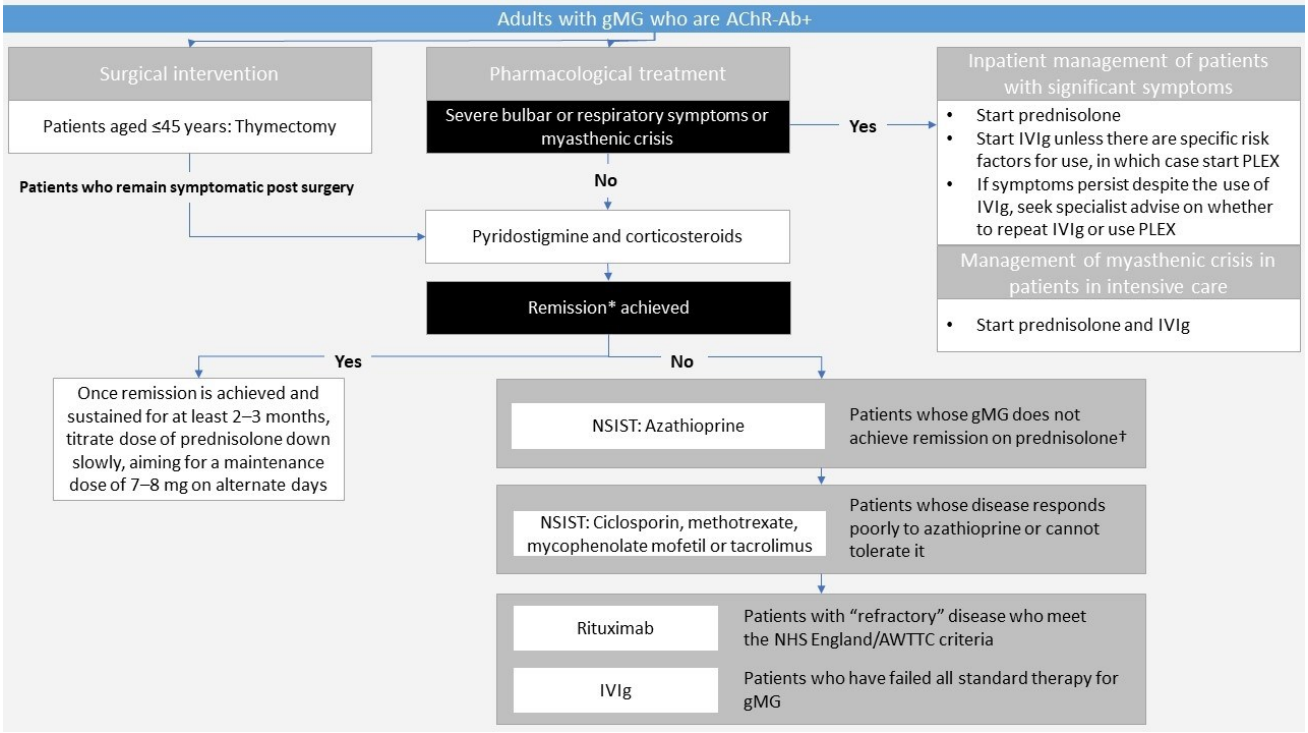
Author	Year	Title
Sussman J et al.[19,117]	2015	Myasthenia gravis: Association of British Neurologists' management guidelines
Narayanaswami P et al.[21]	2020	International consensus guidance for the management of myasthenia gravis (Myasthenia Gravis Foundation of America): update
Sanders DB et al.[20]	2016	International consensus guidance for the management of myasthenia gravis (Myasthenia Gravis Foundation of America)
Farrugia ME and Goodfellow JA[116]	2020	A practical approach to managing patients with myasthenia gravis: opinions and a review of the literature
Melzer N et al.[22]	2016	Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society
Skeie G.O et al.[40]	2010	European Federation of Neurological Societies guidelines for treatment of autoimmune neuromuscular transmission disorders

This submission focuses on the guidelines presented by the Association of British Neurologists (ABN), which UK experts confirm broadly reflects treatment patterns in England and Wales.[30] However, the ABN guidelines, due to be updated in 2023, were originally published in 2015 and therefore do not include all current NHS commissioned treatments for gMG.

Figure 7 describes the current treatment recommendations from the ABN for gMG, as well as the NHS commissioning policies for rituximab and IVIg.[19,31,32,111,117] The ABN guidelines recommend initiating treatment for gMG with pyridostigmine, an AChEi, but most patients do not experience an adequate response to this treatment alone and will require further treatment with corticosteroids as well as NSISTs, such as azathioprine, mycophenolate mofetil, methotrexate, ciclosporin or tacrolimus, in an attempt to control their symptoms.[19] While the treatment schema suggests a stepwise approach through the treatment pathway, in practice conventional therapies are selected according to patient characteristics, comorbidities and severity of symptoms. Treatments may be used individually or in combination, with some treatments starting before others – e.g., corticosteroids – are tapered.

In the ABN guidelines, IVIg and PLEX are broadly reserved for inpatient management for significant symptoms or during myasthenic crisis.[19] However, they note that patients whose disease fails to respond to corticosteroids or cannot tolerate their increasing dose may be considered for IVIg or PLEX following expert neurologist review. Additionally, the NHS England commissioning guidance recommends IVIg outside of the acute setting only as maintenance therapy for chronic gMG when a patient has failed all standard therapy for gMG.[111] Although general guidance is offered in the ABN recommendations, the management of gMG patients whose symptoms remain significantly uncontrolled despite established clinical management are poorly defined and rely on the judgement of treating clinicians in consultation with patients.[19,117]

Figure 7: UK treatment pathway for gMG based on ABN guidelines and national commissioning policies



*Remission of gMG on corticosteroid therapy is defined as the absence of symptoms or signs after pyridostigmine withdrawal.
†A corticosteroid dose above15–20 mg on alternate days is unacceptable for long-term use and is considered an indication to introduce alternative immunosuppression.
Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; PLEX, plasma exchange
Source: Sussman 2015[19]; NHS England 2018[111]; AWTTC 2021[32]; NHS England 2021[31]

B.1.3.3.4 Current UK treatment options for gMG

The following treatments used in gMG are reimbursed in England and Wales[23,118–120]:

- acetylcholinesterase inhibitors (AChEis; pyridostigmine and neostigmine),
- corticosteroids,
- azathioprine and other NSISTs including ciclosporin, mycophenolate mofetil, tacrolimus and methotrexate,
- rituximab,
- IVIg,
- PLEX

Despite treatment with the current standard of care, many patients continue to experience substantial disease burden and debilitating symptoms that profoundly impact their quality of life.[11,34,36,78,121] Just 25% of MG patients are able to achieve pharmacological remission, and only 8% achieve clinical remission. Almost 20% do not benefit from their medication at all. Further, 48% of patients experience treatment-related side effects and 37% report having discontinued therapy in the past (56% of those patients discontinued due to side effects).[41]

B.1.3.3.4.1 AChEis (pyridostigmine)

Pyridostigmine has been used as a treatment for gMG for over 50 years.[122] Pyridostigmine inhibits the hydrolysis of ACh, the key neurotransmitter at the neuromuscular junction, increasing the number of interactions between ACh and the AChR.[24] Having this mechanism of action, AChEi efficacy declines as gMG progresses since the neuromuscular junction becomes more damaged over time.[123] Moreover, AChEis are short-acting and often need to be taken several times a day.[24,119] The use of AChEis is further constrained by the well-defined cholinergic side effects that limit the tolerated dose, and additional treatment is often required to manage side effects.[122]

Despite the widespread use of AChEis, a Cochrane systematic review from 2014 found there is no evidence from RCTs to support using AChEis in MG patients.[124] Recommended dosing schedules are not based on studies but on expert opinion, which considers pyridostigmine suitable as a long-term treatment in patients with mild gMG and as an adjunctive therapy in patients with more active disease who are also receiving immunosuppressive therapy.[22,122,124] Moreover, AChEis do not fully control gMG symptoms in most patients, and patients often need long-term immunosuppression.[20,124]

B.1.3.3.4.2 Thymectomy

Because the thymus promotes the production of autoimmune antibodies, thymectomy is frequently used as a treatment strategy in gMG and can be effective even in patients without thymoma.[125] gMG patients are generally at high risk for surgical intervention due to impaired respiratory function but with the use of current surgical techniques and anaesthesia mortality rates are low (≤1%). Complications related to thymectomy include myasthenic crisis (6%), infections (11%), and recurrent laryngeal nerve / phrenic nerve injury (2%). [126]

B.1.3.3.4.3 Corticosteroids

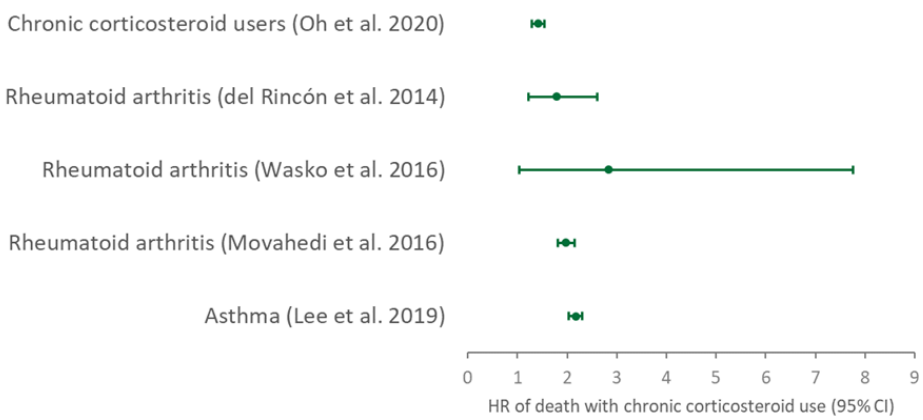
Corticosteroids, which are not approved for treatment of gMG, have a broad, non-specific suppressive effect on immune response; however, their exact mechanism of action in MG remains unknown.

gMG patients who have an inadequate response to AChEis are most commonly treated with oral corticosteroids, but there is limited evidence supporting their use; a Cochrane review concluded limited evidence suggests that corticosteroids offer a short-term benefit compared with placebo.[127] Importantly, the optimal dosing of corticosteroids in gMG, particularly for long-term treatment, has not been established.[24,40] As shown in Figure 7, the ABN guidelines recommend an initial starting dose of 10 mg on alternate days, increasing every three doses until symptoms improve to a maximum of 100mg on alternate days (or 1.5mg/kg). Even after remission is achieved and following slow titration down over up to 14 months, the guidelines recommend patients aim to continue on a maintenance dose of 7 or 8 mg on alternate days. To mitigate the harmful long-term effects of this exposure to significant doses of corticosteroids, treatment strategies in gMG focus on minimising the steroid dose.[19,22,117,128]

In addition to the limited efficacy associated with corticosteroid treatment, the number and severity of adverse events (AEs) increases with duration of treatment and cumulative

dosage.[22,24] Studies in gMG patients indicate that the proportion of patients experiencing at least one side effect while on corticosteroid treatment ranges from 67% to 100%.[129,130] Long-term use of corticosteroids is associated with serious adverse events (SAEs) such as osteoporosis and bone fractures, cancer, hypothalamic–pituitary–adrenal axis suppression, significant weight gain, recurrent infections, hyperglycaemia/diabetes, cardiovascular disease and dyslipidaemia, myopathy, cataracts and glaucoma, and psychiatric disturbances.[24,128,129,131–133] In other autoimmune conditions, including rheumatoid arthritis and asthma, the chronic use of systemic corticosteroids has been associated with an increased risk of death and poor HRQoL (Figure 8).[134–137]

Figure 8: Chronic use of systemic corticosteroids is associated with increased risk of death in patients with chronic diseases



Abbreviations: HR, hazard ratio; CI, confidence interval
Sources: Oh, 2020; del Rincon, 2014; Wasko, 2016; Movahedi, 2016; Lee, 2019[134–138]

B.1.3.3.4.4 NSISTs

NSISTs are non-specific, systemic treatments with broad immunosuppressive mechanisms.[139] Azathioprine is the most commonly prescribed NSIST for gMG, other NSISTs used less frequently for gMG include mycophenolate mofetil, methotrexate, ciclosporin, and tacrolimus.[19–22] All NSISTs are used off-label in this indication with the exception of a liquid formulation of azathioprine (Jayempi®) that was granted regulatory approved by the European Medicines Agency (EMA) in July 2021.[23]

In prospective clinical trials, NSISTs failed to show efficacy in gMG patients.[130,140–144] Specifically, the addition of methotrexate and mycophenolate mofetil, failed to reduce corticosteroid dosages required to maintain disease control, and mycophenolate mofetil, tacrolimus, and methotrexate failed to show significant improvements versus placebo on QMG or MG-ADL scores.[141,142,144] Further, the time to treatment effect can take 6 to 12 months with NSISTs.[145]

Long-term studies of AEs associated with NSISTs are lacking in gMG populations but available data indicate prolonged use of NSISTs may be associated with liver and bone marrow toxicities, malignancies, and increased risk for infection.[21,21,35,38,40] As stated in the International Consensus Guidance, it is usually necessary to maintain immunosuppression for many years, sometimes for life, which predisposes patients to opportunistic infections, an increased risk of cancer, and other severe treatment-related side effects.[21,22,90,91] Treatment

with NSISTs also leads to impaired physical HRQoL, as revealed by significantly lower scores on the SF-36 Physical Component Scale, independent of disease activity.[33]

B.1.3.3.4.5 Intravenous immunoglobulin (IVIg)

IVIg is predominantly used acutely in gMG for treatment of exacerbations in refractory patients and for myasthenic crises. It may also be used as maintenance therapy in patients with chronic gMG where a patient has failed all standard therapy (including steroids and immunosuppression) under the recommendation of a specialist neuromuscular service.[146,147] In the acute setting, a Cochrane review of IVIg found that of three RCTs for gMG, one showed some evidence of efficacy for IVIg versus placebo while two did not show significant differences between IVIg and plasma exchange.[146] A fourth trial also did not show a significant difference between IVIg and oral methylprednisolone.[146] Three of the four studies used change in QMG as primary endpoints, the fourth (published in 1997) used increase in myasthenia muscle score as the primary endpoint.[146]

Overall, the Cochrane review concluded there is insufficient evidence from trials to determine whether IVIg is efficacious as a maintenance treatment in chronic gMG.[146] Sources of data for maintenance IVIg in chronic gMG included one RCT in 15 patients, and one crossover study in 12 patients. Both used change in QMG as the primary endpoint.[148,149]

In addition to the lack of evidence for IVIg efficacy, IVIg therapy is burdensome for patients and healthcare systems. The treatment requires hospitalisation; IVIg is administered slowly over several hours and may require a series of infusions over 3–5 days.[150] IVIg also requires substantial premedication with antihistamines, corticosteroids, or nonsteroidal anti-inflammatory drugs to avoid IVIg-induced AEs, including neutropaenia.[151] Furthermore, IVIg is associated with the risk of acute renal failure and thromboembolic events, including stroke and myocardial infarction.[152]

There are logistical issues with IVIg use as well, since it is a blood-derived product. IVIg has been subject to periodic supply issues, necessitating altered dosing schedules, including postponed infusions, increased intervals between doses, decreased dosages, and substitution of alternative therapy.[111]

B.1.3.3.4.6 Plasmapheresis or plasma exchange (PLEX)

PLEX is believed to act in gMG by removing anti-AChR antibodies from the circulation; it does this by separating plasma from the blood and replacing it with albumin or plasma collected from healthy donors.[153–155] In addition to removing pathogenic autoantibodies, immune complexes and cryoglobulins are also removed.[155] SAEs can occur during PLEX treatment as a result of the removal of plasma proteins.[153,156] PLEX is generally used off-label for myasthenic crises.

A Cochrane review of PLEX for gMG found that no adequate RCTs have been performed to determine whether PLEX improves the short- or long-term outcomes of gMG or MG exacerbation.[153] While some clinical improvements have been reported in case reports, benefits seen with PLEX are short term, and primarily observed in the management of myasthenic crises.

PLEX is also a burdensome treatment option for patients and healthcare systems. As a preventative treatment, PLEX is administered in a hospital or outpatient setting as often as every 24 to 72 hours for three to six treatments and requires two high-volume IV access lines.[153,156,157] Patients who do not have suitable peripheral veins may require central catheters, which are associated with complications such as infection, pneumothorax, and thromboembolism.[24]

B.1.3.3.4.7 Rituximab

A recommendation about the use of rituximab was not included in the ABN guidelines.[19] Although not approved in this indication or supported by robust evidence, rituximab has been commissioned for use in select groups including refractory patients by NHS England[22,25,26,31]:

- gMG patients who demonstrate active disease despite treatment with maximal immunosuppression,
- MG patients with crisis,
- MG patients with frequent relapses,
- MG patients in whom oral immunosuppression is complicated by significant side effects,
- MG patients whose disease onset is “explosive” and are unresponsive to conventional rescue treatments

The NHS England rituximab commissioning policy also notes that there should be a lower threshold to consider the drug in MuSK antibody positive MG patients with bulbar disease (which characterises this form of the condition), responding poorly to IVIg or plasmapheresis, or who demonstrate poor tolerability to immunosuppression.[31]

US international consensus guidelines note that rituximab is unlikely to have a clinically meaningful steroid-sparing effect and that the efficacy of rituximab in refractory AChR-Ab+ gMG is uncertain.[21]

The efficacy of rituximab was evaluated in AChR-Ab+ gMG patients in the BeatMG study, a Phase 2, randomised, double-blind, placebo-controlled trial. Rituximab did not meet the primary endpoint, which was a significant reduction in the dosage of corticosteroids required to maintain disease control compared with placebo.[27] There were also no significant differences compared with placebo in change from baseline to Week 52 in MG-ADL, QMG, or MGC scores.[27]

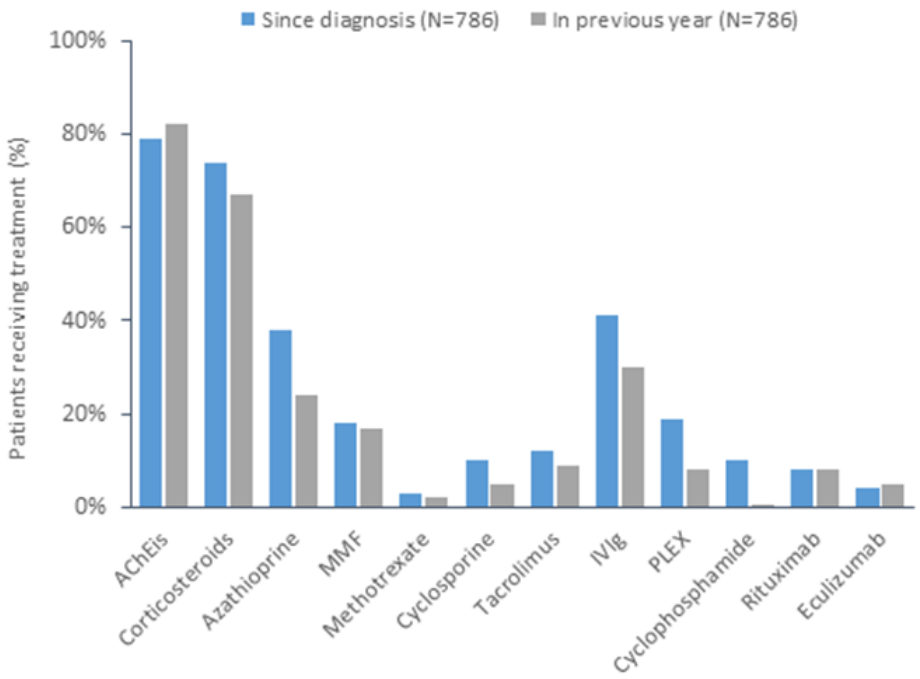
A second randomised, double-blind, placebo-controlled trial—the RINOMAX study—evaluated the efficacy and safety of rituximab as an add on to standard therapy for MG compared with placebo. The study included patients with recent disease onset (within 12 months) and a QMG score of 6 or more.[28] The primary outcome was minimal disease manifestations at 16 weeks (QMG score of 4 or less) with a daily dose of prednisolone of 10 mg or less and no need for rescue treatment from weeks 9 to 16. Although the primary endpoint was met, this study failed to show statistical differences in several important outcome measures including QMG, MG-ADL, and MG-QOL scores.[28]

The safety of rituximab is also important to consider, as it is associated with severe, potentially fatal infusion-related reactions (including cytokine release syndrome), infections, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy.[29] Furthermore, recently published retrospective case reports report found that treatment with rituximab was an important predictor of severe COVID-19 infection in MG patients.[39,158]

B.1.3.3.5 Treatment choice in routine clinical practice

Evidence from registry-based and real-world studies has demonstrated that a large majority of gMG patients receive treatment with corticosteroids and NSISTs, in addition to AChEis.[10,34,36,159] Figure 9 shows the MG treatments patients have taken since their diagnosis and which treatments have been taken in the previous year. Even though most patients had received an AChEi, it was not adequate to control their symptoms, as shown by the high utilisation of corticosteroids and NSISTs (argenx, MyRealWorldMG data on file).

Figure 9: Routine treatments received by participants in the MyRealWorld MG study since diagnosis of MG and in the previous year (N=786)



Abbreviations: AchEi, acetylcholinesterase inhibitor; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MMF, mycophenolate mofetil; PLEX, plasmapheresis or plasma exchange.
Source: argenx, MyRealWorldMG data on file

B.1.3.3.6 Unmet need

Current therapeutic options for gMG in the UK provide limited benefit: patients continue to bear substantial burden, experiencing symptoms and morbidities that negatively impact their mental health, quality of life (QoL), and ability to work, and treatment-related morbidity remains high.[33,160–162] Current pharmacological options are often broadly immunosuppressive, lack robust clinical trial data, have a prolonged time to take clinical effect, and are associated with a high risk of adverse events. Therefore, fast-acting,

efficacious, targeted treatments that are well tolerated are still needed to help gMG patients to manage their lifelong condition.

In the UK, the only approved treatments for gMG are AChEis, eculizumab (Soliris®, licensed only for anti-AChR-Ab+ patients with refractory gMG and not reimbursed by NICE), and an oral suspension of azathioprine (Jayempi®, approved July 2021; oral azathioprine tablets are not approved for the treatment of gMG). Rituximab is not licensed for MG but is commissioned by NHS England for defined patient groups including those who fulfil the criteria for refractory gMG. The frequent use of off-label options and even commissioning of an unlicensed medicine demonstrates the unmet need for patients living with gMG.

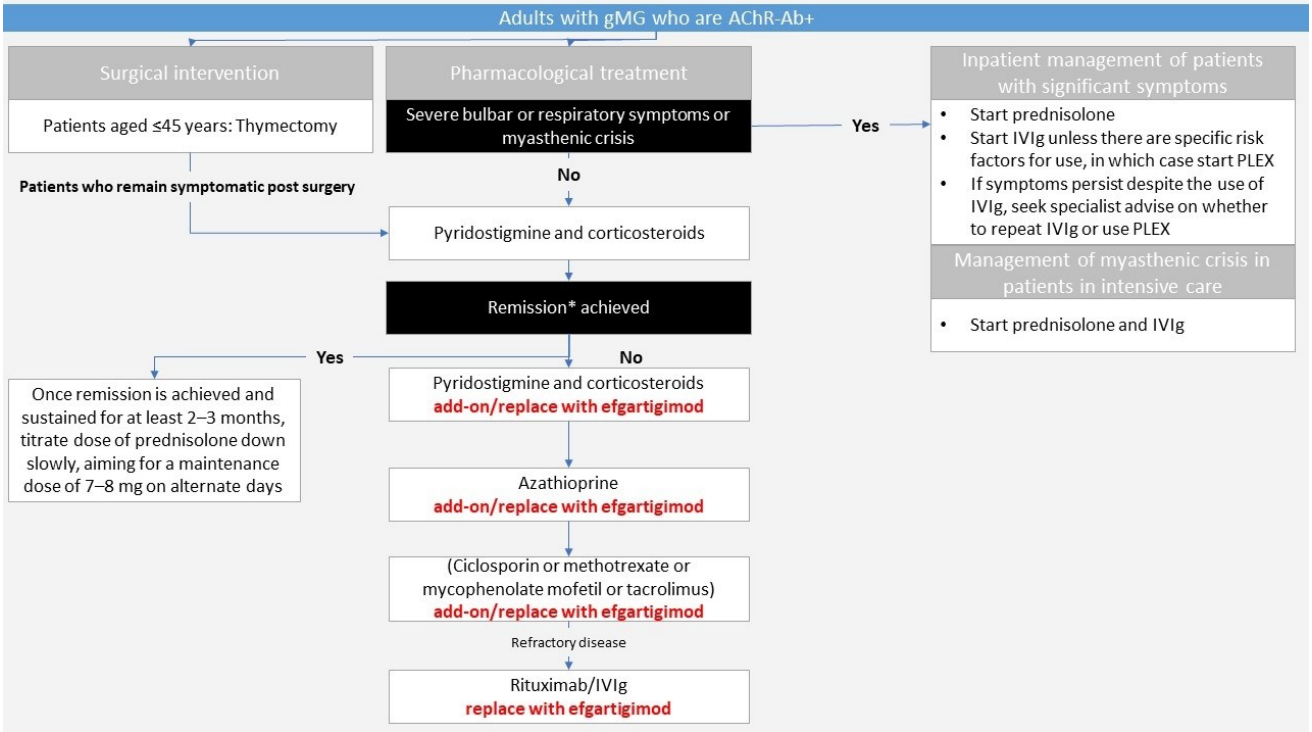
For these reasons, there is a clear unmet need for an effective, well tolerated therapy that can be used to manage gMG patients whose symptoms remain significantly uncontrolled despite established clinical management including corticosteroids and immunosuppressive therapies, with or without IVIg.

With an anticipated indication as an add on to standard therapy for the treatment of adults with gMG who are AChR-Ab+, efgartigimod addresses this need. In recognition of its promising efficacy and acceptable safety profile for a population of patients with high unmet clinical need, efgartigimod was granted promising innovative medicine (PIM) status in November 2021 and a positive scientific opinion by the MHRA under the EAMS in May 2022.[47,48] As of 2 Feb 2023, [redacted] patient requests for efgartigimod were approved from [redacted] specialist centres across England.

B.1.3.3.7 Proposed place of efgartigimod in the current treatment pathway

Efgartigimod is a first-in-class human IgG1 antibody Fc-fragment that blocks FcRn leading to a targeted reduction of IgG, including disease-causing IgG autoantibodies. The anticipated indication for efgartigimod in the UK is aligned with the approved EU indication as an add on to standard therapy for the treatment of adults with gMG who are AChR-Ab+.[50] As discussed in Section B.1.3.3.3, while the treatment schema suggests a stepwise approach through the treatment pathway, in practice conventional therapies are selected according to patient characteristics, comorbidities and severity of symptoms.[30] Treatments may be used alone or in combination, with some starting before others – e.g., corticosteroids – are tapered.[19] Consistent with the anticipated indication, the proposed place of efgartigimod in the current treatment pathway is provided in Figure 10. The figure shows that efgartigimod may be used in addition to, or to replace any of the individual treatments included in the current basket of established clinical management. In gMG patients with refractory disease, efgartigimod may considered in combination with established clinical management as an alternative to rituximab or IVIg.

Figure 10: Proposed place of efgartigimod in the current treatment pathway



While the treatment schema suggests a stepwise approach through the treatment pathway, in practice conventional therapies may be used individually or in combination, with some treatments starting before others – e.g., corticosteroids – are tapered.
*Remission of gMG on corticosteroid therapy is defined as the absence of symptoms or signs after pyridostigmine withdrawal.
Abbreviations: AChR-Ab+, acetylcholinesterase inhibitor antibody positive; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; PLEX, plasma exchange

B.1.4 Equality considerations

No equality issues are anticipated for the appraisal of efgartigimod in this indication.

B.2 Clinical effectiveness

Evidence for this submission comes from the ADAPT trial, a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial designed to evaluate the efficacy, safety and tolerability, and HRQoL impact of efgartigimod treatment in patients with gMG.[42]

- Evidence for the long-term safety, tolerability, and efficacy of efgartigimod is provided by ADAPT+, an ongoing, open-label, single-arm, multicentre, 3-year extension of the ADAPT study.[163,164]
- ADAPT enrolled 167 patients aged ≥18 years with MGFA class II–IV gMG, of whom 129 (77%) patients were AChR-Ab+.[42]
- The patient population enrolled in ADAPT is representative of the gMG patient population in terms of age, gender, and prior and ongoing use of gMG therapies.[42]

ADAPT met its primary endpoint: a statistically significantly higher proportion of AChR-Ab+ patients in the efgartigimod group were MG-ADL responders during Cycle 1 compared with the placebo group (67.7% vs 29.7%; odds ratio [OR] 4.95 [95% CI 2.21, 11.53]; p<0.0001).[42]

- Significantly more AChR-Ab+ patients in the efgartigimod arm were QMG responders during Cycle 1 compared with placebo (OR 10.84 [95% CI 4.18, 31.20]; p<0.0001).[42]
- AChR-Ab+ patients treated with efgartigimod showed a clinically meaningful improvement (CMI) in MG-ADL score for a significantly longer mean percentage of time during the study compared with placebo-treated patients (48.7% vs 26.6%; p=0.0001).[42]
- Efficacy results from ADAPT+ align with those observed in ADAPT study: reductions in mean MG-ADL and QMG scores in the AChR-Ab+ and overall population were repeated with multiple cycles of efgartigimod, showing CMIs from baseline.[163,164]

Overall, AChR-Ab+ patients treated with efgartigimod experienced greater improvements from baseline in QoL compared with the placebo arm.[165]

- QoL measured by EQ-5D-5L visual analogue scale (VAS), EQ-5D-5L UK-weighted utility, and MG-QOL15r was significantly improved from baseline at Week 4 compared with placebo (p<0.0001).[165]
- Patients in the efgartigimod treatment arm showed substantial numeric improvements at 4 weeks in all EQ-5D-5L domains.[165]

Overall, efgartigimod was generally well tolerated in ADAPT, with a favourable safety profile and a lower proportion of patients reporting AEs or SAEs in the efgartigimod arm than in the placebo arm.[42]

- AEs were reported by 77% of patients in the efgartigimod arm and 84% in the placebo arm across the whole ADAPT population, and mostly mild-to-moderate in severity.[42]
- Few patients in ADAPT discontinued treatment due to an AE: 3.6% of patients in each treatment arm.[42]
- The long-term ADAPT+ extension study demonstrated that efgartigimod was well tolerated with repeated cycles of treatment (patients received up to [redacted] cycles).[163,166]

Evidence for a subcutaneous formulation of efgartigimod is provided by the ADAPT-SC trial, which demonstrated noninferiority of efgartigimod SC compared with efgartigimod IV.[46,167]

- ADAPT-SC was a Phase 3, randomised, open-label, parallel-group study comparing the pharmacodynamics, pharmacokinetics, efficacy, safety, tolerability, and immunogenicity of SC injections of efgartigimod PH20 1,000 mg with IV infusions of efgartigimod 10 mg/kg in patients with gMG.[168]
- ADAPT-SC met the primary endpoint of reduction from baseline in total IgG levels at Day 29, demonstrating a least squares mean reduction of 66.4% (95% CI −68.91, −63.86) from baseline in the SC treatment arm, compared with 62.2% (95% CI −64.67, −59.72) in the IV treatment arm.[46,167]
- The proportion of patients achieving a response according to MG-ADL (69.1%) or QMG (65.5%) was similar to the IV arm,[46] including those with AChR-Ab+ gMG.[167]
- Overall, clinical efficacy of efgartigimod PH20 SC was similar to efgartigimod IV after one treatment cycle of four weekly administrations.[167]
- Both efgartigimod PH20 SC and efgartigimod IV were well tolerated and had favourable safety profiles in participants with gMG, consistent ADAPT.[46]

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify randomised clinical studies for efgartigimod and comparator treatments (corticosteroids and immunosuppressive therapies, with or without IV immunoglobulin or plasma exchange) for the management of gMG. Full details of the methodology and results of the SLR are provided in Appendix D

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified two completed Phase 3 studies: ADAPT, and ADAPT-SC, plus data from an interim analysis (data cut-off January 2022) of the ADAPT extension study (ADAPT+); see Table 10 for details. These studies provide evidence on the efficacy and safety of efgartigimod in patients with gMG.

Table 10: Clinical effectiveness evidence

Study	ADAPT[42,169] (ARGX-113-1704; NCT03669588)	ADAPT+[163,164] (ARGX-113-1705; NCT03770403)	ADAPT-SC[167,168] (ARGX-113-2001; NCT04735432)
Study design	Phase 3, randomised, double-blind, placebo-controlled, multicentre	Phase 3, long-term, single-arm, open-label, multicentre	Phase 3, randomised, open-label, parallel-group, multicentre
Population	Adults with gMG	Adults with gMG	Adults with gMG
Intervention(s)	Efgartigimod 10 mg/kg (IV formulation)	Efgartigimod 10 mg/kg (IV formulation)	Efgartigimod PH20 SC 1,000 mg (SC formulation)
Comparator(s)	Placebo	Placebo	Efgartigimod 10 mg/kg (IV formulation)
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	Yes	Yes
Rationale if study not used in model	NA	NA	NA
Reported outcomes specified in the decision problem	• Improvement in MG • Time to clinically meaningful improvement • Mortality • Hospitalisations • AEs of treatment • HRQoL	• AEs of treatment • Improvement in MG (MG-ADL and QMG score changes)	• Improvement in MG (MG-ADL and QMG score changes) • AEs of treatment
All other reported outcomes	• Improvement in MG in Cycle 1	• Levels of total IgG, IgG subtypes, and autoantibodies	• Levels of total IgG, IgG subtypes, and autoantibodies

Study	ADAPT[42,169] (ARGX-113-1704; NCT03669588)	ADAPT+[163,164] (ARGX-113-1705; NCT03770403)	ADAPT-SC[167,168] (ARGX-113-2001; NCT04735432)
	• Proportion of time up to Day 126 with an improvement in MG • Time to no improvement in MG • Early responders • Levels of total IgG, IgG subtypes, and autoantibodies • Magnitude of effect • Time to onset of effect • Duration of response in MG-ADL responders • Repeatability of effect with second treatment cycle • Change in MGC and MG-QOL15r scores		• PK parameters • Number and percentage of MG-ADL and QMG responders • Caregiver competency

Abbreviations: gMG, generalised myasthenia gravis; HRQoL, health-related quality of life; IgG, immunoglobulin G; IV, intravenous; MG, myasthenia gravis; MG-ADL, MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite; MG-QOL15r, 15-item revised version of the Myasthenia Gravis Quality of Life questionnaire; SC, subcutaneous

Source: Howard et al, 2021[2]; argenx DoF, ADAPT CSR 2020[169]; argenx DoF, ADAPT+ Interim CSR 2021[170]; ClinicalTrials.gov (NCT03770403)[171]; Meisel et al, 2022[166]; argenx DoF, ADAPT-SC CSR 2022[167]; ClinicalTrials.gov (NCT04735432)[168]

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

B.2.3.1 ADAPT study

The main study characteristics are detailed in Table 11.

ADAPT is a completed randomised, double-blind, placebo-controlled, multicentre, 26-week, Phase 3 trial to evaluate the efficacy, safety, and tolerability of efgartigimod by IV infusion in adults with gMG.[42] ADAPT took place in Europe, North America and Japan. Patients included in the trial had MG with generalised muscle weakness (patients with ocular weakness only or myasthenic crisis not enrolled), had an MG-ADL total score of ≥5 points with >50% of the total score attributed to non-ocular symptoms, and were on a stable dose of standard of care gMG treatment, that could include AChEis, steroids, and NSISTs alone or in combination.[42] Patients in ADAPT could be AChR-Ab positive or negative; but this submission is for AChR-Ab positive patients only. The inclusion of AChR-Ab− patients was important due to the limited treatment options these patients have and their lack of inclusion in previous clinical trials. However, only a few of these patients were recruited, and the trial was not statistically powered to assess efficacy in this population.[42]

After a 2-week screening period, eligible patients were randomised in a 1:1 ratio to receive efgartigimod 10 mg/kg or matching placebo (solution for IV administration with the same formulation as the efgartigimod solution but without efgartigimod).[42] Treatment was administered as cycles of once weekly infusions for 4 weeks, on the basis of results from a dose-finding trial in healthy subjects.[44]. All patients received an initial cycle; subsequent cycles were initiated according to each patient's clinical evaluation, for individualised treatment intervals (see below). Subsequent cycles started at least 8 weeks from initiation of the previous cycle. A maximum of three cycles was possible in the 26-week trial.[42]

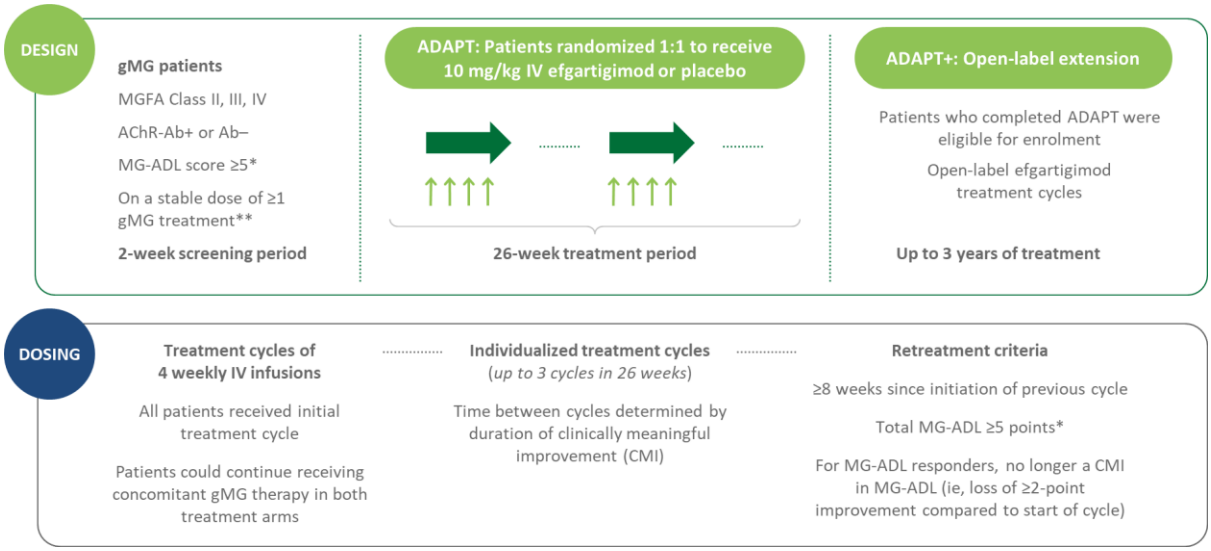
Patients were considered eligible for another cycle of efgartigimod treatment if they met the following criteria:[42]

- Myasthenia Gravis Activities of Daily Living scale (MG-ADL) total score ≥5 points with more than 50% of the total score due to non-ocular symptoms,
- Patients who were MG-ADL responders no longer had a clinically meaningful improvement (CMI) in MG-ADL score, and
- No sooner than 8 weeks from initiation of the previous cycle.

Patients who completed the study or could not complete a cycle before study end (i.e., they met criteria for initiation of a treatment cycle after study Day 126) were able to roll over to the open-label extension study ADAPT+ (see Section B.2.3.2).

A summary of the trial design is shown in Figure 11 and the trial methodology in Table 11. A more detailed overview of the key inclusion and exclusion criteria for ADAPT is provided in Appendix M.

Figure 11: ADAPT trial design



*>50% of the score attributed to non-ocular items
Abbreviations: AChR-Ab+/−, acetylcholine receptor autoantibody positive/negative; CMI, clinically meaningful improvement; gMG, generalised myasthenia gravis; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGFA, Myasthenia Gravis Foundation of America
Source: Based on information included in Howard et al, 2021[2] and ClinicalTrials.gov (NCT03770403)[171]

Table 11: Summary of ADAPT study methodology

Study design	Randomised, double-blind, placebo-controlled, multicentre Phase 3 trial
	Randomisation: patients were randomly assigned 1:1 using interactive response technology, using both web and voice systems, by an independent company. No crossover was allowed
Duration of study	2-week screening period followed by a 26-week treatment period
Settings and locations where data were collected	56 neuromuscular academic and community centres across Japan and 14 countries in Europe and North America
Patient eligibility criteria	**Key inclusion criteria** • Male or female patients aged ≥18 years • Diagnosis of MG with generalised muscle weakness; supported by at least one of the following: o History of abnormal neuromuscular transmission demonstrated by single-fibre electromyography or repetitive nerve stimulation o History of positive edrophonium chloride test o Demonstrated improvement in MG signs on oral AChEis as assessed by the treating physician • MGFA Class II, III or IV • A total MG-ADL score of ≥5 points at screening and baseline with more than 50% of the total score due to non-ocular symptoms • Patients were required to be on a stable dose of ≥1 therapy for gMG, that could include AChEis, steroids, and NSISTs, alone or in combination, prior to screening. Requirements for stable dose treatments were:

	o NSISTs: treatment for ≥6 months prior to screening and no dose change within three months of screening o Steroids: treatment for ≥3 months prior to screening and no dose changes in the month prior to screening o AChEis: treatment with a stable dose with no dose escalation in the 2 weeks prior to screening
	Key exclusion criteria • MGFA Class 1 (ocular weakness only) and Class 5 (myasthenic crisis) patients • Thymectomy when performed <3 months prior to screening or planned to be performed during the study period • Pregnant and lactating women • Patients who had worsening muscle weakness secondary to concurrent infections or medications • Patients with known seropositivity or who tested positive for an active viral infection at screening with HBV (except patients who were seropositive because of HBV vaccination), HCV, or HIV • Use of any monoclonal antibody, such as rituximab or eculizumab, within 6 months of first study dose
Study drugs	Randomised in a 1:1 ratio based on three stratification factors: AChR-Ab status (positive vs. negative), NSISTs (taking vs. not taking), and Japanese nationality (yes vs. no) **Intervention:** efgartigimod 10 mg/kg administered as four IV infusions per cycle (one infusion per week); maximum of three cycles. After each cycle there was a period of ≥5 weeks of follow-up. All patients received an initial cycle; subsequent cycles were initiated according to individual clinical response **Comparator**: matching placebo by IV infusion All patients in the intervention and comparator groups continued to receive concomitant therapy for gMG (limited to AChEis, steroids, and NSISTs) at an unchanged dose
Concomitant medication	**Permitted concomitant medication:** AChEis, steroids, and NSISTs **Prohibited concomitant medication:** any other IgG therapy not listed as permitted medication; change in the type or dose/regimen of concomitant treatment (replacing, adding, or removing treatment, or adjusting dose and/or frequency of established treatment), even if used for indications other than gMG; any monoclonal antibody for immunomodulation; vaccines; rescue therapy (any patient requiring rescue therapy was discontinued from treatment)
Primary outcomes	Proportion of AChR-Ab+ patients who were MG-ADL responders in the first treatment cycle (defined as a patient who had ≥2-point improvement (reduction) in MG-ADL score, sustained for ≥4 consecutive weeks, with the first improvement occurring by week 4 of the cycle (1 week after the fourth infusion)
Other outcomes used in the model/specified in scope	• Time to clinically meaningful improvement • Mortality • Hospitalisations

	• AEs of treatment • HRQoL
Other outcomes of interest	• QMG responders • Proportion of time up to Day 126 with an improvement in MG-ADL • Time to qualify for retreatment • Early responders • Magnitude of effect • Time to onset of effect • Duration of response in MG-ADL responders • Repeatability of effect with second treatment cycle • Change in MGC and MG-QoL15r scores • Levels of total IgG, IgG subtypes, and autoantibodies
Pre-planned subgroups	The percentages of MG-ADL responders were analysed by race, concomitant gMG treatment, MG-ADL total score at baseline category, and the number of administered cycles. An additional subgroup analysis by AChR-Ab serostatus was planned; however, this is not relevant to this submission. Additional *post-hoc* analyses of patient subgroups by baseline disease factors and concomitant gMG treatment were performed for the AChR-Ab+ population
Key publication	Howard et al, 2021[42]
Secondary sources	argenx, 2020 (ADAPT Clinical Study Report)[169]

Abbreviations: AChEis, acetylcholinesterase inhibitors; AChR-Ab(+), acetylcholine receptor autoantibody (positive); gMG, generalised myasthenia gravis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IV, intravenous; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MG-QOL15r, 15-item revised version of the Myasthenia Gravis Quality of Life questionnaire; NSISTs, nonsteroidal immunosuppressive therapies
Sources: argenx DoF, ADAPT CSR 2020;[169] Howard et al, 2021.[2]

B.2.3.1.1 ADAPT study endpoints

Efficacy and HRQoL were assessed via multiple validated physician- and patient-reported instruments for MG. The MG assessment scales and the CMI used to define responders in the efficacy analyses for ADAPT and ADAPT+ are detailed in Section B.1.3.1.2.

Efficacy assessments were done weekly for 8 weeks after the initiation of each cycle and then every 2 weeks, for up to 26 weeks.[42]

Trial endpoints and their definitions are provided in Table 12.

Table 12: Summary of key endpoints in ADAPT

Endpoint/assessment	Definition/measurement
Primary endpoint	
Proportion of AChR-Ab+ patients who were MG-ADL responders in the first treatment cycle	The MG-ADL scale is patient-reported, physician-recorded outcome measure MG-ADL responder defined as a patient with a ≥2-point improvement in MG-ADL score sustained for ≥4 consecutive weeks, with the first improvement occurring no later than one week after the last infusion in a cycle
Secondary endpoints (assessed in hierarchical order)	
Proportion of QMG responders in the AChR-Ab+ population	QMG score is physician assessed and includes quantitative measures QMG responder was defined as a patient with a ≥3-point improvement in the total QMG score for ≥4 consecutive weeks, with the first improvement occurring no later than one week after the last infusion in a cycle
Proportion of MG-ADL responders in the overall population (i.e., AChR-Ab+ and AChR-Ab- patients) in the first treatment cycle	These results are not shown in this submission, as this population includes AChR-Ab- patients
Proportion of time AChR-Ab+ patients had a CMI in MG-ADL score, up to Day 126	CMI in MG-ADL total score defined as having ≥2-point improvement in total MG-ADL score compared with baseline
Time to qualify for retreatment (time from Day 28 to no CMI in the AChR-Ab+ population)	Time from Day 28 (1 week after the fourth infusion in Cycle 1) to qualification for retreatment (i.e., the patient has <2-point reduction in the MG-ADL total score and MG-ADL total score of ≥5 points with >50% of the total score attributed to non-ocular symptoms, compared with baseline of the first cycle) in the AChR-Ab+ population
Proportion of early MG-ADL responders in the AChR-Ab+ population in the first treatment cycle	An early MG-ADL responder was defined as a patient with an MG-ADL improvement of ≥2 points sustained for ≥4 weeks, with the first improvement occurring no later than Week 2
Other QoL outcomes	
Change in MG-QOL15r score	MG-QOL15r was a patient-completed questionnaire
Change in EQ-5D-5L	Patient-completed QoL scale

Endpoint/assessment	Definition/measurement
Change in MGC scale score	MGC scale is a patient and physician assessed scale; CMI is a ≥3-point reduction
Predefined exploratory endpoints	
Onset of effect	Time at which a MG-ADL or QMG response was observed
Proportion of patients achieving minimal symptom expression	Defined as MG-ADL score of 0 or 1
Proportion of patients with increasing levels of MG-ADL and QMG score improvement	Proportion of patients at week 4 in Cycle 1 achieving increasing thresholds of improvement in MG-ADL, or QMG score
Duration of response in MG-ADL responders	Duration of ongoing CMI (≥2-point improvement) in MG-ADL score in patients who were MG-ADL responders
Repeatability of effect with second treatment cycle	Proportion of patients who were MG-ADL responders during cycle 2
Safety endpoints	
Assessment of adverse events and treatment safety	Incidence of adverse events, clinical laboratory evaluations, ECG, vital signs, and immunogenicity
Tertiary endpoints	
Pharmacodynamics	Including levels of total IgG, IgG subtypes, and AChR-Abs autoantibodies

Abbreviations: AChR-Ab(+/-), acetylcholine receptor autoantibody (positive/negative); AE, adverse event; CMI, clinically meaningful improvement; ECGs, electrocardiograms; MG-ADL MGC, Myasthenia Gravis Composite; MG-QOL15r, 15-item revised version of the Myasthenia Gravis Quality of Life questionnaire; QMG, Quantitative Myasthenia Gravis scale; QoL, quality of life
Sources: Howard et al, 2021[2]

B.2.3.2 ADAPT+ study

The main study characteristics are detailed in Table 13.

ADAPT+ is an ongoing, open-label, single-arm, multicentre, 3-year extension of ADAPT evaluating the long-term safety, tolerability, and efficacy of efgartigimod for the treatment of gMG.[170,163,164,171] Study results presented in this dossier include safety and efficacy analyses from the data cut-off of 31 Jan 2022.

Patients who completed ADAPT or patients who met the criteria to initiate a treatment cycle that could not be completed within the timeframe of ADAPT were eligible for enrolment in ADAPT+.[170] Patients were required to be on a stable dose of any concomitant gMG treatment (i.e., AChEis, steroids, and NSISTs) prior to study entry.

Exclusion criteria for ADAPT+ included:[170,171]

- Patients who discontinued early from ADAPT or patients who discontinued early from treatment for pregnancy or rescue reasons or an SAE that might jeopardise the safety of the patient in that trial.
- Pregnant and lactating women.
- Patients with known seropositivity for HBV, HCV, or HIV.

ADAPT+ follows the dosing regimen of ADAPT; Treatment was administered as cycles of once weekly infusions for 4 weeks.[170] Subsequent treatment cycles were initiated according to individual clinical response (an MG-ADL score ≥5 and within 2 points of baseline), with an interval of at least 4 weeks from the last infusion.[164]

Table 13: Main study characteristics for ADAPT+

Trial name	ADAPT+ (A long-term, single-arm, open-label, multicentre, Phase 3 follow-on study of ARGX 113-1704 to evaluate the safety and tolerability of ARGX-113 in patients with myasthenia gravis having generalised muscle weakness)
NCT number	NCT03770403
Objective	ADAPT+ is a follow-on study to ADAPT to evaluate the long-term safety and tolerability of efgartigimod in patients with gMG
Publications – title, author, journal, year	argenx. Efgartigimod (ARGX-113-1705) Clinical Study Report (Interim Analysis 4): A Long-term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Study of ARGX 113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT+). Data on file. 2022:1-165.[163] Howard JF Jr, Bril V, Vu T, et al. Poster #108: Long-term safety, tolerability, and efficacy of efgartigimod in patients with generalized myasthenia gravis. Presented at the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting, Nashville, TN, USA. 21-24 September, 2022.[164]
Trial type and design	Single-arm, open-label, Phase 3
Follow-up time	3 years (currently ongoing)
Primary and secondary endpoints	Primary endpoint is safety and tolerability in the AChR-Ab+ population. Secondary endpoints are focused on safety and tolerability in the overall population

Exploratory endpoints	Other endpoints included MG-ADL and QMG total score changes from baseline of treatment period
Method of analysis	This study was designed to collect additional safety data on efgartigimod and provide continued treatment to patients who completed ADAPT. The primary and secondary endpoints were summarised in the safety analysis set by descriptive statistics. Frequency tables were prepared for all binary variables by cycle and overall. Summary statistics were provided for the continuous endpoints in terms of absolute values and changes from baseline.
Subgroup analyses	No subgroup analyses were performed.

Abbreviations: AChR-Ab+, acetylcholine receptor positive autoantibody; gMG, generalised myasthenia gravis
Sources: argenx, 2021;[170] ClinicalTrials.gov (NCT03770403);[171] Meisel et al, 2022;[166] argenx, 2022;[163] Howard et al, 2022.[164]

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

B.2.4.1 ADAPT study

B.2.4.1.1 Analysis sets

Efficacy analyses were performed in the modified intention-to-treat population (mITT), which included all randomised patients who had a valid baseline MG-ADL assessment and at least one post-baseline MG-ADL assessment.[42] Safety analyses were evaluated in all patients who received at least one dose or part of a dose of study treatment.[42]

B.2.4.1.2 Statistical analyses

The primary analysis tested the null hypothesis that there is no difference in proportion of MG-ADL responders between patients treated with placebo and efgartigimod. The trial was powered at 90% using significance level of 5% 2-sided to test the alternative hypothesis of that the difference in the proportion of responders is 29% in favour of patients treated with efgartigimod. The proportion MG-ADL responders amongst patients treated with placebo was hypothesised to be 30%. In order to test this alternative hypothesis, a sample size of 150 patients is needed, with this allowing for 10% attrition rate.[169] Sample size was based on allowing enrolment of up to 20% AChR-Ab− patients.[42] Based on this quota, a sample size of 150 provided power of 96% in the primary population of AChR-Ab+ patients to detect a difference of 35% in the proportion of responders with 120 patients.[42]

To control the type I error, the primary endpoint and secondary endpoints were tested in strict hierarchical order.[42,169] If the primary endpoint met significance at the 5% two-sided α level, secondary endpoints were tested at a 5% two-sided significance level in hierarchical order using a fixed sequence approach.[42]

The primary endpoint (and other endpoints involving binary variables, i.e., responder/non-responder) was tested using a two-sided exact test using a logistic regression model with baseline MG-ADL total score as a covariate and the three stratification factors as variables.[42] The treatment effect is presented as an OR with 95% CI and two-sided p value. Percentage of time patients showed a clinically meaningful improvement in MG-ADL score in the AChR-

Ab+ population was analysed using an analysis of covariance (ANCOVA) model. In this analysis, randomised treatment group and the stratification variables were included as factors, and baseline total MG-ADL score was included as a covariate. Time from Day 28 to not having clinically meaningful improvement in the AChR-Ab+ population was estimated using Kaplan–Meier time-to-event analysis and compared by means of a stratified log-rank test, stratified for the stratification variables. Additional endpoints assessing efficacy, safety, pharmacodynamics, and immunogenicity were analysed in a descriptive manner.[42]

Statistical analyses were done using SAS, version 9.2 or higher, and the software package R, where applicable.[42]

B.2.4.1.3 Patient flow in ADAPT

See Appendix D1.2 for full details of patient flow in the ADAPT study.

A total of 167 patients were enrolled and randomised to receive efgartigimod (n=84) or placebo (n=83); 152 (91%) patients completed treatment.[42] Overall, 15 (9%) patients discontinued treatment during the study: 5 (6%) patients in the efgartigimod group and 10 (12%) in the placebo group.[42]

B.2.4.1.4 Patient baseline characteristics

Table 14 presents the patient baseline characteristics for the AChR-Ab+ patient population in ADAPT.

Between September 2018 and November 2019, 167 adult patients with gMG were enrolled, randomly assigned, and treated; 129 (77%) were AChR-Ab+, and 38 (23%) were AChR-Ab−, of whom six (4%) were MUSK antibody positive.[42]

Overall, patient characteristics were representative of the gMG population and well balanced between treatment groups, with the exception that more patients receiving efgartigimod than placebo had undergone thymectomy.[42] Most patients were <65 years old, and receiving immunosuppressive treatment (either corticosteroids or NSISTs, alone or in combination) at baseline. The mean time since diagnosis of gMG was around 9–10 years. Baseline MG-ADL and QMG scores indicated an ongoing substantial disease burden for patients, despite receiving treatment.[42]

Table 14: ADAPT baseline demographics and clinical characteristics of the AChR-Ab+ patient population

	Efgartigimod (n=65)	Placebo (n=64)
Mean age (SD), years	44.7 (15)	49.2 (15.5)
Age category, n (%)		
18 to <65 years	57 (87.7)	51 (79.7)
≥65 years	8 (12.3)	13 (20.3)
Sex, n (%)		
Female	46 (70.8)	40 (62.5)
Male	19 (29.2)	24 (37.5)

	Efgartigimod (n=65)	Placebo (n=64)
Race, n (%)		
Asian	7 (10.8)	4 (6.3)
Black or African American	1 (1.5)	3 (4.7)
White	54 (83.1)	56 (87.5)
Other*	3 (4.6)	1 (1.6)
Mean time since diagnosis, years (SD)	9.7 (8.3)	8.9 (8.2)
Previous thymectomy, n (%)	45 (69.2)	30 (46.9)
MGFA class at screening, n (%)		
II	28 (43.1)	25 (39.1)
III	35 (53.8)	36 (56.3)
IV	2 (3.1)	3 (4.7)
Total MG-ADL score, mean (SD)	9.0 (2.5)	8.6 (2.1)
Total QMG score, mean (SD)	16.0 (5.1)	15.2 (4.4)
Total MGC score, mean (SD)	18.6 (6.1)	18.1 (5.2)
Total MG-QOL15r score, mean (SD)	15.7 (6.3)	16.6 (5.5)
At least one previous NSIST, n (%)	47 (72.3)	43 (67.2)
gMG therapy at baseline, n (%)		
Any steroid	46 (70.8)	51 (79.7)
Any NSIST	40 (61.5)	37 (57.8)
Steroid + NSIST	34 (52.3)	31 (48.4)
No steroid or NSIST	13 (20.0)	6 (9.4)

Ranges of the clinical outcome assessments are as follows: MG-ADL total score 0–24, QMG score 0–39, MGC 0–50, and MG-QOL15r 0–30; for each instrument, higher scores are indicative of more active disease
*Includes American Indian or Alaska Native, multiple reported, or not reported
Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; gMG, generalised myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite scale; MGFA, Myasthenia Gravis Foundation of America; MG-QOL15r, Myasthenia Gravis Quality of Life revised; NSIST, nonsteroidal immunosuppressive therapy; QMG, Quantitative Myasthenia Gravis; SD, standard deviation
Sources: Howard et al, 2021[42]; argenx, 2020.[172]

B.2.4.2 ADAPT+ study

B.2.4.2.1 Statistical testing of primary analysis of primary outcome

Safety analyses were evaluated in all patients who received at least one dose or part of a dose of study treatment.[163] As with ADAPT, the efficacy of efgartigimod was assessed in ADAPT+ using MG-ADL and QMG scores, each compared with the corresponding cycle baseline in the AChR-Ab+ population.

B.2.4.2.2 Patient baseline characteristics

Overall, 151 patients from ADAPT rolled over into ADAPT+, and 145 patients received at least 1 dose of efgartigimod as of the January 2022 database lock: 84 patients were from the efgartigimod group and 83 patients were from the placebo group.[163,164] A total of [redacted] patients were AChR-Ab+.[163]

Overall, [redacted] patients have discontinued treatment during ADAPT+.[163] The primary reason for discontinuation from treatment was treatment failure in [redacted] patients and AEs in [redacted] patients.[163] Patients could also choose to exit ADAPT+ in order to enrol in the ADAPT-SC study, and this was [redacted] for discontinuation from ADAPT+ [redacted] patients; Section B.2.12).[163]

Baseline patient demographics and characteristics are summarised in Table 15.

Table 15: ADAPT+, baseline patient demographics and characteristics

Characteristic	AChR-Ab+ (n=[redacted])	All patients (n=145)
Mean age (SD, years)	47.1 (15.5)	47.0 (14.8)
Age category, n (%)		
18–<65 years	93 (83.8)	124 (85.5)
≥65 years	18 (16.2)	21 (14.5)
Sex, n (%)		
Female	75 (67.6)	103 (71.0)
Male	36 (32.4)	42 (29.0)
Race, n (%)		
Asian	8 (7.2)	11 (7.6)
Black or African American	3 (2.7)	5 (3.4)
White	97 (87.4)	126 (86.9)
American Indian or Alaska Native	2 (1.8)	2 (1.4)
Multiple	1 (0.9)	1 (0.7)
Mean time since diagnosis (SD), years	9.7 (7.9)	9.7 (8.2)
Mean MG-ADL score (SD)	9.5 (3.1)	9.8 (3.2)
Mean QMG score (SD)	15.3 (5.7)	15.4 (5.7)
Concomitant gMG treatment, n (%)		
NSISTs	67 (60.4)	89 (61.4)
No NSISTs	44 (39.6)	56 (38.6)

Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NSIST, nonsteroidal immunosuppressive therapy; QMG, Quantitative Myasthenia Gravis scale; SD, standard deviation

Source: argenx, 2022.[163]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

B.2.5.1 Quality assessment of clinical studies

Quality assessment of ADAPT was conducted using the NICE Single Technology Assessment: User Guide for Company Evidence Submission template, adapted from Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking

reviews in health care (University of York Centre for Reviews and Dissemination; Table 16). This quality assessment was a critical appraisal of methodological quality with the goal of identifying how potential biases may have affected the generalisability of the study findings to the overall population. While this quality assessment covers the entire trial population, the population of interest for this submission is those with AChR-Ab+ gMG.

Table 16: Quality assessment checklist for the ADAPT study

Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was the randomisation method adequate?	Yes	Central randomisation was conducted using voice and web interactive response technology. Three stratification factors were applied: acetylcholine receptor antibody status (positive vs negative), NSISTs (taking vs not taking), and Japanese nationality (yes vs no). Randomisation was done across centres rather than within centres.
Was the allocation adequately concealed?	Yes	Central randomisation was conducted using voice and web interactive response technology.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline disease characteristics were balanced between groups, including duration of MG, median MG-ADL total score, and median QMG total score. There were no imbalances in prior or concomitant gMG treatments, except for the proportion of patients who had undergone thymectomy for gMG (efgartigimod: 70%; placebo: 43%).* *Upon further analysis, efgartigimod was found to be efficacious regardless of prior thymectomy status; thus, the higher prevalence of thymectomy in the efgartigimod treatment group did not appear to favour efgartigimod (see Appendix E1).
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Investigators, patients, study personnel, clinic staff, and funders were masked to treatment conditions for the duration of the study. Placebo was matched to efgartigimod in appearance and supplied in identical containers.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Yes and yes	Overall treatment discontinuation was numerically higher in the placebo group (n=10) than the efgartigimod group (n=5). The primary reason for discontinuation from treatment was the occurrence of an AE, which was reported in six patients overall: 3 patients in the efgartigimod group and three patients in the placebo group. Withdrawal due to participant's decision was reported for three patients in the placebo group (none in the efgartigimod group). Administration of rescue therapy

Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
		resulted in the discontinuation of treatment in three patients overall: 1 patient in the efgartigimod group and two patients in the placebo group. Additional discontinuations were due to prohibited medication use (n=1, placebo); protocol deviation (n=1, efgartigimod); and sponsor decision (n=1, placebo).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes were reported in the Clinical Study Report.
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 and yes	Efficacy was analysed on a mITT basis (patients with a valid baseline MG-ADL assessment and at least one post-baseline MG-ADL assessment). Safety analysis included all patients who received at least one dose or part of a dose. Rules for handling missing data were clearly described in an a priori statistical analysis plan. A sensitivity analysis was performed to assess the imputation impact for missing values.
Did the authors of the study publication declare any conflicts of interest?	Yes	Several interests have been declared, including individual author support from various manufacturers conducting MG research. The study itself was sponsored by argenx.

Checklist adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care.[173]
Abbreviations: AE, adverse event; gMG, generalised myasthenia gravis; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; mITT, modified intention-to-treat; NSIST, nonsteroidal immunosuppressive therapy
Source: Howard et al, 2021;[42] argenx, 2020.[169]

B.2.5.2 Relevance of outcomes assessed in clinical studies to clinical benefits and HRQoL expected in practice

The efficacy outcome measures used for the primary and secondary endpoints in ADAPT included validated and specific MG assessment scales for disease activity that are clinically meaningful, including the MG-ADL, the QMG, and the MGC (see Section B.1.3.1.2 for more details about each measure). The MG-ADL is a patient-reported, physician-administered outcome scale that assesses the impact on daily function of eight signs or symptoms that are typically observed in gMG.[74,174] Each item is assessed on a 4-point scale, where a score of 0 represents normal function and a score of 3 represents a loss of ability to perform that function (total score can range from 0 to 24). A reduction of ≥2 points in the MG-ADL total score is considered the threshold for a CMI.[74,72] QMG is a direct physician assessment scoring system that quantifies disease activity based on objective measures of impairments of body functions and structures.[74] A 3-point reduction in the total QMG score is the threshold for a CMI. The MGC combines patient– and physician-reported outcome measures. A ≥3-point reduction in the MGC score reliably indicates clinical improvement that is meaningful to patients.[175,176]

Quality of life measurements in ADAPT were assessed with the disease-specific MG-QOL15r, which uses patient-reported outcome measures to assess each patient's perception of impairment and disability. The 15-item Quality of Life scale for Myasthenia Gravis (MG-QOL15) is a validated HRQoL questionnaire specifically developed for assessing MG patients,[177,71] and its scoring correlates positively with other clinical measures, including the MG-ADL, the QMG, and the MGC.[178] The MG-QOL15 evaluates 4 domains: mobility (9 items), MG symptoms (3 items), general contentment (1 item), and emotional well-being (2 items). Responses for each item are given on a 5-point scale: not at all (0), a little bit (1), somewhat (2), quite a bit (3), and very much (4); the total score ranges from 0 to 60, with higher scores indicating a greater impact on QoL.

B.2.5.3 Factors influencing applicability of study results to patients in routine clinical practice in England

Of the 129 AChR-Ab+ patients included in the ADAPT study, 66 (51%) were from European countries.[169] Overall, the patient population in the study reflects the demographic characteristics of the general patient population with gMG, and is generalisable to European gMG patients. Prior or concomitant gMG treatments received by patients in ADAPT included AChEis, NSISTs, and steroids. These medications represent the standard therapy currently used in the UK.[116,117]

B.2.5.4 Limitations of the evidence base

Limitations of the ADAPT trial and open-label extension largely derive from the fact that gMG is a rare disease, and is therefore associated with all of the challenges associated with evidence generation for conditions where there is a limited number of patients eligible to be included in clinical trials. However, despite the fact that the AChR-Ab+ population in ADAPT was only 129 patients, enrolment was still sufficient to demonstrate statistical significance for the primary endpoint vs. placebo (Section B.2.6.2).[42] In the ADAPT+ study, [redacted] of enrolled patients chose to exit the study in order to continue efgartigimod treatment in the ADAPT-SC study, which is also ongoing.[163,168]

Another study limitation was the length of follow-up, which is a consistent challenge in NICE appraisals, irrespective of the rarity of a disease. In this case, the Company is committed to ongoing data collection, including the ongoing open-label extension study, which enrolled the majority of patients previously included in ADAPT as of the January 2022 data cut-off, and has already generated a substantial quantity of data. Efgartigimod is also available via the MHRA-approved EAMS at specialist gMG centres. As of 2 Feb 2023, [redacted] patient requests for efgartigimod were approved from [redacted] specialist centres across England; the scheme continues to expand and patient and clinician experience from these requests will continue to accrue throughout the NICE appraisal timelines.

Finally, as the symptoms of gMG can fluctuate over time (see Section B.1.3.2) it is challenging to select a clinical trial endpoint that can measure gMG progression. As described in Section B.1.3.1.2, the Company believes that the MG-ADL is the most appropriate measure for assessing efficacy and disease activity; this approach is consistent with published and ongoing clinical trials in gMG, and ADAPT demonstrated consistency across four MG-specific scales (Section B.2.6.4.1).[42]

B.2.6 ADAPT study, clinical effectiveness results

B.2.6.1 Treatment duration in the overall study population

The mean (standard deviation [SD]) duration in the study (i.e., period starting from the first dose until end of study) was 151.5 (22.4) days in the efgartigimod group and 151.7 (29.6) days in the placebo group.[42,169] The cumulative duration of treatment exposure was 34.9 patient-years for the efgartigimod group and 34.5 patient-years for the placebo group.[169]

In the overall population, the mean time to the second treatment cycle in the efgartigimod alfa group was 13 weeks (SD: 5.5 weeks) and the median time was 10 weeks (8–26 weeks) from the initial infusion of the first treatment cycle.[179] Patients received a maximum of three cycles, regardless of study group. In the efgartigimod group, 21 (25%) patients received 1 cycle, 56 (66.7%) patients received 2 cycles, and 7 (8.3%) patients received 3 cycles. In the placebo group, 26 (31.3%) patients received 1 cycle, 54 (65.1%) patients received 2 cycles, and 3 (3.6%) patients received 3 cycles.[42]

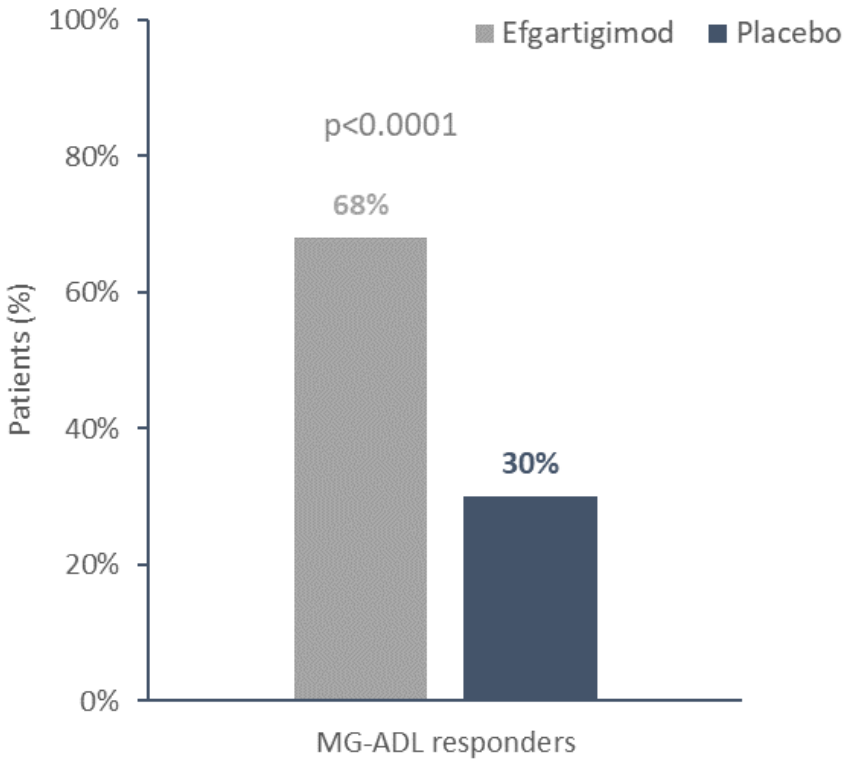
B.2.6.2 Primary endpoint: MG-ADL responders in Cycle 1, AChR-Ab+ population

The primary efficacy endpoint in ADAPT was the proportion of AChR-Ab+ patients who were MG-ADL responders in the first treatment cycle.[42] An MG-ADL responder was defined as a patient with a ≥2-point improvement in MG-ADL score sustained for ≥4 consecutive weeks, with the first improvement occurring no later than one week after the last infusion in a cycle.[42] A 2-point change in this patient-reported outcome measure is considered clinically meaningful, and reliability is high.[74,72]

In ADAPT, a significantly higher proportion of AChR-Ab+ patients in the efgartigimod group were MG-ADL responders (44/65; 68%) during Cycle 1 compared with the placebo group (19/64; 30%; OR 4.95 [95% CI 2.21, 11.53]; p<0.0001; Figure 12).[42] This is a clinically relevant result, because a difference of total MG-ADL responder rate of 35% between the placebo and the AChR-Ab+ population is considered to be clinically relevant.[42]

The onset of response was rapid; [redacted] of efgartigimod-treated patients who were Cycle 1 MG-ADL responders had CMI in MG-ADL score by Week 1 and 84% (37/44) by Week 2.[42,169]

Figure 12: Proportion of MG-ADL responders, AChR-Ab+ population, Cycle 1 (mITT analysis set)



Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; mITT, modified intention-to-treat
Source: Howard et al, 2021[42]

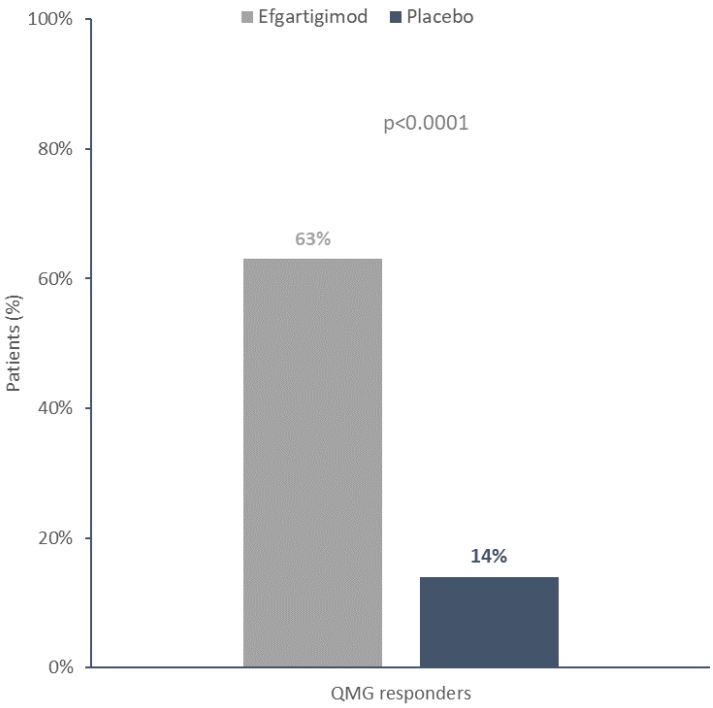
B.2.6.3 Secondary endpoints

B.2.6.3.1 QMG responders in Cycle 1, AChR-Ab+ population

A patient was considered a QMG responder if there was a ≥3-point improvement in the total QMG score for at least four consecutive weeks, with the first improvement occurring no later than one week after the last infusion in a cycle.[42] A statistically significantly higher proportion of AChR-Ab+ patients in the efgartigimod group were QMG responders during Cycle 1 (41/65; 63%) compared with the placebo group (9/64; 14%; OR 10.84 [95% CI 4.18, 31.20]; p<0.0001; Figure 13 and Table 17).[42]

The statistically significantly greater proportion of both MG-ADL and QMG responders in the efgartigimod treatment group during Cycle 1 demonstrates a consistency of clinically meaningful improvement across different scales that measure the manifestations of gMG.[42]

Figure 13: Proportion of QMG responders, AChR-Ab+ population, Cycle 1 (mITT analysis set)



Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; mITT, modified intention-to-treat; QMG, Quantitative Myasthenia Gravis scale
Source: Howard et al, 2021[42]

B.2.6.3.2 Proportion of time up to Day 126 with a CMI in MG-ADL, AChR-Ab+ population

AChR-Ab+ patients treated with efgartigimod showed a CMI (≥2-point improvement) in MG-ADL score for a significantly longer mean percentage of time between the start of the study and Day 126 (48.7%; 95% CI 36.5, 60.9), compared with placebo-treated patients (26.6%; 95% CI 14.1, 39.2; p=0.0001;Table 17).[42,169]

B.2.6.3.3 Time to qualify for retreatment, AChR-Ab+ patients

The time to no CMI was defined as the time from Day 28 (1 week after the fourth infusion of Cycle 1) to qualifying for retreatment (retreatment was initiated upon loss of response [defined as no longer exhibiting a decrease of ≥2 points on the total MG-ADL score compared with the corresponding treatment cycle baseline] and an MG-ADL total score of ≥5 points with >50% of the total score attributed to non-ocular symptoms). A longer time to no CMI indicates a longer duration of treatment effect. The median time from Day 28 to no CMI was numerically longer in AChR-Ab+ patients receiving efgartigimod compared with patients receiving placebo (35 days vs 8 days; Figure 14). Although a log-rank test did not identify this difference as being statistically significant (p=0.26), a Wilcoxon test done *post hoc* found a significant difference (p=0.013).[42]

Figure 14: Time to no CMI in the AChR-Ab+ population

Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive
Source: argenx, 2020[169]

B.2.6.3.4 Early MG-ADL responders in Cycle 1 (AChR-Ab+ population)

Patients with a ≥2-point improvement in MG-ADL score sustained for at least 4 weeks, with the first improvement occurring no later than Week 2 of the first treatment cycle were considered early responders.[42]

A higher proportion of AChR-Ab+ patients treated with efgartigimod were early MG-ADL responders compared with patients receiving placebo (57% [37/65] vs 25% [16/64]), but this was not tested for significance because a statistically significant difference between the efgartigimod and placebo groups was not attained in the previous endpoint in the hierarchy.[42]

B.2.6.3.5 Summary of secondary endpoints

A summary of secondary efficacy endpoints and results from ADAPT (AChR-Ab+ patients only) is shown in Table 17.

Table 17: Summary of secondary endpoints and results from ADAPT (mITT analysis set)

Secondary endpoint type	Measure	Population	Time	Efgartigimod	Placebo	p value
Response	QMG responder	AChR-Ab+	Cycle 1	63% (41/65)	14% (9/64)	<0.0001 OR (95% CI): 10.84 (4.18, 31.20)
Duration	Time (%) with CMI in MG-ADL	AChR-Ab+	Until Day 126*	48.7%	26.6%	0.0001
Duration	Time from Day 28 to no CMI	AChR-Ab+	Full study	Median 35 days, (IQR 18–71 days)	Median 8 days (IQR 1–57 days)	0.26
Onset	Early MG-ADL responder	AChR-Ab+	Cycle 1	57% (37/65)	25% (16/64)	Not tested**

*Day 126 was the last day on which it was possible to start and complete a subsequent treatment cycle within the study; **Secondary endpoints were tested in hierarchical order. The last secondary endpoint was not tested as the prior secondary endpoint did not achieve statistical significance.
Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; CI, confidence interval; CMI, clinically meaningful improvement; IQR, interquartile range; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; OR, odds ratio; QMG, Quantitative Myasthenia Gravis scale
Source: Howard et al, 2021.[42]

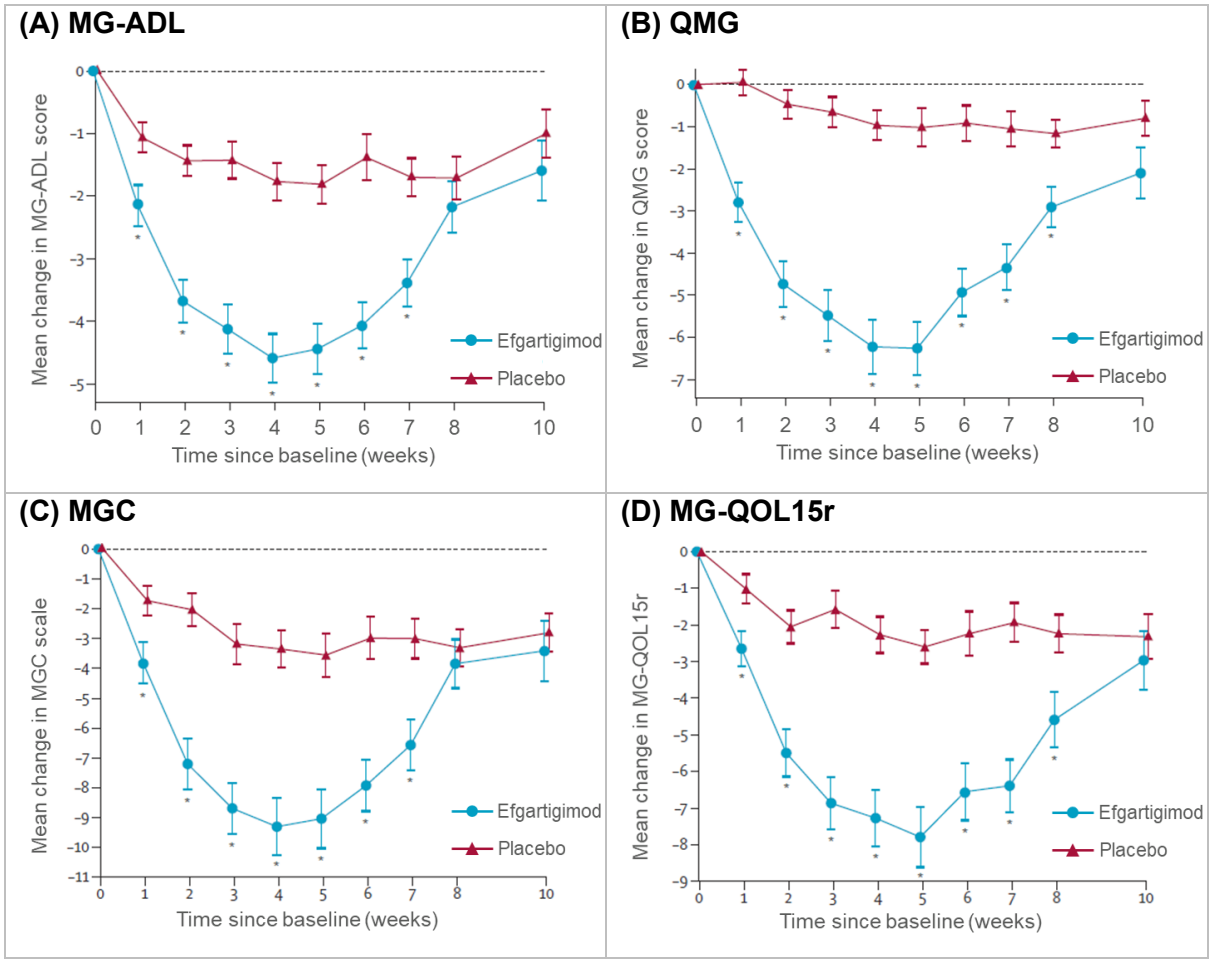
B.2.6.4 Exploratory analyses (AChR-Ab+ population)

Predefined exploratory endpoints provide important information, including time to onset of effect; magnitude of effect, including proportion of patients achieving minimal symptom expression (defined as MG-ADL score of 0 or 1) and the proportion of patients with increasing levels of MG-ADL and QMG improvement in each cycle; duration of response in MG-ADL responders; repeatability of effect with second treatment cycle; and the change in MGC and MG-QOL15r scores.[42]

B.2.6.4.1 Magnitude of effect: change from baseline in total mean score (MG-ADL, QMG, MGC, MG-QOL15r)

Clinically meaningful and sustained improvements were consistently demonstrated across the four MG scales. In the AChR-Ab+ population, patients treated with efgartigimod had greater improvements than those treated with placebo in MG-ADL, QMG, MGC, and MG-QOL15r total mean scores in Cycle 1, and statistically significant differences from baseline observed from Week 1 through Week 7 (Figure 15).[42] These results demonstrate that response to efgartigimod was rapid, with significant and clinically meaningful improvements from baseline observed as early as one week after the initial dose and sustained through at least Week 7 across all measures.

Figure 15: Mean change in total scores from baseline for MG-ADL (A), QMG (B), MGC (C), and MG-QOL15r (D) during cycle 1, AChR-Ab+ patients



Error bars show standard error; *p<0.05
Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite scale; MG-QOL15r, Myasthenia Gravis 15-item Quality of Life revised scale QMG, Quantitative Myasthenia Gravis
Source: Howard et al, 2021[42]

A summary of the mixed model for repeated measures analyses conducted for changes from baseline in total mean scores across efficacy (MG-ADL, QMG, MGC) and HRQoL (MG-QOL15r) scales is shown in Table 18.

Table 18: Summary of MMRM analyses for MG-ADL, QMG, MGC, and MG-QOL15r (Cycle 1)

Scale	Max improvement timepoint	Mean change from baseline (95% CI)		LS mean difference (SE)	p value
		Efgartigimod	Placebo		
MG-ADL	Week 4	−4.10 (−5.01, −3.20)	−1.27 (−2.20, −0.34)	−2.84 (0.49)	p<0.0001
QMG	Week 4	−5.77 (−7.02, −4.51)	−0.54 (−1.85, −0.77)	−5.23 (0.71)	p<0.0001
MGC	Week 4	−8.91 (SE: 0.97)	−2.87 (SE: 1.01)	NA	p<0.0001
MG-QOL15r	Week 5	NA	NA	Mean difference >5 points Effect size: 0.94*	p<0.0001

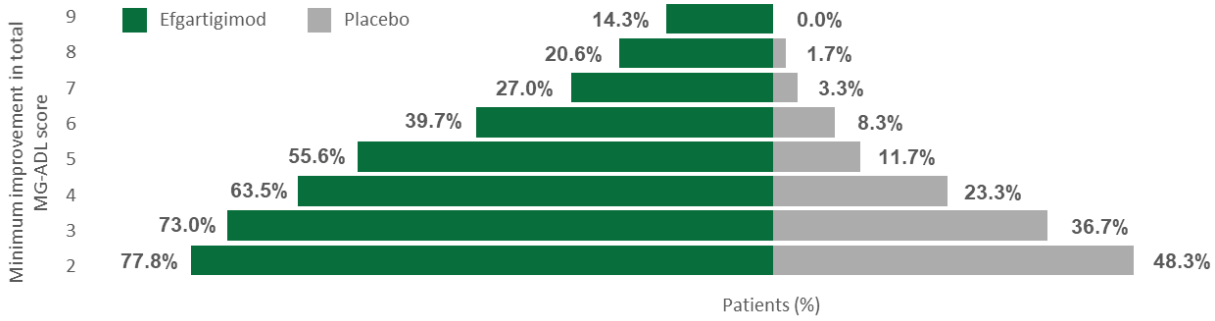
*An effect size >0.8 is considered a large effect size
Abbreviations: LS, least squares; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite scale; MG-QOL15r, Myasthenia Gravis 15-item Quality of Life revised scale; MMRM, mixed model for repeated measures; NA, not applicable; QMG, Quantitative Myasthenia Gravis scale; SE, standard error; W, week
Source: argenx, 2020.[169]

B.2.6.4.2 Magnitude of effect: minimum point improvement in total score (MG-ADL and QMG)

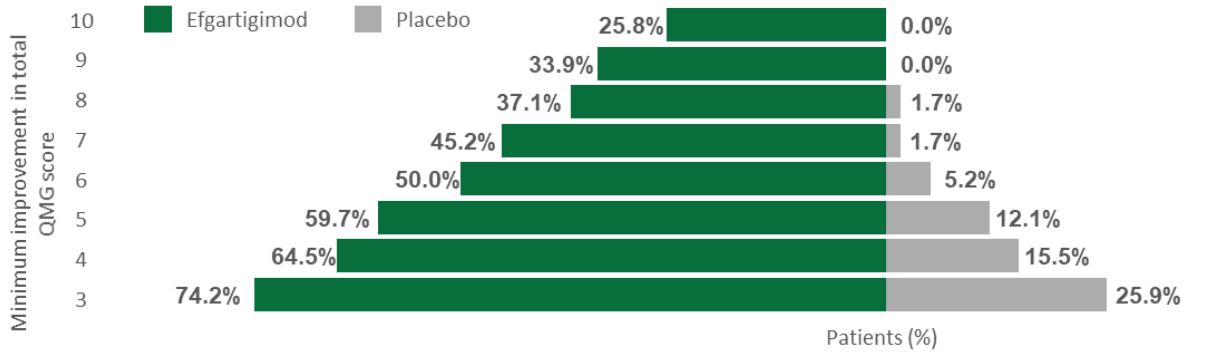
Treatment with efgartigimod showed a substantial magnitude of effect on both the MG-ADL and QMG scales as demonstrated by the level of improvement in scores among patients. One week after the last infusion of Cycle 1, the time of maximum pharmacodynamic effect, a greater proportion of AChR-Ab+ patients treated with efgartigimod achieved higher levels of reduction in both MG-ADL and QMG scores than patients treated with placebo (Figure 16). For example, 55.6% of patients treated with efgartigimod achieved at least a 5-point reduction in MG-ADL score versus 11.7% of those treated with placebo; likewise, a ≥10-point improvement in QMG score was observed in 25.8% vs 0%, respectively.[42]

Figure 16: Proportion of AChR-Ab+ patients with point reduction of at least 2–9 points in MG-ADL (A) and 3–10 points in QMG (B) scores at Week 4 of cycle 1

(A) MG-ADL



(B) QMG



Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QMG, Quantitative Myasthenia Gravis scale
Source: Howard et al, 2021[42]

B.2.6.4.3 Magnitude of effect: Minimal symptom expression (MG-ADL)

Minimal symptom expression is defined as an MG-ADL total score of 0 or 1. In the AChR-Ab+ population, 40% (26/65) of patients in the efgartigimod group attained an MG-ADL score of 0 or 1 at any point in Cycle 1, indicating no or minimal symptoms, compared with 11% (7/63) in the placebo group ($p<0.0001$).[42]

B.2.6.4.4 Onset of effect: MG-ADL and QMG responders

As demonstrated with the mean changes in total MG-ADL and QMG scores (Figure 15), rapid onset of effect was also observed upon further analysis of these two measures. Among AChR-Ab+ patients who were MG-ADL and QMG responders to efgartigimod in Cycle 1, 84% and 83%, respectively, experienced an onset of response by Week 2 (one week after the second infusion) of the treatment cycle.[169]

B.2.6.4.5 Duration of response: MG-ADL and QMG responders

The duration of response for AChR-Ab+ patients who were MG-ADL or QMG responders to efgartigimod during Cycle 1, defined as the period over which a CMI was maintained, is presented in Figure 17.

For MG-ADL, the duration of response was ≥6 weeks in [redacted] of responders, ≥8 weeks in [redacted] of responders, and ≥12 weeks in [redacted] of responders. The duration of QMG response was ≥6 weeks in [redacted] of responders, ≥8 weeks in [redacted] of responders, and ≥12 weeks in [redacted] of responders.[169]

The 8- and 12-week response results for both the MG-ADL and QMG scales demonstrate that a substantial proportion of responders have extended clinical benefit during treatment with efgartigimod. The prolonged treatment response beyond 12 weeks for a considerable portion of the study population further supports the use of an individualised treatment approach for patients (approach outlined in Section B.2.3.1).

Figure 17: Duration of responses for efgartigimod treated MG-ADL and QMG responders from Cycle 1

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QMG, Quantitative Myasthenia Gravis scale
Source: argenx, 2020[42,169]

B.2.6.4.6 Repeatability of effect: MG-ADL and QMG responders in Cycle 2

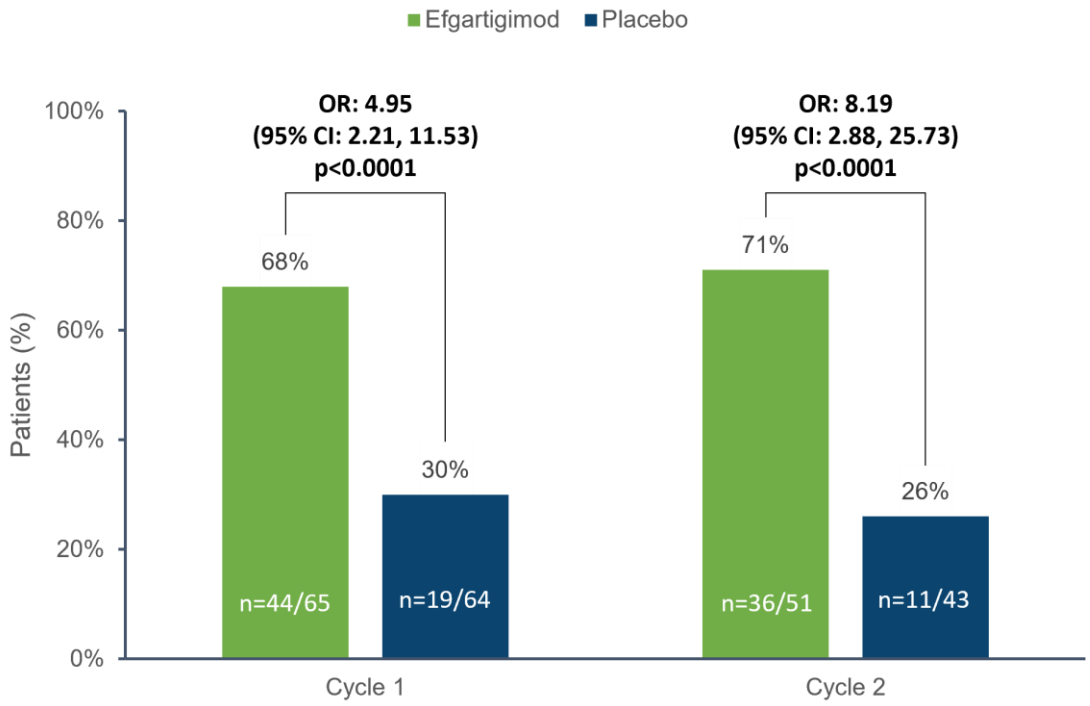
MG-ADL responder rates in Cycle 2 were similar to those in Cycle 1. In AChR-Ab+ patients who received a second treatment cycle, 71% (36/51) of patients in the efgartigimod group were MG-ADL responders compared with 26% (11/43) of patients in the placebo group (Figure 18), demonstrating that the effect of efgartigimod is repeatable across treatment cycles.[42]

Moreover, patients who have limited benefit in the first cycle may still respond with a second cycle.[42] Among the 21 AChR-Ab+ patients in the efgartigimod group who were not MG-ADL responders in Cycle 1, 19 patients received a subsequent treatment cycle and 7 (37%) were MG-ADL responders in Cycle 2.[42]

Across Cycles 1 and 2, 78.5% (51/65) of efgartigimod-treated patients were MG-ADL responders.

Six (86%) of seven patients in the efgartigimod group who received a third cycle were MG-ADL responders.[42]

Figure 18: Proportion of MG-ADL responders during Cycle 1 and Cycle 2 in the AChR-Ab+ population

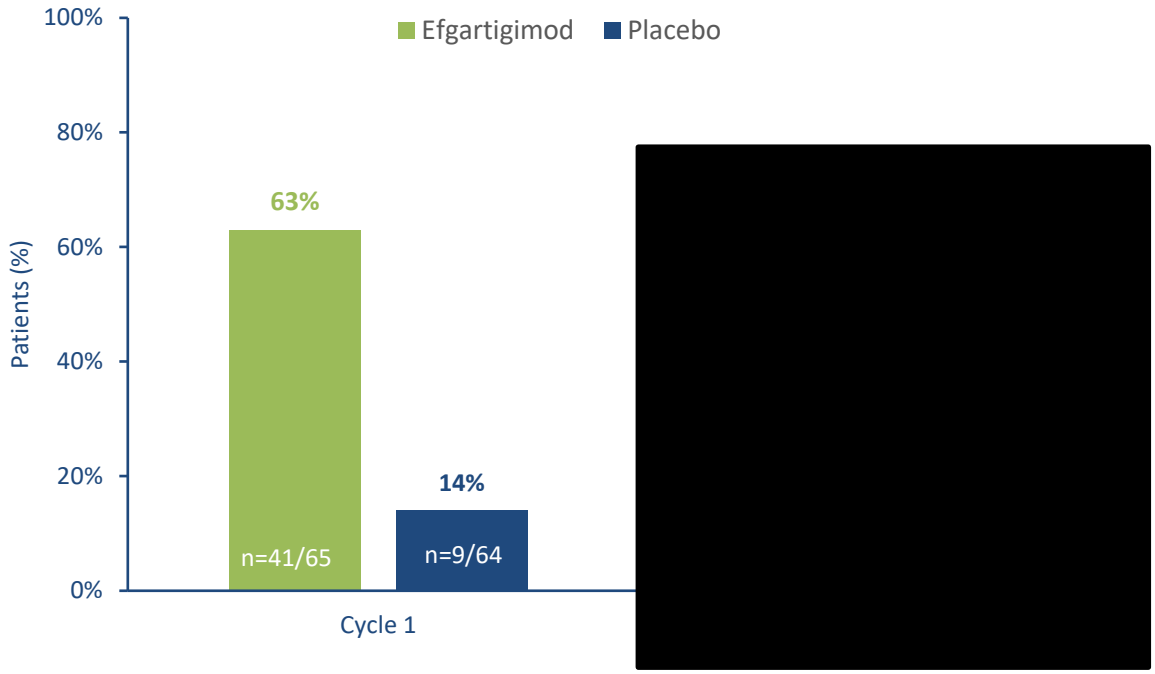


Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Source: Howard et al, 2021.[42]

QMG responder rates in Cycle 2 were similar to those in Cycle 1. In AChR-Ab+ patients who received a second treatment cycle, [redacted] of patients in the efgartigimod group were QMG responders compared with [redacted] of patients in the placebo group (Figure 19).[169]

The lower proportion of QMG responders in Cycle 2 is explained by the durability of improvement in QMG from Cycle 1 at the time of initiation of Cycle 2. Patients were considered eligible for a new treatment cycle on the basis of their MG-ADL score only, which means that a cycle could be administered despite a patient retaining a CMI in their QMG score. Eighteen of the 51 patients who received a second cycle had a clinically meaningful improvement in QMG score (i.e. ≥3 point reduction) at the start of the second cycle, compared with their QMG score at study entry, including 16 patients who were QMG responders in Cycle 1.[169]

Figure 19: Proportion of QMG responders during Cycle 1 and Cycle 2 in the AChR-Ab+ population

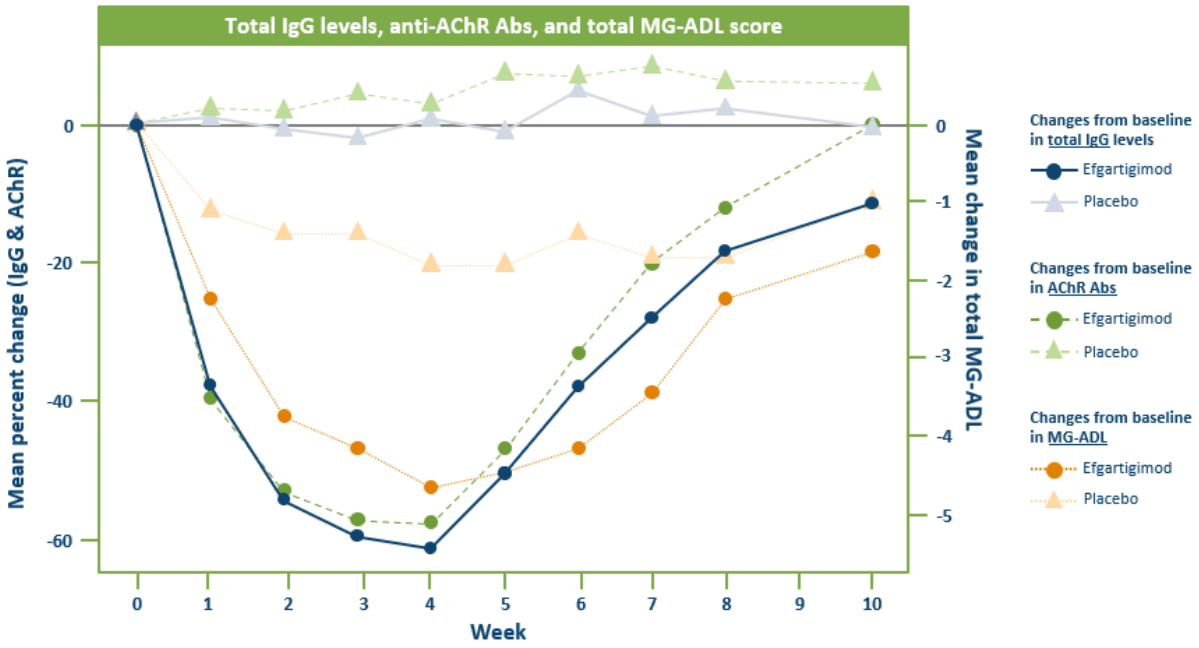


Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; QMG, Quantitative Myasthenia Gravis scale
Source: Howard et al, 2021;[42] argenx, 2020.[169]

B.2.6.5 Selected tertiary endpoints

Pharmacodynamic analyses conducted were levels of total IgG, IgG subtypes, and autoantibodies measured from blood samples using validated methods. Consistent reductions in total IgG levels and anti-AChR antibodies were observed in all cycles in the AChR-Ab+ population. The reduction in IgG levels and anti-AChR antibodies followed a similar time course as improvements in MG-ADL (Figure 20).[42]

Figure 20: Total IgG levels, AChR-Ab levels and change in mean MG-ADL score, AChR-Ab+ patients, Cycle 1



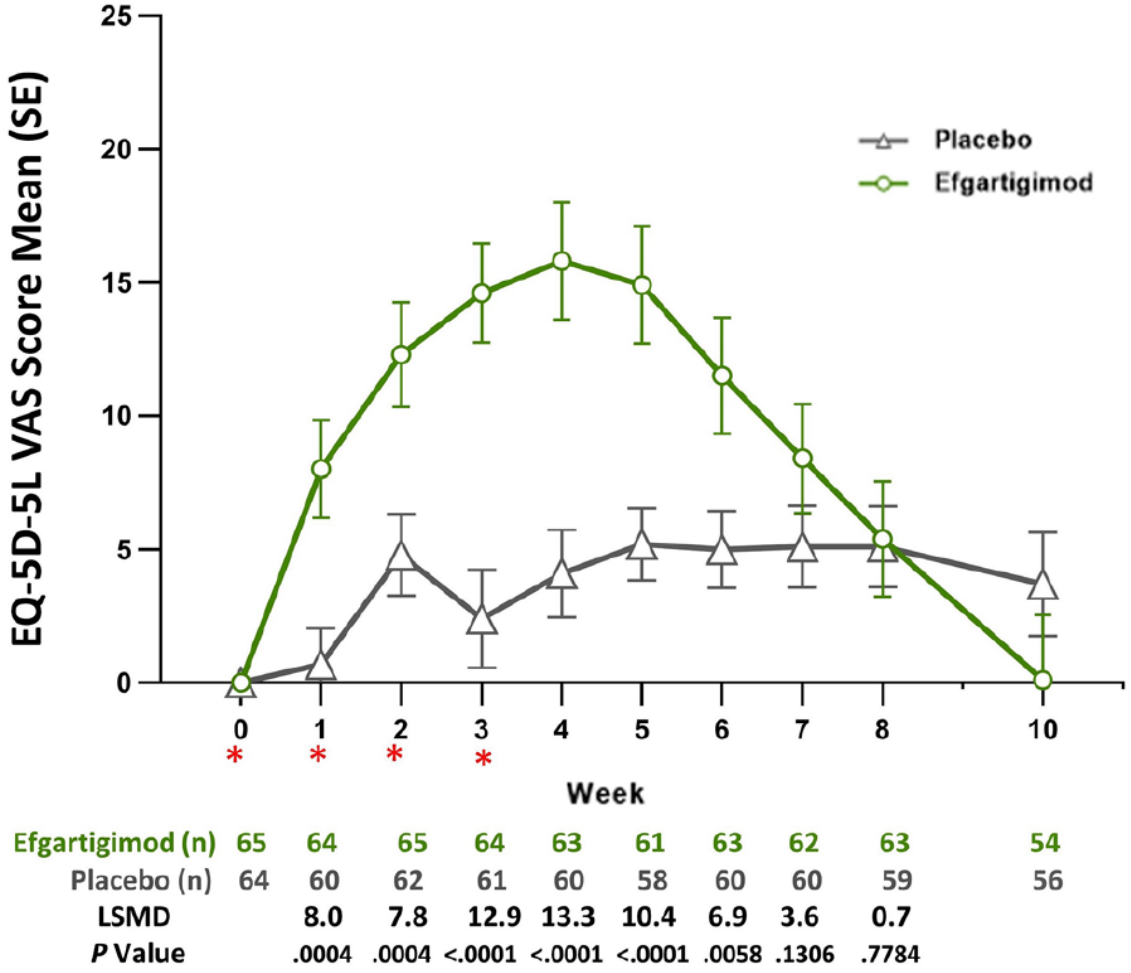
Abbreviations: Ab, antibodies; AChR-Ab+, acetylcholine receptor autoantibody-positive; IgG, immunoglobulin G; MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Source: adapted from Howard et al, 2021[42]

B.2.6.6 HRQoL and patient-reported outcomes

B.2.6.6.1 EQ-5D-5L VAS

Results of the mean change from baseline on the VAS of the EQ-5D-5L during Cycle 1 in the AChR-Ab+ population are presented in Figure 21.[165] Positive changes indicate a higher HRQoL as reported by the patient. The maximum mean (standard error, SE) change in the EQ-5D-5L VAS at Week 4 in the AChR-Ab+ population was 15.8 (2.20) in the efgartigimod group compared with 4.1 (1.64) in the placebo group.[165,169] During Cycle 1, the change from baseline was statistically significantly different between treatment arms at weeks 1–6 ($p<0.05$).[165]

Figure 21: EQ-5D-5L VAS: Mean change from baseline in the AChR-Ab+ population; Cycle 1



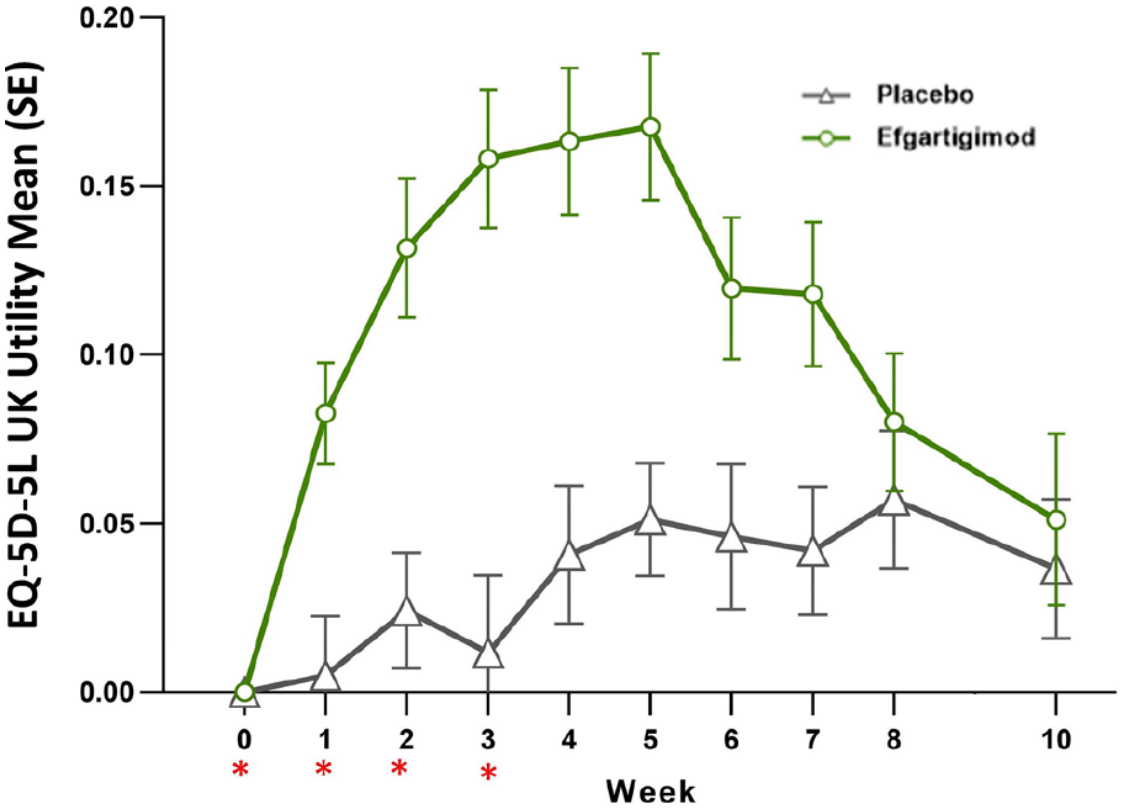
*Indicates treatment administration (efgartigimod or matching placebo).
Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; LMSD, least squares mean difference; SE, standard error; VAS, visual analogue scale.
Source: Saccà et al, 2023.[165]

B.2.6.6.2 EQ-5D-5L UK utility

At baseline, patients had EQ-5D-5L health utility scores of 0.62–0.66, potentially reflecting the substantial quality of life burden of gMG, despite all patients being on stable treatment at screening.[165]

Results of utility scores from ADAPT were calculated using the UK standardised value set as weighting; these results from Cycle 1 in the AChR-Ab+ population are shown in Figure 22.[165] During Cycle 1, the change from baseline was statistically significantly different between treatment arms at weeks 1–8 ($p<0.05$).[165]

Figure 22: EQ-5D-5L UK utility: Mean change from baseline in the AChR-Ab+ population; Cycle 1



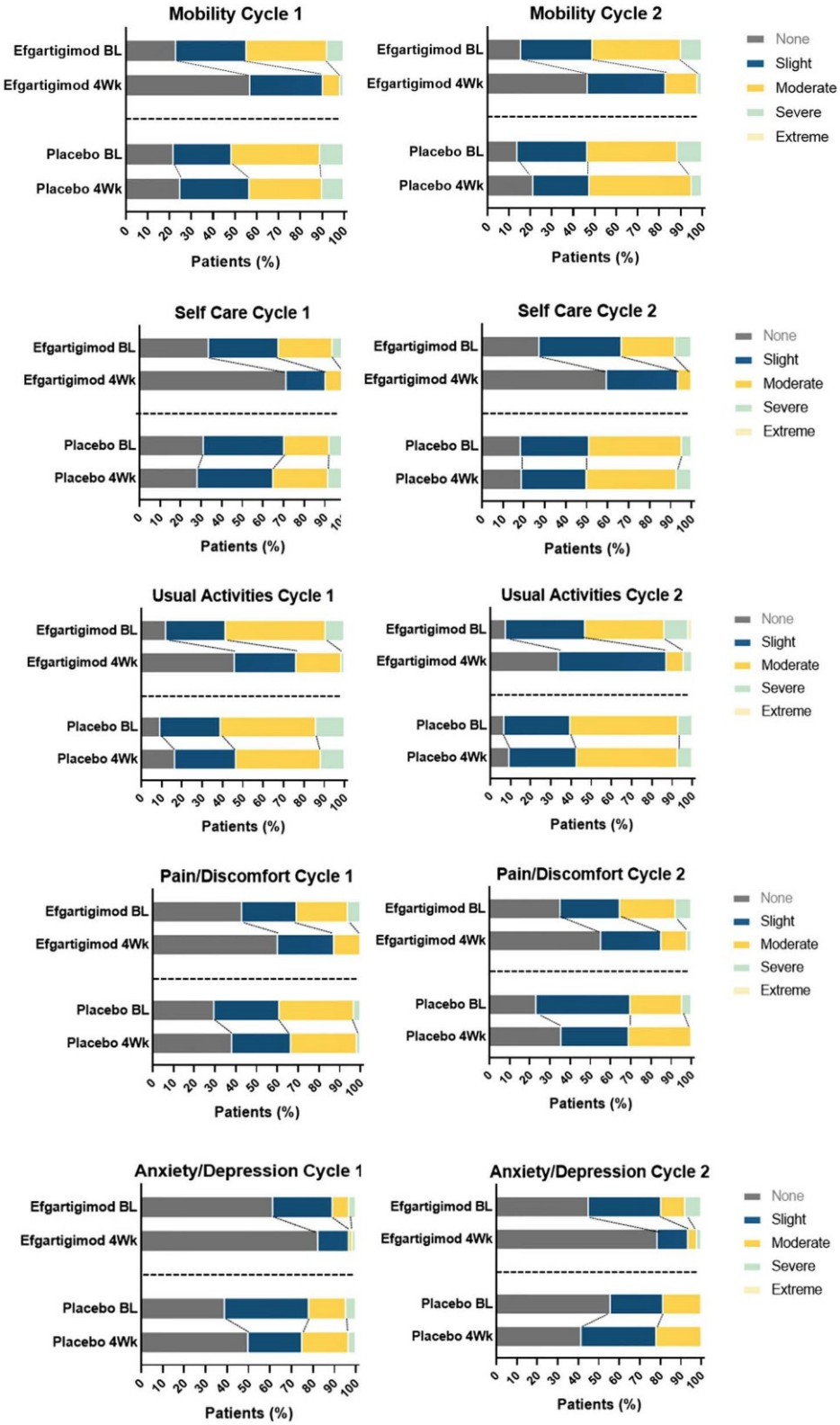
*Indicates treatment administration (efgartigimod or matching placebo).
Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; LMSD, least squares mean difference; SE, standard error; VAS, visual analogue scale.
Source: Saccà et al, 2023.[165]

B.2.6.6.3 EQ-5D-5L domain responses

Responses for individual EQ-5D-5L domains by cycle are shown in Figure 23. Patients in the efgartigimod treatment arm showed numeric improvements at 4 weeks in each domain for both Cycle 1 and 2, whereas patients in the placebo arm did not.[165]

For mobility, the increase in proportion of participants reporting no problems (averaged over Cycle 1 and Cycle 2) was 38%-points for the efgartigimod group vs 7%-points for placebo. For self-care, the averaged increase in participants reporting no problems was 36%-points for the efgartigimod group vs an averaged decrease of 1.5%-points for the placebo group. For usual activities, the efgartigimod group had an averaged increase in reporting no problems of 30%-points vs 9.5%-points for placebo; for pain/discomfort, increase for efgartigimod was 19%-points vs 11%-points for placebo; and for anxiety/depression, efgartigimod was an increase of 13%-points vs a decrease of 1.5%-points for the placebo group.[165]

Figure 23: EQ-5D-5L domain responses by treatment cycle in the AChR-Ab+ population



Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; BL, baseline; Wk, week.
Source: Saccà et al, 2023.[165]

B.2.6.7 Area under the curve (AUC) efficacy analyses (*post-hoc* analysis)

After an initial treatment cycle, patients enrolled in ADAPT received a subsequent treatment cycle with efgartigimod according to clinical response as measured by the MG-ADL. Patients therefore received different numbers of treatment cycles and had variable time between treatment cycles (i.e., time periods in which no efgartigimod treatment was received). To confirm the efficacy of efgartigimod compared with placebo over the complete study period rather than in predefined cycles, a *post hoc* efficacy analysis was conducted using an AUC analysis for the change in total MG-ADL, QMG, and MG-QOL15r scores from baseline to Week 26.[180]

For all three scales, the mean differences in the AUC from baseline to Week 26 were [redacted][180]

[redacted]

[redacted][180]

B.2.7 ADAPT+ study, clinical effectiveness results

B.2.7.1 Treatment duration

As of the 31 Jan 2022 interim database cut-off date, 145 patients received at least one cycle (or part of a cycle) of efgartigimod.[163,164]

The mean (SD) total duration of treatment and follow-up was 548.0 (231.79) days, resulting in 217.55 patient-years of observation.[163,164] The median (range) study duration was 588.0 (40–924) days, and the majority of patients in the total efgartigimod cohort had a combined treatment and follow-up duration of ≥18 months (Table 19).[163] Patients received up to [redacted] treatment cycles.[163]

Table 19: Duration of treatment and follow-up in patients treated with efgartigimod

Duration of treatment and follow-up	Total efgartigimod group (N=145) Patients, n (%)
<6 months	[redacted]
6 to <12 months	[redacted]
12 to <18 months	[redacted]

Duration of treatment and follow-up	Total efgartigimod group (N=145) Patients, n (%)
18 to <24 months	[redacted]
≥24 months	[redacted]

Source: argenx, 2022.[163]

B.2.7.2 Efficacy: MG-ADL total score

There were repeated improvements in MG-ADL with each cycle of treatment. The mean change from baseline in the MG-ADL total score at Week 3 of Cycles 1 through 14 in the efgartigimod AChR-Ab+ population is shown in Figure 24, demonstrating clinically meaningful improvements with each cycle.[163,164] The Week 3 time point was selected due to the limited number of scheduled visits (i.e., no visits were scheduled at Weeks 4, 5, and 6).

For all cycles, [redacted] of patients in the AChR-Ab+ population had an improvement from cycle baseline in the MG-ADL total score of at least 2 and 3 points, respectively.[163]

Figure 24: ADAPT+, mean change from cycle baseline to Week 3 of cycle in MG-ADL total score in AChR-Ab+ patients

Blue line at -2 represents the CMI threshold (≥2-point improvement in total MG-ADL score)
Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; CMI, clinically meaningful improvement; MG-ADL, Myasthenia Gravis Activities of Daily Living scale.
Source: argenx, 2022.[163]

B.2.7.3 Efficacy: QMG score

There were consistent and repeated improvements in QMG with each cycle of treatment.[170,166] The mean change from baseline in QMG score at Week 3 of Cycles 1 through 7 in the efgartigimod AChR-Ab+ population is shown in Figure 25, demonstrating clinically meaningful improvements with each cycle.

Figure 25. Mean change from cycle baseline to Week 3 of cycle in QMG total score in AChR-Ab+ patients

Blue line at -3 represents the CMI threshold (≥3-point improvement in total QMG score)
Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; CMI, clinically meaningful improvement; QMG, Quantitative Myasthenia Gravis scale
Source: argenx, 2022.[163]

B.2.8 Subgroup analysis

B.2.8.1 Efficacy subgroup analyses (AChR-Ab+ population)

Post hoc subgroup analyses demonstrated that efgartigimod was effective in a broad population of patients, with improvements over placebo that were consistent regardless of concomitant therapy, baseline disease activity, or prior NSIST exposure.[51]

See Appendix E for a summary of the results for subgroups.

B.2.9 Meta-analysis

Not applicable

B.2.10 Indirect and mixed treatment comparisons

To date, no published positive reimbursement decisions exist for treatment of gMG in England, Scotland, or Wales. In England and Wales, commissioning statements recommend use of biosimilar rituximab for a limited population (patients whose disease is refractory to standard therapy after referral and assessment within a myasthenia clinic in specialised neuroscience centres) (Section B.1.3.3.2);[31] however, this is not reflected in the current ABN disease management guidelines.[117] In England, commissioning guidance also recommends IVIg in patients requiring acute treatment, or as maintenance therapy for patients who have failed all standard therapy.[111] These commissioning decisions mean rituximab and IVIg are part of established clinical practice and may therefore be relevant therapies against which to conduct an indirect/mixed treatment comparison.[21,27,28,146]

As described in Section B.1.3.3.2, the published evidence base for clinical trials of therapies for the management of gMG is limited, and recommendations are often based on established clinical practice rather than RCTs.[20,21,40] In the cases of rituximab and IVIg, evidence of clinical benefit is particularly limited. Section B.1.3.3.4 above describes a Cochrane review for IVIg that concluded there is insufficient evidence from trials to determine whether IVIg is efficacious as a maintenance treatment in chronic gMG.[146] For rituximab, both the BeatMG and RINOMAX studies failed to demonstrate a statistically significant clinical benefit for rituximab vs. placebo.[27,28] Given the insufficient level of evidence available a reliable indirect treatment comparison was considered not feasible.

B.2.11 Adverse reactions

B.2.11.1 ADAPT study

Overall, efgartigimod was generally well tolerated, with a favourable safety profile.

The most common treatment-emergent adverse events (AEs) in all patients in ADAPT (including the AChR-Ab+ population) are presented in Table 20. Overall, 65 (77%) of 84 patients in the efgartigimod group and 70 (84%) of 83 in the placebo group had at least one AE.[42] The most frequently reported AEs in the efgartigimod group were headache (29%), nasopharyngitis (12%), nausea (8%), diarrhoea (7%), upper respiratory tract infections (11%), and urinary tract infections (10%). Most AEs were mild or moderate in

severity; 9 (11%) and 8 (10%) patients in the efgartigimod and the placebo groups, respectively, experienced severe events (Grade ≥3).

There were no clinically meaningful changes in haematology or chemistry parameters, including albumin, electrocardiograms, or vital signs in either group.[42]

Administration of rescue therapy resulted in the discontinuation of treatment in 1 (1.2%) patient in the efgartigimod group and 2 (2.4%) patients in the placebo group.[42]

Table 20: Common (≥5% in any group) AEs by preferred term, n (%); ADAPT study, all patients

AE	Efgartigimod (n=84)	Placebo (n=83)
≥1 AE	65 (77.4)	70 (84.3)
Bronchitis	5 (6.0)	2 (2.4)
Nasopharyngitis	10 (11.9)	15 (18.1)
Upper respiratory tract infection	9 (10.7)	4 (4.8)
Urinary tract infection	8 (9.5)	4 (4.8)
System organ class 'Infections and infestations'	39 (46.4)	31 (37.3)
Dizziness	3 (3.6)	5 (6.0)
Headache	24 (28.6)	23 (27.7)
Diarrhoea	6 (7.1)	9 (10.8)
Nausea	7 (8.3)	9 (10.8)
Myalgia	5 (6.0)	1 (1.2)
Cough	3 (3.6)	5 (6.0)
Oropharyngeal pain	3 (3.6)	7 (8.4)
Hypertension	3 (3.6)	6 (7.2)

Abbreviations: AE, adverse event
Source: Howard et al, 2021[42]; argenx, 2020[169]

Infections were regarded as treatment-emergent AEs of special interest (AESIs) and were reported in 39 (46%) of patients in the efgartigimod group and 31 (37%) of patients in the placebo group.[42] The most frequently reported AESIs in either group were nasopharyngitis, upper respiratory tract infection, urinary tract infection, and bronchitis (see Table 20 for rates). Most infectious events were reported as mild to moderate in severity and there were no discontinuations due to an infectious event.[42,169]

Four (5%) patients treated with efgartigimod had a treatment-emergent serious AE (SAE), including thrombocytosis, rectal adenocarcinoma, MG worsening, and depression.[42] Thrombocytosis, rectal adenocarcinoma and MG worsening led to treatment discontinuation.[42] In the placebo group, 7 (8%) patients had an SAE, including myocardial ischaemia, atrial fibrillation, and spinal ligament ossification, all of which led to treatment discontinuation; upper respiratory infection, spinal compression fracture, MG worsening, and myasthenic crisis were also reported but did not lead to treatment discontinuations. No deaths occurred during the study in either arm.[42]

Discontinuation from treatment due to AEs was reported in six patients overall: 3 (4%) patients in the efgartigimod group and 3 (4%) patients in the placebo group.[42]

For longer-term safety outcomes from ADAPT+ study, see Section B.2.11.2.

B.2.11.2 ADAPT+ study

This long-term extension study demonstrated that efgartigimod was well tolerated with repeated cycles of treatment.[166]

A summary of the most frequently reported treatment-emergent AEs (≥5% patients) in the overall population of ADAPT+ by preferred term is provided in Table 21. The most commonly reported AEs were headache, nasopharyngitis and COVID-19.[163] Most AEs were mild or moderate in severity.[163] AEs of severity grade ≥3 occurred in 38 (26.2%) patients.[163] Events with severity grade ≥3 reported in ≥2 patients in either cohort were COVID-19 pneumonia, pneumonia, urinary tract infection, headache, and MG. None of these events were assessed by the investigator as related to efgartigimod treatment, other than an AE of urinary tract infection that the investigator judged to be probably related to efgartigimod.[163]

Table 21: Most frequently reported AEs (≥8% patients) by preferred term in ADAPT+, n (%); overall safety population

AE, n (%)	All patients (N=145)
≥1 AE	123 (84.8)
Headache	36 (24.8)
Nasopharyngitis	20 (13.8)
COVID-19	18 (12.4)
Diarrhoea	14 (9.7)
Urinary tract infection	13 (9.0)
Arthralgia	12 (8.3)

Abbreviations: AE, adverse event
Source: argenx, 2022.[163]

Infections (as reported in Table 21) were considered AESIs in ADAPT+. The majority of AESIs were mild to moderate in severity; Grade ≥3 AESIs included COVID-19 pneumonia, urinary tract infection, septic shock, COVID-19, dysentery, pneumonia, pneumonia *Escherichia*, pharyngitis streptococcal, influenza, and pseudomonal sepsis. The incidence rate of AESIs did not increase with subsequent efgartigimod cycles and no opportunistic infections were reported.[163]

At least one treatment-emergent SAE occurred in 34 (23.4%) patients. One Grade 1 SAE of infusion-related reaction in one patient was considered related to efgartigimod treatment.[163] Five patients have died in ADAPT+; no deaths were considered related to treatment with efgartigimod.[163]

Overall, 12 [8.3%] patients have discontinued treatment during ADAPT+ due to AEs.[163]

B.2.12 Supporting evidence from ADAPT-SC study

Efgartigimod co-formulated with recombinant human hyaluronidase PH20 (rHuPH20) for subcutaneous (SC) administration (efgartigimod PH20 SC) 1,000 mg is a new formulation

expected to receive UK approval by the end of 2023. This new formulation will allow/enable patients to opt for self-administration. The primary objective of this study was to demonstrate the noninferiority (NI) of the SC formulation compared with the IV formulation using total IgG percent reduction at Day 29 based on an NI margin of 10%. The main study characteristics are detailed in Table 22.

Table 22: Main study characteristics for ADAPT-SC study

Study name	ADAPT-SC (a Phase 3, randomised, open-label, parallel-group study to compare the pharmacodynamics, pharmacokinetics, efficacy, safety, tolerability, and immunogenicity of multiple SC injections of efgartigimod PH20 SC with multiple IV infusions of efgartigimod in patients with gMG)
NCT number	NCT04735432
Objective	The aim of this study was to investigate the PD, PK, safety, tolerability, immunogenicity, and clinical efficacy of efgartigimod co-formulated with recombinant human hyaluronidase PH20 (rHuPH20) administered SC (efgartigimod PH20 SC) as compared to efgartigimod IV infusion (efgartigimod IV) in patients with gMG
Study type and design	ADAPT-SC was a randomised, multicentre, open-label Phase 3 study. All patients were centrally assigned to randomised study intervention using an interactive response technology
Follow-up time	10 weeks
Inclusion criteria	• Adult patients who were diagnosed with gMG with confirmed documentation and supported by at least one of the following: o History of abnormal neuromuscular transmission demonstrated by single-fibre electromyography or repetitive nerve stimulation o History of positive edrophonium chloride test o Demonstrated improvement in MG signs upon treatment with oral AChEis as assessed by the treating physician • An MG-ADL total score of ≥5 points, with >50% of the total score attributed to non-ocular symptoms, at screening and baseline • Receiving a stable dose of concomitant therapy for gMG
Primary endpoint	Percentage reduction from baseline in total immunoglobulin G (IgG) levels at Day 29 (i.e., 7 days after the fourth IV or SC administration)
Secondary endpoints	Absolute values, change from baseline, and percent reduction from baseline in: • Total IgG levels over time • AChR-Ab levels in AChR-Ab+ patients over time • IgG subtype levels (IgG1, IgG2, IgG3, and IgG4) over time AUEC of the percentage reduction from baseline total IgG and AUEC for each IgG subtype per dosing interval (Days 1–8, Days 8–15, Days 15–22, and Days 22–29), Days 1–29, and over the entire study (Days 1–71) PK parameters: • Cmax (after all doses for the IV treatment arm) • Ctrough (after all doses for the IV and SC treatment arms) Incidence and prevalence of antidrug antibodies against efgartigimod and against rHuPH20 in the SC treatment arm Incidence and severity of AEs, SAEs, and changes in laboratory test results, physical examination results, vital signs, and ECG results

	Number and percentage of MG-ADL and QMG responders Change from baseline in MG-ADL total score and QMG score over time
Method of analysis	Efficacy analyses were performed on the ITT population set, which included all randomised participants who were exposed to study treatment. PD analyses were performed on the mITT analysis set, which included all randomised participants with a value for total IgG levels at baseline and at least one post-baseline time point. Safety analyses were evaluated in all randomised participants who were exposed to study treatment. PK analyses were performed on a subset of the safety analysis set with at least one post-dose PK measurement The primary endpoint was analysed using an ANCOVA model with treatment as a factor and total IgG levels at baseline as a covariate. The NI evaluation was based on a percent reduction from baseline in total IgG levels at day 29 (Week 4) using a noninferiority margin of 10%
Subgroup analyses	[redacted]

Abbreviations: AChEi, acetylcholinesterase inhibitor; AChR-Ab, acetylcholine receptor autoantibody; AE, adverse events; ANCOVA, analysis of covariance; AUEC, area under the effect curve; Cmax, maximum concentration; Ctrough, concentration observed pre-dose; ECG, electrocardiogram; gMG, generalised myasthenia gravis; ITT, intention-to-treat; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; mITT, modified intent-to-treat; PD, pharmacodynamics; PK, pharmacokinetics; QMG, Quantitative Myasthenia Gravis; SAE: serious adverse events
Source: argenx, 2022;[167] ClinicalTrials.gov (NCT04735432).[168]

B.2.12.1 ADAPT-SC study design

ADAPT-SC is a Phase 3, randomised, open-label, parallel-group study comparing the pharmacodynamics, pharmacokinetics, efficacy, safety, tolerability, and immunogenicity of SC injections of efgartigimod PH20 with IV infusions of efgartigimod in patients with gMG.[168] The primary objective of the study was to demonstrate that the PD effect of SC injections of 1,000 mg efgartigimod PH20 was noninferior to that of IV (10 mg/kg) infusions of efgartigimod. The primary endpoint was the reduction from baseline in total IgG levels at Day 29.[168] The study enrolled adult patients with gMG who had an MG-ADL total score ≥5 points, with greater than 50% of the total score attributed to non-ocular symptoms, at screening and baseline.[167]

B.2.12.2 ADAPT-SC results summary

A total of [redacted] participants were enrolled in the study and randomised 1:1 to either the efgartigimod IV 10 mg/kg treatment arm or the efgartigimod PH20 SC 1,000 mg treatment arm once weekly for four administrations.(argenx 2022c) There were 110 patients in the safety analysis, ITT, and mITT analysis sets (55 in each arm).[167](argenx 2022c)

The primary endpoint was met; efgartigimod SC demonstrated a least squares mean total IgG reduction of 66.4% (95% CI −68.91, −63.86) from baseline at Day 29, compared with 62.2% (95% CI −64.67, −59.72) with IV efgartigimod, meaning that the SC route was noninferior to IV administration.[46,167]

The clinical efficacy of efgartigimod PH20 SC was measured using the participant-reported MG-ADL scale and the physician assessed QMG scale. As well as a reduction in total IgG, a

large proportion of participants with gMG treated with efgartigimod PH20 SC achieved a response measured by MG-ADL or QMG (69.1% and 65.5%, respectively),[46] including those with AChR-Ab+ gMG, [redacted].[167] Overall, clinical efficacy of efgartigimod PH20 SC was similar to efgartigimod IV after one treatment cycle of four weekly administrations.(argenx 2022c)

Both efgartigimod PH20 SC and efgartigimod IV were well tolerated and had favourable safety profiles in participants with gMG, consistent with the Phase 3 ADAPT study (see Section B.2.11).[46] Most AEs were mild to moderate in severity, with the most frequent AE reported for efgartigimod PH20SC being injection-site rash.[46,167]

B.2.13 Ongoing studies

The ongoing ADAPT+ study is presented above (Section B.2.3.2, B.2.4.2, and B.2.7). A final data cut from ADAPT+ is anticipated within the next 12 months.

B.2.13.1 ADAPT-SC+

A long-term, single-arm, open-label Phase 3 study of the subcutaneous formulation (ADAPT-SC+; NCT04818671) is also in progress. This study will close in April 2023.

B.2.13.2 ADAPT NXT

A Phase 3b, randomised, open-label, parallel-group, multicentre study investigating different IV dosing regimens is ongoing (ADAPT NXT; NCT04980495). Estimated study completion is April 2025.

B.2.14 Interpretation of clinical effectiveness and safety evidence

The clinical efficacy and safety of efgartigimod has been demonstrated in the pivotal ADAPT RCT, which provides the main body of evidence for efgartigimod for the treatment of gMG. The clinical trial included 167 patients from 56 clinical sites in 15 countries, representing a large and broad population of patients, especially considering the low prevalence of gMG, which is an orphan disease.[42] The patient population enrolled in the study is representative of the gMG patient population in terms of age, gender, and prior and ongoing use of gMG therapies. As shown by the MG-ADL and QMG scores at baseline, all participants were experiencing debilitating symptoms despite their current treatment for gMG.[42] Therefore, the results of ADAPT are generalisable across different subpopulations based on demographic and baseline disease characteristics.

The study was well-controlled and demonstrated robust and statistically significant treatment effects of efgartigimod on the study's primary efficacy endpoint – the proportion of MG-ADL responders. The primary endpoint was supported by several secondary endpoints, including percentage of QMG responders, a measure that was examined under a rigorous type-1 error rate. The treatment effects on the MG-ADL and the QMG scores confirm that the observed treatment effects are clinically meaningful in the improvement of disease symptoms that affect patients' activities of daily living.[42]

The efficacy analyses used in ADAPT are validated clinical outcome scales and the endpoints were stringent, combining the accepted CMI thresholds with the requirement for improvement to be sustained for at least four consecutive weeks. Results for AChR-Ab+ patients showed clinically meaningful and sustained improvements in symptoms and HRQoL across multiple treatment cycles, as assessed by four MG scales in ADAPT (MG-ADL, QMG, MGC, MG-QOL15R) and across multiple cycles in ADAPT+. There was a rapid onset of response, occurring as early as one week after the initial dose of efgartigimod, and a substantial magnitude of effect, with more patients achieving and surpassing CMI thresholds on the MG-ADL and QMG scales in the efgartigimod group than the placebo group.[42,169]

The safety and tolerability of efgartigimod in patients with gMG have been further characterised in ADAPT+, over a mean total duration of treatment and follow-up of 548.0 days and up to [redacted] cycles, confirming that continued treatment with efgartigimod was again associated with consistent and repeated improvements in MG-ADL and QMG scores, and that efgartigimod was well tolerated by patients.[50,163,164,163,170]

The International Consensus Guidance notes that gMG requires an individualised treatment approach.[20] Supported by robust data from the Phase 3 ADAPT and ADAPT+ studies, efgartigimod offers individualised dosing based on clinical response.[50] The individualised patient-dosing approach in ADAPT allowed patients with ongoing clinical benefits to extend the time to initiation of the next cycle. Since around one-third of AChR-Ab+ patients experienced an extended clinical benefit in ADAPT, there is potential for fewer treatment cycles per year for a substantial portion of patients.[42] In summary, initiation of subsequent treatment cycles according to clinical evaluation is supported by the efficacy demonstrated in the clinical studies with repeatable improvements and by a proportion of patients experiencing extended clinical benefit.

Finally, real-world experiences with efgartigimod confirm its effectiveness in the management of gMG. In an Expanded Early Access Program in Italy, treatment with

efgartigimod resulted in significant improvement across three MG scales (MG-ADL, QMG, and MGC), reduced need for rescue therapy, and a reduction in steroid dose without clinical worsening. No major AEs or infusion-related reactions were reported.[133]

Overall, results from the ADAPT and ADAPT+ studies, and preliminary real-world data, have demonstrated that efgartigimod is effective in AChR-Ab+ gMG patients, providing clinically meaningful, rapid, and repeated clinical benefits over time. In addition, the studies showed that efgartigimod is efficacious in AChR-Ab+ gMG patients regardless of concomitant gMG therapy, reinforcing its utility as add on therapy. As such, efgartigimod addresses the unmet need for patients with AChR-Ab+ gMG whose symptoms remain sub-optimally controlled despite standard therapy.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify relevant economic evaluations of treatments for gMG patients who are AChR-Ab+ who remain symptomatic despite receiving established clinical management. A detailed description of the review methods and results are reported in Appendix G.

The SLR identified one published economic evaluation of the cost-effectiveness of efgartigimod as an add-on to established clinical management of gMG (see Section B.3.1 and Appendix G). Tice and colleagues, on behalf of ICER in the US, evaluated the cost effectiveness of eculizumab plus conventional therapy vs conventional therapy alone in patients with refractory anti-AChR antibody positive gMG as defined in the REGAIN trial and efgartigimod plus conventional therapy vs conventional therapy alone in gMG patients, including those with or without anti-AChR antibodies.[181] A quality assessment of this study is presented in Appendix G.

The ICER model has a number of issues that limit its applicability to the current decision problem. Of critical importance is the use of the QMG to define rudimentary health states (response yes/no) and utility values. In particular, the Company believes that the health states used in the ICER model are overly simplistic, and do not capture either the differences in disease activity between patients or differences in disease activity across a patient's lifetime. As an example, a 3-point reduction in the QMG – which the ICER model defines as a "response" irrespective of baseline value – has substantially different implications for a patient with baseline QMG of 4, compared with a patient with baseline QMG of 20. As a consequence, the model oversimplifies assumptions on the quality of life experienced by gMG patients. Analysis conducted by the Company demonstrates that, while QMG is significantly associated with EQ-5D utility values, QMG scores alone are not sufficient to capture the HRQoL gained from efgartigimod and conventional therapy compared to placebo and conventional therapy.[182]

In its use of the QMG, ICER also relied on assumptions to derive the response rate values and utility inputs for the model, by generating pseudo-patient-level data for efgartigimod. The response rates based on QMG score were derived from clinical trials by bootstrapping the mean change in QMG at certain time points using the mean and standard deviation and assuming a normal distribution.

The ICER model – which was conducted from a US perspective and therefore has limited generalisability to the UK – also used a 2-year time horizon. The Company believes that such a short time horizon is not appropriate for modelling a chronic disease such as gMG.

The Company identified other issues with the ICER model; its full response to ICER is included in the submission reference pack, titled "argenx ICER Draft Evidence Report Letter Final 8-18-21"[183]

Table 23 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*	2022	Efgartigimod plus CT vs CT in gMG patients, four-state model	Not stated	Efgartigimod + CT: 1.27 CT alone: 0.98	Efgartigimod + CT: US$692,700 CT alone: US$94,800	US$2,076,000

Abbreviations: CT, conventional therapy; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

B.3.2 Economic analysis

Given the limitations associated with the only published economic model for gMG including the availability of patient-level trial data, the Company developed a de novo economic model to assess the cost-effectiveness of efgartigimod plus established clinical management including corticosteroids and immunosuppressive therapies vs. established clinical management without efgartigimod including corticosteroids and immunosuppressive therapies for treating patients with AChR-Ab+ gMG.

No published economic evaluations submitted to NICE within the gMG setting are available to be used alongside publications identified within the economic SLR to inform the de novo model structure, assumptions and data sources.

B.3.2.1 Patient population

The cost-effectiveness analysis presented considers adults with AChR-Ab+ gMG, per the clinical indication under review. The starting population in the model includes only those patients with an MG-ADL score ≥5 despite use of conventional therapy.

B.3.2.2 Model structure

The de novo cost-effectiveness model was developed in Microsoft Excel® as a state-transition Markov model with a lifetime horizon and a 4-weekly model cycle length. The model structure has six health states that capture the levels of disease activity based on the MG-ADL scale*; 'MG-ADL <5'*, *'MG-ADL 5–7' 'MG-ADL 8–9', 'MG-ADL ≥10', 'crisis',* and *'death'*.

The Myasthenia Gravis – Activities of Daily Living (MG-ADL) score is a discrete scoring system based on a patient's assessment of their disease. The MG-ADL scale comprises questions examining disease activity; eight questions assess ocular function, speech, chewing, swallowing, respiratory function, and strength of proximal upper and lower extremities. Each item is scored from 0 to 3, resulting in a total score of 0–24 points; higher scores are indicative of more active disease (i.e., more symptoms).

There are no established MG-ADL cut-offs to define levels of disease activity in gMG. The health-states MG-ADL cut-offs were defined based on the following rationale:

- *MG-ADL<5* health-state: likely to represent a minimally symptomatic disease stage, as defined by the clinical expert involved in the validation of the model. This is

supported by the MG-ADL cut-off used to define the population in the current cost-effectiveness analysis, i.e., MG-ADL of at least 5, which is also the main criteria to define eligibility for re-treatment with efgartigimod (in line with ADAPT study and its open label extension).

- *MG-ADL 5-7*, *MG-ADL 8-9* and *MG-ADL ≥10* health-states: likely to represent considerably symptomatic disease, as suggested by the clinical expert involved in the validation of the model. The MG-ADL cut-offs for these 3 health-states were defined in line with the subgroup analysis conducted for the ADAPT study as listed in the associated Statistical Analysis Plan.[184] Moreover, clustering (a machine learning technique) was used to identify appropriate categorical groupings based on the MG-ADL score and HRQoL data from ADAPT (EQ-5D an MG-QoL15):
    - The objective was to create homogeneous groups out of heterogeneous observations. This is achieved by minimising the intra-cluster distance and maximising the inter-cluster distance.
    - Specifically, the K-means clustering approach was used where each record is assigned to the cluster based on the distance from each cluster by averaging of the data.
    - Both the analysis on EQ-5D and the MG-QoL as a quality of life measure supported a MG-ADL threshold of 10 to define the cohort with the most considerable disease activity.
    - Given that as a minimum, a 2-point change in the MG-ADL scale represents a meaningful clinical improvement,[75,174] the category from 5-9 was divided into two sub-categories: 5-7 and 8-9 in order to show differences in treatment patterns which may be observed in established clinical management.
- *Crisis* health-state: occurrence of a myasthenic crisis event which is defined as the worsening of myasthenic weakness requiring intubation, with or without mechanical ventilation. Unlike an acute exacerbation, myasthenic crisis takes an average of 4 weeks to be resolved (which is the duration of a model cycle) and requires interruption of ongoing maintenance therapy to receive rescue treatment. Myasthenic crisis is also associated with increased mortality.[85,101,103,185–188] For these reasons, it was decided to define crisis as a separate health state rather than an acute event within the other health states. This approach was validated with clinical experts.

The model structure was selected based on the following:

- The structure is consistent with the primary outcome (MG-ADL) and eligibility criteria (MG-ADL ≥5) in the ADAPT study.
- The model captures the highly variable nature of gMG, including fluctuating symptoms and the rapid transition between health states as patients experience disease exacerbations or myasthenic crises.

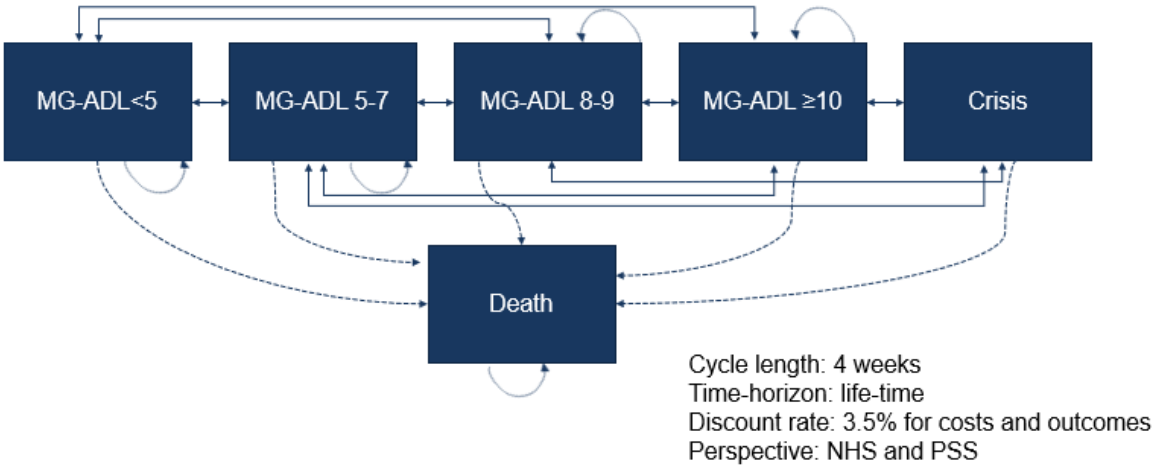
Alternative measures of disease activity were considered during the model conceptualisation phase, however none appeared better suitable than MG-ADL in defining health-states to simulate changes in disease activity and related treatment administration:

- The Myasthenia Gravis Foundation of America (MGFA) is a classification system to assess clinical features or severity of disease that may indicate different prognoses or responses to therapy over time. The MGFA classification allows the classification of disease severity in five broader classes (MGFA I, II, III, IV and V). As an established classification system, MGFA stages may have been considered more suitable to define health-states in the model. The main limitation of this approach is that MGFA was not collected as an endpoint in the ADAPT trial, because this instrument is not designed to capture changes in the severity of the disease, and it was merely recorded at baseline to define the trial eligible population. Exploratory analysis on the correlation between MGFA and MG-ADL were performed to attempt to define MG-ADL cut-offs for each MGFA class. Nevertheless, the correlation between these two measures was not sufficiently strong and some overlapping in the cut-off threshold was observed. Thus, using MGFA classification was considered unsuitable for defining health-states in the model since it would not be possible to model changes in MGFA over the time-horizon of the analysis for efgartigimod and the comparator.
- The Quantitative Myasthenia Gravis (QMG) score was included as a secondary endpoint in the ADAPT study and similarly to MG-ADL is a discrete measure with no established cut-offs of gMG disease activity. Therefore, the QMG score would not have provided a better measure than MG-ADL to inform the discrete definition of the health-states in the model. Moreover, treatment eligibility criteria for efgartigimod treatment are based on MG-ADL rather than QMG score, thus, using QMG would not provide a clear cut-off score for treatment and re-treatment with efgartigimod in the model.

The model structure and permitted flow of patients is shown in Figure 26. All patients enter the model in the '*MG-ADL 5–7', 'MG-ADL 8–9', or 'MG-ADL ≥10'* health states, based on the proportion of AChR-Ab+ patients in each of these categories at baseline of ADAPT. The proportion of patients allocated to each category as baseline was validated by UK clinical experts consulted by the Company. Over the time-horizon of the analysis, the cohort may transition to any of the other MG-ADL health-states or remain in the same health-state based on observed MG-ADL changes in the ADAPT and its open extension study. Within each MG-ADL health state, patients are at risk of 'crisis' or 'death'. Patients who enter *'crisis'* state can return to any one of the MG-ADL health states or transition to "death". That is, *'crisis'* is a transitory health-state since the assumption is that the cohort would not spend more than one model cycle in the state. '*Death'* is an absorbing state. Transitions between health states are based on observed effects during treatment cycles in the ADAPT and ADAPT+ studies.[42,43] See Section B.3.3.4 for details of the transition probabilities used in the model.

Within each of the MG-ADL health states, the model considers the impact of acute exacerbations that require hospitalisations on costs and HRQoL; the impact of the chronic use of corticosteroids on mortality, HRQoL and costs and the impact of grade ≥3 treatment related adverse events on costs. In addition to the impact of gMG disease activity on patients' HRQoL, the model also considers the impact of the disease on caregivers' HRQoL.

Figure 26: Model structure



MG-ADL, Myasthenia Gravis Activities of Daily Living scale

B.3.2.2.1 Time horizon and model cycle length

The base case analysis adopts a 'lifetime' horizon of approximately 55 years. This is considered long enough to capture the lifetime of patients in this setting (mean start age for patients in the model is 45.2 years, aligned with the baseline characteristics of the UK population meeting ADAPT inclusion criteria in the MyRealWorld MG study). The time horizon is implemented by tracking patients up to the model cycle where they reach the age of 100 years. A model cycle length of 4 weeks is used to adequately capture and reflect changes in health and is short enough to capture the dosing schedules of efgartigimod and established clinical management. The model includes half-cycle correction implemented by applying the trapezoidal rule.

B.3.2.2.2 Discount rate and perspective

As per the NICE reference case, all health effects were measured in quality-adjusted life years (QALYs) and a 3.5% discount rate is used for QALYs and costs. The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) for costs and health effects.[189]

B.3.2.2.3 Features of the economic analysis

Table 24 Features of the economic analysis

	Current evaluation	
Factor	**Chosen values**	**Justification**
Model type	Markov	
Perspective	NHS and PSS	As per NICE reference case
Time horizon	Life-time	As per NICE reference case: lifetime horizon since the condition is chronic
Model cycle length	4 weeks	Considered short enough to capture changes in health and captures the dosing schedules
Discount rate	3.5% for costs and QALYs	As per the NICE reference case
Outcome measure	QALYs	As per the NICE reference case
Source of transitions between MG-ADL health-states	ADAPT and ADAPT+ data in AChR+	Pivotal trial of efgartigimod and its open label extension, as per the NICE reference case
Source of health-states utilities	MG-ADL health-state: ADAPT and ADAPT+ AChR-Ab+ population 'crisis' health-state: literature	EQ-5D utilities collected from the relevant population within the clinical study, as per the NICE reference case. Literature values used for *'crisis'* and scenarios where data from the study population is not available.
Source of costs	BNF PSSRU NHS Cost Collection	As per the NICE reference case

B.3.2.3 Intervention technology and comparators

The intervention in the analysis is IV efgartigimod 10 mg/kg per infusion, administered as 4 weekly infusions within an 8-week treatment cycle, as per the approved posology in the EU product label.[50] Health effects (i.e., health-state transitions) for patients receiving efgartigimod in the model are based on the efgartigimod arm from ADAPT, as well as the ADAPT+ extension study (in which all patients received efgartigimod). Consistent with the approved indication and the design of the ADAPT study, the efgartigimod arm is modelled as efgartigimod as an add-on to conventional therapy .[42,50]

The comparator, established clinical management, consists of existing therapy for AChR-Ab+ gMG currently used in England and Wales, defined in consultation with clinical experts

working in England. Based on the experts' input, the components of established clinical management in England and Wales include not only the conventional therapy for gMG recorded in the ADAPT study – corticosteroids, AChEis, and NSISTs (azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide) – but also rituximab in a minority of patients, and maintenance IVIg in a subset of patients, the proportion of which increases with increasingly active disease (as measured by MG-ADL score). Thus, to reflect clinical practice in England and Wales more closely, established clinical management in the model consists of these treatments in the proportions shown in Table 25.

Health effects for patients receiving established clinical management in the model are based on the placebo arm from ADAPT until trial data are available to define health-state transitions. Thereafter, the model assumes that the cohort would be distributed as observed at baseline in ADAPT and maintained stable at a population level for the entire duration of the simulation. This represents a conservative assumption for the analysis, meaning that the condition will not worsen for the entire patient's lifetime. This means that the baseline distribution in ADAPT is representative of the distribution expected to be observed at the population-level in patients treated with established clinical management, i.e., there may be some patients improving and some patients worsening because of changes in treatment dosing/schedule, but the population level distribution is expected to remain constant. Following the same rationale, although patients receiving rituximab or IVIg were excluded from ADAPT, the cost-effectiveness analysis assumes that the inclusion of these treatments for a proportion of the cohort in each health-state does not influence the population-level distribution between health-states of the cohort on established clinical management. This assumption is further supported by the lack of evidence on efficacy of rituximab and IVig in gMG (as detailed in Section 1.3.3.4) and was tested with UK clinical experts.

Table 25. Components of established clinical management in the model

Therapy **Health state**	**Proportion of cohort, %**
Corticosteroid*	75.2
AChEi*	88.4
NSIST*	59.7
Rituximab†	
MG-ADL <5	12.5
MG-ADL 5–7	12.5
MG-ADL 8–9	12.5
MG-ADL ≥10	0.0
Maintenance IVIg†	
MG-ADL <5	0.0
MG-ADL 5–7	12.5
MG-ADL 8–9	50.0
MG-ADL ≥10	100.0

AChEi, acetylcholinesterase inhibitor; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale NSIST, nonsteroidal immunosuppressive therapy;
*Conventional therapy; included in the efgartigimod and established clinical management arms
†Included in the established clinical management arm only; defined in MyRealWorld MG as concomitant

treatment in 12 months prior to study baseline
Sources: *argenx, 2020[169]; †argenx, MyRealWorld MG data on file and clinical expert working in England

As described in Section B.1.1, due to the lack of supportive evidence on the use of PLEX outside of the acute setting in the management of acute episodes (exacerbations or myasthenic crisis), PLEX is not included as among treatments in the established clinical management arm of the model. The impact of an alternative assumption, considering the additional costs of some use of PLEX on a recurrent basis as part of established clinical management, is explored in a scenario analysis (see Section B.3.11.3).

B.3.3 Clinical parameters and variables

The principal sources of data used to inform the economic analysis are the pivotal ADAPT trial, and the long-term extension study, ADAPT+. These data comprise the key evidence base concerning the use of efgartigimod as a treatment for patients with AChR-Ab+ gMG who continue to experience symptoms despite treatment with established clinical management. Clinical data for the following inputs, endpoints and events are used to inform the estimation of costs and effects within the model:

- Baseline characteristics (Section B.3.3.1)
- Efficacy (MG-ADL) (Section B.3.3.2)
- Source of transition probabilities (Section B.3.3.3)
- Transition probabilities between MG-ADL health-states (Section B.3.3.4)
- gMG exacerbations (Section B.3.3.5)
- Probability of transitioning into or out of myasthenic crisis (Section B.3.3.7)
- Safety (Section B.3.3.8)
- Mortality (Section B.3.3.9)

B.3.3.1 Baseline patient characteristics

The base-case population considered in the model – adult patients with AChR-Ab+ gMG – is consistent with the approved indication in the European SmPC and with the expected MHRA-licensed population for efgartigimod.[50] To ensure the population of the model is representative of the patients' population in England and Wales, cohort characteristics were obtained from the baseline characteristics of the UK patient population included in the MyRealWorld MG study who fulfilled the ADAPT inclusion criteria (n=25). Because data on bodyweight were not available from the MyRealWorld MG study, the bodyweight of the cohort is assumed to be the same as reported in the ADAPT trial for AChR+ EU population (n=52) in ADAPT (Table 26).[34] The company was unable to obtain additional bodyweight data specific to gMG patients treated in England and Wales despite enquiring with clinical experts; however, the experts considered the average weight is generalisable between ADAPT and the patient population in England and Wales with gMG and a MG-ADL ≥5 despite established clinical management.

Table 26. Baseline model cohort characteristics

Characteristic	Model input
Initial age, years	[redacted]
Female, %	[redacted]
Weight, kg	[redacted]
Cohort with weight >80kg, %	[redacted]
Cohort with weight 80-90kg, %	[redacted]

Sources: MyRealWorld MG data on file; argenx, data derived from ADAPT

The distribution of the simulated cohort between health-states at model entry was based on baseline MG-ADL of the AChR+ population in the ADAPT study (n=129) (Table 27). This distribution was considered to be representative of the gMG population with MG-ADL>5 despite receiving established clinical management in England and Wales by UK-based clinical experts.

Table 27. Health-state distribution of the cohort at model entry

Health-state	Model input
MG-ADL <5, %	[redacted]
MG-ADL 5–7, %	[redacted]
MG-ADL 8–9, %	[redacted]
MG-ADL ≥10, %	[redacted]
Crisis, %	[redacted]

MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Source: argenx, data derived from ADAPT

B.3.3.2 Efficacy (MG-ADL)

The treatment effect is modelled as changes in MG-ADL score. Reduced MG-ADL score is also modelled as being associated with a lower probability of myasthenic crises (i.e., the probability of having a crisis is higher in health states with greater disease activity).[190] Thus, changes in MG-ADL score also impact the probability of transitioning to the crisis health state. Moreover, the MG-ADL<5 is associated with steroid-sparing and, therefore, prevention of the adverse systemic corticosteroid impact considered in the model. The analysis also considers the effect of treatment on the incidence of MG exacerbations.

Changes in MG-ADL from baseline to 4 weeks of each treatment cycle from the efgartigimod arm of ADAPT and the ADAPT+ were used to define the on-treatment cycle transition probabilities in the efgartigimod arm of the model. Changes in MG-ADL from baseline to 4 weeks and every 4 weeks thereafter from the placebo arm of the ADAPT study were used to define cycle transition probabilities in the established clinical management arm of the model. No data on the established clinical management arm alone are available from that extension study since all patients who received placebo in the ADAPT study and rolled over into ADAPT+ started receiving efgartigimod treatment as add-on to established clinical management.

ADAPT provides the data for comparison of efgartigimod as an add-on to conventional therapy versus placebo (conventional therapy alone).

The follow-up period in ADAPT was 26 weeks. At date of submission, the latest data cut available from ADAPT+ was Interim Analysis (IA) 4, data cut-off date November 2021, which provided approximately 2 years follow-up.

To be fully aligned with the anticipated indication for efgartigimod, only AChR-Ab+ patients were used to inform the effectiveness of efgartigimod in the model. In addition, the patients in ADAPT who did not respond to two consecutive cycles were not included in the trial population used to estimate the model parameters for effectiveness of efgartigimod, because the model assumes that the efgartigimod cohort that does not respond to two cycles of efgartigimod permanently interrupts treatment and incurs the costs and the health effect of established clinical management arm of the model. This approach was validated by the UK clinical experts who were consulted for this submission, one of whom is a coauthor of the Association of British Neurologists' management guidelines for MG.[48,75]

B.3.3.3 Source of transition probabilities

The efgartigimod cohort in the cost-effectiveness analysis is assumed to receive a cycle of treatment (4 weekly infusions) and to remain off treatment for 4 weeks, which represents the minimum treatment interval in ADAPT.[42] The only exception is the cohort in the MG-ADL <5 health state, which is assumed to remain off treatment for a minimum of 4 weeks or until the transition to the MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health states (i.e., by treatment eligibility criteria, patients would not receive a treatment cycle unless they have an MG-ADL score ≥5). During the off-treatment period, the efgartigimod cohort is assumed to be treated with conventional therapy alone, in line with ADAPT.[42,170]

To obtain transition probabilities that adequately describe the effect observed during the efgartigimod on-treatment period (i.e., while patients receive the 4 weekly infusions), each treatment cycle in ADAPT and ADAPT+ was considered in isolation. Patient-level changes in MG-ADL scores from baseline to week 4 of each treatment cycle in ADAPT and ADAPT+ were used to estimate the transition probabilities during the on-treatment periods. The transition probabilities in the off-treatment model cycles, were informed by observations in the placebo arm of ADAPT. For the cohort in the MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health states at the end of the on-treatment model cycle, the off-treatment transitions were based on patient-level changes in MG-ADL from week 4 to week 8. For the cohort in MG-ADL<5 health-state at the end of the on-treatment model cycle, the off-treatment transitions were based on patient-level changes in MG-ADL every 4 weeks from week 4, following patients who maintained MG-ADL<5 over-time. Since a subsequent treatment cycle in ADAPT was not initiated unless the MG-ADL score was ≥5, the number of off-treatment model cycles in the MG-ADL <5 health state was indefinite (i.e., efgartigimod treatment was only recommenced upon transitioning to one of the health states with MG-ADL ≥5).

Health-state changes from the start of each treatment cycle in ADAPT and ADAPT+ were considered independently of chronological time from study entry because of challenges posed by the innovative design of the trial, which permitted efgartigimod dosing in a highly individualised manner. In each treatment cycle, patients in ADAPT and ADAPT+ were treated with 4 weekly infusions of efgartigimod or placebo. In ADAPT, patients were then allowed to start another treatment cycle after week 8 from the start of the cycle, provided that they met specific criteria, requiring an MG-ADL total score of ≥5 points, with >50% of the

total score attributed to non-ocular symptoms. Thus, due to the individualised nature of the subsequent-treatment criteria, the duration of this off-treatment period varied from patient to patient and, for each patient, from period to period. This posed a challenge in modelling because, after the eighth week from the trial baseline, the efgartigimod cohort comprised a mixture of patients in on- and off-treatment states. If the periods used to estimate the treatment effect were based only on the chronological distance of each timepoint from baseline, the treatment effect on the transition probabilities would be impossible to isolate beyond the first 8 weeks due to the mixed nature of the cohort after this timepoint.

In contrast, there is no need to isolate the treatment effect in the context of the placebo arm since the conventional therapy is administered constantly over time and only the placebo is administered intermittently. Therefore, it is possible to use the placebo data from ADAPT based on chronological distance from the trial baseline and to disregard the corresponding treatment cycles. Indeed, even if the cohort comprises a mixture of patients on-(placebo) treatment and off-(placebo) treatment after the eighth week, this has no influence on the effect of the standard therapy. Only ADAPT was used to inform the transition matrices for the established clinical management arm in the model because there is no control arm in ADAPT+.

The patients included in ADAPT were allowed to roll over into ADAPT+ and receive additional treatment cycles with efgartigimod. An analysis of the change in the MG-ADL score between baseline and week 4 of each treatment cycle in ADAPT+ showed that the change from week 0 to week 4 of each treatment cycle is similar over time. Thus, the data suggest that at every subsequent treatment cycle, the effect of treatment is similar to the effect of treatment in the previous cycle. This allowed for the model to consider the treatment cycles of ADAPT+ as consecutive to those in ADAPT, which meant that the number of treatment cycles could be counted progressively from baseline in ADAPT to the ADAPT+ study cut-off date. In addition, data could be pooled for patients in the same treatment cycle regardless of whether this occurred in ADAPT or ADAPT+ study (e.g., the observations of a patient completed treatment cycle 2 while in ADAPT would be combined with observations of a patient who completed treatment cycle 2 in ADAPT+).

Detailed of method for pooling of data in ADAPT and ADAPT+ to define the on-treatment transition matrices in the efgartigimod arm

The main obstacle encountered by pooling treatment cycle data in the two studies is related to the timing of the study visits. In ADAPT, visits for each treatment cycle were conducted weekly until the eighth week and then bi-weekly thereafter. In ADAPT+, visits for each treatment cycle were conducted weekly only until the third week and then monthly thereafter. This generates two issues:

1. In ADAPT+, the observations do not follow the same 4-week pattern observed in ADAPT, since after the third week the subsequent visits are conducted at odd-numbered timepoints (third week, seventh week, eleventh week, etc). This poses a challenge both because of the resulting misalignment with the observations in ADAPT, which are conducted at even-numbered timepoints (fourth week, eighth week, twelfth week, etc), and because of the resulting misalignment with the 4-week cycles adopted in the Markov model.[42]

2. The last infusion of efgartigimod is administered at the end of the third week of each treatment cycle. Therefore, the visit at the fourth week of each treatment cycle allows the full treatment effect of efgartigimod to be captured. In ADAPT, this is demonstrated by the average MG-ADL score at the fourth week being the lowest in each treatment cycle, making week 4 the maximum improvement timepoint. The lack of the Week 4 visit in ADAPT+ is, therefore, a major limitation in the ability to fully capture the effect of efgartigimod.

To overcome these issues, the fourth week of ADAPT+ was reconstructed based on the difference between the fourth and the third week observed in ADAPT.[42] The MG-ADL scores at the fourth week of the first treatment cycle in ADAPT were regressed on the MG-ADL scores at the third week using a linear regression model. A cross-validation technique was used to identify the best least-square estimators of the regression coefficients. The coefficients were then used to predict the values of the fourth week of each treatment cycle in ADAPT+.

The approach described above allows for the observations of the ADAPT and ADAPT+ studies up to the fourth week of each treatment cycle to be pooled. The maximum number of treatment cycles obtained by pooling the two trials is 19. However, due to declining patient numbers over time, only the first 13 cycles from the baseline of ADAPT were used to inform the model (i.e., beyond 13 treatment cycles the number of patients who started a new treatment cycle was 10 or less).

B.3.3.4 Transition probabilities

The probabilities of entering a specific health state during each cycle of the Markov model are based on the number of patients who, in the ADAPT and the ADAPT+ studies, shifted between health states during the pre-specified periods. The number of patients in each health state at the start and end of a period is used to estimate the transition probability matrices that are then applied over the time horizon of the analysis in the efgartigimod and established clinical management arms of the model. The following paragraphs describe how the transition matrices are calculated and applied in the model.

B.3.3.4.1 Efgartigimod

As described previously, separate transition probabilities are estimated for the on- and off-treatment periods, based on ADAPT and ADAPT+ observations. The cohort enters the simulation and receives a first treatment cycle (i.e., 4 weekly infusions). Following the first treatment cycle, the cohort located in the MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health states remain off-treatment for one model cycle (i.e., 4 weeks) and transitions between health states based on probabilities estimated from patient-level changes in MG-ADL from week 4 to week 8 in the placebo arm of ADAPT(i.e. while off-treatment the cohort received only treatment with conventional therapy) .[42] The cohort located in the MG-ADL <5 health state at the end of the first model cycle remains in this health state for a minimum of 4 weeks or until it worsens to MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10. In ADAPT and ADAPT+, patients did not receive a subsequent cycle of treatment with efgartigimod as long as they remained in the MG-ADL <5 health state. The probabilities of transitioning out of the MG-ADL <5 health state was estimated by following patients in the placebo arm with MG-ADL <5 at week 4 of the first cycle in ADAPT.[42] This schema is repeated over the time

horizon of the analysis. MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states are therefore separated into on- and off-treatment sub-states, and tunnel states within the MG-ADL<5 health-state are used to trace the cohort from time of entry

B.3.3.4.2 Non-responder stopping rule

Overall, 18% of the efgartigimod treatment arm is classified as non-responsive to efgartigimod therapy and has treatment permanently discontinued. Post permanent discontinuation, the costs and effects of the established clinical management arm are applied to the cohort. The percentage ([redacted]) is derived by dividing the number of patients in ADAPT who did not respond to two consecutive treatment cycles ([redacted]) by the total number of patients who started treatment in the efgartigimod arm (n=65).

To avoid complex simulation of transition probabilities, the non-responder cohort is separated from the responder cohort at the beginning of the simulation, but the cost of two cycles of efgartigimod alfa treatment is still applied. The non-responder cohort excluded from treatment with efgartigimod is thereafter assumed to receive established clinical management. The costs, effects, and HRQoL of the established clinical management arm are therefore applied to this proportion of the cohort from discontinuation across the entire time horizon.

B.3.3.4.3 On-treatment transition probabilities

As described above, the transition probabilities for the first model cycle were calculated based on the number of patients in each health state at baseline of the first treatment cycle in ADAPT and the shifts to other health states that occurred by week 4 of the same cycle. In line with the population at baseline in ADAPT, at the beginning of the simulation, the entire cohort is distributed between MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states. The transition matrix defining the cycle probabilities applied in the first model cycle is shown in Table 28.

Table 28. On-treatment health-state transition probabilities, efgartigimod model Cycle 1

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL 5–7	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 8–9	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

The on-treatment transition probabilities applied in the model after cycle 1 were estimated by averaging the observed health-state transitions between baseline and week 4 of each treatment cycle, combining ADAPT and ADAPT+ data to permit consideration of cycles 2 to 13. Table 29 shows the resulting on-treatment cycle transition probabilities applied after model cycle 1.

Table 29. On-treatment health-state transition probabilities, efgartigimod beyond model Cycle 1

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL 5–7	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 8–9	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

B.3.3.4.4 Off-treatment transition probabilities in the MG-ADL <5 health state

The proportion of the cohort in the MG-ADL <5 health state at the end of each on-treatment model cycle is considered to remain off-treatment for a minimum of 4 weeks or until worsening to the MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health states. Tunnel states were created in the model to simulate cycle transition probabilities that varied by time of entry into a given state, as observed in data from ADAPT. After one model cycle (i.e., 4 weeks) in the MG-ADL <5 health state, the cohort is at risk of worsening to the MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health state, which would lead to starting a new treatment cycle. Observations in the placebo arm of the ADAPT trial were used to inform transition probabilities since patients in MG-ADL <5 remain on conventional therapy only (i.e., offefgartigimod treatment) until they worsen to MG-ADL of 5 or higher. Patients with MG-ADL<5 at week 4 in the ADAPT study were tracked for 16 weeks (from week 4 to week 20 of the first treatment cycle in ADAPT). Beyond week 20 the number of observations was too low to be informative. After the last tunnel state, the probabilities of the last time interval (from week 16 to week 20) are recycled. Clinical experts validated this approach.

Table 30 shows the transition matrix used to inform the probabilities to shift from the MG-ADL <5 health state to any of the non–MG-ADL <5 health states during each tunnel state.

Table 30. Off-treatment probabilities from the MG-ADL <5 health state to any other non–MG-ADL <5 health state from time of entry into state, efgartigimod model arm

Probability from entry in MG-ADL <5 at:	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
Model cycle 1 (w4 to w8)	[redacted]	[redacted]	[redacted]	[redacted]	1.00
Model cycle 2 (w8 to w12)	[redacted]	[redacted]	[redacted]	[redacted]	1.00
Model cycle 3 (w12 to w16)	[redacted]	[redacted]	[redacted]	[redacted]	1.00
Model cycle 4+ (w16 to w20, applied thereafter)	[redacted]	[redacted]	[redacted]	[redacted]	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale; w: week
Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00.

B.3.3.4.5 Off-treatment probabilities in MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states

The proportion of the cohort in MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states at the end of each on-treatment cycle is assumed to remain off-treatment for 4 weeks (as

previously explained) before a new treatment cycle is started. The transition probabilities during the off-treatment model cycle were informed by patient-level changes in MG-ADL from week 4 to week 8 in the first treatment cycle in the placebo arm in ADAPT. Table 31 presents the resulting transition probabilities applied to define transitions from MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 off-treatment substate.

Table 31. Off-treatment probabilities from MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states in the off-treatment model cycle, efgartigimod arm

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL 5–7	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 8–9	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00

B.3.3.4.6 Established clinical management

To model the transition probabilities in the established clinical management arm, observations in the placebo arm of ADAPT were used.

The number of patients in ADAPT who shifted to a different health state during each 4-week period starting from baseline up to week 16 is used to calculate the transition matrices of the first four model cycles. After the fifth model cycle, the cohort is assumed to return towards baseline health-state distribution and remain in the same health state unless a crisis or death occurs. The rationale behind this assumption is that the distribution between health-states observed at baseline in the ADAPT study is overall representative of the expected population-level distribution of disease activity in gMG patients with MG-ADL of at least 5 despite treatment with established clinical management. This assumption is supported by the clinical expert involved in the model validation. The cohort in the established clinical management arm is assumed to be treated constantly over the entire time horizon.

Table 32 to Table 36 show the transition matrices used to define the probabilities from MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 in the established clinical management arm at the first, second, third, fourth, fifth, and from the sixth cycle of the model, respectively.

Table 32. Transition matrix used for the established clinical management arm during the first model cycle

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL 5–7	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 8–9	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00

Table 33. Transition matrix used for the established clinical management arm during the second model cycle

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL <5	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 5–7	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 8–9	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00

Table 34. Transition matrix used for the established clinical management arm during the third model cycle

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL <5	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 5–7	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 8–9	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00

Table 35. Transition matrix used for the established clinical management arm during the fifth model cycle (return to baseline health-state distribution)

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL <5	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 5–7	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 8–9	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00

Table 36. Transition matrix used for the established clinical management arm during and after the fifth model cycle (identity matrix)

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL <5	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 5–7	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL 8–9	[redacted]	[redacted]	[redacted]	[redacted]	1.00
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Identity matrix is included to model recycling of the cohort in the same health-state.

B.3.3.5 Transitions between MG-ADL health-states after efgartigimod permanent discontinuation

The cohort on efgartigimod permanently discontinuing treatment is assumed to receive treatment with established clinical management. The costs, effect and HRQoL of established clinical management are therefore applied.

In line with the long-term health-state distribution simulated in the established clinical management arm, the model therefore assumes that post permanent discontinuation the cohort in the efgartigimod arm worsen towards baseline health-states distribution, i.e., disease activity recorded at trial entry in ADAPT study.

As previously described, the distribution between health-states observed at baseline in the ADAPT study is overall representative of the expected population level distribution of disease activity in gMG patients with MG-ADL of at least 5 despite treatment with established clinical management. This assumption is supported by the clinical expert involved in the model validation.

The worsening towards baseline health-state distribution is assumed to occur gradually over 6 months from discontinuation. Tunnel states were therefore introduced in the model to allow the cohort to be tracked from the time of discontinuation.

B.3.3.6 gMG exacerbations

The cost-effectiveness analysis considers only gMG exacerbations that require hospitalisation since exacerbations not requiring inpatient treatment are expected to have minimal impact on costs and quality of life. gMG exacerbations are included in the analysis as acute events requiring in-hospital care; these may occur in any health state except crisis and death. At the occurrence of exacerbation, the corresponding cost and reduction in utility is applied in the model. As exacerbations are modelled as an acute event and not a separate health state, ongoing treatment is assumed to be maintained as relevant for the respective health state.

The rate of MG exacerbations was obtained by treatment arm in ADAPT. The mITT population was considered, instead of the AChR-Ab+ population, to allow for a larger sample size given the small number of events occurring. During ADAPT, two patients in the placebo arm and one in the efgartigimod arm had an MG exacerbation. Considering a total follow-up period of [redacted] and [redacted] weeks in the placebo and efgartigimod arms, respectively, the resulting model-cycle (i.e., 4 weeks) rate of MG exacerbation was [redacted] for the cohort in the established clinical management arm and [redacted] in the efgartigimod arm.

B.3.3.7 Probability of transitioning into or out of myasthenic crisis

Myasthenic crisis is modelled as a health state rather than as an event (as in the case of exacerbations) because crises are longer in duration than exacerbations, carry the potential for death, and involve an interruption of maintenance treatment for rescue therapy to be administered along with ICU-specific treatment algorithms.[12,85,116] The probability of transition to the crisis health state was based on the literature and assumed to apply to the MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states only.[188] The percentage of MG patients that present with myasthenic crisis is variable among studies, ranging from 5.6% to 9.6%.[185,190] The probability of crisis was based on a registry study by Ramos-Fransi et al, 2015, which analysed data from 648 gMG patients.[190] For the model, a cycle probability of transitioning to crisis of 0.09% from MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states were estimated, independent of baseline treatment.[190]

The probability of transitioning out of the crisis (the worst health state possible in terms of disease severity and the need for constant monitoring in the ICU and ventilatory support) is assumed to be 100%—that is, the cohort remains in the crisis health state for only 1 cycle. This assumption was taken due to a lack of evidence on what proportion of patients

experiencing myasthenic crisis would remain in crisis longer than 4 weeks (i.e., beyond the cycle length). This assumption can be considered conservative given that a greater proportion of the cohort in the comparator arm than in the efgartigimod arm experience a crisis. It was assumed in the model that all patients transition from crisis to the MG-ADL ≥10 health state, considering that after an ICU stay, patients require specific in-hospital treatments and rehabilitation programs to achieve full recovery. After an episode of myasthenic crisis, patients could require mechanical ventilation at discharge or inpatient rehabilitation/discharge to rehabilitation centres.

In line with clinical practice, ongoing treatments for gMG are suspended in the model when patients enter the crisis health state. Rescue therapy is administered, and ongoing gMG treatment is not resumed until the cohort transitions out of the crisis health state.

B.3.3.8 Adverse reactions

In the model, only grade ≥3 treatment-emergent AEs are considered since these events are expected to have measurable impact on costs and HRQoL. Likewise, treatment-emergent AEs were included in the model as acute events, at rates specific to the treatment administered. At any cycle, AEs may occur for a proportion of the cohort in a specific treatment arm.

Based on the number of grade ≥3 AEs reported for efgartigimod and placebo arms in ADAPT (Table 37), the incidence of treatment-emergent AEs was implemented in the model in the efgartigimod and established clinical management arms, respectively. In addition to acute AEs, the model considers the chronic impact of corticosteroid use on mortality, HRQoL, and costs (see Sections B.3.4.5.2 and B.3.5.1.2).

Table 37. Treatment-emergent grade ≥3 AEs (overall population; safety analysis set)

AE	N events in ADAPT		Cycle rate in model	
	Placebo	Efgartigimod	Established clinical management	Efgartigimod
Infection	1	2	0.002	0.004
Asthenia (fatigue)	1	0	0.002	0.000
Cardiovascular disorders (incl. thrombosis)	1	0	0.002	0.000
Eyelid disorders	1	0	0.002	0.000
Myalgia	0	1	0.000	0.002
Headache or procedural pain	1	1	0.002	0.002
Gastrointestinal	0	1	0.000	0.002
Other	3	4	0.007	0.009

AE, adverse event; SoC, standard-of-care therapy
Source: ADAPT CSR, Table 14.3.1.6.2[169]

B.3.3.9 Mortality

B.3.3.9.1 Mortality in MG

The natural, untreated course of MG has been associated with high mortality and persistence of symptoms in most patients.[191] In 1960, mortality rates were as high as 50%–

80%, but due to faster recognition of crises and improvements in intensive respiratory care and rescue treatments, and the introduction of immunosuppressive therapies, the mortality rate has fallen over time.[185] Currently, myasthenic crisis remains the main cause of MG-related deaths; however, reports on mortality are heterogeneous, and this proportion changes across studies, usually ranging from 5%–22%.[85]

B.3.3.9.2 Mortality by health state

Evidence of mortality related to gMG, independent of crises and complications due to corticosteroids, is scarce. Therefore, the model assumes that the mortality in each health state is the same as the general population (i.e., a hazard ratio [HR] of 1 is assumed), except in crisis. This assumption can be regarded as being conservative. General population mortality by age and sex was obtained from UK life tables from the Office for National Statistics and was applied to the model cohort over the time horizon based on cohort age and proportion of females.[192]

B.3.3.9.3 Probability of death in myasthenic crisis

Following a targeted literature review to estimate the probability of death for crises, a 12% probability of death during myasthenic crisis was implemented in the model, estimated as the average of the rate of death reported in seven studies.[85,101,103,185–188]

B.3.3.9.4 Mortality associated with chronic corticosteroid use

An SLR was conducted to estimate the impact of chronic corticosteroid use on mortality, HRQoL, and costs.[193] For mortality, three UK studies retrieved from the SLR were used to calculate average HRs for mortality based on high- and low-dose corticosteroid use.[88,136,194] The SLR conducted to evaluate the impact of chronic corticosteroid use on mortality is presented in Appendix O.[195]

Table 38. Average hazard ratios for mortality in the UK based on high- and low-dose corticosteroid use

Corticosteroid regimen	HR of death vs no corticosteroid use
High-dose (≥10 mg/day)	2.10
Low-dose (<10 mg/day)	1.11

HR, hazard ratio
Sources: Movahedi et al, 2016[136]; Mebrahtu et al, 2019[88]; Wilson et al, 2017[194]

B.3.4 Measurement and valuation of health effects

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

In the ADAPT trial, EQ-5D-5L and MG-QOL15r questionnaires were administered to enrolled patients at each treatment cycle initiation (±1 day), then weekly (±1 day) throughout each treatment cycle, weekly (±1 day) for 4 weeks after completion of each treatment cycle, then every 2 weeks for ≤26 weeks thereafter.[165]

B.3.4.2 Mapping EQ-5D-5L to EQ-5D-3L

The utility values assigned to the MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states were estimated by regressing the EQ-5D utilities on the health state and the treatment arm using observations in the ADAPT study. In ADAPT, EQ-5D-5L data were collected at 1-week intervals while patients were on treatment and at 2-week intervals while patients were off treatment. The UK EQ-5D-5L value sets were applied to obtain utility values applicable to the population in England.[196] Data were mapped to EQ-5D-3L to derive utility values according to the mapping function developed by the Decision Support Unit, using the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) dataset.[196,197]

The regression was implemented using a mixed model with fixed and random effects. The analysis was based on the ADAPT AChR-Ab+ population, in line with the cohort simulated in the model.

The mixed model is an extension of the linear model and is used to analyse longitudinal data from multiple patients. With longitudinal data, the EQ-5D observations belonging to the same patient have a higher correlation. Because of that, the results of a linear model could be misleading as they may reflect a pattern that is only observable in the aggregate data, but different from what would be observed if the data from a single patient were considered. The mixed model addresses this issue by acknowledging that the longitudinal EQ-5D observations from each patient may have a different pattern. Thus, the parameters of the model, which refer to the entire population and not to a specific patient, are subject to a certain degree of uncertainty and vary randomly within a certain range. A fixed and a random term are introduced in the model for each parameter assumed to differ between patients. The fixed term represents the expected value of the parameter in the entire sample, while the random term represents its variability.

In the present analysis, a random term for the intercept is introduced, meaning that the average EQ-5D utility of the entire sample is assumed to vary among the patients. The corresponding fixed term represents the expected EQ-5D utility value. The EQ-5D utility in the MG-ADL <5 health state in the efgartigimod alfa arm is used as a reference (model intercept). All other values by health state and treatment arm are coefficients representing the difference in EQ-5D utility vs the reference value (Table 39). The health-state utility values in the model base case were therefore estimated based on the mixed effect model using ADAPT data (Table 40).

Table 39. Coefficients of the mixed model on ADAPT data used to derive utility values by health state in the base-case analysis

Variable	Mixed model		
	Coefficient	SE	p value
Intercept (MG-ADL <5)	[redacted]	0.018	0.00000
MG-ADL 5–7	[redacted]	0.007	0.00000
MG-ADL 8–9	[redacted]	0.008	0.00000
MG-ADL ≥10	[redacted]	0.009	0.00000
Placebo	[redacted]	0.025	0.00004

MG-ADL, Myasthenia Gravis Activities of Daily Living scale; SE, standard error

Table 40. Utility values by health state derived from mixed model regression on ADAPT data – base-case analysis

Health state	Efgartigimod	Established clinical management
MG-ADL <5	[redacted]	[redacted]
MG-ADL 5–7	[redacted]	[redacted]
MG-ADL 8–9	[redacted]	[redacted]
MG-ADL ≥10	[redacted]	[redacted]

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

From a theoretical point of view, health states in a Markov model are meant to fully capture discrete disease stages, including their associated QoL utility, and therefore a treatment effect is generally not considered appropriate. However, in the current case, the treatment effect is a statistically significant variable in the regression analysis for EQ-5D, indicating that MG-ADL is not fully capturing the effect of efgartigimod on gMG patients. Therefore, if the treatment effect were to be neglected and utilities estimated only based on health-state effect, the benefit of efgartigimod would likely be underestimated.

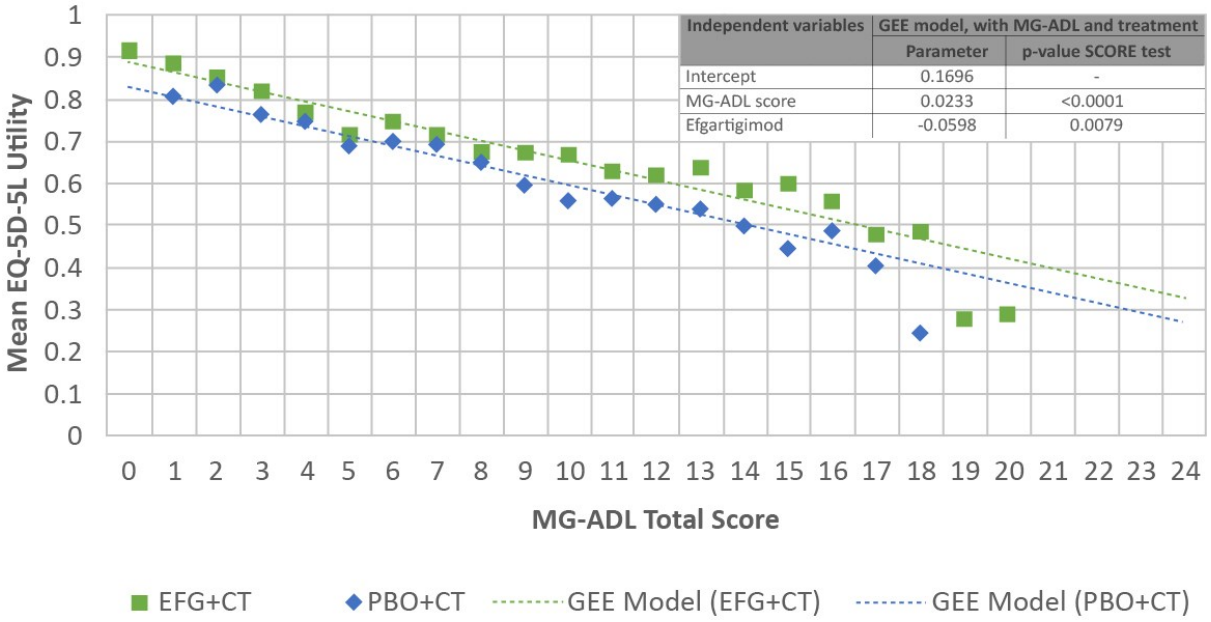
When a treatment effect is present and significant in the regression, this can be considered in two ways:

1. The health states are not granular enough, i.e., two patients in the same health state can have a different utility because the health state is too broad. If this is the case, when health states are redefined to offer greater granularity, the treatment effect disappears from the regression.

2. If the treatment effect does not disappear, it means that the instrument used to define health states, in this case, MG-ADL is not capturing something that is instead captured by EQ-5D or vice versa. In the absence of being able to redefine the health states, the use of a treatment effect may be acceptable.

A recently published regression analysis of data from ADAPT, where MG-ADL is treated as a continuous variable, confirmed the existence of a treatment effect (Figure 27). This means that the granularity of health states is not a concern in this specific case. The same analysis assessed that individual MG-ADL items of the total score contributed differently to quality of life values as measured by EQ-5D-5L, meaning that patients in the same MG-ADL-defined health state may experience a different measure of quality of life.[198] For these reasons we believe that in this specific case, it is appropriate to consider a treatment effect in the calculation of QALYs, to fully capture the benefit provided by the treatment.

Figure 27: Regression analysis of QoL ADAPT data, considering MG-ADL as a continuous variable



Source: Dewilde et al, 2023.[198]

To further explore the uncertainty in the definition of health states utilities, the model includes the flexibility to run the analysis using utility values estimated from a mixed model regression on data from the MyRealWorld MG (ARG-MG-2019-01) study, with MG-ADL <5 as the reference (i.e., intercept). The coefficients for this regression analysis are reported in Table 41. The resulting utility values by health state are applied to both the efgartigimod and established clinical management arms of the model (Table 42). The impact of this alternative option is explored in a scenario analysis.

Table 41. Coefficients of the mixed model on MyRealWorld MG data used to derive utility values by health state in scenario analysis

Variable	Mixed model		
	Coefficient	SE	p value
Intercept (MG-ADL <5)	[redacted]	0.007	0.00000
MG-ADL 5–7	[redacted]	0.009	0.00000
MG-ADL 8–9	[redacted]	0.011	0.00000
MG-ADL ≥10	[redacted]	0.012	0.00000

MG-ADL, Myasthenia Gravis Activities of Daily Living scale; SE, standard error

Table 42. Utility values by health state derived from mixed model regression on MyRealWorld MG data – scenario analysis

Health state	Utility value
MG-ADL <5	[redacted]
MG-ADL 5–7	[redacted]
MG-ADL 8–9	[redacted]
MG-ADL ≥10	[redacted]

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Although up to 20% of gMG patients experience a myasthenic crisis at least once in their lifetime, no patient had a crisis during ADAPT. Thus data from the MyRealWorld MG study were used to inform the utility value in the crisis health state. In the MyRealWorld MG study, EQ-5D-5L data were collected at 1-month intervals.[3,12,199] To calculate the HRQoL related to crises, all the timepoints were pooled and the observations were stratified by their baseline MGFA class. The average utility of the MGFA Class V of [redacted] was used in the model to define the utility value in the crisis health state (argenx, MyRealWorld MG data on file).

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

An SLR to identify relevant HRQoL studies was conducted. Appendix H provides full details of the methods, overview of studies and results of the identified studies, together with the quality assessments. The results of the utility review are presented in **Error! Reference source not found.** and **Error! Reference source not found.**. Only limited data were identified capturing the effects of MG and relevant treatments on HRQoL using the EQ-5D or SF-36.

The primary source of utilities used in this submission is the Phase 3 ADAPT Study. The UK EQ-5D-5L value sets were applied to obtain utility values applicable to the population in England. Data were mapped to EQ-5D-3L to derive utility values according to the mapping function developed by the Decision Support Unit, using the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) dataset. The only other source of EQ-5D data identified through the SLR for this population is captured in the MyRealWorldMG observational study which collected patient data using a smartphone app. The resulting utilities are included in an exploratory scenario analysis within the submission.

B.3.4.3.1 Utilities used in previous appraisals

There are no previous NICE appraisals in gMG.

B.3.4.4 Adverse reactions

The mixed model regression used to derive utilities by MG-ADL health-states in the model was developed based on ADAPT data. The impact of adverse reactions on HRQoL is assumed to be represented within the health-state utilities as these was based on the same trial used to derive the rates of adverse events used in the model. Therefore, no additional impact was considered separately.

B.3.4.5 Other utility decrements

B.3.4.5.1 Utility decrements due to exacerbations

Exacerbations are associated with a temporary reduction of HRQoL. This is reflected in the model by introducing a utility decrement at the occurrence of each exacerbation. The disutility is applied for each exacerbation for an average duration of 20.73 days, calculated as the average of the durations of hospitalisation for gMG exacerbations reported in four studies.[101,103,200,201] The disutility per exacerbation was derived from Van Wilder et al., 2019, assuming severe allergic rhinitis as a proxy since both conditions require the use of high-dose corticosteroids and hospitalisation (Table 43).[202]

Table 43. Temporary HRQoL decrement per exacerbation

Variable	Value in the model	Sources
Disutility of exacerbation	-0.16	Van Wilder et al, 2019 (assuming severe allergic rhinitis as a proxy)[203] [202]
Average exacerbation duration, days	20.73	Gummi et al, 2018[200]; Sakaguchi et al, 2012[201]; Mandawat et al, 2010[103]; Alshekhlee et al, 2009[101]

HRQoL, health-related quality of life

B.3.4.5.2 Corticosteroid-related utility decrements

Among the available immunosuppressive therapies, oral corticosteroids remain a first-line treatment option and are still the most common agents used for long-term immunosuppression for the management of MG.[203] Corticosteroids have been widely prescribed in several chronic conditions for their immunosuppressant and anti-inflammatory effects. Corticosteroid-related complications, particularly in patients on high-dose and/or long-term regimens, can have a negative impact on patient quality of life.[204]

A systematic literature review on the humanistic and economic burden of corticosteroids was conducted (see Appendix O).[193] No studies were identified that reported the impact of corticosteroids on HRQoL in gMG patients, but evidence on the impact of corticosteroid use in other chronic diseases was found. Considering only studies that reported utility values by corticosteroid dose, two studies were identified for inclusion to define the utility decrements associated with high-dose and low-dose systemic corticosteroid use compared with no corticosteroid treatment. Bexelius et al[205] conducted a Swedish study that evaluated the impact of corticosteroid use on HRQoL and costs in systemic lupus erythematosus patients. Corticosteroid dosage was a statistically significant predictor for total costs and HRQoL, with a lower HRQoL reported in the high-dose and low-dose groups (EQ-5D 0.61 for both groups) vs the no-corticosteroid group (0.70). The second study, by Sullivan et al,[206] was conducted in US and UK cohorts and explored the impact of systemic corticosteroid use on HRQoL in a range of chronic conditions. Corticosteroid use was associated with a significantly lower EQ-5D score compared to no exposure, and the greatest adverse impact was reported for patients on high-dose corticosteroids. The current model includes a utility decrement related to corticosteroid use differentiated by dose (high vs low), estimated by averaging the utility decrements obtained from these two studies (Table 44).

Table 44. Utility decrements associated with systemic corticosteroid use

Systemic corticosteroid use	Utility decrement
High-dose (≥10 mg/day)	-0.18
Low-dose (<10 mg/day)	-0.07

Sources: Bexelius et al, 2013[205]; Sullivan et al, 2017.[206]

B.3.4.5.3 Caregiver utility decrements

No studies were identified reporting caregiver disutility in gMG. Therefore, an ad hoc search was conducted to identify caregiver disutility in conditions characterised by progressive

disability (disease worsening), with stages of severity that could be linked to the gMG disease activity scale (MG-ADL) used in the current analysis.

Caregiver disutility at different severity stages of multiple sclerosis (MS) as measured using the Patient Determined Disease Steps (PDDS) scale was therefore used as a proxy for caregiver disutility in the different gMG health states in the established clinical management arm, based on caregiver HRQoL data reported in the MS study by Acaster et al., 2013.[207] No difference in caregiver disutility between treatment arms was assumed for a given health state (Table 45).

Table 45. Caregiver disutility values by health state

Health state	PDDS Stage (proxy)	Caregiver disutility
MG-ADL <5	0–1	-0.002
MG-ADL 5–7	2–3	-0.045
MG-ADL 8–9	4	-0.142
MG-ADL ≥10	5	-0.160
Crises	6	-0.180

MG-ADL, Myasthenia Gravis Activities of Daily Living scale; PDDS, Patient Determined Disease Steps
Source: Acaster et al, 2013[207]

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

The gender- and age-specific utility of the general population was used to adjust the utility values of the cohort over the time horizon of the analysis. Following the latest NICE guidelines, the general population utility by age and gender, was estimated using the utilities reported in the Supplementary file of the publication by Hernandez et al. 2022.[208]

A summary of the utility values for cost-effectiveness analysis is shown in Table 46.

Table 46 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
MG-ADL <5 Efgartigimod Established clinical management	[redacted]	[redacted]	Section B.3.4.2, page 102	Derived from mixed model regression on ADAPT data
MG-ADL 5–7 Efgartigimod Effective clinical management	[redacted]	[redacted]	Section B.3.4.2, page 102	Derived from mixed model regression on ADAPT data
MG-ADL 8–9 Efgartigimod Effective clinical management	[redacted]	[redacted]	Section B.3.4.2, page 102	Derived from mixed model regression on ADAPT data
MG-ADL ≥10 Efgartigimod Effective clinical management	[redacted]	[redacted]	Section B.3.4.2, page 102	Derived from mixed model regression on ADAPT data
Crisis	[redacted]	[redacted]	Section B.3.4.2, page 102	Derived from MGFA V in MyRealWorld MG study
Death	0.000	N/A	Section B.3.4, page 101	
Exacerbations	-0.160	-0.191; -0.129	Section B.3.4.5.1, page 105	Van Wilder et al, 2019 (assuming severe allergic rhinitis as a proxy)[202]
Corticosteroid use High dose Low dose	 -0.175 -0.070	 -0.209; -0.141 -0.084; -0.056	Section B.3.4.5.2, page 106	Bexelius et al, 2013[205]; Sullivan et al, 2017[206]
Caregivers MG-ADL <5 MG-ADL 5–7 MG-ADL 8–9 MG-ADL ≥10 Crises	 -0.002 -0.045 -0.142 -0.160 -0.180	 -0.002; -0.002 -0.054; -0.036 -0.170; -0.114 -0.191; -0.129 -0.215; -0.145	Section B.3.4.5.3, page 107	Acaster et al, 2013[207], mapping of multiple sclerosis stages to MG-ADL health-states

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

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

An SLR was undertaken to identify cost and resource use studies for gMG. Full details of the SLR methods, identified studies and results are presented in Appendix I.

HCRU and costs for the following healthcare components were considered in the analysis:

- Drug acquisition and administration
- Patient monitoring
- Management of complications associated with the chronic use of corticosteroids
- Rescue treatments
- Management of treatment-emergent AEs
- End-of-life care

The current analysis was developed with the aim of including healthcare resources and costs that would closely represent the actual HCRU and costs of gMG treatment in England and Wales. Conservative estimates of the least expensive medications were used instead of a weighted average based on sales data. Where available, costs for previous years were inflated to 2022 values using the Consumer Price Index (CPI) published by the Office of National Statistics, with July 2015 set as reference point for the CPI index.[209]

B.3.5.1 Drug acquisition and administration costs

Efgartigimod IV is dosed at 10 mg per kg of body weight per administration.[50] The model base case estimates the number of vials based on the weight distribution of the European AChR-Ab+ patient population in ADAPT (n=52), in which [redacted] patients weighed <80 kg, [redacted]) weighed between 80 and 90kg, and [redacted] weighed >90kg. Patients weighing <80kg require 2 vials and patients weighing >90kg require 3 vials. Based on real-world observations from US practice, approximately [redacted] of patients weighing 80–90kg require 2 vials, and the remaining [redacted] require 3 vials (see Appendix P for full details of the analysis). Therefore, in total, [redacted] of patients require 2 vials and [redacted] of patients require 3 vials yielding an average of [redacted] vials per administration in the simulated cohort. As efgartigimod is administered as four weekly administrations during any treatment cycle, four administrations are considered per treatment cycle in the on-treatment substates. A relative dose intensity of [redacted] is considered for efgartigimod based on the observation in ADAPT+ of [redacted] administrations out of 4 planned during a treatment cycle (argenx, data derived from ADAPT+).

Conventional therapy includes corticosteroids, AChEis, and NSISTs. Conventional therapy was assumed to be administered continuously over the entire time horizon unless patients transitioned to the crisis health state, where they would receive rescue therapy. The proportion of the cohort treated with each therapy was informed based on the patient distribution in ADAPT. The cohort treated with corticosteroids was further divided into high- and low-dose groups, with the high-dose threshold defined as 10 mg/day. Within the high- and low-dose groups, the average daily dose was estimated at 20.59 mg and 4.77 mg, respectively. These doses were applied to 74.2% and 25.8% of patients, respectively, based on ADAPT (argenx, data derived from ADAPT). Reflecting clinical practice guidelines and clinical expert validation, the cohort in MG-ADL <5 is assumed to discontinue corticosteroids.[19]

As previously mentioned, a proportion of the cohort in the established clinical management arm of the model also received recurrent treatment with immunoglobulin and rituximab. Immunoglobulin therapy is administered as an intravenous infusion (IVIg) in the UK, dosed at 1 g/kg, yielding an average of 1 and 8 vials per administration for the 2.5 mg/25 mL and 10 mg/100 mL formulations, respectively. IVIg is administered once every 4 weeks: therefore

one administration per model cycle is considered. Rituximab is administered as intravenous infusion dosed at 2000 mg every 6 months, yielding an average of 4 vials. This usage was validated by a clinical expert working in England.

To calculate drug costs, the supplied sizes and prices were retrieved from the British National Formulary (BNF).[210] Drug dosing regimens were obtained from the literature and online sources. Administration costs for efgartigimod and rituximab were applied based on an outpatient IV administration tariff, while administration costs for IVIg incorporated both IV administration plus a short-stay hospitalisation for observation. Corticosteroids, AChEis, and NSISTs are administered orally, and therefore, no administration cost is applied. The intervention and comparator prices are presented in Appendix K.1.1 and K.1.2 and costs per cycle used in the model are presented in Table 47 and Table 48.

Table 47. Drug cost per cycle (efgartigimod, IVIg, rituximab)

Drug	Admin per cycle	Drug cost per vial, £	Drug cost per admin, £	Drug cost per cycle, £	Admin cost per admin, £	Admin cost per cycle, £
Efgartigimod[1]	4.00* [redacted]	[redacted]	[redacted]	[redacted]	155.58	622.32
IVIg (2.5 mg/2 5mL)	1.00	172.50	690.00	5,520.00	1,765.92	1,765.92
IVIg (10 mg/100 mL)	1.00	690.00	4,830.00			
Rituximab	0.15	785.84	3,143.36	481.90	155.58	23.85

Admin, administration; IVIg, intravenous immunoglobulin
1) applies to on-treatment sub-state of the model, 2) Relative dose intensity = [redacted], 3) list price including PAS

Table 48. Standard therapy cost per cycle

Therapy	Cost per cycle, £
Corticosteroid	6.44
AChEi	76.34
NSIST	44.60
Standard therapy mix	98.93

AChEi, acetylcholinesterase inhibitor; NSIST, nonsteroidal immunosuppressive therapy

B.3.5.1.1 Discontinuation due to unplanned reasons

In both ADAPT and ADAPT+,[42,169,170] patients could stop ongoing efgartigimod treatment due to unplanned reasons. To inform the per-cycle probability of discontinuing the efgartigimod treatment due to unplanned reasons, the treatment duration during the pooled ADAPT and ADAPT+ studies was used.[42,170]

The time between the date of first treatment exposure in ADAPT and the date of the last observation in either ADAPT or ADAPT+ was calculated for each patient and used to produce a Kaplan–Meier (KM) curve of the time-on-treatment (ToT). Only the AChR+ patients in the efgartigimod arm of ADAPT were considered for the analyses. The observations of patients who did not respond to two consecutive cycles were not considered to avoid double counting of patients discontinuing in the model because of no response (as previously described). Finally, patients who discontinued because they moved to the subcutaneous trial of efgartigimod (Study 131-2002) were censored.

The KM ToT curve covers a time horizon shorter than the model time horizon; therefore, extrapolation is needed. Parametric fitting of KM curves was performed to extrapolate beyond the observation period using the following distributions: Exponential, Weibull, Log-Normal, Log-Logistic, Gompertz, and Gamma (Figure 28). The parametric function was pre-selected based on Akaike information criterion/Bayesian information criterion (AIC/BIC), visual inspection, and internal and external validity. In the base case, a piecewise approach is used where the KM points are used to define the probability of discontinuations until available data (i.e., 33 months) and thereafter, the best-fitting parametric model is applied. The Exponential parametric function was selected since it is the best-fitting curve based on AIC/BIC values. Table 49 summarises the AIC/BIC values associated with each parametric function.

Figure 28. Observed ToT data from ADAPT and ADAPT+, and parametric extrapolations

KM, Kaplan–Meier
Source: argenx, data derived from ADAPT and ADAPT+

Table 49. AIC/BIC values of each parametric function

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Gamma
AIC+BIC	**203.41**	**208.73**	**208.67**	**208.76**	**328.80**	**214.79**
AIC	100.72	102.39	102.36	102.41	162.40	104.44
BIC	102.69	106.34	106.31	106.35	166.40	110.35

AIC, Akaike information criterion; BIC, Bayesian information criterion

B.3.5.1.2 Reduction in corticosteroid use with efgartigimod

Due to the large burden of chronic corticosteroid use on mortality, HRQoL, and costs, an important benefit of efgartigimod treatment is the reduction in corticosteroid use. An Italian study of an Early Access Program for efgartigimod found that a majority of patients receiving steroids were able to reduce their steroid dose without clinical worsening.[133]

Initial discussions with clinicians indicate that patients on efgartigimod will receive much lower doses of corticosteroids, and ideally, there will be no corticosteroid use in MG-ADL <5 patients. This is also supported by treatment guidelines which advise the reduction /removal of corticosteroid treatment as soon as the disease is under control. Given the corticosteroid AE profile, MG-specific treatment guidelines recommend a gradual tapering once treatment goals are reached and continuing with the lowest effective corticosteroid dose as maintenance therapy.[19]

The ADAPT trial cannot be used as a source of evidence to model changes in corticosteroid use since the treatment schedule could not be modified as per study protocol; however, based on existing gMG treatment guidelines that recommend reducing corticosteroid dose as soon as possible, the cohort in the MG-ADL <5 health state in both treatment arms of the model is assumed to have 0% corticosteroid use.[19,117]

B.3.5.1.3 Patient-monitoring

Monitoring healthcare resource use by health state was obtained from the MyRealWorld MG study and a survey with clinicians in the UK. For the latter, experts in the treatment of gMG in England, Wales, and Ireland were recruited to complete a survey on healthcare resources used in their clinical practice, the frequency/quantity for which they are used per patient, and the percentage of the patient population that use them, across three scenarios: (1) during patient monitoring, (2) during gMG exacerbation and (3) during gMG crisis. A descriptive analysis was conducted on these data and a final set of validated HCRU assumptions was created using the mean responses from the UK experts (England and Wales). These assumptions were then implemented in the economic model.

The study data allowed the estimation of the annual frequency of monitoring visits by health state (Table 50). The annual frequency was divided by 12 to transform it into the model cycle frequency. Costs were inflated to 2022 amounts to calculate the monitoring cost per cycle.[209]

Table 50. Annual average frequency of monitoring visits by health state

HCRU	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10
General practitioner	1.4	1.9	3.3	4.1
Hospital outpatient	1.1	1.3	2.6	3.1
Nurse visit (general)	0.0	0.0	0.5	1.0
Physiotherapist	0.0	0.1	1.0	1.7
Neurologist/MG specialist	2.4	2.9	4.0	5.3
Language/speech therapist	0.4	1.1	2.5	3.6
Nurse visit (specialist)	0.8	1.0	1.8	2.6

HCRU, healthcare resource utilisation; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MG, myasthenia gravis
Source: argenx, MyRealWorldMG data on file

Table 51. Healthcare resource unit cost

HCRU	Unit cost, £		Source
	Original	Inflated to 2022	
General practitioner visit/ nurse visit (specialist)	33.00	35.90	PSSRU, Unit Costs of Health & Social Care 2021. See Chapter 10 pages 110-6[211]
Specialist visit, hospital	197.00	197.00	NHS National tariff workbook (2022/23). Assumed as General Internal Medicine Service (HRG Code:300). First attendance[212]
Nurse, hospital	159.00	172.99	National Schedule of NHS Reference Costs 2020/1, WF01A136
Physiotherapist	159.00	172.99	National Schedule of NHS Reference Costs 2020/1. WF01A136
Specialist visit, neurology outpatient	226.00	245.88	National Schedule of NHS Reference Costs 2020/1. WF01A136
Speech therapy services	107.00	116.41	PSSRU, Unit Costs of Health & Social Care 2021 [211]

HCRU, healthcare resource utilisation

Table 52. Patient monitoring cost by health state, per cycle

Health state	Cost per cycle, £
MG-ADL <5	78.28
MG-ADL 5–7	102.09
MG-ADL 8–9	185.46
MG-ADL ≥10	253.80

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

B.3.5.1.4 Complications associated with chronic corticosteroid use

The association between chronic corticosteroid use and costs has been reported in the literature, including the extra expenditure required to treat complications and corticosteroid-related AEs. In addition, studies have reported the impact of high and low corticosteroid doses on total annual cost—increases in HCRU, costs, and complications were more pronounced with higher doses of corticosteroids.[213,214]

The SLR covering the humanistic and economic burden of chronic corticosteroid use, previously described in this dossier, was used as a source of evidence to define the additional costs associated with the consequences of chronic systemic corticosteroid use (Appendix 2). As no studies in England were identified, the geographical scope was broadened to the UK and Nordic countries. From the studies included in the SLR, two studies conducted in Sweden and one in the UK were selected to populate the extra costs associated with the consequences of systemic corticosteroids in the model.[205,215,216] These costs are applied to patients receiving high- or low-dose corticosteroids as maintenance therapy. The average cost was estimated by corticosteroid dose and the extra cost per cycle among corticosteroid users was implemented in the model (Table 53).

Table 53. Complications of chronic corticosteroid use, extra cost per cycle

Corticosteroid dose	Cost per cycle, £
High (≥10 mg/day)	934.95
Low (<10 mg/day)	440.51

Sources: Voorham et al, 2019[216]; Janson et al, 2018[215]; Bexelius et al, 2013[205]

B.3.5.1.5 Rescue treatment

The cost of disease management for gMG exacerbations requiring hospitalisation and myasthenic crises was estimated considering that the proportion of the cohort experiencing acute deterioration of gMG incurs different consumption of healthcare resources than the rest of the cohort. Both inputs (gMG exacerbation cost per event and myasthenic crisis cost per cycle) were estimated based on the resources required by each health condition, and its quantity. These resources were obtained from the aforementioned survey conducted with clinical experts in the UK. NHS codes associated with each intervention were identified and the aggregate costs of the resources used were calculated.

The price of medicines used for rescue treatment are show in Appendix K.1.3. Calculations of drug utilisation and associated costs for exacerbations and myasthenic crises incorporate the inputs shown in Table 54 and Table 55.

Table 54. Dosing of drugs used for rescue treatment

Therapy	Recommended dose	Units per week	Total mg/unit	Treatment duration, weeks	Assumptions	References
IVIg	1g/kg	78.9	10000	2	Recommended: 1g/kg for first dose, only receiving a further 1g/kg if there is deterioration or no response.	NHS England, 2018[111]; Whittington Health NHS, 2015[217]
Prednisolone	100 mg alternate days	80	5	2	Association of British Neurologists' management guidelines: proposed dosing for ventilated gMG patients.	Sussman et al, 2015[19]
IV hydrocortisone	100–500 mg, ≤4 times a day	84	100	2	Slow IV infusion over at least 30 secs repeated as required. Assumed 300 mg every 6 hours.	MIMS, 2021[218]

IV, intravenous, IVIg, intravenous immunoglobulin; MIMS, Monthly Index of Medical Specialities

Table 55. Costs of drugs used for rescue treatment

Therapy	Units	Cost per unit, £	Proportion of cohort, %		Total cost, £	
			Exacerbation	Crisis	Exacerbation	Crisis
IVIg	5	690.00	55.5	63.3	6,127.20	6,992.00
Prednisolone	32	1.60	64.8	57.2	33.15	29.23
IV hydrocortisone	2	11.00	10.1	14.8	2.22	3.26

IV, intravenous, IVIg, intravenous immunoglobulin

Other healthcare resources required for managing gMG exacerbations and myasthenic crises in clinical practice in England were identified in consultation with a clinical expert, and corresponding tariffs were retrieved (Table 56). The proportion of patients estimated by the clinician to require a given resource was used to calculate the total cost for each resource, as shown in Table 57.

Table 56. Healthcare resources required for rescue therapy, and associated unit costs

Resource	Unit cost, £	Inflated cost, £	DRG code	Assumptions	Source
Healthcare visits					
Physician	115.00	125.12	NA	GP cost per hour including direct care	Jones & Burns, 2021[211]
Psychologist	65.00	70.72	PSSRU	Clinical psychologist cost per working hour (Community-based scientific and professional staff, Band 7)	Jones & Burns, 2021[211]
MG specialist/ neurologist	226.00	245.88	WF01A	Consultant-led outpatient follow-up in neurology. MG as a speciality is not identified in the reference costs.	NHS England, 2021[219]
Specialist nursing - adult	159.00	172.99	WF01A	Costs for "specialist nurse" not specifically identified. WF01A cost is for a follow-up outpatient attendance that is non-consultant led.	NHS England, 2021[219]
Physiotherapist	159.00	172.99	WF01A	As above	NHS England, 2021[219]
Occupational therapist	81.00	88.13	PSSRU	None	Jones & Burns, 2021[211]
Language therapy	107.00	116.41	PSSRU	Speech therapy services	Jones & Burns, 2021[211]
Dietician	92.00	100.09	PSSRU	None	Jones & Burns, 2021[211]
Emergency resources					
Ambulance	357.00	388.41	ASS02	Ambulance services cost for see, treat and convey	NHS England, 2021[219]
Emergency care	207.00	225.21	VB06Z	Emergency Medicine care unit costs vary widely according to type of treatment given. Value chosen is a mid-point in the range but cannot be specifically validated.	NHS England, 2021[219]
Inpatient resources					
Hospital stay	300.00	326.39	WF01B	There is no identified cost for "hospitalisation". WF01B refers to a first outpatient hospital attendance in neurology.	NHS England, 2021[219]

Resource	Unit cost, £	Inflated cost, £	DRG code	Assumptions	Source
Critical care/ organ support	1,889.00	2,055.18	XC06Z	ICU costs vary according to how many organs are supported. Value selected is for general adult critical care with one organ supported.	NHS England, 2021[219]
Oxygen assessment and monitoring	334.00	363.38	DZ38Z	None	NHS England, 2021[219]
Invasive ventilatory support	873.00	873.00	DZ27N	Multiple values exist depending on level of intervention. DZ27N relates to Respiratory Failure with Multiple Interventions, with CC Score 0-10.	NHS England, 2021[219]
Tracheostomy	6,609.00	7,190.40	CA63Z	None	NHS England, 2021[219]
Non-invasive ventilation support assessment	78.00	84.86	DZ37A	Value selected with reference to underlying specialty of neurology	NHS England, 2021[219]

DRG, diagnosis-related group; GP, general practitioner; ICU, intensive care unit; MG, myasthenia gravis

Table 57. Proportion of patients requiring resources for rescue therapy, and associated costs

Resource	Proportion of cohort, %		Units		Total cost, £	
	Exacerbation	Crisis	Exacerbation	Crisis	Exacerbation	Crisis
Healthcare visits						
Psychologist	8.3	0.0	0.9	0.0	5.5	0.0
MG specialist/ neurologist	90.0	93.3	7.5	18.2	1659.7	4183.0
Specialist nursing - adult	76.8	75.0	6.5	19.5	860.4	2529.9
Physiotherapist	89.1	95.0	3.7	11.0	569.2	1800.9
Occupational therapist	62.9	0.0	4.8	0.0	265.1	0.0
Language therapy	85.7	0.0	7.1	0.0	704.7	0.0
Dietician	39.5	0.0	3.9	0.0	153.9	0.0
Emergency resources						
Ambulance	50.5	91.7	0.8	1.0	162.1	345.4
Emergency care	89.5	96.7	1.0	1.0	192.5	211.2
Inpatient resources						
Hospital stay	100.01	100.0	7.0	22.8	2269.9	7425.4
Critical care/ organ support	12.5	100.0	0.9	3.8	220.2	7764.0

Resource	Proportion of cohort, %		Units		Total cost, £	
	Exacerbation	Crisis	Exacerbation	Crisis	Exacerbation	Crisis
Oxygen assessment and monitoring	100.0	100.0	5.7	1.5	2060.7	545.1
Invasive ventilatory support	7.0	28.3	0.3	0.6	17.4	141.8
Tracheostomy	0.0	32.5	0.0	0.7	0.0	1606.6
Non-invasive ventilation support assessment	55.8	82.5	0.8	0.9	36.3	61.3

MG, myasthenia gravis. 1) By definition, the model considers only exacerbations requiring hospitalisation

In addition, PLEX was identified by the clinical expert as a procedure undergone by 17% of patients with gMG exacerbations and 32% of those experiencing myasthenic crises. PLEX was assigned a unit cost of £779.00 (inflated to £847.53) based on the general DRG code SA44A (plasma exchange 2–9 units) in the absence of an MG-specific code.[219] Assuming use of 5 units for both exacerbations and crises, the total cost of PLEX associated with these events was estimated at £590.4 and £1,087.7, respectively.

Adding all of the above components, the overall cost of gMG exacerbations and myasthenic crises was as shown in Table 58.

Table 58. Cost of gMG-related hospitalisations

Event	Cost, £
gMG exacerbation (per event)	34,726.62
Myasthenic crisis (per cycle)	15,930.62

gMG, generalised myasthenia gravis

B.3.5.2 Adverse reaction unit costs and resource use

The unit (one-off) cost of each treatment-emergent grade 3 AE is applied per event to the proportion of the cohort having each respective AE at each cycle of the analysis. The cost of the AEs was informed based on the National Schedule of NHS Costs (Year 2020-2021).[219]

Table 59. Cost of adverse events

Adverse event	Cost, £
Infection	1,788
Asthenia (fatigue)	2,198
Cardiovascular disorders (including thrombosis)	1,850
Eyelid disorders	1,631
Myalgia	1,228
Headache or procedural pain	1,244
Gastrointestinal	905
Other	882

B.3.5.3 End-of-life care

An end-of-life care cost was applied in the model to patients who died. This was set at £382, based on the end-of-life cost for inpatients reported in the compendium of unit costs of health and social care from the Personal Social Services Research Unit (PSSRU) at the University of Kent.[211]

B.3.6 Severity

Table 60 summarises the key features for the QALY shortfall analysis. Table 61 summarises the utilities and undiscounted time spent in each health state for the established clinical management arm. This results in a total number of undiscounted QALYs of [redacted] for patient with gMG treated with established clinical management, compared to 16.09 QALYs for the general population with the same sex and age, as presented in Table 63. This means that for the population of interest for this submission, the threshold for a QALY modifier was not met.

Table 60: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Proportion female	[redacted]	B.3.3.1
Starting age	[redacted]	B.3.3.1

Table 61: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years current treatment
MG-ADL <5	[redacted] (0.02)	0.07
MG-ADL 5-7	[redacted] (0.02)	7.33
MG-ALG 8-9	[redacted] (0.02)	11.53
MG-ALG ≥ 10	[redacted] (0.02)	13.96
Crises	[redacted] (0.08)	0.03

Table 62: Summary of QALY shortfall analysis

Expected total discounted QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
16.09	[redacted]	[redacted]	[redacted]

B.3.7 Uncertainty

As described in Section B.2.5.4, there are a number of issues relating to gMG that impact on the ability to generate high-quality evidence. In particular, the fact that gMG is a rare disease limits the potential pool of patients eligible for enrolment in the ADAPT, ADAPT+, ADAPT-SC and ADAPT-SC+ studies. However, despite the fact that the AChR-Ab+ population in ADAPT was only 129 patients, enrolment was still sufficient to demonstrate statistical significance for the primary endpoint vs. placebo (Section B.2.6.2).

Moreover, as the symptoms of gMG can fluctuate over time (see Section B.1.3.2) it is challenging to select a clinical trial endpoint that can measure gMG progression. As described in Section B.1.3.1.2, the Company believes that the MG-ADL is the most appropriate measure for assessing efficacy and disease activity; this approach is consistent with published and ongoing clinical trials in gMG, and ADAPT demonstrated consistency across four MG-specific scales (Section B.2.6.4.1).[42] Moreover the Company has explored the impact of the distribution of patients across the MG-ADL-derived health states in sensitivity analyses, as well as exploring the impact of different assumptions on treatments patients in the most severe MG-ADL health state would receive.

Overall, gMG is a challenging therapy area in which to assess cost-effectiveness. In the absence of published cost-effectiveness models that reflect UK practice, and without previous NICE precedent to rely on for gMG, the Company has developed a de novo model designed to reflect both the lived experience of gMG patients, and UK clinical practice and treatment patterns. For the latter, the Company has explored multiple methods of data generation to support reducing uncertainty in this appraisal, notably through a survey of healthcare resource use, as well as multiple discussions with UK clinical experts.

B.3.8 Managed access proposal

The Company believes that the current submission provides appropriate evidence that efgartigimod can be approved within its licensed indication for routine NHS commissioning.

B.3.9 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

Table 63 provides summary of base-case settings for the cost-effectiveness analysis.

Table 63. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
General parameters			
Discount rate, costs	3.5%	Fixed	B.3.2.2.2
Discount rate, outcomes	3.5%	Fixed	
Time horizon, years	[redacted]	Fixed	B.3.2.2.1
Baseline age, years	[redacted]	Fixed	B.3.3.1
Female, %	[redacted]	Fixed	
Weight ≥80kg, % cohort	[redacted]	Fixed	
Weight 80-90kg, % cohort	[redacted]	Fixed	
Parametric curves			
ToT curve	Exponential parametric model: [redacted]	[redacted] (Cholesky)	B.3.5.1.1
Utilities			
Efgartigimod			B.3.4.2
MG-ADL <5	[redacted]	0.02 (Beta)	
MG-ADL 5–7	[redacted]	0.02 (Beta)	
MG-ADL 8–9	[redacted]	0.02 (Beta)	
MG-ADL ≥10	[redacted]	0.02 (Beta)	
Established Clinical Management			
MG-ADL <5	[redacted]	0.02 (Beta)	
MG-ADL 5–7	[redacted]	0.02 (Beta)	
MG-ADL 8–9	[redacted]	0.02 (Beta)	
MG-ADL ≥10	[redacted]	0.02 (Beta)	
Crises	[redacted]	0.08 (Beta)	
Exacerbations	-0.16	0.02 (Normal)	B.3.4.5.1
Duration of exacerbation (days)	20.72	2.07 (Normal)	
Corticosteroid related			B.3.4.5.2
High dose	-0.18	0.02 (Normal)	
Low dose	-0.17	0.01 (Normal)	
Caregiver			
MG-ADL <5	-0.002	0.0002 (Normal)	B.3.4.5.3
MG-ADL 5–7	-0.045	0.0045 (Normal)	
MG-ADL 8–9	-0.142	0.0142 (Normal)	
MG-ADL ≥10	-0.160	0.0160 (Normal)	
Crises	-0.180	0.0180 (Normal)	
Drug costs			
Efgartigimod IV	[redacted]	Fixed	Appendix K.1.1
IVIg (2.5mg/25mL)	£172.50	Fixed	Appendix K.1.2
IVIg (10mg/100mL)	£690.00	Fixed	
Rituximab	£785.84	Fixed	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Azathioprine	£2.04	Fixed	
Methotrexate	£2.65	Fixed	
Ciclosporin	£13.05	Fixed	
Tacrolimus	£55.69	Fixed	
Mycophenolate	£8.21	Fixed	
Cyclophosphamide	£9.66	Fixed	
Prednisolone	£12.76	Fixed	
Pyridostigmine	£45.44	Fixed	
Efgartigimod RDI	[redacted]	Fixed	B.3.5.1
Distribution of treatments			
Maintenance IVIg in established clinical management			
MG-ADL <5	0%	Fixed	B.3.2.3
MG-ADL 5–7	12.5%	0.01 (Beta)	
MG-ADL 8–9	50%	0.05 (Beta)	
MG-ADL ≥10	100%	0.1 (Beta)	
Rituximab in established clinical management			
MG-ADL <5	12.5%	0.01 (Beta)	B.3.2.3
MG-ADL 5–7	12.5%	0.01 (Beta)	
MG-ADL 8–9	12.5%	0.01 (Beta)	
MG-ADL ≥10	0%	Fixed	
Conventional therapy treatments			
Cohort on corticosteroid	75.2%	0.08 (Beta)	B.3.2.3
Cohort on AChEi	88.4%	0.08 (Beta)	
Cohort on NSIST	59.7%	0.06 (Beta)	
Corticosteroid use in conventional therapy			
On high dose	74.2%	0.07 (Beta)	B.3.5.1
Average dose/day, high dose	20.59	2.06 (Gamma)	
Average dose/day, high dose	4.77	0.48 (Gamma)	
% change in corticosteroid use vs baseline			
MG-ADL <5	-100%	Fixed	B.3.5.1
MG-ADL 5–7, 8–9 and ≥10	0%	Fixed	
% on corticosteroid high-dose			
MG-ADL <5	0%	Fixed	B.3.5.1
MG-ADL 5–7, 8–9 and ≥10	74.2%	0.07 (Beta)	
Administration costs			
Hospital administration, IVIG	1765.9	176.6 (Gamma)	B.3.5.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: SE (distribution)	Reference to section in submission
Hospital administration, IV	155.6	15.6 (Gamma)	
Other costs			
Cost of crises per cycle	£34,727	3,473 (Gamma)	B.3.5.1.5
Cost of exacerbation/event	£15,931	1,593 (Gamma)	
Health state monitoring costs, per cycle			
MG-ADL <5	£78	8 (Gamma)	B.3.5.1.3
MG-ADL 8–9	£185	19 (Gamma)	
MG-ADL ≥10	£254	25 (Gamma)	
Complications of chronic corticosteroid use, per cycle			
High dose CS use	£934.9	93.49 (Gamma)	B.3.5.1.4
Low dose CS use	£440.5	44.05 (Gamma)	
Adverse events			
Infection	£1,788	178.76 (Gamma)	B.3.5.2
Asthenia	£2,198	219.75 (Gamma)	
Cardiovascular disorders (including thrombosis)	£1,850	185.01 (Gamma)	
Eyelid disorders	£1,631	163.05 (Gamma)	
Myalgia	£1,228	122.80 (Gamma)	
Headache or procedural pain	£1,244	124.39 (Gamma)	
Gastrointestinal	£905	90.50 (Gamma)	
Other	£882	88.21 (Gamma)	
End of life care cost	£382	38.20 (Gamma)	B.3.5.3

Assumptions

Table 64: Summary of key model assumptions

Topic	Assumption	Justification/reason	Sensitivity
Cycle length	4 weeks	Short enough to capture the dosing schedules of efgartigimod and established clinical management.	N/A
Time horizon	Lifetime (55 years)	Long enough to capture the lifetime of patients in this setting	N/A
Efficacy	Treatment effect is modelled as changes in MG-ADL score	MG-ADL was the primary outcome of the ADAPT study	N/A
	Extrapolation of effect in efgartigimod alfa arm is based on recycling of pooled observations in ADAPT and ADAPT+ studies	The effect observed after any subsequent cycle of efgartigimod alfa treatment in ADAPT and ADAPT+ is greater or equal to the effect in previous cycle.	A scenario is provided where transition matrices in efgartigimod arm are based on ADAPT only

Topic	Assumption	Justification/reason	Sensitivity
	In established clinical management arm, cohort is assumed to return to baseline MG-ADL health state beyond ADAPT observations	Baseline distribution in the ADAPT study is assumed to be representative of population level distribution in patients with MG-ADL of at least 5 despite treatment with established clinical management	N/A
Mortality	Differences in mortality between model arms are assumed to come solely from occurrence of crisis and use of systemic corticosteroids	The literature on gMG does not suggest evidence of increased mortality in patients at any MG-ADL level, unless crisis occurs. Evidence on systemic use of corticosteroid from the literature suggests that high-dose corticosteroid on recurrent use impacts survival.	N/A
Treatment (dis)continuation	The cohort not responding to 2 consecutive cycles is excluded from treatment with efgartigimod	These patients are thereafter assumed to receive conventional therapy treatment. The costs, effects and HRQoL of conventional therapy are therefore applied to this proportion of the cohort excluded from treatment with efgartigimod This is based on the response definition in ADAPT	N/A
	Patients in the crisis health state stop treatment and receive rescue therapy	Treatment is started again once the cohort transit out of the Crisis health state.	N/A
	Unplanned discontinuation is considered using a piecewise approach with KM curve until available and exponential parametric model	The probability of discontinuation is based on the time to treatment discontinuations estimated on ADAPT and ADAPT + data, AChR+ responders (censoring lost to follow-up between ADAPT and ADAPT+ and patients who discontinued because they moved to SC trial 113-2002).	N/A
	Post-discontinuation of efgartigimod the cohort is applied the return to baseline waning effect probability over 6 months.	Discontinued cohort is assumed to be the same as established clinical management cohort. Baseline distribution in the ADAPT study is assumed to be representative of population level distribution in patients with MG-ADL of at least 5 despite treatment with established clinical management.	N/A

Topic	Assumption	Justification/reason	Sensitivity
Utilities	Health state utilities are based on a mixed model considering health state and treatment, based on ADAPT data	In line with the NICE reference case, health-state utilities were obtained from the pivotal trial of efgartigimod.	A scenario is provided where utilities by health state based on MRWMG data are applied
	Caregiver disutilities are considered, and are based on caregiver disutilities in multiple sclerosis	In line with the NICE reference care, caregiver disutilities were considered since gMG has an important impact on the QoL of carers. Caregiver disutilities in gMG are not available, thus multiple sclerosis was selected as a proxy since, as in gMG patients have progressive movement impairment.	N/A
Vial sharing	No vial sharing considered	In line with the NICE reference case	N/A
Drug administration	Maintenance IVIG in established clinical management is administered to the following proportions: • MG-ADL <5 = 0% • MG-ADL 5-7 =12.5% • MG-ADL 8-9 =50% • MG-ADL ≥10 = 100%	This was based on evidence from MyRealWorld MG study in patients meeting ADAPT eligibility criteria and supported by clinical experts in the UK	A scenario is provided where IVIG is only administered in MG-ADL 8-9 and MG-ADL≥10 Another scenario is provided where in MG-ADL≥10 90% of patients are administered IVIG, and the remaining are administered PLEX
	The number of vials per administration for efgartigimod was based on the distribution of weight in the ADAPT study (EU AChR-Ab+ patients) at baseline.	Real world usage from US registry, suggest that only 50% of patients with weight between 80 and 90 kg would receive the third vial.	N/A
	The definition of high-dose corticosteroids is >10mg/day	Clinical expert opinion	A scenario is provided where the definition of high-dose corticosteroids in >5mg/day
Subsequent treatments	Patients that discontinue efgartigimod are assumed to be treated with established clinical management	No other licenced treatments are available for the population of interest	N/A

Abbreviations:

B.3.10 Base-case results

Because this submission includes a simple PAS, a full set of results with PAS are presented in B.3.10, and results without PAS are presented in Appendix N. All results of this analysis concern the IV formulation of efgartigimod.

A decision by the MHRA on the application for marketing authorisation of a SC formulation of efgartigimod is expected in [redacted]. At the current stage the price for this formulation has not yet been set. This first needs to be set with the DoH in the context of the VPAS program. If considering the cost effectiveness of the SC formulation, it is expected that the same model with the same effectiveness inputs should be used. The SC formulation will be given at a dose of 1000 mg per week for 4 weeks per cycle, therefore, the only difference would be in the acquisition and administration costs of efgartigimod. The Company expects the SC formulation to have a similar cost-effectiveness as the IV formulation.

B.3.10.1 Base-case incremental cost-effectiveness analysis results

Table 65 presents summary results of the base-case cost-effectiveness analysis considering the efgartigimod list price with a [redacted] PAS for efgartigimod versus established clinical management, from the third-party payer perspective in England and Wales. Over the lifetime time horizon, there was a substantial gain in QALYs for patients who received efgartigimod ([redacted]) compared with those who received established clinical management. This is partially attributable to gains in HRQoL in the efgartigimod arm as a result of more years spent in the least active health state (i.e., MG-ADL <5), the higher utility associated with efgartigimod, and the lower mortality associated with a decrease in the corticosteroid dose. Table 66 presents the net health benefit for the base case analysis.

Table 65: Base-case results with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,066
Established clinical management	[redacted]	[redacted]	[redacted]	-	-	-	-

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

Table 66: Net health benefit with PAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	-1.16	0.19
Established clinical management	[redacted]	[redacted]	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; NHB, net health benefit

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to assess the robustness of the model to parameter uncertainty. In the PSA, 1,000 simulations were performed in which model parameters were varied simultaneously by sampling at random from hypothetical distributions. The distributions used for each variable in the PSA are reported in the model.

In the PSA, most iterations are in the North-East quadrant of the cost-effectiveness plane (i.e., positive incremental benefit and higher incremental cost) (Figure 29). The base-case ICER and the PSA mean ICER were similar, confirming the overall robustness of the model results (Table 67).

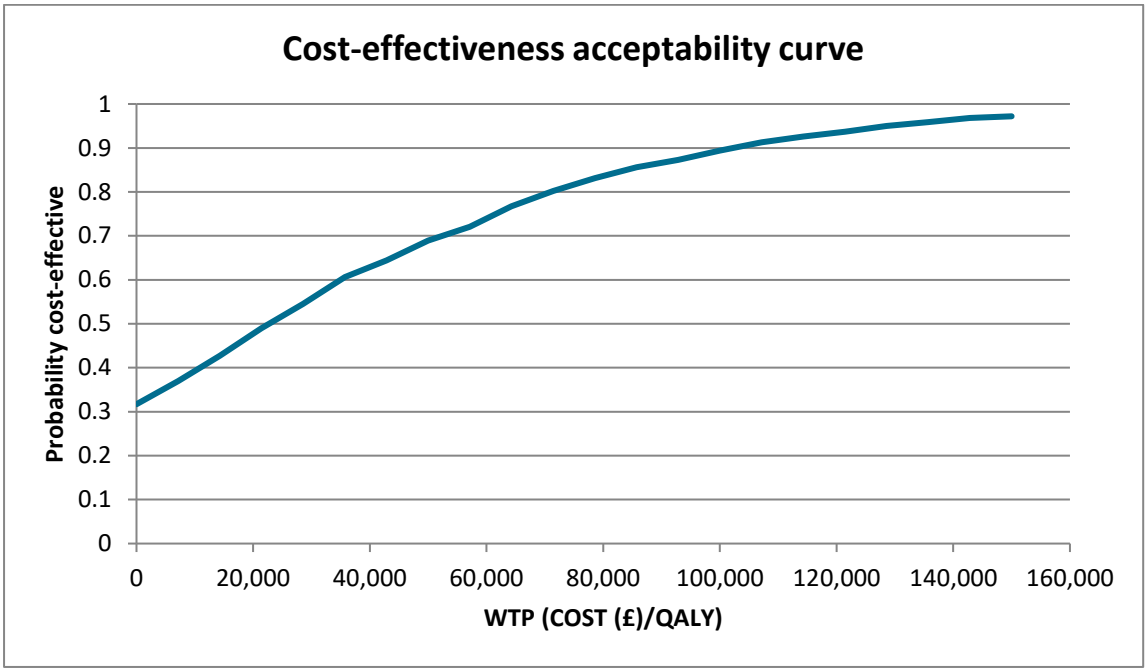
Figure 29 Incremental cost and QALY cloud in the cost-effectiveness plane with PAS

Table 67. Comparison of the base case and PSA results with PAS

	Cost, £			QALYs			ICER (£/QALY)
	Efgartigimod	ECM	Incremental	Efgartigimod	ECM	Incremental	
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,066
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24,764
PSA 95%CI lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-50,165
PSA 95%CI upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	150,613

ICER, incremental cost-effectiveness ratio; ECM: established clinical management; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year

Figure 30. Cost-effectiveness acceptability curve with PAS



QALY, quality-adjusted life-year; WTP, willingness to pay

B.3.11.2 Deterministic sensitivity analysis

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way sensitivity analyses was performed in which key model parameters were varied one at a time around their base-case values. When the SE was not reported, 10% of the base-case value was used as a proxy for SE. Each parameter was varied to assess the impact on incremental LYs, QALYs, and costs. High and low values used in the one-way sensitivity analyses are presented in Table 68.

Table 68. Parameter limits used in the univariate sensitivity analyses

Parameter name	Base case	Lower value	Upper value
Discount rate outcomes	0.035	0.000	0.060
Discount rate costs	0.035	0.000	0.060
Initial age (years)	[redacted]	[redacted]	[redacted]
Proportion of females	[redacted]	[redacted]	[redacted]
Proportion with weight >80kg	[redacted]	[redacted]	[redacted]
Proportion with weight 80-90kg	[redacted]	[redacted]	[redacted]
Weight, kg	[redacted]	[redacted]	[redacted]
Proportion cohort in MG-ADL <5 health state	[redacted]	[redacted]	[redacted]
Proportion cohort of patients in MG-ADL 5-7 health state	[redacted]	[redacted]	[redacted]
Proportion cohort of patients in MG-ADL 8-9 health state	[redacted]	[redacted]	[redacted]
Proportion cohort of patients in MG-ADL ≥10 health state	[redacted]	[redacted]	[redacted]
Efgartigimod non-responders	[redacted]	[redacted]	[redacted]
Prob of crises from MG-ADL <5	0.000	0.000	0.000
Prob of crises from MG-ADL 5-7	0.001	0.001	0.001
Prob of crises from MG-ADL 8-9	0.001	0.001	0.001

Parameter name	Base case	Lower value	Upper value
Prob of crises from MG-ADL ≥10	0.001	0.001	0.001
Transition prob - From Crises to MG-ADL <5	0.000	0.000	0.000
Transition prob - From Crises to MG-ADL 5-7	0.000	0.000	0.000
Transition prob - From Crises to MG-ADL 8-9	0.000	0.000	0.000
Transition prob - From Crises to MG-ADL ≥10	1.000	0.804	1.000
Prob of exacerbations – established clinical management	[redacted]	[redacted]	[redacted]
Prob of exacerbations - Efgartigimod	[redacted]	[redacted]	[redacted]
Mortality HR vs general population in health state MG-ADL <5	1.000	1.000	1.196
Mortality HR vs general population in health state MG-ADL 5-7	1.000	1.000	1.196
Mortality HR vs general population in health state MG-ADL 8-9	1.000	1.000	1.196
Mortality HR vs general population in health state MG-ADL ≥10	1.000	1.000	1.196
Prob of death during Crises	0.123	0.099	0.147
Extra mortality associated with corticosteroid use - Corticosteroid high-dose	2.101	1.689	2.513
Extra mortality associated with corticosteroid use - Corticosteroid low-dose	1.110	0.892	1.328
AEs incidence - established clinical management - Infection	0.002	0.002	0.003
AEs incidence - established clinical management - Asthenia (fatigue)	0.002	0.002	0.003
AEs incidence - established clinical management - Cardiovascular disorders (incl. thrombosis)	0.002	0.002	0.003
AEs incidence - established clinical management - Eyelid disorders	0.002	0.002	0.003
AEs incidence - established clinical management - Myalgia	0.000	0.000	0.000
AEs incidence - established clinical management - Headache or procedural pain	0.002	0.002	0.003
AEs incidence - established clinical management - Gastrointestinal	0.000	0.000	0.000
AEs incidence - established clinical management - Other	0.007	0.005	0.008
AEs incidence - Efgartigimod - Infection	0.004	0.004	0.005
AEs incidence - Efgartigimod - Asthenia (fatigue)	0.000	0.000	0.000
AEs incidence - Efgartigimod - Cardiovascular disorders (incl. thrombosis)	0.000	0.000	0.000
AEs incidence - Efgartigimod - Eyelid disorders	0.000	0.000	0.000
AEs incidence - Efgartigimod - Myalgia	0.002	0.002	0.003
AEs incidence - Efgartigimod - Headache or procedural pain	0.002	0.002	0.003
AEs incidence - Efgartigimod - Gastrointestinal	0.002	0.002	0.003
AEs incidence - Efgartigimod - Other	0.009	0.007	0.011
Utility - MG-ADL <5, established clinical management	[redacted]	[redacted]	[redacted]
Utility - MG-ADL <5, efgartigimod	[redacted]	[redacted]	[redacted]
Utility - MG-ADL 5-7, established clinical management	[redacted]	[redacted]	[redacted]
Utility - MG-ADL 5-7, efgartigimod	[redacted]	[redacted]	[redacted]

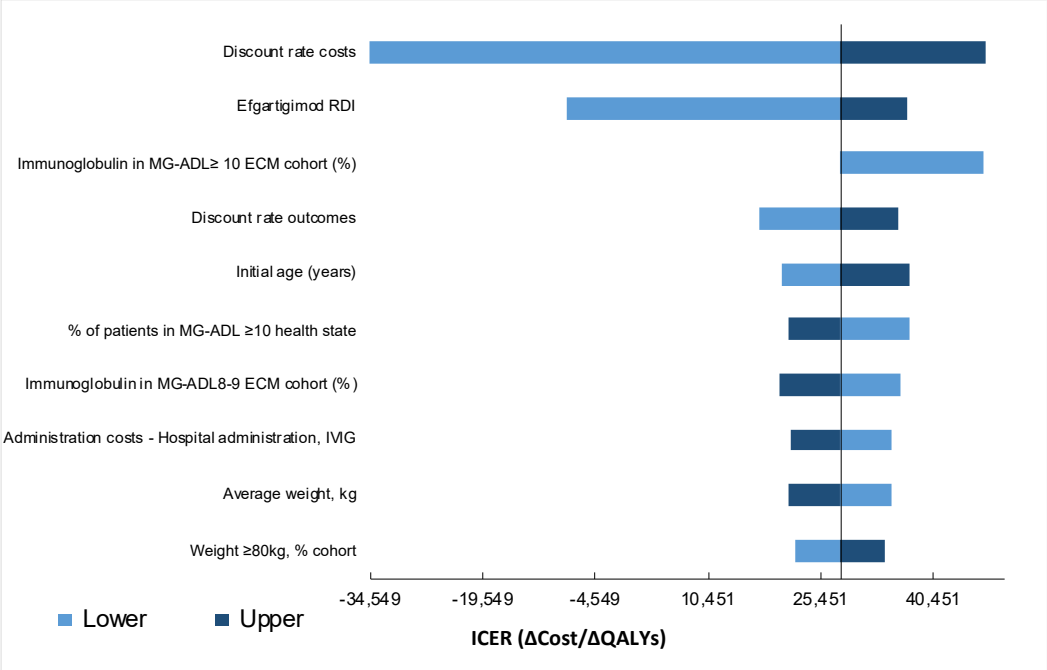
Parameter name	Base case	Lower value	Upper value
Utility - MG-ADL 8-9, established clinical management	[redacted]	[redacted]	[redacted]
Utility - MG-ADL 8-9, efgartigimod	[redacted]	[redacted]	[redacted]
Utility - MG-ADL ≥10, established clinical management	[redacted]	[redacted]	[redacted]
Utility - MG-ADL ≥10, efgartigimod	[redacted]	[redacted]	[redacted]
Utility - Crises	[redacted]	[redacted]	[redacted]
Disutility per exacerbation event	-0.160	-0.191	-0.129
Exacerbation duration (days)	20.725	16.663	24.787
Utility decrement - High-dose corticosteroid	-0.175	-0.209	-0.141
Utility decrement - Low-dose corticosteroid	-0.070	-0.084	-0.056
Impact of MG on the QoL of caregivers - MG-ADL <5	-0.002	-0.002	-0.002
Impact of MG on the QoL of caregivers - MG-ADL 5-7	-0.045	-0.054	-0.036
Impact of MG on the QoL of caregivers - MG-ADL 8-9	-0.142	-0.170	-0.114
Impact of MG on the QoL of caregivers - MG-ADL ≥10	-0.160	-0.191	-0.129
Impact of MG on the QoL of caregivers - Crises	-0.180	-0.215	-0.145
Efgartigimod 80-90Kg on 3 vials, proportion of cohort	[redacted]	[redacted]	[redacted]
Efgartigimod RDI	[redacted]	[redacted]	[redacted]
Immunoglobulin in MG-ADL<5, established clinical management cohort (proportion of cohort)	0.000	0.000	0.000
Immunoglobulin in MG-ADL5-7, established clinical management cohort (proportion of cohort)	0.125	0.101	0.150
Immunoglobulin in MG-ADL8-9, established clinical management cohort (proportion of cohort)	0.500	0.402	0.598
Immunoglobulin in MG-ADL≥ 10, established clinical management cohort (proportion of cohort)	1.000	0.804	1.000
Rituximab in MG-ADL<5, established clinical management cohort (proportion of cohort)	0.125	0.101	0.150
Rituximab in MG-ADL5-7, established clinical management cohort (proportion of cohort)	0.125	0.101	0.150
Rituximab in MG-ADL8-9, established clinical management cohort (proportion of cohort)	0.125	0.101	0.150
Rituximab in MG-ADL≥ 10, established clinical management cohort (proportion of cohort)	0.000	0.000	0.000
Conventional therapy treatments - Cohort on corticosteroid, proportion of cohort	0.752	0.605	0.899
Conventional therapy treatments - Cohort on AChEi, proportion of cohort	0.884	0.711	1.000
Conventional therapy treatments - Cohort on NSIST, proportion of cohort	0.597	0.480	0.714
Corticosteroid use in conventional therapy - proportion of cohort on corticosteroid high-dose	0.742	0.597	0.888
Corticosteroid use in conventional therapy - Average dose/day, high-dose	20.592	16.556	24.628
Corticosteroid use in conventional therapy - Average dose/day, low-dose	4.767	3.833	5.702
Proportion of cohort with change in CS use vs baseline - MG-ADL <5	-1.000	-1.000	-0.804
Proportion of cohort with change in CS use vs baseline - MG-ADL 5-7	0.000	0.000	0.000

Parameter name	Base case	Lower value	Upper value
Proportion of cohort with change in CS use vs baseline - MG-ADL 8-9	0.000	0.000	0.000
Proportion of cohort with change in CS use vs baseline - MG-ADL ≥10	0.000	0.000	0.000
Proportion of cohort with on corticosteroid high-dose - MG-ADL <5	0.000	0.000	0.000
Proportion of cohort with on corticosteroid high-dose - MG-ADL 5-7	0.742	0.597	0.888
Proportion of cohort with on corticosteroid high-dose - MG-ADL 8-9	0.742	0.597	0.888
Proportion of cohort with on corticosteroid high-dose - MG-ADL ≥10	0.742	0.597	0.888
Administration costs - Hospital administration, IVIG	1765.919	1419.799	2112.039
Administration costs - Hospital administration, IV	155.580	125.086	186.074
Cost of MG related hospitalisations - Cost of crises/cycle (£)	34726.620	27920.202	41533.037
Cost of MG related hospitalisations - Cost of exacerbation/event (£)	15930.625	12808.222	19053.027
Disease monitoring (HC visits, examinations) - MG-ADL <5	78.284	62.941	93.628
Disease monitoring (HC visits, examinations) - MG-ADL 5-7	102.093	82.083	122.103
Disease monitoring (HC visits, examinations) - MG-ADL 8-9	185.462	149.111	221.812
Disease monitoring (HC visits, examinations) - MG-ADL ≥10	253.798	204.054	303.543
Corticosteroid related chronic conditions cost - High dose CS use	934.949	751.699	1118.198
Corticosteroid related chronic conditions cost - Low dose CS use	440.508	354.168	526.847
Adverse events costs - Infection	1787.581	1437.216	2137.947
Adverse events costs - Asthenia (fatigue)	2197.534	1766.817	2628.251
Adverse events costs - Cardiovascular disorders (incl. thrombosis)	1850.150	1487.520	2212.779
Adverse events costs - Eyelid disorders	1630.549	1310.961	1950.136
Adverse events costs - Myalgia	1227.982	987.298	1468.667
Adverse events costs - Headache or procedural pain	1243.928	1000.118	1487.738
Adverse events costs - Gastrointestinal	905.036	727.649	1082.423
Adverse events costs - Other	882.069	709.183	1054.954
End of life care cost	382.000	307.128	456.872

AChEi, acetylcholinesterase inhibitor; AE, adverse event; CS, corticosteroid; HC, healthcare; HR, hazard ratio; IV, intravenous; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NSIST, nonsteroidal immunosuppressive therapy; Prob, probability; QoL, quality of life

In the one-way sensitivity analysis, the variable with the greatest influence on the ICER was the discount rate for costs in the model (Figure 31). Other influential variables were the proportion of patients using immunoglobulin in MG-ADL ≥10 in ECM cohort, the actual number of infusions per cycle of efgartigimod treatment (RDI), the discount rate for outcomes, the initial age (years), the proportion of patients in MG-ADL ≥10 health state, utilisation of IVIg in MG-ADL 8-9 in ECM cohort, the administration cost of IVIg in hospital, weight (kg) of the cohort.

Figure 31. Results of the one-way sensitivity analysis with PAS



ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QALY, quality-adjusted life-year; ECM, established clinical management

Table 69. Percentage change in base case results with PAS following lower and upper variation in the 10 most influential parameters

Parameter	Lower value	Upper value
Discount rate costs	-230%	69%
Efgartigimod RDI	-130%	31%
Immunoglobulin in MG-ADL≥ 10 ECM cohort (%)	68%	0%
Discount rate outcomes	-39%	28%
Initial age (years)	-28%	33%
% of patients in MG-ADL ≥10 health state	32%	-25%
Immunoglobulin in MG-ADL8-9 ECM cohort (%)	28%	-28%
Administration costs - Hospital administration, IVIG	24%	-24%
Average weight, kg	24%	-24%
Weight ≥80kg, % cohort	-21%	21%

ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QALY, quality-adjusted life-year; ECM, established clinical management

Table 70. Detailed results of the one-way sensitivity analysis with PAS

Parameter	ICER (£/QALY)	
	Lower	Upper
Discount rate costs	-36,368	47,519
Efgartigimod RDI	-8,477	36,851
Immunoglobulin in MG-ADL≥ 10 ECM cohort (%)	47,088	28,066
Discount rate outcomes	17,225	35,846
Initial age (years)	20,202	37,212
% of patients in MG-ADL ≥10 health state	37,142	21,074
Immunoglobulin in MG-ADL8-9 ECM cohort (%)	36,008	20,123
Administration costs - Hospital administration, IVIG	34,803	21,328
Average weight, kg	34,778	21,324
Weight ≥80kg, % cohort	22,050	34,081

ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QALY, quality-adjusted life-year; ECM, established clinical management

B.3.11.3 Scenario analysis

Results of the scenario analyses are shown in Table 71. Variation in the source of evidence to model the extrapolation of efgartigimod effect does not appear to impact the results importantly, thus supporting the current modelling approach. The health-state utility values obtained from MyRealWorld MG study provide greater differentiation in HRQoL between the model health-states, thereby explaining the improvement in the ICER as consequence of greater QALYs gained. This scenario may suggest greater cost-effectiveness of efgartigimod vs established clinical management in the real-world practice, i.e. more representative of actual impact of gMG on patients' HRQoL. Finally, the largest ICER difference from the base-case scenario was observed with the alternative definition of threshold for high-dose corticosteroid in chronic use, i.e. 5mg/day instead of 10mg/day. This is expected since a lower threshold implies lower overall complications associated with systemic corticosteroid use, which most impact the cohort in the established clinical management arm of the model.

Table 71. Scenario analyses for efgartigimod vs Established Clinical Management with PAS

	Scenario description	Efgartigimod vs Established Clinical Management			
		Incr Cost, £	Incr QALYs	ICER £/QALY	ICER % change vs basecase
0	Base case	[redacted]	[redacted]	28,066	-
1	IVIG only in MG-ADL 8-9 and MG-ADL>10	[redacted]	[redacted]	32,312	15.1%
2	Updated distribution of treatments in established clinical management MG-ADL>10 (the other health states remain the same): IVIG: 90% PLEX: 10%	[redacted]	[redacted]	32,057	14.2%
3	Transition matrices in efgartigimod arm based on ADAPT only (i.e., no ADAPT +)	[redacted]	[redacted]	34,497	22.9%

	Scenario description	Efgartigimod vs Established Clinical Management			
		Incr Cost, £	Incr QALYs	ICER £/QALY	ICER % change vs basecase
4	Utilities by health-state based on MyRealWorld MG	[redacted]	[redacted]	25,983	-7.4%
5	Definition of high-dose corticosteroid in systemic use: >5mg/day	[redacted]	[redacted]	37,418	33.3%
6	From year 2 onwards it is assumed that 100% of patients receive administration of efgartigimod at home at no cost (supported by argenx)	[redacted]	[redacted]	26,097	-7.0%

Incr, incremental; ICER, incremental cost-effectiveness ratio; IV, intravenous; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; PLEX, plasma exchange; UK, United Kingdom; QALY, quality-adjusted life-years; y, year

B.3.12 Subgroup analysis

Not applicable

B.3.13 Benefits not captured in the QALY calculation

Section B.1.3.2.2 summarises the substantial everyday patient burden associated with gMG. The fluctuating and unpredictable nature of symptoms affects patients' ability to plan for the short-, medium- and long-term and diminishes all aspects of a patient's life.[89] Patients describe how the muscle weakness and fatigue that they experience with gMG means they have to make continuous adaptations and trade-offs when working or taking care of themselves or their family, leading to a sense of loss due to restrictions in activity and limitations in life choices.[89] They rely on coping mechanisms such as long-term planning, frequent breaks, reducing the amount or type of work they do, proactively cancelling plans if necessary and adapting the ways in which they conduct activities of daily living such as eating or personal hygiene.[89]

The fluctuating nature of gMG, and the fact that many gMG patients simply adapt their everyday lives to cope with symptoms, both have the potential to underestimate the quality of life, and thus utility, decrement associated with the condition. Given that this is the first assessment by NICE of a therapy for gMG, and that there is therefore no precedent available for the utility impact of gMG, the Company would request that the Committee take this into consideration.

Beyond the aptitude to complete work tasks, gMG patients are also often concerned about the emotional stresses of gMG manifesting in the workplace, or, conversely, the stress of work negatively impacting their disease.[89] Employer attitudes vary considerably, and can even affect the treatments gMG patients are able to commit to; for example, they may not feel able to take time away from work to receive infused treatments.[89] As a result of all of these factors, unemployment rates are high, with an estimated 55% of gMG patients unable to work at all.[15] Even in those who were still employed, MG patients were 9 times more likely to take long-term sick leave than the general population.[98] Many of these issues are also relevant to the ability of both children and adults with gMG to pursue educational activities.[89] None of the economic impacts outlined above are captured in the QALY.

B.3.14 Validation

Validation of cost-effectiveness analysis

The model conceptual schema, comparator, population characteristics, key assumptions behind the model structure, extrapolation of effects, health-care resource use were validated with gMG clinical experts in the UK. Overall, all clinical experts agree that the conceptual model is appropriate, and inputs included are reflective of disease management in the given country. The model has also been subjected to a thorough quality assessment by an experienced health economist using the transparency and validation checklist from Eddy et al. 2012. Table 72 presents the results of the technical validation of the economic model.

Table 72. Model technical validation

Scenario testing	Outcome	Corrections made
Make treatment costs equal - sense check results.	This is a difficult scenario to test because the treatment is given at different intervals for different treatments. We instead set efgartigimod, Ig and rituximab cost = 0 and any reduction is CS = 0, crises rate = 0, then the total drug cost in each arm should be equal. A higher cost was noticed in efgartigimod arm, this was because the AChEi and NSIST treatment was taking into account also cohort in crises and death health-state. After correcting, the drug total cost was equal between health-state.	Yes, in efgartigimod engine the range used to apply AChEi and NSIST treatment was adjusted to consider only cohort in relevant health-states
Make treatment costs for each arm very high - sense check results.	Yes, only drug costs increase	
Treatment Costs: Turn off all health state costs and set AE rates to 0. Total costs should now only include treatment costs; ensure that intervention treatment costs reflect expectations given inputs.	Costs for drug administration, health-state monitoring, CS consequences, crises, exacerbations were set to 0. AE incidence was set = 0 in both arms. Total cost was equal to drug cost.	
Make AE rates equal; check that associated costs are equal (assuming AE-specific costs), and that LY or QALY results change in the right direction.	Treatment AEs in both arms were set equal. Only costs were impacted since we do not consider impact of AEs on survival or QoL	
If a survival treatment effect exists, examine relative time in states and make sure times make sense given transition probabilities. Use judgement on LY per state, make sure nothing looks unrealistic.	If prob of crises = 0 and no CS reduction, Lys in each arm are the same, as expected. If HR>1 is applied to MG-ADL 8-9 and MG-ADL>10 health-states, the incremental Lys for efgartigimod vs established clinical practice is greater, which is expected given that greater proportion of cohort in these health-states is found in the established clinical management arm.	
If a treatment effect exists, set baseline event rates equal across arms, RR/HR to 1 and AE/other event rates to zero/equivalence, total LY	It is not possible to run this test because of the different substates which had to be considered to accommodate the intermittent treatment schedule of efgartigimod.	

Scenario testing	Outcome	Corrections made
and QALYs should be equal between arms.		
Make both arms entirely equal (all costs, AE rates, OS, PFS). 1) Total LY and QALYs should be equal between arms. 2) Total costs should be equal between arms 3) Total costs per health state should be equal between arms.	It is not possible to run this test because of the different substates which had to be considered to accommodate the intermittent treatment schedule of efgartigimod.	
If a survival treatment effect exists, turn off transition probability to specific health states, one at a time (assuming multiple health states). Make sure time in state = 0 for each given health state.	If probability of crises = 0, then time in state for crises = 0	
If QoL effect exists, make all utilities and disutilities = 0. Make sure total QALYs = 0	Health-state utilities and all disutilities (CS, exacerbations, caregiver) = 0. Then total QALYs in both arms = 0	
If QoL effect exists, make all utilities = 1 and disutilities = 0. Make sure total QALYs = total LYs.	Health-state utility =1, all disutilities (CS, exacerbations, caregiver) = 0, general population utilities = 1, Then total QALYs in both arms = total LYs	
General check		
Using Formulas | Formula Auditing | Show Formulas, check to ensure consist formulas are used, where necessary.	No issues found	
Check that discount rates are being applied correctly.	Checked in both Markov engine sheets in setting part and LYs, QALYs and costs. No issues found. Scenarios with 0% discount for outcomes first and then costs were run to check only respective outputs were impacted.	
Ensure all linked cells refer back to the original source (no spider webs)	No issues found	
Check that cells have appropriate formatting (currency, same number of decimals where appropriate, etc)?	No issues found	
Markov/Survival analysis		
Are the discount rates for costs and outcomes correctly calculated?	Yes	
Does the time spent in the health states add up to 1?	Yes. In both arms, the sum was done for cohort on and off treatment together	
Does the number of subjects remain constant over model cycles?	Yes = 1	
Check that time horizon/ cycles/ age are linked in correctly.	Checked in look-up and the Markov engines sheet and no issues were found	
Confirm that the first row of the Markov Trace refers to the correct input.	No issues found	
Confirm that cost formulas in Markov Trace refer to the right cells.	No issues found	
Confirm that QALY, LY and PFLY formulas in Markov Trace refer to the right cells.	No issues found	

Scenario testing	Outcome	Corrections made
Is the model type (Weibull, Exponential, Gompertz, etc) calculated correctly?	Checked with respect to ToT curve and no issues were found	
Check that PFS is never greater than OS (check that they never cross).	N/A	
Check that the choice of survival functions (e.g., for Weibull) has been justified (see log-likelihood, AIC, BIC, visual inspection, etc).	The Exponential function was selected based on objective fit based on BIC and AIC	
If hazard ratios have been used, check they have been applied correctly	No issues found related to mortality HRs versus general population	
Check that the hazard of death in the model doesn't fall below that of the general population.	No issues found	
OWSA		
Check results for OWSA - do they make sense?	Yes, variations around basecase ICER in all parameters move in expected direction.	
Are there any problems with the OWSA macro?	No	
Check the graphs (example: tornado) - does the scale make sense? Are all axes labeled properly? Is there a legend for the graph? Is the base case result clearly labeled on the graph? Is the diagram sorted?	The axis title in the Tornado diagram was missing and was added, everything else is appropriate	
Do the high and low values make sense?	All high and low values were checked, and no issues were found. Confidence intervals were used when available and if not upper and lower values were estimated based on standard deviation.	
For custom high/low values, is there data validation to ensure the range makes sense (ensure that the high range can't be lower than the low range; bounded appropriately)	Yes, all proportions were fixed to max 1 as upper value	
PSA		
Do the results of the PSA make sense?	yes	
Are there any problems with the PSA macro?	No	
Check the scatterplot and CEAC graphs - do these make sense based on the base case results?	Yes, the CEA cloud is centered around basecase results and what the CEAC shows is in line with finding of approx. 57% of simulations being falling under WTP	
Check that the average cost and outcomes calculated from PSA array are close to their point estimate values.	No issues found. Mean PSA ICER is slightly lower than basecase results.	
Check distributions (appropriateness of types of distributions - normal, beta, gamma) and low and high estimates (95% CI and SE).	No issues found	

Scenario testing	Outcome	Corrections made
In the event of negative ICERs, was a net monetary benefit analysis included? Do the graph and results make sense?	N/A	

B.3.15 Interpretation and conclusions of economic evidence

A pharmacoeconomic model has been developed in which health-state transitions and associated costs for patients with AChR-Ab+ gMG are compared between efgartigimod as an add-on to standard of care and Established Clinical Management. The model incorporates key clinical data from the ADAPT RCT and ADAPT+, the open-label extension of ADAPT, as well as real-world data derived from the UK population in the MyRealWorld study. The model is also customised to the healthcare setting in England and Wales and several key model parameters were validated by clinical experts.

All results of this analysis concern the IV formulation of efgartigimod. A decision by the MHRA on the application for marketing authorisation of a SC formulation of efgartigimod is expected in [redacted]. At the current stage the price for this formulation has not yet been set. This first needs to be set with the DoH in the context of the VPAS program. If considering the cost effectiveness of the SC formulation, it is expected that the same model with the same effectiveness inputs should be used. The SC formulation will be given at a dose of 1000 mg per week for 4 weeks per cycle, therefore, the only difference would be in the acquisition and administration costs of efgartigimod. The Company expects the SC formulation to have a similar cost-effectiveness as the IV formulation.

Over the lifetime horizon, there was a gain of [redacted] QALYs for patients who received efgartigimod compared with those who received Established Clinical Management. This is partially attributable to gains in HRQoL in the efgartigimod arm as a result of more years spent in the least symptomatic health state (i.e., MG-ADL <5), the higher utility associated with efgartigimod, and the lower mortality associated with a decrease in the corticosteroid dose.

Incorporating the simple PAS with a [redacted], the resulting ICER for efgartigimod compared with Established Clinical Management was £28,066/QALY.

An orphan drug designation (ODD) is expected for efgartigimod in gMG; the application was filed concurrently with the marketing authorisation application, and is expected at the same time as the marketing authorisation is received.

Interpreting the results of this cost-effectiveness analysis should consider the value of a clinically efficacious drug treating a small and well-defined group of rare disease patients with a serious chronic condition that has thus far lacked clinically proven treatment options. Moreover, current management is suboptimal, with clinicians resorting to several off-label products. Therefore, efgartigimod should be viewed as a cost-effective breakthrough to reduce the burden of gMG on patients, caregivers, and society.

B.4 References

1. Gilhus NE. Myasthenia gravis. *N Engl J Med*. 2016;375(26):2570-2581. doi:10.1056/NEJMra1602678
2. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in myasthenia gravis. *BMC Neurol*. 2010;10:46. doi:10.1186/1471-2377-10-46
3. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve*. 2008;37(2):141-149. doi:10.1002/mus.20950
4. Behin A, Le Panse R. New pathways and therapeutic targets in autoimmune myasthenia gravis. *J Neuromuscul Dis*. 2018;5(3):265-277. doi:10.3233/JND-170294
5. Shen C, Lu Y, Zhang B, et al. Antibodies against low-density lipoprotein receptor-related protein 4 induce myasthenia gravis. *J Clin Invest*. 2013;123(12):5190-5202. doi:10.1172/JCI66039
6. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nat Med*. 2001;7(3):365-368. doi:10.1038/85520
7. Juel VC, Massey JM. Myasthenia gravis. *Orphanet J Rare Dis*. 2007;2:44. doi:10.1186/1750-1172-2-44
8. Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Myasthenia gravis - autoantibody characteristics and their implications for therapy. *Nat Rev Neurol*. 2016;12(5):259-268. doi:10.1038/nrneurol.2016.44
9. Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia gravis: epidemiology, pathophysiology and clinical manifestations. *J Clin Med*. 2021;10(11):2235.
10. Cortes-Vicente E, Alvarez-Velasco R, Segovia S, et al. Clinical and therapeutic features of myasthenia gravis in adults based on age at onset. *Neurology*. 2020;94(11):e1171-e1180. doi:10.1212/WNL.0000000000008903
11. Ruiter AM, Verschuuren J, Tannemaat MR. Prevalence and associated factors of fatigue in autoimmune myasthenia gravis. *Neuromuscul Disord*. 2021;31(7):612-621. doi:10.1016/j.nmd.2021.04.002
12. Wendell LC, Levine JM. Myasthenic crisis. *Neurohospitalist*. 2011;1(1):16-22. doi:10.1177/1941875210382918
13. Lee I, Kaminski HJ, Xin H, Cutter G. Gender and quality of life in myasthenia gravis patients from the myasthenia gravis foundation of America registry. *Muscle Nerve*. 2018;58(1):90-98. doi:10.1002/mus.26104
14. Guptill JTMAKASDB, Author A, Department of, et al. Cost analysis of myasthenia gravis from a large U.S insurance database. *Muscle Nerve*. 2011;44(6):907-911. doi:10.1002/mus.22212
15. Guastafierro E, Tramacere I, Toppo C, et al. Employment in Myasthenia Gravis: A Systematic Literature Review and Meta-Analysis. *Neuroepidemiology*. 2020;54(4):304-312. doi:10.1159/000506310

16. Sharma N, Bisen R, Rawat NS, Afaque A, Gupta S. Economic Burden of Myasthenia Gravis in the US: A Literature Review. *Value Health*. 2018;21:S252. doi:10.1016/j.jval.2018.04.1703

17. Harris L, Graham S, MacLachlan S, Exuzides A, Jacob S. A retrospective longitudinal cohort study of the clinical burden in myasthenia gravis. *BMC Neurol*. 2022;22(1):172. doi:10.1186/s12883-022-02692-4

18. Uzawa A, Ozawa Y, Yasuda M, Onishi Y, Akamine H, Kuwabara S. Minimal symptom expression achievement over time in generalized myasthenia gravis. *Acta Neurol Belg*. Published online January 2, 2023. doi:10.1007/s13760-022-02162-1

19. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. *Pr Neurol*. 2015;15(3):199-206. doi:10.1136/practneurol-2015-001126

20. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology*. 2016;87(4):419-425. doi:10.1212/WNL.0000000000002790

21. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021;96(3):114-122. doi:10.1212/WNL.0000000000011124

22. Melzer N, Ruck T, Fuhr P, et al. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. *J Neurol*. 2016;263(8):1473-1494. doi:10.1007/s00415-016-8045-z

23. Jayempi® (azathioprine 10 mg/mL oral suspension) Summary of Product Characteristics. Published 2022. https://www.medicines.org.uk/emc/product/12745

24. Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of myasthenia gravis. *Neurol Clin*. 2018;36(2):311-337. doi:10.1016/j.ncl.2018.01.011

25. Tandan R, Hehir MK 2nd, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: A systematic review. *Muscle Nerve*. 2017;56(2):185-196. doi:10.1002/mus.25597

26. Marino M, Basile U, Spagni G, et al. Long-lasting rituximab-induced reduction of specific-but not total-igg4 in musk-positive myasthenia gravis. *Front Immunol*. 2020;11:613. doi:10.3389/fimmu.2020.00613

27. Nowak RJ, Coffey CS, Goldstein JM, et al. Phase 2 trial of rituximab in acetylcholine receptor antibody-positive generalized myasthenia gravis: The BeatMG Study. *Neurology*. 2022;98(4):e376. doi:10.1212/WNL.0000000000013121

28. Piehl F, Eriksson-Dufva A, Budzianowska A, et al. Efficacy and safety of rituximab for new-onset generalized myasthenia gravis: The RINOMAX randomized clinical trial. *JAMA Neurol*. Published online September 19, 2022:e222887. doi:10.1001/jamaneurol.2022.2887

29. MabThera® (rituximab 100/500 mg concentrate for solution for infusion) Summary of Product Characteristics. Published July 14, 2022.

https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf

30. argenx. Data on file: UK advisory board report.
31. NHS England. Clinical commissioning policy statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults).
32. All Wales Therapeutics and Toxicology Centre. OW12: Rituximab for myasthenia gravis. Accessed December 20, 2022. https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/one-wales-rituximab-for-myasthenia-gravis-ow12/
33. Boldingh MI, Dekker L, Maniaol AH, et al. An up-date on health-related quality of life in myasthenia gravis -results from population based cohorts. *Health Qual Life Outcomes*. 2015;13:115. doi:10.1186/s12955-015-0298-1
34. Twork S, Wiesmeth S, Klewer J, Pohlau D, Kugler J. Quality of life and life circumstances in German myasthenia gravis patients. *Health Qual Life Outcomes*. 2010;8:129. doi:10.1186/1477-7525-8-129
35. Mantegazza R, Bonanno S, Camera G, Antozzi C. Current and emerging therapies for the treatment of myasthenia gravis. *Neuropsychiatr Treat*. 2011;7:151-160. doi:10.2147/NDT.S8915
36. Cutter G, Xin H, Aban I, et al. Cross-sectional analysis of the Myasthenia Gravis Patient Registry: disability and treatment. *Muscle Nerve*. 2019;60(6):707-715. doi:10.1002/mus.26695
37. Szczudlik P, Sobieszczuk E, Szyluk B, Lipowska M, Kubiszewska J, Kostera-Pruszczyk A. Determinants of quality of life in myasthenia gravis patients. *Front Neurol*. 2020;11(1094):553626. doi:10.3389/fneur.2020.553626
38. Hart IK, Sathasivam S, Sharshar T. Immunosuppressive agents for myasthenia gravis. *Cochrane Database Syst Rev*. 2007;(4):CD005224. doi:10.1002/14651858.CD005224.pub2
39. Jakubikova M, Tyblova M, Tesar A, et al. Predictive factors for a severe course of COVID-19 infection in myasthenia gravis patients with an overall impact on myasthenic outcome status and survival. *Eur J Neurol*. 2021;28(10):3418-3425. doi:10.1111/ene.14951
40. Skeie GO, Apostolski S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol*. 2010;17(7):893-902. doi:10.1111/j.1468-1331.2010.03019.x
41. Lehnerer S, Jacobi J, Schilling R, et al. Burden of disease in myasthenia gravis: taking the patient's perspective. *J Neurol*. 2022;269(6):3050-3063. doi:10.1007/s00415-021-10891-1
42. Howard JF Jr, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2021;20(7):526-536. doi:10.1016/S1474-4422(21)00159-9
43. Gable KL, Guptill JT. Antagonism of the neonatal Fc receptor as an emerging treatment for myasthenia gravis. *Front Immunol*. 2020;10:3052. doi:10.3389/fimmu.2019.03052

44. Ulrichts P, Guglietta A, Dreier T, et al. Neonatal Fc receptor antagonist efgartigimod safely and sustainably reduces IgGs in humans. *J Clin Invest*. 2018;128(10):4372-4386. doi:10.1172/JCI97911

45. Howard J, Bril V, Vu T, et al. Long-term Safety, Tolerability, and Efficacy of Efgartigimod in Patients With Generalized Myasthenia Gravis: Interim Results of the ADAPT+ Study (S25.004). *Neurology*. 2022;98(18 Supplement). Accessed January 19, 2023. https://n.neurology.org/content/98/18_Supplement/2770

46. argenx. argenx Announces Positive Topline Phase 3 Data from ADAPT-SC Study Evaluating Subcutaneous Efgartigimod for Generalized Myasthenia Gravis. businesswire. Published March 22, 2022. Accessed February 7, 2023. https://www.businesswire.com/news/home/20220321005941/en/

47. Early access to medicines scheme (EAMS): scientific opinions. GOV.UK. Published May 27, 2022. Accessed January 26, 2023. https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions

48. argenx Announces the UK MHRA has Granted Early Access to Efgartigimod for Generalized Myasthenia Gravis. Argenx. Accessed January 26, 2023. https://www.argenx.com/news/argenx-announces-uk-mhra-has-granted-early-access-efgartigimod-generalized-myasthenia-gravis

49. Sesarman A, Vidarsson G, Sitaru C. The neonatal Fc receptor as therapeutic target in IgG-mediated autoimmune diseases. *Cell Mol Life Sci*. 2010;67(15):2533-2550. doi:10.1007/s00018-010-0318-6

50. Vyvgart™ (efgartigimod alfa 20 mg/mL concentrate for solution for infusion) Summary of Product Characteristics. Published September 26, 2022. https://www.ema.europa.eu/en/documents/product-information/vyvgart-epar-product-information_en.pdf

51. Takahashi M, Howard JF Jr, Bril V, et al. Efgartigimod demonstrates consistent improvements in myasthenia gravis across patient populations. In: *Japanese Society of Neurology Annual Meeting*. ; 2022.

52. European Medicines Agency (EMA). Vyvgart (efgartigimod alfa): An overview of Vyvgart and why it is authorised in the EU. Published August 2022. https://www.ema.europa.eu/documents/overview/vyvgart-epar-medicine-overview_en.pdf

53. Habib A. The therapeutic potential for FcRn blockade in myasthenia gravis - antibodies and antibody clearance. *Neurol Rev*. 2020;Suppl:34-36.

54. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM. Myasthenia gravis. *Nat Rev Dis Primer*. 2019;5(1):1-19. doi:10.1038/s41572-019-0079-y

55. Koneczny I, Herbst R. Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture. *Cells*. 2019;8(7):671. doi:10.3390/cells8070671

56. Drachman DB, Adams RN, Josifek LF, Self SG. Functional activities of autoantibodies to acetylcholine receptors and the clinical severity of myasthenia gravis. *N Engl J Med*. 1982;307(13):769-775. doi:10.1056/NEJM198209233071301

57. Drachman DB, Angus CW, Adams RN, Michelson JD, Hoffman GJ. Myasthenic antibodies cross-link acetylcholine receptors to accelerate degradation. *N Engl J Med*. 1978;298(20):1116-1122. doi:10.1056/NEJM197805182982004

58. Cole RN, Ghazanfari N, Ngo ST, Gervásio OL, Reddel SW, Phillips WD. Patient autoantibodies deplete postsynaptic muscle-specific kinase leading to disassembly of the ACh receptor scaffold and myasthenia gravis in mice. *J Physiol*. 2010;588(Pt 17):3217-3229. doi:10.1113/jphysiol.2010.190298

59. Engel AG, Arahata K. The membrane attack complex of complement at the endplate in myasthenia gravis. *Ann N Y Acad Sci*. 1987;505:326-332. doi:10.1111/j.1749-6632.1987.tb51301.x

60. Ward ES, Zhou J, Ghetie V, Ober RJ. Evidence to support the cellular mechanism involved in serum IgG homeostasis in humans. *Int Immunol*. 2003;15(2):187-195. doi:10.1093/intimm/dxg018

61. Ghetie V, Hubbard JG, Kim JK, Tsen MF, Lee Y, Ward ES. Abnormally short serum half-lives of IgG in β2-microglobulin-deficient mice. *Eur J Immunol*. 1996;26(3):690-696. doi:10.1002/eji.1830260327

62. Bubuioc AM, Kudebayeva A, Turuspekova S, Lisnic V, Leone MA. The epidemiology of myasthenia gravis. *J Med Life*. 2021;14(1):7-16.

63. Hehir MK, Silvestri NJ. Generalized myasthenia gravis: classification, clinical presentation, natural history, and epidemiology. *Neurol Clin*. 2018;36(2):253-260. doi:10.1016/j.ncl.2018.01.002

64. Mané-Damas M, Molenaar PC, Ulrichts P, et al. Novel treatment strategies for acetylcholine receptor antibody-positive myasthenia gravis and related disorders. *Autoimmun Rev*. 2022;21(7):103104. doi:10.1016/j.autrev.2022.103104

65. Gelinas D, Parvin-Nejad S, Phillips G, et al. The humanistic burden of myasthenia gravis: A systematic literature review. *J Neurol Sci*. 2022;437:120268. doi:10.1016/j.jns.2022.120268

66. Ruiter AM, Verschuuren JJGM, Tannemaat MR. Fatigue in patients with myasthenia gravis. A systematic review of the literature. *Neuromuscul Disord*. 2020;30(8):631-639. doi:10.1016/j.nmd.2020.06.010

67. Jacob S. Myasthenia Gravis – A Review of Current Therapeutic Options. *Eur Neurol Rev*. 2018;13(2):86-92.

68. National Institute of Neurological Disorders or Stroke. Myasthenia Gravis Fact Sheet. Accessed December 19, 2022. https://www.ninds.nih.gov/myasthenia-gravis-fact-sheet

69. Priola AM, Priola SM. Imaging of thymus in myasthenia gravis: from thymic hyperplasia to thymic tumor. *Clin Radiol*. 2014;69(5):e230-245. doi:10.1016/j.crad.2014.01.005

70. Jaretzki A, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology*. 2000;55(1):16-23. doi:10.1212/wnl.55.1.16

71. Burns TM, Sadjadi R, Utsugisawa K, et al. International clinimetric evaluation of the MG-QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r. *Muscle Nerve*. 2016;54(6):1015-1022. doi:10.1002/mus.25198

72. Muppidi S, Silvestri NJ, Tan R, Riggs K, Leighton T, Phillips GA. Utilization of MG-ADL in myasthenia gravis clinical research and care. *Muscle Nerve*. 2022;65(6):630-639. doi:10.1002/mus.27476

73. Dewilde S, Kousoulakou H, Janssen M, et al. Digital data collection to measure the impact of myasthenia gravis on patients' quality of life in the real world: report at baseline [Presented at the Virtual International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2021 conference, 30 November - 3 December 2021]. *Value Health*. 2022;25(1 Suppl):S246.

74. Thomsen JLS, Andersen H. Outcome measures in clinical trials of patients with myasthenia gravis. *Front Neurol*. 2020;11:596382. doi:10.3389/fneur.2020.596382

75. Barnett C, Herbelin L, Dimachkie MM, Barohn RJ. Measuring clinical treatment response in myasthenia gravis. *Neurol Clin*. 2018;36(2):339-353. doi:10.1016/j.ncl.2018.01.006

76. Carey IM, Banchoff E, Nirmalananthan N, et al. Prevalence and incidence of neuromuscular conditions in the UK between 2000 and 2019: A retrospective study using primary care data. *PLoS One*. 2021;16(12):e0261983. doi:10.1371/journal.pone.0261983

77. National Institute for Health and Care Excellence. Final scope: Efgartigimod for treating generalised myasthenia gravis. Accessed December 20, 2022. https://www.nice.org.uk/guidance/indevelopment/gid-ta10986/documents

78. Petersson M, Feresiadou A, Jons D, et al. Patient-reported symptom severity in a nationwide myasthenia gravis cohort: cross-sectional analysis of the Swedish GEMG study. *Neurology*. 2021;97(14):e1382-e1391. doi:10.1212/WNL.0000000000012604

79. Muley S, Gelinas D, Sani JM, Ruzhansky K. Patient burden of generalized myasthenia gravis. In: ; 2021.

80. Saccà F, Dewilde S, Nivelle E, et al. Combining RCT and real-world data to model the benefit of efgartigimod on productivity losses. Presented at 17th International Congress on Neuromuscular Diseases. *J Neuromuscul Dis*. 2022;9(Supplement 1):S108-S109.

81. Andersen LK, Jakobsson AS, Revsbech KL, Vissing J. Causes of symptom dissatisfaction in patients with generalized myasthenia gravis. *J Neurol*. 2022;269(6):3086-3093. doi:10.1007/s00415-021-10902-1

82. Law C, Flaherty CV, Bandyopadhyay S. A Review of Psychiatric Comorbidity in Myasthenia Gravis. *Cureus*. 2020;12(7):e9184. doi:10.7759/cureus.9184

83. Zhou X, Cao S, Hou J, Gui T, Zhu F, Xue Q. Association between myasthenia gravis and cognitive disorders: a PRISMA-compliant meta-analysis. *Int J Neurosci*. 2022;0(0):1-12. doi:10.1080/00207454.2022.2031183

84. Zaninotto P, Batty GD, Allerhand M, Deary IJ. Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. *J Epidemiol Community Health*. 2018;72(8):685-694. doi:10.1136/jech-2017-210116

85. Neumann B, Angstwurm K, Mergenthaler P, et al. Myasthenic crisis demanding mechanical ventilation: a multicenter analysis of 250 cases. *Neurology*. 2020;94(3):e299-e313. doi:10.1212/WNL.0000000000008688

86. Hansen JS, Danielsen DH, Somnier FE, et al. Mortality in myasthenia gravis: A nationwide population-based follow-up study in Denmark. *Muscle Nerve*. 2016;53(1):73-77. doi:10.1002/mus.24697

87. Westerberg E, Punga AR. Mortality rates and causes of death in Swedish Myasthenia Gravis patients. *Neuromuscul Disord NMD*. 2020;30(10):815-824. doi:10.1016/j.nmd.2020.08.355

88. Mebrahtu TF, Morgan AW, Keeley A, Baxter PD, Stewart PM, Pujades-Rodriguez M. Dose dependency of iatrogenic glucocorticoid excess and adrenal insufficiency and mortality: a cohort study in England. *J Clin Endocrinol Metab*. 2019;104(9):3757-3767. doi:10.1210/jc.2019-00153

89. Law N, Davio K, Blunck M, Lobban D, Seddik K. The Lived Experience of Myasthenia Gravis: A Patient-Led Analysis. *Neurol Ther*. 2021;10(2):1103-1125. doi:10.1007/s40120-021-00285-w

90. Piponniau L, Kittleson M, Patel J, et al. Mycophenolate not azathioprine is associated with increased risk for skin cancer after heart transplant. *J Heart Lung Transpl*. 2013;32(4, Supplement):S199. doi:10.1016/j.healun.2013.01.490

91. Gallagher MP, Kelly PJ, Jardine M, et al. Long-term cancer risk of immunosuppressive regimens after kidney transplantation. *J Am Soc Nephrol*. 2010;21(5):852-858. doi:10.1681/asn.2009101043

92. Kassardjian CD, Widdifield J, Paterson JM, et al. Serious infections in patients with myasthenia gravis: population-based cohort study. *Eur J Neurol*. 2020;27(4):702-708. doi:10.1111/ene.14153

93. Bozovic I, Ilic Zivojinovic J, Peric S, et al. Long-term outcome in patients with myasthenia gravis: one decade longitudinal study. *J Neurol*. 2022;269(4):2039-2045. doi:10.1007/s00415-021-10759-4

94. Blum S, Lee D, Gillis D, McEniery DF, Reddel S, McCombe P. Clinical features and impact of myasthenia gravis disease in Australian patients. *J Clin Neurosci Off J Neurosurg Soc Australas*. 2015;22(7):1164-1169. doi:10.1016/j.jocn.2015.01.022

95. Dewilde S, Philips G, Paci S. Patient -reported burden of Myasthenia Gravis: Baseline results of the International Prospective, Observational, Longitudinal Real-World Digital Study MyRealWorld-MG. *BMJ Open Print*.

96. Zhou T, Guan H, Wang L, Zhang Y, Rui M, Ma A. Health-related quality of life in patients with different diseases measured with the EQ-5D-5L: a systematic review. *Front Public Health*. 2021;9:675523. doi:10.3389/fpubh.2021.675523

97. Muppidi S. The myasthenia gravis--specific activities of daily living profile. *Ann N Y Acad Sci*. 2012;1274:114-119. doi:10.1111/j.1749-6632.2012.06817.x

98. Frost ASMLRJSCMNCVLT, Author A, The N, et al. Labour market participation and sick leave among patients diagnosed with myasthenia gravis in Denmark 1997-2011: A Danish nationwide cohort study. *BMC Neurol*. 2016;16:1 Article Number: 224. doi:10.1186/s12883-016-0757-2

99. Landfeldt E, Pogoryelova O, Sejersen T, Zethraeus N, Breiner A, Lochmüller H. Economic Costs of Myasthenia Gravis: A Systematic Review. *PharmacoEconomics*. 2020;38(7):715-728. doi:10.1007/s40273-020-00912-8

100. Tomaras D, Marshall S, Forsythe A. PND100 THE HUMANISTIC AND ECONOMIC BURDEN OF MYASTHENIA GRAVIS (MG) - A DEBILITATING & COSTLY DISEASE. *Value Health*. 2020;23:S279. doi:10.1016/j.jval.2020.04.992

101. Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. *Neurology*. 2009;72(18):1548-1554. doi:10.1212/WNL.0b013e3181a41211

102. Souayah N, Nasar A, Suri MFK, Kirmani JF, Ezzeddine MA, Qureshi AI. Trends in Outcomes and Hospitalization Charges among Mechanically Ventilated Patients with Myasthenia Gravis in the United States. *Int J Biomed Sci IJBS*. 2009;5(3):209-214.

103. Mandawat A, Kaminski HJ, Cutter G, Katirji B, Alshekhlee A. Comparative analysis of therapeutic options used for myasthenia gravis. *Ann Neurol*. 2010;68(6):797-805. doi:10.1002/ana.22139

104. Omorodion JO, Pines JM, Kaminski HJ. Inpatient cost analysis for treatment of myasthenia gravis. *Muscle Nerve*. 2017;56(6):1114-1118. doi:10.1002/mus.25624

105. Tiamkao S, Pranboon S, Thepsuthammarat K, Sawanyawisuth K. Prevalence of factors associated with poor outcomes of hospitalized myasthenia gravis patients in Thailand. *Neurosci Riyadh Saudi Arab*. 2014;19(4):286-290.

106. Furlan JC, Barth D, Barnett C, Bril V. Cost-minimization analysis comparing intravenous immunoglobulin with plasma exchange in the management of patients with myasthenia gravis. *Muscle Nerve*. 2016;53(6):872-876. doi:10.1002/mus.24960

107. Heatwole C, Johnson N, Holloway R, Noyes K. Plasma Exchange versus Intravenous Immunoglobulin for Myasthenia Gravis Crisis: An Acute Hospital Cost Comparison Study. *J Clin Neuromuscul Dis*. 2011;13(2):85. doi:10.1097/CND.0b013e31822c34dd

108. Harris L, Aban IB, Xin H, Cutter G. Employment in refractory myasthenia gravis: A Myasthenia Gravis Foundation of America Registry analysis. *Muscle Nerve*. 2019;60(6):700-706. doi:10.1002/mus.26694

109. National Institute for Health and Care Excellence. Ravulizumab for treating generalised myasthenia gravis. Accessed November 29, 2022. https://www.nice.org.uk/guidance/indevelopment/gid-ta10987

110. efgartigimod alfa (Vyvgart). Scottish Medicines Consortium. Accessed December 9, 2022. https://www.scottishmedicines.org.uk/medicines-advice/efgartigimod-alfa-vyvgart-full-smc2561/

111. NHS England. Updated Commissioning Guidance for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England December 2018. Published December 2018. https://www.england.nhs.uk/wp-content/uploads/2019/03/PSS9-Immunoglobulin-Commissioning-Guidance-CQUIN-1920.pdf

112. National Institute for Health and Care Excellence. Suspected neurological conditions: recognition and referral (NG127). Accessed December 2, 2022. https://www.nice.org.uk/guidance/ng127

113. National Institute for Health and Care Excellence. Suspected neurological conditions: recognition and referral (QS198). Accessed December 3, 2022. https://www.nice.org.uk/guidance/qs198

114. National Institute for Health and Care Excellence. Eculizumab for treating refractory myasthenia gravis (terminated appraisal). Accessed November 29, 2022. https://www.nice.org.uk/guidance/ta636

115. eculizumab (Soliris). Scottish Medicines Consortium. Accessed December 9, 2022. https://www.scottishmedicines.org.uk/medicines-advice/eculizumab-soliris-nonsub-smc-2236/

116. Farrugia ME, Goodfellow JA. A practical approach to managing patients with myasthenia gravis—opinions and a review of the literature. *Front Neurol*. 2020;11:604. doi:10.3389/fneur.2020.00604

117. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. The Association of British Neurologists' myasthenia gravis guidelines. *Ann N Y Acad Sci*. 2018;1412(1):166-169. doi:10.1111/nyas.13503

118. Soliris® (eculizumab 300 mg concentrate for solution for infusion) Summary of Product Characteristics. Published 2022. https://www.medicines.org.uk/emc/product/362

119. Mestinon® (pyridostigmine bromide 60 mg tablets) Summary of Product Characteristics. Published 2018. https://www.medicines.org.uk/emc/product/962/smpc

120. Neostigmine methylsulfate (injection BP 2.5 mg in 1 mL) Summary of Product Characteristics. Published 2021. https://www.medicines.org.uk/emc/product/6268/smpc

121. Alhaidar MK, Abumurad S, Soliven B, Rezania K. Current Treatment of Myasthenia Gravis. *J Clin Med*. 2022;11(6):1597. doi:10.3390/jcm11061597

122. Maggi L, Mantegazza R. Treatment of myasthenia gravis: focus on pyridostigmine. *Clin Drug Investig*. 2011;31(10):691-701. doi:10.2165/11593300-000000000-00000

123. Howard JF Jr. Myasthenia gravis: the role of complement at the neuromuscular junction. *Ann N Acad Sci*. 2018;1412(1):113-128. doi:10.1111/nyas.13522

124. Mehndiratta MM, Pandey S, Kuntzer T. Acetylcholinesterase inhibitor treatment for myasthenia gravis. *Cochrane Database Syst Rev*. 2014;(10):CD006986. doi:10.1002/14651858.CD006986.pub3

125. Harris L, Graham S, MacLachlan S, Exuzides A, Jacob S. Healthcare resource utilization by patients with treatment-refractory myasthenia gravis in England. *J Med Econ*. 2019;22(7):691-697. doi:10.1080/13696998.2019.1592180

126. Aydin Y, Ulas AB, Mutlu V, Colak A, Eroglu A. Thymectomy in Myasthenia Gravis. *Eurasian J Med*. 2017;49(1):48-52. doi:10.5152/eurasianjmed.2017.17009

127. Schneider-Gold C, Gajdos P, Toyka KV, Hohlfeld RR. Corticosteroids for myasthenia gravis. *Cochrane Database Syst Rev*. 2005;(2):CD002828. doi:10.1002/14651858.CD002828.pub2

128. Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. *Ther Adv Neurol Disord*. 2019;12:1756286419832242. doi:10.1177/1756286419832242

129. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. *Ann Neurol*. 1984;15(3):291-298. doi:10.1002/ana.410150316

130. Gajdos P, Elkharrat D, Chevret S, et al. A randomised clinical trial comparing prednisone and azathioprine in myasthenia gravis. Results of the second interim analysis. Myasthenia Gravis Clinical Study Group. *J Neurol Neurosurg Psychiatry*. 1993;56(11):1157-1163. doi:10.1136/jnnp.56.11.1157

131. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9(1):30. doi:10.1186/1710-1492-9-30

132. Reddel SW, Morsch M, Phillips WD. Clinical and scientific aspects of muscle-specific tyrosine kinase-related myasthenia gravis. *Curr Opin Neurol*. 2014;27(5):558-565. doi:10.1097/WCO.0000000000000136

133. Frangiamore R, Antozzi C, Rinaldi E, et al. Anti-FcRn treatment for generalized myasthenia gravis: A real world experience with efgartigimod. In: ; 2022.

134. Oh TK, Song IA. Trends in long-term glucocorticoid use and risk of 5-year mortality: a historical cohort study in South Korea. *Endocrine*. 2020;69(3):634-641. doi:10.1007/s12020-020-02382-6

135. del Rincon I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheumatol*. 2014;66(2):264-272. doi:10.1002/art.38210

136. Movahedi M, Costello R, Lunt M, Pye SR, Sergeant JC, Dixon WG. Oral glucocorticoid therapy and all-cause and cause-specific mortality in patients with rheumatoid arthritis: a retrospective cohort study. *Eur J Epidemiol*. 2016;31(10):1045-1055. doi:10.1007/s10654-016-0167-1

137. Lee H, Ryu J, Nam E, et al. Increased mortality in patients with corticosteroid-dependent asthma: a nationwide population-based study. *Eur Respir J*. 2019;54(5):1900804. doi:10.1183/13993003.00804-2019

138. Chester Wasko M, Dasgupta A, Ilse Sears G, Fries JF, Ward MM. Prednisone Use and Risk of Mortality in Patients With Rheumatoid Arthritis: Moderation by

Use of Disease-Modifying Antirheumatic Drugs. *Arthritis Care Res Hoboken*. 2016;68(5):706-710. doi:10.1002/acr.22722

139. Sathasivam S. Steroids and immunosuppressant drugs in myasthenia gravis. *Nat Clin Pr Neurol*. 2008;4(6):317-327. doi:10.1038/ncpneuro0810

140. Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. *Neurology*. 1998;50(6):1778-1783. doi:10.1212/wnl.50.6.1778

141. Pasnoor M, He J, Herbelin L, et al. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. *Neurology*. 2016;87(1):57-64. doi:10.1212/WNL.0000000000002795

142. Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. *Neurology*. 2008;71(6):400-406. doi:10.1212/01.wnl.0000312374.95186.cc

143. Tindall RS, Phillips JT, Rollins JA, Wells L, Hall K. A clinical therapeutic trial of cyclosporine in myasthenia gravis. *Ann N Acad Sci*. 1993;681:539-551. doi:10.1111/j.1749-6632.1993.tb22937.x

144. Yoshikawa H, Kiuchi T, Saida T, Takamori M. Randomised, double-blind, placebo-controlled study of tacrolimus in myasthenia gravis. *J Neurol Neurosurg Psychiatry*. 2011;82(9):970-977. doi:10.1136/jnnp-2011-300148

145. European Medicines Agency. Orphan Maintenance Assessment Report : Vyvgart (efgartigimod). Published online August 10, 2022. https://www.ema.europa.eu/en/documents/orphan-maintenance-report/vyvgart-epar-orphan-maintenance-assessment-report_en.pdf

146. Gajdos PCSTK, Author A, Raymond Poincaré Hospital APHP c o, et al. Intravenous immunoglobulin for myasthenia gravis. *Cochrane Database Syst Rev*. (2006)(2):CD002277.

147. Alcantara M, Sarpong E, Barnett C, Katzberg H, Bril V. Chronic immunoglobulin maintenance therapy in myasthenia gravis. *Eur J Neurol*. 2021;28(2):639-646. doi:10.1111/ene.14547

148. Wolfe GI, Barohn RJ, Foster BM, et al. Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis. *Muscle Nerve*. 2002;26(4):549-552. doi:10.1002/mus.10224

149. Rønager J, Ravnborg M, Hermansen I, Vorstrup S. Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. *Artif Organs*. 2001;25(12):967-973. doi:10.1046/j.1525-1594.2001.06717.x

150. Myasthenia Gravis Foundation of America. Brochures - Learn More About MG: Intravenous immunoglobulin. Published 2021. https://myasthenia.org/What-is-MG/MG-Materials-Webinars/Brochures-Learn-More-About-MG

151. Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. *Front Immunol*. 2018;9:1299. doi:10.3389/fimmu.2018.01299

152. Privigen® immune globulin intravenous (human), 10% liquid, highlights of Prescribing Information. Published March 2019.

http://cslbehring.vo.llnwd.net/o33/u/central/PI/US/Privigen/EN/Privigen-Prescribing-Information.pdf

153. Gajdos PCSTK, Author A, Intensive Care Unit RP, et al. Plasma exchange for myasthenia gravis. *Cochrane Database Syst Rev*. (2002)(4):CD002275.

154. Ipe TS, Davis AR, Raval JS. Therapeutic plasma exchange in myasthenia gravis: a systematic literature review and meta-analysis of comparative evidence. *Front Neurol*. 2021;12:662856. doi:10.3389/fneur.2021.662856

155. Kumar R, Birinder SP, Gupta S, Singh G, Kaur A. Therapeutic plasma exchange in the treatment of myasthenia gravis. *Indian J Crit Care Med*. 2015;19(1):9-13. doi:10.4103/0972-5229.148631

156. Myasthenia Gravis Foundation of America. Brochures - Learn More About MG: Therapeutic Plasma Exchange (TPE). Published 2021. https://myasthenia.org/What-is-MG/MG-Materials-Webinars/Brochures-Learn-More-About-MG

157. Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. *Ther Adv Neurol Disord*. 2018;11:1756285617749134. doi:10.1177/1756285617749134

158. Calabrese CM, Kirchner E, Husni EM, et al. Breakthrough SARS-CoV-2 infections in immune mediated disease patients undergoing B cell depleting therapy: A retrospective cohort analysis. *Arthritis Rheumatol Hoboken Nj*. Published online July 6, 2022:10.1002/art.42287. doi:10.1002/art.42287

159. Phillips GA, Li Y, Abreu C, et al. PND27 Cost-of-illness for adults with generalized myasthenia gravis in the US [Presented at the Virtual International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2021 conference, 17–20 May 2021]. *Value Health*. 2021;24(Suppl 1):S163. doi:10.1016/j.jval.2021.04.811

160. Suh J, Goldstein JM, Nowak RJ. Clinical Characteristics of Refractory Myasthenia Gravis Patients. *Yale J Biol Med*. 2013;86(2):255-260.

161. Gilhus NE. Eculizumab: a treatment option for myasthenia gravis? *Lancet Neurol*. 2017;16(12):947-948. doi:10.1016/S1474-4422(17)30363-0

162. Silvestri NJ, Wolfe GI. Treatment-refractory myasthenia gravis. *J Clin Neuromuscul Dis*. 2014;15(4):167-178. doi:10.1097/CND.0000000000000034

163. argenx. Efgartigimod (ARGX-113-1705) Clinical Study Report (Interim Analysis 4): A Long-term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Study of ARGX 113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT+). Published online 2022:1-165.

164. Howard JF Jr, Bril V, Vu T, et al. #108: Long-term safety, tolerability, and efficacy of efgartigimod in patients with generalized myasthenia gravis. In: *Poster Presented at the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting, Nashville, TN, USA*. Vol 21-24 September. ; 2022.

165. Saccà F, Barnett C, Vu T, et al. Efgartigimod improved health-related quality of life in generalized myasthenia gravis: results from a randomized, double-blind,

placebo-controlled, phase 3 study (ADAPT). *J Neurol*. Published online January 4, 2023. doi:10.1007/s00415-022-11517-w

166. Meisel A, Bril V, Vu T, kar, Peric S. Long-term safety and efficacy of efgartigimod in patients with generalised myasthenia gravis. *Eur J Neurol*. 2022;29, Suppl 1(62):OPR-021.

167. argenx. Efgartigimod (ARGX-113-2001) Clinical Study Report: A Phase 3, Randomized, Open-label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of Efgartigimod PH20 SC With Multiple Intravenous Infusions of Efgartigimod in Patients With Generalized Myasthenia Gravis (ADAPTSC). Published online 2022:1-122.

168. ClinicalTrials.gov. *Evaluating the Pharmacodynamic Noninferiority of Efgartigimod PH20 SC Administered Subcutaneously as Compared to Efgartigimod Administered Intravenously in Patients With Generalized Myasthenia Gravis (ADAPTsc)*.; 2022. Accessed December 12, 2022. https://clinicaltrials.gov/ct2/show/NCT04735432?term=adaptsc&cond=Myasthenia+Gravis&draw=2&rank=1

169. argenx. Efgartigimod (ARGX-113-1704) Clinical Study Report: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT). Published online 2020:1-171.

170. argenx. Efgartigimod (ARGX-113-1705) Clinical Study Report (Interim Analysis 3): A Long-term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Study of ARGX 113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT+). Published online 2021:1-146.

171. ClinicalTrials.gov. *A Safety and Tolerability Study of ARGX-113 in Patients With Myasthenia Gravis Who Have Generalized Muscle Weakness. (ADAPT+)*.; 2022. Accessed December 12, 2022. https://clinicaltrials.gov/ct2/show/NCT03770403?term=adapt%2B&draw=2&rank=2

172. argenx. *Efgartigimod (ARGX-113-1704) Clinical Study Report: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT)*.; 2020.

173. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. Published January 2009. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf

174. Muppidi S, Wolfe GI, Conaway M, Burns TM, MG Composite and MG-QOL15 Study Group. MG-ADL: still a relevant outcome measure. *Muscle Nerve*. 2011;44(5):727-731. doi:10.1002/mus.22140

175. Katzberg HD, Barnett C, Merkies IS, Bril V. Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial. *Muscle Nerve*. 2014;49(5):661-665. doi:10.1002/mus.23988

176. Burns TM, Conaway M, Sanders DB, Composite MG, MG-QOL15 Study Group. The MG Composite: a valid and reliable outcome measure for myasthenia gravis. *Neurology*. 2010;74(18):1434-1440. doi:10.1212/WNL.0b013e3181dc1b1e

177. Burns TM, Grouse CK, Wolfe GI, Conaway MR, Sanders DB. The MG-QOL15 for following the health-related quality of life of patients with myasthenia gravis. *Muscle Nerve*. 2011;43(1):14-18. doi:10.1002/mus.21883

178. Diez Porras L, Homedes C, Alberti MA, Velez Santamaria V, Casasnovas C. Quality of life in myasthenia gravis and correlation of MG-QOL15 with other functional scales. *J Clin Med*. 2022;11(8):2189. doi:10.3390/jcm11082189

179. European Medicines Agency (EMA). Vyvgart: summary of product characteristics. Published online 2022. https://www.ema.europa.eu/en/documents/product-information/vyvgart-epar-product-information_en.pdf

180. argenx. *Data on File: Area under the Curve Efficacy Analyses (ADAPT Study)*.

181. Tice JATDRLPWAFNDPSD, Author A, Division of General Internal M, et al. The effectiveness and value of eculizumab and efgartigimod for generalized myasthenia gravis. *J Manag Care Spec Pharm*. 1AD;28(1):119-124. doi:10.18553/JMCP.2022.28.1.119

182. DeWilde S, Qiu Z, Janssen M, et al. The association between QMG Scores and Health-related Quality of Life in Myasthenia Gravis Patients. In: *International Congress on Neuromuscular Diseases (ICNMD) | July 05–09, 2022 | Brussels, Belgium*. ; 2022.

183. Argenx. ICER Draft Evidence Report Letter Final 8-18-21 [included in submission reference pack].

184. argenx. MyRealWorld® MG: an international, prospective,observational,digital study of the impact of myasthenia gravis in the real world - Statistical Analyses Plan v3.0. Published online 2020.

185. Liu F, Wang Q, Chen X. Myasthenic crisis treated in a Chinese neurological intensive care unit: clinical features, mortality, outcomes, and predictors of survival. *BMC Neurol*. 2019;19(1):172. doi:10.1186/s12883-019-1384-5

186. Liu C, Wang Q, Qiu Z, et al. Analysis of mortality and related factors in 2195 adult myasthenia gravis patients in a 10-year follow-up study. *Neurol India*. 2017;65(3):518-524. doi:10.4103/neuroindia.NI_804_16

187. Spillane J, Hirsch NP, Kullmann DM, Taylor C, Howard RS. Myasthenia gravis--treatment of acute severe exacerbations in the intensive care unit results in a favourable long-term prognosis. *Eur J Neurol*. 2014;21(1):171-173. doi:10.1111/ene.12115

188. Soleimani A, Moayyeri A, Akhondzadeh S, Sadatsafavi M, Tavakoli Shalmani H, Soltanzadeh A. Frequency of myasthenic crisis in relation to thymectomy in generalized myasthenia gravis: a 17-year experience. *BMC Neurol*. 2004;4:12. doi:10.1186/1471-2377-4-12

189. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. Published January 31, 2022. Accessed December 13,

2022. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

190. Ramos-Fransi A, Rojas-García R, Segovia S, et al. Myasthenia gravis: descriptive analysis of life-threatening events in a recent nationwide registry. *Eur J Neurol*. 2015;22(7):1056-1061. doi:10.1111/ene.12703

191. Rath J, Brunner I, Tomschik M, et al. Frequency and clinical features of treatment-refractory myasthenia gravis. *J Neurol*. 2020;267(4):1004-1011. doi:10.1007/s00415-019-09667-5

192. Office for National Statistics. National life tables, United Kingdom, period expectation of life, based on data for the years 2018-2020. Published September 23, 2021. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/previousReleases

193. Duarte AA, De Francesco M, Iannazzo S. Systematic literature review of the survival, humanistic and economic impact of systemic corticosteroid use [Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2022 conference, Vienna, Austria, 6-9 November 2022]. *Value Health*. 2022;In press.

194. Wilson JC, Sarsour K, Collinson N, et al. Serious adverse effects associated with glucocorticoid therapy in patients with giant cell arteritis (GCA): A nested case-control analysis. *Semin Arthritis Rheum*. 2017;46(6):819-827. doi:10.1016/j.semarthrit.2016.11.006

195. Systematic Literature Review of the Survival, Humanistic and Economic Impact of Systemic Corticosteroid Use. ISPOR | International Society For Pharmacoeconomics and Outcomes Research. Accessed February 9, 2023. https://www.ispor.org/heor-resources/presentations-database/presentation/euro2022-3565/120390

196. Hernandez Alava M, Wailoo A, Grimm S, et al. EQ-5D-5L versus EQ-5D-3L: the impact on cost effectiveness in the United Kingdom. *Value Health*. 2018;21(1):49-56. doi:10.1016/j.jval.2017.09.004

197. Hernandez Alava M, Wailoo A, Pudney S, Gray L, Manca A. Mapping clinical outcomes to generic preference-based outcome measures: development and comparison of methods. *Health Technol Assess*. 2020;24(34):1-68. doi:10.3310/hta24340

198. Dewilde S, Qi C, Philips G, Iannazzo S, Janssen MF. Association Between Myasthenia Gravis-Activities of Daily Living (MG-ADL) and EQ-5D-5L Utility Values: The Additional Effect of Efgartigimod on Utilities. *Adv Ther*. Published online accepted 2023.

199. Berrih-Aknin S, Claeys KG, Law N, et al. Patient-reportedimpact of myasthenia gravis in the real world: protocol for a digital observational study (MyRealWorld MG). *BMJ Open*. 2021;11(7):e048198. doi:10.1136/bmjopen-2020-048198

200. Gummi RR, Kukulka NA, Deroche CB, Govindarajan R. Factors associated with acute exacerbations of myasthenia gravis. *Muscle Nerve*. 2019;60(6):693-699. doi:10.1002/mus.26689

201. Sakaguchi H, Yamashita S, Hirano T, et al. Myasthenic crisis patients who require intensive care unit management. *Muscle Nerve*. 2012;46(3):440-442. doi:10.1002/mus.23445

202. Van Wilder L, Rammant E, Clays E, Devleesschauwer B, Pauwels N, De Smedt D. A comprehensive catalogue of EQ-5D scores in chronic disease: results of a systematic review. *Qual Life Res*. 2019;28(12):3153-3161. doi:10.1007/s11136-019-02300-y

203. Imai T, Utsugisawa K, Murai H, et al. Oral corticosteroid dosing regimen and long-term prognosis in generalised myasthenia gravis: a multicentre cross-sectional study in Japan. *J Neurol Neurosurg Psychiatry*. 2018;89(5):513-517. doi:10.1136/jnnp-2017-316625

204. Johnson S, Katyal N, Narula N, Govindarajan R. Adverse side effects associated with corticosteroid therapy: a study in 39 patients with generalized myasthenia gravis. *Med Sci Monit*. 2021;27:e933296. doi:10.12659/MSM.933296

205. Bexelius C, Wachtmeister K, Skare P, Jönsson L, van Vollenhoven R. Drivers of cost and health-related quality of life in patients with systemic lupus erythematosus (SLE): a Swedish nationwide study based on patient reports. *Lupus*. 2013;22(8):793-801. doi:10.1177/0961203313491849

206. Sullivan PW, Ghushchyan VH, Globe G, Sucher B. Health-related quality of life associated with systemic corticosteroids. *Qual Life Res*. 2017;26(4):1037-1058. doi:10.1007/s11136-016-1435-y

207. Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. *BMC Health Serv Res*. 2013;13:346. doi:10.1186/1472-6963-13-346

208. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *PharmacoEconomics*. Published online November 30, 2022. doi:10.1007/s40273-022-01218-7

209. Office for National Statistics. Consumer price inflation tables. Published September 2022. https://www.ons.gov.uk/economy/inflationandpriceindices/datasets/consumerpriceinflation/current

210. British National Formulary. Published September 28, 2022. https://bnf.nice.org.uk/

211. Jones K, Burns A. Unit costs of health and social care 2021. Published 2021. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/

212. NHS England. 2022/23 National Tariff Payment System: Annex A - National tariff workbook. Published September 2, 2022. https://www.england.nhs.uk/publication/national-tariff-payment-system-documents-annexes-and-supporting-documents/

213. Dalal AA, Duh MS, Gozalo L, et al. Dose-response relationship between long-term systemic corticosteroid use and related complications in patients with

severe asthma. *J Manag Care Spec Pharm*. 2016;22(7):833-847. doi:10.18553/jmcp.2016.22.7.833

214. Chen SY, Choi CB, Li Q, et al. Glucocorticoid use in patients with systemic lupus erythematosus: association between dose and health care utilization and costs. *Arthritis Care Res Hoboken*. 2015;67(8):1086-1094. doi:10.1002/acr.22574
215. Janson C, Lisspers K, Stallberg B, et al. Health care resource utilization and cost for asthma patients regularly treated with oral corticosteroids - a Swedish observational cohort study (PACEHR). *Respir Res*. 2018;19(1):168. doi:10.1186/s12931-018-0855-3
216. Voorham J, Xu X, Price DB, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy*. 2019;74(2):273-283. doi:10.1111/all.13556
217. Whittington Health NHS. Intravenous immunoglobulin use. Published November 2015. https://www.whittington.nhs.uk/document.ashx?id=6073
218. Monthly Index of Medical Specialities (MIMS). Hydrocortisone. Published 2021. https://www.mims.co.uk/drugs/endocrine/inflammatory-disorders/hydrocortisone
219. NHS England. National Schedule of NHS Costs Year : 2020-21 - All NHS trusts and NHS foundation trusts - HRG Data. Published 2021. https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of Information for Patients (SIP)

20 March 2023

File name	Version	Contains confidential information	Date
ID4003_Vyvgart_gMG_SIP	2.0	No	20 March 2023

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):

Efgartigimod alfa (VYVGART)

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

Efgartigimod is used for the treatment of adults with generalised myasthenia gravis (gMG), a rare, long-term condition that causes muscle weakness (1–5). "Generalised" means that the condition affects muscle groups throughout the body, bringing with it wide-ranging symptoms of muscle weakness (6–9). These have a significant negative impact on the quality of life of patients, and their carers (10–13). Some adults with gMG continue to experience symptoms of the condition despite receiving existing medicines (14). They would greatly benefit from another treatment option to help reduce their symptoms. Use of efgartigimod in these patients is the focus of this submission.

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 European Commission issued a marketing authorisation for efgartigimod throughout the European Union (EU) on August 10, 2022.

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued a marketing authorisation for efgartigimod on March, 14, 2023. MHRA approval is an important step towards ensuring that patients have access to new medicines, like efgartigimod

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:

Working with patient groups

As a responsible pharmaceutical company, argenx partners with relevant patient organisations to support endeavours to improve the treatment and care of people affected with myasthenia gravis and to improve our understanding of the condition. We are in regular dialogue with such groups, which, in the UK, includes both MyAware and Muscular Dystrophy UK (MDUK). This is common practice, and we adhere closely to industry guidelines and regulations that are in place.

International patient-reported outcomes study

argenx sponsor a long-term study called MyRealWorldMG to understand better the burden of myasthenia gravis (15). This has included adults with myasthenia gravis from the USA, Japan, Germany, France, Italy, Spain, Canada, Belgium and the UK (15). The study is observational, meaning participation in it does not influence which type of treatment participants receive, and is intended to assess MG in a “normal” setting. Participants use a smartphone application (app) called MyRealWorld MG to regularly enter data about their MG, its management and its impact on their lives (15).

argenx designed the study in close collaboration with the MG community, including patient organisations and patient representatives. The study is overseen by a Scientific Advisory Board (SAB), which plays an important role in ensuring that it is of high quality and that the information it produces is valuable to the understanding of the condition. The SAB includes at least one patient organisation or patient representative from every country participating in the study.

UK patient organisation involvement

The UK was represented by MDUK, who participated in the MyRealWorldMG app protocol development and testing. MDUK did not receive any financial support from argenx in relation to their participation in this study, except for

accommodation costs for an MDUK representative who participated in a face-to-face meeting.

For more information on MyRealWorldMG, please see:

Berrih-Aknin S, Claeys KG, Law N, et al. Patient-reported impact of myasthenia gravis in the real world: protocol for a digital observational study (MyRealWorld MG). BMJ Open 2021;11:e048198. doi:10.1136/ bmjopen-2020-048198

No other collaborations exist that could be considered a potential conflict of interest.

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.

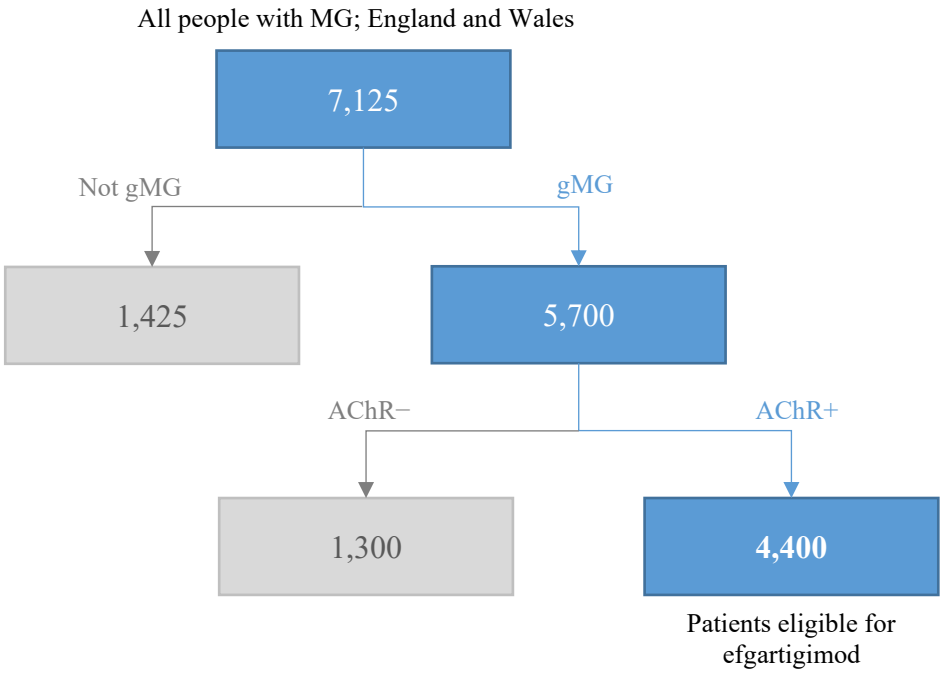
Myasthenia Gravis

Myasthenia gravis (MG) is the name given to a rare, long-term condition that causes muscle weakness (7). It is an autoimmune condition which means that the body's immune system makes antibodies that attack a part of the body itself. In MG, the antibodies interrupt the communication between nerves and muscles; therefore the nerves are not able to make the muscles contract as well as normal, leading to muscle weakness (3–5).

"Generalised" myasthenia gravis, or gMG, describes when the condition has an impact on muscle groups throughout the body. As a result, it can have a disabling effect on several different body functions, including movement, speaking, swallowing, and breathing (6–9).

Number of patients with gMG

The number of people with myasthenia gravis is thought to be around 15 per 100,000 population, making it a rare condition (2). Considering that not all people with MG have gMG, the number of people with gMG in England and Wales (the full remit of NICE's appraisal) is around 5,700, of which around 4,400 would be considered eligible for treatment with efgartigimod bearing in mind that its use is expected to be only for the AChR+ form of the condition (see below).



Efgartigimod is being assessed as a treatment for the most common (though not only) type of gMG, often given the shorthand name “AChR+” (6,7). This refers to the particular type of antibodies which, in patients with this form of the condition, attack the neuromuscular junction (i.e. the point where the nerve transmits signals from the brain to muscle), causing muscle weakness.

The main symptom of gMG is severe muscle weakness throughout the body. This is not usually life-threatening, though it can be where the respiratory muscles are affected, and people cannot breathe without emergency treatment. This is known as a myasthenic crisis (16,17).

People with gMG report that they experience a considerable negative impact on their quality of life due to having the condition, and may be unable to work or carry out usual activities of day-to-day living (2,13,18,19)[25,90]. The condition can also be unpredictable – suddenly getting much worse or even leading to crisis – which can further burden mental and physical health (20).

In addition, problems are caused by several of the treatments which are frequently used in the treatment of gMG, particularly steroids (12). Many patients find taking high, or sustained, doses of steroids to be challenging, because of their side effects. This can lead to poor compliance and worsening of gMG symptoms.

Due to the burden of the disease and available treatment options, new treatments, which target the underlying cause of the condition, are urgently needed.

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 and Testing

Myasthenia gravis is often, though not always, experienced first as a condition affecting the eyes where a persistently drooping eyelid is a common symptom. “Generalised” myasthenia gravis (gMG) refers to when the disease affects muscles throughout the body (6–9). Patients are typically diagnosed with gMG in a neurology department, and have often been referred from eye care or from their GP.

People with symptoms suggestive of gMG will undergo a blood test to look for elevated levels of antibodies characteristic of the condition (8,21). This test can also be used to identify whether the patient has the form of gMG which would be appropriate for treatment with efgartigimod. Therefore, no additional diagnostic tests are required to determine a patient’s suitability for treatment with efgartigimod.

Other tests, such as electrical tests of the nerves and muscles or a magnetic resonance imaging (MRI) scan of the thymus gland (problems which are associated with gMG), may be done (22).

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.

Treatment of gMG

Most treatments used for gMG are not licensed specifically for the condition, and the evidence for their effectiveness is variable. Additionally, many treatments have significant side effects that can be a burden for gMG patients and their carers (23). A reasonable estimate is that around one in five gMG patients have symptoms that remain uncontrolled despite the use of existing treatments (14,24). The need for new and better treatments is therefore significant.

The first treatment often prescribed for gMG is an acetylcholinesterase inhibitor, usually pyridostigmine bromide (which is licensed for the condition) (8,25). Pyridostigmine has been in use for gMG since the 1950s, and while it can be

effective for some people, it is common for them to receive further treatments. The usual next choice is steroids, a type of drug that reduces the activity of the immune system. These can be used either instead of, or in addition to, pyridostigmine (8,25).

Doctors treating gMG will try to find the right balance in order to keep the patient's condition under control while minimising the risk from the side effects, particularly those of steroids (8). This can be extremely difficult, especially if the individual has another health condition, such as diabetes, where steroids should not be used (26–29).

Given the potential difficulties associated with steroid treatment, many patients will also need various other treatments known to suppress the immune system. The usual first choice of treatment to do this is azathioprine, a type of medicine called an immunosuppressant (30). Immunosuppressants reduce the effect of the body's immune system. Several other immunosuppressants are commonly used, either together or one after the other, depending on how the patient responds to the treatment, its potential side effects and the severity of their condition (8,31–33). This includes rituximab which NHS England funds (and which the AWTTC in Wales approves) as a treatment for gMG for patients whose disease is still active despite having received other forms of immunosuppression (34).

None of these immunosuppressant treatments works by targeting the underlying cause of gMG. These treatments, like steroids, can also cause side effect issues, and choice is often determined by their safety profile rather than particular expectations of effectiveness (2,35).

Patients who continue to experience symptoms despite progressing through these treatments may have regular treatment with immunoglobulin, which is used to treat several autoimmune conditions. This is usually given intravenously. Intravenous immunoglobin, or IVIg, is also used in cases of sudden worsening or as an emergency treatment for myasthenia crisis (36,37). Another treatment used to manage certain aspects of the condition, known as plasma exchange, or PLEX, involves removing plasma from the blood to reduce the number of harmful antibodies.

For some patients, removing the thymus gland (an operation called thymectomy) might be considered a treatment option (41).

Though several types of treatment are therefore used for gMG, it is still the case that a significant number of people continue to suffer with the condition and/or with the side-effect consequences of those treatments (2,42–44). A common estimate for this number is around one gMG patient in five (14,24). Therefore, a significant need for new treatments remains.

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.

Furthering our understanding of gMG

argenx has a strong commitment to working with people with gMG to better understand the condition and to gather evidence that is relevant to them about myasthenia gravis and how it is treated. This is shown, for example, by our support for the MyRealWorldMG study discussed below (15). We also involved patient groups in the design of the ADAPT trial, which provides the key evidence for efgartigimod; the individualised dosing schedule adopted for that trial was partly as a result of that involvement.

Published evidence

There is relatively little published evidence on the topic of the lived experience with gMG. However, some important understanding was gathered from a study, published in 2021, based on research among 48 people with gMG as well as six carers (12). This included people from around the world including the UK and the work was led by a global Patient Council that comprised nine people with the condition.

This work produced a total of 114 patient insights which showed that, overall, gMG has a significant impact on many aspects of life. The authors of the study summarised their findings into five themes describing the experience of living with the condition (12):

- living with fluctuating and unpredictable symptoms
- a constant state of adaptation, continual assessment and trade-offs in all aspects of life
- treatment inertia, often resulting in under-treatment
- a sense of disconnect with healthcare professionals
- feelings of anxiety, frustration, guilt, anger, loneliness and depression.

A study published in 2010, based on questionnaires filled out by over 1,500 people with MG in Germany, found that, despite receiving recommended therapy, many with the condition were still significantly burdened by it (13). In particular, people in

this study reported that both their mobility and mental well-being were affected and their quality of life was markedly reduced (13).

MyRealWorldMG

argenx are the sponsor of MyRealWorldMG, a long-term study observing the effects of myasthenia gravis based on patient-reported experiences (15). This covers the USA, Japan, Germany, France, Italy, Spain, Canada, Belgium and the UK (15). Participants use a smartphone application (app), MyRealWorld MG (Vitaccess Limited, London), to enter regular data about their MG, its management and its impact on their lives over approximately two years (15).

The digitally collected data from this study have confirmed the considerable impact of myasthenia gravis on quality of life (45). Moreover, an impact was seen for people with all levels of severity of the condition and the findings were consistent between the different ways in which quality of life was measured in the study (19). Among other findings, one third of participants reported difficulties in performing day-to-day activities with the condition and nearly one third (according to one recording measure used) said that they had either moderate or severe anxiety problems.

For more information on the MyRealWorldMG, please see (15):

Berrih-Aknin S, Claeys KG, Law N, et al. Patient-reported impact of myasthenia gravis in the real world: protocol for a digital observational study (MyRealWorld MG). BMJ Open 2021;11:e048198. Doi:10.1136/ bmjopen-2020-048198

Commitment to patient-based outcomes

Data for efgartigimod come principally from the ADAPT study, as well as ADAPT+, where patients were given a longer opportunity to be treated with efgartigimod (46,47). In both ADAPT and ADAPT+, data on the effectiveness of efgartigimod were collected using the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale. This is a patient-reported measure in which doctors collect data on the patient's symptoms related to MG, and as reported by patients from their experiences in the previous week (48). Additionally, safety data were collected to ensure that the safety profile of efgartigimod is well-understood, and appropriate for patients with gMG (46,47).

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.

The cause of gMG

For a muscle to contract, a substance called acetylcholine is released from a nerve and attaches to molecules called receptors on the muscle cells. This causes muscles to “activate” and to do their job (14).

gMG is caused by the immune system mistakenly producing antibodies (also sometimes called autoantibodies) that attack and damage the body’s acetylcholine receptors. These autoantibodies belong to a particular class called IgG. The damage done to the acetylcholine receptors by these IgG autoantibodies means that the nerves cannot make the muscles contract as well as normal, leading to muscle weakness (3,4,6,49–54).

A protein in the body (called neonatal Fc receptor (FcRn)) is known to increase the number of IgG autoantibodies in the blood (55,56). Efgartigimod binds to this protein and, by blocking its action, thereby reduces the number of such autoantibodies. As a result, there are fewer that can attack and damage the acetylcholine receptors and therefore less weakening of the muscles (57). This is the basis for efgartigimod being an effective treatment for gMG (58,59).

Efgartigimod has no impact on other parts of the immune system (60). It is therefore a targeted treatment for gMG, unlike many other treatments that are used that rely on a more general immunosuppressive effect. Because the immune system is important to the body, its general suppression can be problematic, and this helps explain why side-effects are a common feature of many existing gMG treatments.

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.

Efgartigimod is expected to be used alongside commonly available treatments (i.e. those described above) for adults with gMG caused by AChR+ antibodies.

Patients in the ADAPT trials (see section 3d below) were already receiving standard gMG treatments and still had symptoms when they entered the studies (46). Therefore, efgartigimod has been studied in combination with these existing treatments and there is evidence of it being effective in patients receiving acetylcholinesterase inhibitors, steroids and immunosuppressant therapies that are not steroids (46).

In ADAPT, patients had to continue their existing treatments and the dose could not be changed (61). Any impact that efgartigimod might have on reducing steroid use could not therefore be shown in that trial. Nevertheless, it is expected that using efgartigimod will enable other treatments (especially steroids) to be reduced or stopped, which would be beneficial given the side-effects associated with these treatments.

There is some emerging evidence from open-label extension studies and in "real world" observations that this may be the case and argenx will analyse these data as they get more mature.

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?

Individualised dosing

Efgartigimod is a long-term treatment for gMG with dosing that is adjusted to the individual needs of each patient (62). Efgartigimod is given as an intravenous infusion, which is a method of injecting drugs into the bloodstream, usually into a vein in the arm. Some other treatments for gMG are given in a similar way, though several can be taken as tablets.

Each efgartigimod infusion takes one hour and is administered by a doctor or a nurse (62). Efgartigimod can also be given in a patient's home so long as this is overseen by a properly qualified person. Such "homecare" delivery is now a common occurrence where people need to have treatment given to them on a repeat basis.

Treatment cycles

Efgartigimod is given in treatment cycles. A treatment cycle consists of one infusion per week for four weeks (46,62). Additional treatment cycles are given based on an assessment of a patient's symptoms. Therefore, the time between

cycles will be different for each patient as each person's need for treatment will also be different. In the ADAPT trial, the average time to the second treatment cycle was 13 weeks from the start of the previous one, although this will vary from person to person (62).

The dose of treatment for each administration will be calculated based on the patient's weight. The dose is 10 mg of efgartigimod per kilogram of the patient's body weight (62).

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, completion dates, etc. Please provide references to further information about the trials or publications from the trials.

The table below summarises the two main clinical trials upon which the evidence for efgartigimod is based (ADAPT and ADAPT+) as well as the ADAPT-SC trial which studied a formulation of efgartigimod that is given as an injection under the skin (known as sub-cutaneous injection). This sub-cutaneous formulation will be subject to a future separate application for marketing authorisation. Data about the clinical effectiveness of the sub-cutaneous formulation are included in argenx's submission to NICE.

Study	ADAPT (ARGX-113-1704; NCT03669588) (46,61)	ADAPT+ (ARGX-113-1705; NCT03770403) (47,63)	ADAPT-SC (ARGX-113-2001; NCT04735432) (64,65)
Study design	Phase 3, randomised, double-blind, placebo-controlled, multicentre	Phase 3, long-term, single-arm, open-label, multicentre	Phase 3, randomised, open-label, parallel-group, multicentre
Population	Adults with gMG	Adults with gMG	Adults with gMG
Intervention(s)	Efgartigimod 10 mg/kg (IV formulation)	Efgartigimod 10 mg/kg (IV formulation)	Efgartigimod PH20 SC 1,000 mg (SC formulation)
Comparator	Placebo	No comparator, all received efgartigimod	Efgartigimod 10 mg/kg (IV formulation)
Number of patients	167 patients with gMG, including 129 AChR+ patients	151 patients with gMG including 111 AChR+ patients	111 patients with gMG including 91 AChR+ patients
Completion Date	April 2020	June 2022	December 2021
Main Reported outcomes	• Improvement in MG • Time to clinically meaningful improvement	• Adverse events of treatment • Improvement in MG	• Improvement in MG (Adverse events of treatment

	• Mortality • Hospitalisations • Adverse events of treatment • Quality of Life		
Inclusion/Exclusion Criteria	The key inclusion criterion was that patients had to be over 18 with a diagnosis of gMG meeting the commonly accepted definition of the condition. For more detail on inclusion and exclusion criteria, please refer to the trial entry in clinicaltrials.com (reference number: NCT03669588)	Patients entering ADAPT+ were those who had been treated in ADAPT and who had not, for any reason, discontinued treatment during that trial. For more detail on inclusion and exclusion criteria, please refer to the trial entry in clinicaltrials.com (reference number: NCT03770403)	The key inclusion criteria were similar to ADAPT though additionally patients must have shown an improvement in myasthenia gravis with treatment with oral acetylcholinesterase inhibitors as assessed by the treating doctor For more detail on inclusion and exclusion criteria, please refer to the trial entry in clinicaltrials.com (reference number: NCT04735432)

3e) Efficacy

Efficacy measures 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.

Efgartigimod was studied in a clinical study called ADAPT. In this study, 167 gMG patients, including 129 AChR+ patients, received either efgartigimod or an inactive dummy treatment (referred to as placebo) given the same way as efgartigimod (46). The study was double blinded, meaning neither the patients nor the doctors knew whether it was efgartigimod or placebo being administered. All patients in the study were experiencing symptoms of gMG despite their current gMG treatments, and all patients, whether they were given efgartigimod or placebo, continued to receive those treatments (46).

How treatment was given

Efgartigimod was given in treatment cycles of one infusion treatment every week for four weeks (four weeks of infusions = one treatment cycle) (46). After the first treatment cycle, additional cycles were given depending on how long the benefit of

the previous cycle lasted. The time between cycles, and the number of cycles each patient received, varied depending on the needs of each individual patient and how their symptoms were changing.

Significant improvement demonstrated vs. standard therapies alone

In the 129 AChR+ patients in the trial, disease symptoms improved significantly in those who received efgartigimod compared with those who received placebo (46). This benefit was shown using symptom scores commonly used in gMG studies, including the Myasthenia Gravis-specific Activities of Daily Living (MG-ADL). Using MG-ADL, patients reported the impact of the disease on their daily activities.

Approximately two of every three (68%) patients treated with efgartigimod showed improvement on the MG-ADL scale, compared to under a third (30%) of the patients who received placebo (46). This had to be sustained for at least four weeks, during their first treatment cycle, Likewise, in the second cycle, results for MG-ADL were similar to the first cycle (71% of efgartigimod patients achieved a meaningful, sustained MG-ADL scale score improvement) (46). Across the first two cycles of treatment a total of 79% of patients who received efgartigimod reported this meaningful improvement in their MG-ADL score (46).

The improvements in symptoms were also confirmed on three other MG scales that included measures of strength and assessed quality of life.

Efgartigimod also showed a quick onset of effect and depth of response. During the first cycle of treatment 40% of patients receiving efgartigimod reported no or very few symptoms (shown by recording an MG-ADL score of 0 or 1) compared to 11% of patients receiving placebo (46). This is sometimes referred to as achieving Minimal Symptom Expression, or MSE.

Duration of effect

Thirty-four percent of patients in the study had a response to their first efgartigimod treatment cycle that lasted longer than 12 weeks (46). In other words, was longer before they needed to receive another 4-week cycle of treatment.

Most patients received two cycles during the time they were in the trial (61).

Repeated improvements with multiple treatment cycles

After this study, patients could enter a longer study (called ADAPT+) that continued to measure how effective efgartigimod was (46,47). In this study, the improvement in gMG symptoms was seen with repeated cycles of treatment (47,63).

Overall, results from the studies have shown that efgartigimod is effective in AChR+ gMG patients. As such, efgartigimod is an important new option for patients.

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

What is the clinical evidence for t 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.

In the ADAPT study, several methods were used to measure the effect of efgartigimod on symptom reduction: measures of strength, the ability to perform daily activities, and impact on quality of life (46,61).

A patient-reported outcome measurement tool called the MG-QOL15r was used to assess quality of life directly. The MG-QOL15r was specially developed to let patients with myasthenia gravis report how the disease affects their quality of life (46,61,66,67). This is done by patients rating four aspects of their quality of life often made worse by gMG: mobility, MG symptoms, general contentment, and emotional well-being (68).

Other outcome measures used in the ADAPT study were the Myasthenia Gravis Composite scale (MGC), which records outcomes reported by patients and doctors, and a quality of life questionnaire completed by patients that is not specific to MG (called EQ-5D-5L) (46,61,67).

The ADAPT study found that efgartigimod improved patients' quality of life (as measured by the MG-QOL15r and on the other measures) more than for patients who received placebo (69). Patients treated with efgartigimod had, as rated by themselves, fewer symptoms caused by muscle weakness. and reduced impact of the condition as assessed by doctors.

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 about 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.

Efgartigimod was generally well tolerated by patients in the ADAPT studies. In ADAPT, where patients received either efgartigimod or placebo (in addition to their existing treatments), fewer patients receiving efgartigimod reported side effects

than those receiving placebo. The side effects were mainly reported as being mild or moderate in severity (46,61).

The most reported side effects following treatment with efgartigimod were infections of the nose and throat, reported by 10.7%, and urinary tract infections, reported by 9.5% of patients.

Other common side effects included:

- Bronchitis (inflammation of the airway passages of the lungs)
- Myalgia (muscle pain)
- Headache during or after the administration of efgartigimod alfa

In the ADAPT+ study efgartigimod continued to be well tolerated during multiple cycles of treatment (47,63).

3h) Summary of key benefits of treatment for patients

Addressing the unmet need

Currently used treatments for gMG, most of which are not licensed specifically for the condition, have variable effectiveness and can impose a significant treatment burden (1,10,13,70). Around one in five patients have gMG that remains uncontrolled despite current treatments (13,14,24). Efgartigimod offers an important new treatment option for those patients.

Targets the underlying cause of gMG

Efgartigimod has been shown to be an effective treatment for people with gMG (46,47). Unlike existing treatments, efgartigimod targets the underlying cause of gMG, reducing the autoantibodies that cause the muscle weakness (57–59).

Effectiveness and tolerability shown in robust clinical trials

The beneficial impact of efgartigimod – both on the symptoms of gMG and on the quality of life of patients – has been shown in a controlled clinical trial against a placebo comparator, as well as in a longer-term study demonstrating sustained effect (46,47,63,69).

Efgartigimod had a quick onset of effect and many patients experienced marked improvement in their symptoms, ability to perform everyday activities and in their quality of life (46,47,63,69). These studies have also shown that efgartigimod was well tolerated and is likely to have less burdensome side effects than are known to occur with long-term steroid use and with other immunosuppressants (1,10,13,70).

Individualised dosing

Efgartigimod also offers an individualised approach to treatment. This means that patients receive subsequent treatment cycles based on their individual symptoms and only receive treatment when they need it. In some patients there was an

extended beneficial effect resulting in less frequent treatment cycles (46). Since gMG is a long-term chronic condition, managing treatment according to clinical need over a sustained period is important not only for patients and doctors, but also to the NHS.

gMG patients in England and Wales are already able to access efgartigimod under the Early Access to Medicines Scheme (EAMS). Since May 2022, when EAMS began, there has been a good response to the programme with requests for patient access across several treatment centres. In order to be part of EAMS, efgartigimod had to be designated as a Promising Innovative Medicine (PIM) based on its efficacy and safety profile. The MHRA gave this designation in November 2021. EAMS exists to allow patients to receive such medicines ahead of them being licensed for treatment, where the need is considered greatest.

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 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 method of administration
- What is the impact of any disadvantages highlighted compared with current treatments

In a condition that is difficult to treat and control for a significant proportion of patients, efgartigimod will provide an important new and effective treatment option. Hospital capacity constraints may pose some challenges for patients to receive repeated cycles of treatment, but argenx will be supporting a homecare delivery service which should help to address this in most cases.

Efgartigimod is administered as an intravenous infusion (46). A sub-cutaneous injection formulation is in an advanced state of development and, subject to marketing authorisation, will be made available as soon as possible (71). Some other treatments for myasthenia gravis are also administered in these injectable forms, though several can be taken as tablets. Although this may be a consideration for some people, we would expect effectiveness and the potential for side-effects to be the key drivers of patient choice.

3i) 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.

Cost-effectiveness assessment of new medicines

In assessing whether a medicine represents a cost-effective use of NHS resources, NICE refers to a measure called the incremental cost-effectiveness ratio (ICER) (72). This looks at the cost-effectiveness of the product in question – in this case, efgartigimod – against other treatments currently used to treat the condition.

The incremental cost-effectiveness ratio is measured in terms of what needs to be spent to gain one QALY, where QALY stands for "quality-adjusted life year". The QALY is a measure of disease burden and includes both the quality and quantity of life lived. A treatment can increase the number of QALYs a patient experiences by either extending life, or increasing the quality of life, or both.

In the case of efgartigimod, treating a condition that is not generally life-shortening, the "QALY gains" are mainly in the form of improved quality of life. Efgartigimod has shown in the ADAPT study that it can improve a person's quality of life by reducing the symptoms of gMG (46). The improvement in quality of life through reducing someone's dependence on steroids is also a factor included in the economic analysis.

NICE's approval of a treatment is based around how much the NHS is willing to pay for each extra QALY the treatment can deliver, compared with existing treatment (72). The starting point in this type of appraisal is that cost-effective treatments should cost between £20,000-30,000 for each QALY gained (72). This is the accepted standard on which NICE assess a vast majority of new medicines.

How the economic assessment of efgartigimod in gMG was conducted

argenx has developed an economic model for efgartigimod which it is presenting to NICE as part of its appraisal submission. This looks at the benefits and costs of efgartigimod against the comparator treatments that NICE has selected and extends over what is called a life-time horizon. This means that all the QALY gains

a patient might expect from being treated with efgartigimod are added up over the patient's lifetime, as are all the costs that would be incurred treating the patient for that period. This is the commonly accepted method for calculating cost-effectiveness with a long-term chronic condition such as gMG.

The patient population used for the model are those with AChR+ gMG taken from the ADAPT trial. This will correspond to the expected licence for efgartigimod and reflects argenx's belief that the need for efgartigimod is across the whole of this population where the condition and its symptoms are uncontrolled with existing treatments alone.

gMG health states

In the economic model, patients are assumed to be in one of several "health states" that correspond to different levels of the severity of their gMG. These states have been defined according to a range of scores on the MG-ADL scale which is itself an accepted measure of the impact of gMG on a patient's day-to-day activity. It was also the main measure used in the ADAPT study of efgartigimod to assess its efficacy (46). The model aims to capture the highly variable nature of gMG. This includes fluctuating symptoms and the rapid transition between health states as patients experience increased levels of symptoms or myasthenic crises (crisis is a separate defined health state in the model).

Each of these health states has associated with it a different level of quality of life and the long-term impact of treatment on quality of life is calculated by modelling how patients move between these health states over the life-time period. Data for how patients are expected to move between the health states come from the ADAPT study. Since this has data for both efgartigimod treated patients (from the active treatment arm) and patients treated with "conventional" care (from the placebo arm) direct values for both efgartigimod and comparator treatments can be put into the model.

Assumptions and limitations

A limitation with this type of model (and any modelling for long-term conditions) is that data from a time-limited study have to be extrapolated over a life-time period. There are several accepted statistical techniques for handling this difficulty which argenx have followed in its modelling, and several assumptions have to be made.

Based on ADAPT, for example, argenx has assumed that patients will not receive a new cycle of efgartigimod treatment if their MG-ADL score is below five (46). The average treatment usage this leads to in the model may, over a long-term period, turn out to be either an over- or under-estimate; this is inherently difficult to predict, given that efgartigimod is designed to be an individualised treatment where patients are re-treated depending on their response and individual need.

Assumptions are also needed for modelling what proportion of patients are receiving treatment with different comparator medicines: data here can come partly from ADAPT, but in clinical practice in England and Wales, patients are also

receiving treatment with interventions such as rituximab or immunoglobulins, which were not part of that trial (46,61).

The value proposition for efgartigimod

Based on the modelling approach summarised above, the treatment with efgartigimod resulted in additional QALYs compared with established clinical management and an overall incremental cost-effectiveness ratio under £30,000 per QALY. This suggests that the treatment with efgartigimod is a cost-effective option for patients with gMG in England and Wales.

The overall ICER for efgartigimod is based on a cost of the product that is intended to ensure it is cost-effective. In order to fulfil our commitment to ensuring that patients can have access to efgartigimod, argenx have put forward a price that will be part of an officially-approved Patient Access Scheme (PAS).

NICE and its assessors will review the cost-effectiveness model and its underlying assumptions/inputs to determine whether it is suitable for decision making. NICE will then make a recommendation based on the ICER using the committee's preferred assumptions.

3j) 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)

Specific, targeted medicine

Efgartigimod is a first-in-class treatment with a mechanism of action that selectively acts to reduce the level of the autoantibodies that are the cause of gMG (57). This differentiates it from long-standing conventional treatments. As well as being reflected in its efficacy in gMG, this selective mechanism of action does not result in widespread immunosuppression, unlike many other treatments in routine clinical use for the treatment of gMG (57–59).

Individualised treatment developed to match patient needs

International clinical consensus on gMG calls for an individualised treatment approach (31). Efgartigimod provides such an approach based on the ADAPT trial, which allowed patients with ongoing clinical benefits to extend the time to initiation of the next treatment cycle. Since around one-third of AChR+ patients who were responders to their first cycle of treatment experienced an extended clinical benefit in ADAPT, there is, therefore potential for fewer treatment cycles per year for a substantial portion of patients (46).

High unmet clinical need

Recognition that efgartigimod is both innovative and that it addresses an area of high unmet clinical need was given in November 2021 when the MHRA designated it as a Promising Innovative Medicine (PIM) (73,74). This designation is important in its own right and opens the way to giving patients access to efgartigimod through the Early Access to Medicines Scheme (EAMS). Since May 2022, when EAMS began, there has been a good response to the programme with requests for patient access across several treatment centres.

3k) 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

The efgartigimod assessment raises no equality issues.

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.

MDUK resources

- Fatigue guidance: YouTube video and MDUK Fatigue Guide
- Myasthenia gravis muscles matter video - https://www.youtube.com/watch?v=FZhZpbM6tmQ&feature=youtu.be
- Treatments information: https://www.musculardystrophyuk.org/get-involved/campaign/our-campaigns/fast-track/ravulizumab

External resources

- Rare diseases website: https://rarediseases.org/rare-diseases/myasthenia-gravis/?filter=ovr-ds-resources
- NHS website: https://www.nhs.uk/conditions/myasthenia-gravis/
- Myaware - https://www.myaware.org/ and https://www.myaware.org/emotional-support
- Practical information on prescriptions: https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/who-can-get-free-prescriptions/
- Practical information via .GOV website on driving
- https://www.gov.uk/myasthenia-gravis-and-driving

Further information

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: https://www.eupati.eu/guidance-patient-involvement/
- 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: http://www.inahta.org/wp-

content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Antibodies - these are proteins the immune system makes to bind to and remove unwanted substances from the body (75,76).

Autoantibodies - antibodies that attack part of the individual's own body

AWTTC - All Wales Therapeutics and Toxicology Centre, an advisory body on medicines in Wales

Cycle - a period when the patient is treated with the medicine, after which they will have no treatment until the next cycle (77).

Double blind - a clinical study where the patients being treated in the study and the researchers conducting the study do not know which of the study medicines the patient is receiving (e.g. they are unaware whether they are receiving efgartigimod or placebo) (78).

ICER – incremental cost-effectiveness ratio. Measure of the cost-effectiveness of a medicine against other treatments currently used to treat the condition

Immunoglobulin - immunoglobulin is another word for antibody. Immunoglobulin treatment is antibodies taken from blood donations (76,79).

Licence/Licensed - see **Marketing authorisation** (78).

Marketing authorisation - permission to sell a medicine after the evidence around it (on safety, quality, and efficacy) has been assessed. This is different from NICE's appraisal of a medicine, which also considers whether the medicine is cost-effective for the NHS (78).

MRI - magnetic resonance imaging (MRI) takes images inside the body using magnetic fields (80).

Open-label - a clinical study where both patients and researchers know what study medicine the patient is receiving (81).

Parallel-group - a clinical study where two different things are compared, (this could be two different medicines, or a medicine and a placebo) (82).

Phase 3 - a clinical study that investigates how safe and efficacious a medicine is. The medicine will previously have been tested in Phase 1-2 studies, which test whether the medicine is safe enough to use in humans and whether it has an effect on the disease (83).

Placebo-controlled - when a patients in a clinical study receive either the medicine or a fake, dummy medicine (a placebo) in order to test the study medicine (78).

Protein - complex molecules that play many critical roles in the body (84).

QALY – quality-adjusted life year. A measure of disease burden, including both the quality and quantity of life lived, used for the economic assessment of medicines.

Randomised - when patients in a clinical study are randomly assigned to a group in the trial (e.g. the group being given the medicine or the group being given a placebo) (78).

Single-arm - a clinical study that has a single group of patients (i.e. to see the effects of a single medicine in these patients) (78).

Steroid - an anti-inflammatory medication (note: this is different from the anabolic steroids used by some people to increase muscle mass) (85).

Thymus gland - a small gland in the chest that produces cells for the immune system (86).

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:

Response:

1. Ruiter AM, Verschuuren J, Tannemaat MR. Prevalence and associated factors of fatigue in autoimmune myasthenia gravis. Neuromuscul Disord. 2021/05/27 ed. 2021 Apr 24;31(7):612–21.

2. Boldingh MI, Dekker L, Maniaol AH, Brunborg C, Lipka AF, Niks EH, et al. An up-date on health-related quality of life in myasthenia gravis -results from population based cohorts. Health Qual Life Outcomes. 2015/08/02 ed. 2015 Aug 1;13:115.

3. Juel VC, Massey JM. Myasthenia gravis. Orphanet J Rare Dis. 2007/11/08 ed. 2007 Nov 6;2:44.

4. Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Myasthenia gravis - autoantibody characteristics and their implications for therapy. Nat Rev Neurol. 2016/04/23 ed. 2016 May;12(5):259–68.

5. Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia gravis: epidemiology, pathophysiology and clinical manifestations. J Clin Med [Internet]. 2021/06/03 ed. 2021 May 21;10(11). Available from: https://www.ncbi.nlm.nih.gov/pubmed/34064035 https://mdpi-res.com/d_attachment/jcm/jcm-10-02235/article_deploy/jcm-10-02235-v2.pdf

6. Behin A, Le Panse R. New pathways and therapeutic targets in autoimmune myasthenia gravis. J Neuromuscul Dis. 2018/07/17 ed. 2018;5(3):265–77.

7. Cortes-Vicente E, Alvarez-Velasco R, Segovia S, Paradas C, Casasnovas C, Guerrero-Sola A, et al. Clinical and therapeutic features of myasthenia gravis in adults based on age at onset. Neurology. 2020/02/20 ed. 2020 Mar 17;94(11):e1171–80.

8. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. Pr Neurol. 2015/05/16 ed. 2015 Jun;15(3):199–206.

9. Mané-Damas M, Molenaar PC, Ulrichts P, Marcuse F, De Baets MH, Martinez-Martinez P, et al. Novel treatment strategies for acetylcholine receptor antibody-positive myasthenia gravis and related disorders. Autoimmun Rev. 2022 Jul 1;21(7):103104.

10. Petersson M, Feresiadou A, Jons D, Ilinca A, Lundin F, Johansson R, et al. Patient-reported symptom severity in a nationwide myasthenia gravis cohort: cross-sectional analysis of the Swedish GEMG study. Neurology. 2021/08/12 ed. 2021 Aug 10;97(14):e1382–91.

11. Andersen LK, Jakobsson AS, Revsbech KL, Vissing J. Causes of symptom dissatisfaction in patients with generalized myasthenia gravis. J Neurol. 2022 Jun 1;269(6):3086–93.

12. Law N, Davio K, Blunck M, Lobban D, Seddik K. The Lived Experience of Myasthenia Gravis: A Patient-Led Analysis. Neurol Ther. 2021 Oct 23;10(2):1103–25.

13. Twork S, Wiesmeth S, Klewer J, Pohlau D, Kugler J. Quality of life and life circumstances in German myasthenia gravis patients. Health Qual Life Outcomes. 2010/11/13 ed. 2010 Nov 11;8:129.

14. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM. Myasthenia gravis. Nat Rev Dis Primer. 2019 May 2;5(1):1–19.

15. Berrih-Aknin S, Claeys KG, Law N, Mantegazza R, Murai H, Sacca F, et al. Patient-reported impact of myasthenia gravis in the real world: protocol for a digital observational study (MyRealWorld MG). BMJ Open. 2021/07/22 ed. 2021 Jul 20;11(7):e048198.

16. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve. 2007/12/07 ed. 2008 Feb;37(2):141–9.

17. Wendell LC, Levine JM. Myasthenic crisis. Neurohospitalist. 2011/01/01 ed. 2011 Jan;1(1):16–22.

18. argenx. Epidemiology, burden of illness, and unmet need in the treatment of myasthenia gravis, Version 1.0 [Internal report]. 2020.

19. Dewilde S, Kousoulakou H, Janssen M, Claeys K, Friconneau M, Jacob S, et al. Digital data collection to measure the impact of myasthenia gravis on patients' quality of life in the real world: report at baseline [Presented at the Virtual International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2021 conference, 30 November - 3 December 2021]. Value Health. 2022 Nov 30;25(1 Suppl):S246.

20. Law C, Flaherty CV, Bandyopadhyay S. A Review of Psychiatric Comorbidity in Myasthenia Gravis. Cureus. 2020;12(7):e9184.

21. National Institute of Neurological Disorders or Stroke. Myasthenia Gravis Fact Sheet [Internet]. [cited 2022 Dec 19]. Available from: https://www.ninds.nih.gov/myasthenia-gravis-fact-sheet

22. Priola AM, Priola SM. Imaging of thymus in myasthenia gravis: from thymic hyperplasia to thymic tumor. Clin Radiol. 2014 May;69(5):e230-245.

23. Lehnerer S, Jacobi J, Schilling R, Grittner U, Marbin D, Gerischer L, et al. Burden of disease in myasthenia gravis: taking the patient's perspective. J Neurol. 2021/11/21 ed. 2022 Jun;269(6):3050–63.

24. argenx. Data on file: UK advisory board report.

25. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. The Association of British Neurologists' myasthenia gravis guidelines. Ann N Acad Sci. 2017/11/10 ed. 2018 Jan;1412(1):166–9.

26. Oh TK, Song IA. Trends in long-term glucocorticoid use and risk of 5-year mortality: a historical cohort study in South Korea. Endocrine. 20200616th ed. 2020 Sep;69(3):634–41.

27. del Rincon I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis Rheumatol. 2014/02/08 ed. 2014 Feb;66(2):264–72.

28. Movahedi M, Costello R, Lunt M, Pye SR, Sergeant JC, Dixon WG. Oral glucocorticoid therapy and all-cause and cause-specific mortality in patients with rheumatoid arthritis: a retrospective cohort study. Eur J Epidemiol. 20160602nd ed. 2016 Oct;31(10):1045–55.

29. Lee H, Ryu J, Nam E, Chung SJ, Yeo Y, Park DW, et al. Increased mortality in patients with corticosteroid-dependent asthma: a nationwide population-based study. Eur Respir J. 2019/09/14 ed. 2019 Nov;54(5):1900804.

30. Sathasivam S. Steroids and immunosuppressant drugs in myasthenia gravis. Nat Clin Pr Neurol. 2008/05/22 ed. 2008 Jun;4(6):317–27.

31. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology. 2016/07/01 ed. 2016 Jul 26;87(4):419–25.

32. Narayanaswami P, Sanders DB, Wolfe G, Benatar M, Cea G, Evoli A, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. Neurology. 2020/11/05 ed. 2021 Jan 19;96(3):114–22.

33. Melzer N, Ruck T, Fuhr P, Gold R, Hohlfeld R, Marx A, et al. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. J Neurol. 2016/02/18 ed. 2016 Aug;263(8):1473–94.

34. NHS England. Clinical commissioning policy statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults).

35. Szczudlik P, Sobieszczuk E, Szyluk B, Lipowska M, Kubiszewska J, Kostera-Pruszczyk A. Determinants of quality of life in myasthenia gravis patients. Front Neurol. 2020/10/20 ed. 2020 Sep;11(1094):553626.

36. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev. 2012/12/14 ed. 2012 Dec 12;12(12):CD002277.

37. Alcantara M, Sarpong E, Barnett C, Katzberg H, Bril V. Chronic immunoglobulin maintenance therapy in myasthenia gravis. Eur J Neurol. 2021 Feb;28(2):639–46.

38. Gajdos P, Chevret S, Toyka K. Plasma exchange for myasthenia gravis. Cochrane Database Syst Rev. 2002;(4):CD002275.

39. Ipe TS, Davis AR, Raval JS. Therapeutic plasma exchange in myasthenia gravis: a systematic literature review and meta-analysis of comparative evidence. Front Neurol. 2021/09/18 ed. 2021;12:662856.

40. Kumar R, Birinder SP, Gupta S, Singh G, Kaur A. Therapeutic plasma exchange in the treatment of myasthenia gravis. Indian J Crit Care Med. 2015 Jan;19(1):9–13.

41. Harris L, Graham S, MacLachlan S, Exuzides A, Jacob S. Healthcare resource utilization by patients with treatment-refractory myasthenia gravis in England. J Med Econ. 2019 Jul 3;22(7):691–7.

42. Suh J, Goldstein JM, Nowak RJ. Clinical Characteristics of Refractory Myasthenia Gravis Patients. Yale J Biol Med. 2013 Jun 13;86(2):255–60.

43. Gilhus NE. Eculizumab: a treatment option for myasthenia gravis? Lancet Neurol. 2017 Dec;16(12):947–8.

44. Silvestri NJ, Wolfe GI. Treatment-refractory myasthenia gravis. J Clin Neuromuscul Dis. 2014 Jun;15(4):167–78.

45. Dewilde S, Philips G, Paci S. Patient -reported burden of Myasthenia Gravis: Baseline results of the International Prospective, Observational, Longitudinal Real-World Digital Study MyRealWorld-MG. BMJ Open Print.

46. Howard JF Jr, Bril V, Vu T, Karam C, Peric S, Margania T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2021/06/20 ed. 2021 Jul;20(7):526–36.

47. Howard JF Jr, Bril V, Vu T, Karam C, Peric S, De Bleecker JL, et al. #108: Long-term safety, tolerability, and efficacy of efgartigimod in patients with generalized myasthenia gravis. In: Poster presented at the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) annual meeting, Nashville, TN, USA. Nashville, TN, USA; 2022.

48. Muppidi S, Silvestri NJ, Tan R, Riggs K, Leighton T, Phillips GA. Utilization of MG-ADL in myasthenia gravis clinical research and care. Muscle Nerve. 2022/01/07 ed. 2022 Jun;65(6):630–9.

49. Gilhus NE. Myasthenia gravis. N Engl J Med. 2016/12/29 ed. 2016 Dec 29;375(26):2570–81.

50. Koneczny I, Herbst R. Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture. Cells. 2019 Jul 2;8(7):671.

51. Drachman DB, Adams RN, Josifek LF, Self SG. Functional activities of autoantibodies to acetylcholine receptors and the clinical severity of myasthenia gravis. N Engl J Med. 1982 Sep 23;307(13):769–75.

52. Drachman DB, Angus CW, Adams RN, Michelson JD, Hoffman GJ. Myasthenic antibodies cross-link acetylcholine receptors to accelerate degradation. N Engl J Med. 1978 May 18;298(20):1116–22.

53. Cole RN, Ghazanfari N, Ngo ST, Gervásio OL, Reddel SW, Phillips WD. Patient autoantibodies deplete postsynaptic muscle-specific kinase leading to disassembly of the ACh receptor scaffold and myasthenia gravis in mice. J Physiol. 2010 Sep 1;588(Pt 17):3217–29.

54. Engel AG, Arahata K. The membrane attack complex of complement at the endplate in myasthenia gravis. Ann N Y Acad Sci. 1987;505:326–32.

55. Ward ES, Zhou J, Ghetie V, Ober RJ. Evidence to support the cellular mechanism involved in serum IgG homeostasis in humans. Int Immunol. 2003 Feb;15(2):187–95.

56. Ghetie V, Hubbard JG, Kim JK, Tsen MF, Lee Y, Ward ES. Abnormally short serum half-lives of IgG in β2-microglobulin-deficient mice. Eur J Immunol. 1996;26(3):690–6.

57. Sesarman A, Vidarsson G, Sitaru C. The neonatal Fc receptor as therapeutic target in IgG-mediated autoimmune diseases. Cell Mol Life Sci. 2010/03/11 ed. 2010 Aug;67(15):2533–50.

58. Gable KL, Guptill JT. Antagonism of the neonatal Fc receptor as an emerging treatment for myasthenia gravis. Front Immunol. 2020/01/31 ed. 2020;10:3052.

59. Ulrichts P, Guglietta A, Dreier T, van Bragt T, Hanssens V, Hofman E, et al. Neonatal Fc receptor antagonist efgartigimod safely and sustainably reduces IgGs in humans. J Clin Invest. 20180724th ed. 2018 Oct 1;128(10):4372–86.

60. Vyvgart™ (efgartigimod alfa 20 mg/mL concentrate for solution for infusion) Summary of Product Characteristics [Internet]. Gent, Belgium: argenx BV; 2022. p. 1–29. Available from: https://www.ema.europa.eu/en/documents/product-information/vyvgart-epar-product-information_en.pdf

61. argenx. Efgartigimod (ARGX-113-1704) Clinical Study Report: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT). 2020;1–171.

62. European Medicines Agency (EMA). Vyvgart: summary of product characteristics [Internet]. 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/vyvgart-epar-product-information_en.pdf

63. argenx. Efgartigimod (ARGX-113-1705) Clinical Study Report (Interim Analysis 4): A Long-term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Study of ARGX 113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT+). 2022;1–165.

64. ClinicalTrials.gov. Evaluating the Pharmacodynamic Noninferiority of Efgartigimod PH20 SC Administered Subcutaneously as Compared to Efgartigimod Administered Intravenously in Patients With Generalized Myasthenia Gravis (ADAPTsc) [Internet]. 2022 Feb [cited 2022 Dec 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT04735432?term=adaptsc&cond=Myasthenia+Gravis&draw=2&rank=1

65. argenx. Efgartigimod (ARGX-113-2001) Clinical Study Report: A Phase 3, Randomized, Open-label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of Efgartigimod PH20 SC With Multiple Intravenous Infusions of Efgartigimod in Patients With Generalized Myasthenia Gravis (ADAPTSC). 2022;1–122.

66. Thomsen JLS, Andersen H. Outcome measures in clinical trials of patients with myasthenia gravis. Front Neurol. 2021/01/12 ed. 2020;11:596382.

67. Barnett C, Herbelin L, Dimachkie MM, Barohn RJ. Measuring clinical treatment response in myasthenia gravis. Neurol Clin. 2018/04/16 ed. 2018 May;36(2):339–53.

68. Burns TM, Sadjadi R, Utsugisawa K, Gwathmey KG, Joshi A, Jones S, et al. International clinimetric evaluation of the MG-QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r. Muscle Nerve. 2016/05/26 ed. 2016 Dec;54(6):1015–22.

69. Saccà F, Barnett C, Vu T, Peric S, Phillips GA, Zhao S, et al. Efgartigimod improved health-related quality of life in generalized myasthenia gravis: results from a randomized, double-blind, placebo-controlled, phase 3 study (ADAPT). J Neurol. 2023 Jan 4;

70. Cutter G, Xin H, Aban I, Burns TM, Allman PH, Farzaneh-Far R, et al. Cross-sectional analysis of the Myasthenia Gravis Patient Registry: disability and treatment. Muscle Nerve. 2019/09/06 ed. 2019 Dec;60(6):707–15.

71. argenx. argenx Announces Positive Topline Phase 3 Data from ADAPT-SC Study Evaluating Subcutaneous Efgartigimod for Generalized Myasthenia Gravis [Internet]. businesswire. 2022 [cited 2023 Feb 7]. Available from: https://www.businesswire.com/news/home/20220321005941/en/

72. NICE. Guide to the methods of technology appraisal. Available Httpswwwniceorgukprocesspmg36 Last Accessed 01042022. 2022;

73. Early access to medicines scheme (EAMS): scientific opinions [Internet]. GOV.UK. 2022 [cited 2023 Jan 26]. Available from: https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions

74. argenx Announces the UK MHRA has Granted Early Access to Efgartigimod for Generalized Myasthenia Gravis [Internet]. Argenx. [cited 2023 Jan 26]. Available from: https://www.argenx.com/news/argenx-announces-uk-mhra-has-granted-early-access-efgartigimod-generalized-myasthenia-gravis

75. Antibodies: Definition, Types & Function [Internet]. Cleveland Clinic. [cited 2023 Feb 11]. Available from: https://my.clevelandclinic.org/health/body/22971-antibodies

76. Explainer: What Is Immunoglobulin? [Internet]. [cited 2023 Feb 11]. Available from: https://www.cslbehring.com/vita/2022/explainer-what-is-immunoglobulin

77. Definition of treatment cycle - NCI Dictionary of Cancer Terms - NCI [Internet]. 2011 [cited 2023 Feb 11]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/treatment-cycle

78. Glossary [Internet]. NICE. NICE; [cited 2023 Feb 11]. Available from: https://www.nice.org.uk/glossary?letter=b

79. Intravenous Immunoglobulin [Internet]. myaware. 2020 [cited 2023 Feb 11]. Available from: https://www.myaware.org/ivig-information-sheet

80. MRI scan [Internet]. nhs.uk. 2017 [cited 2023 Feb 11]. Available from: https://www.nhs.uk/conditions/mri-scan/

81. Definition of open label study - NCI Dictionary of Cancer Terms - NCI [Internet]. 2011 [cited 2023 Feb 11]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/open-label-study

82. https://careboxhealth.com. Blog | Lilly TrialGuide [Internet]. [cited 2023 Feb 11]. Available from: https://trials.lilly.com/en-US/blog/clinical-trial-design-parallel-crossover-studies

83. What Are Clinical Trials and Studies? [Internet]. National Institute on Aging. [cited 2023 Feb 11]. Available from: https://www.nia.nih.gov/health/what-are-clinical-trials-and-studies

84. What are proteins and what do they do?: MedlinePlus Genetics [Internet]. [cited 2023 Feb 11]. Available from: https://medlineplus.gov/genetics/understanding/howgeneswork/protein/

85. Steroids [Internet]. nhs.uk. 2017 [cited 2023 Feb 11]. Available from: https://www.nhs.uk/conditions/steroids/

86. Myasthenia Gravis | National Institute of Neurological Disorders and Stroke [Internet]. [cited 2023 Feb 11]. Available from: https://www.ninds.nih.gov/health-information/disorders/myasthenia-gravis#toc-how-is-myasthenia-gravis-diagnosed-and-treated-

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Response to clarification questions

March 2023

File name	Version	Contains confidential information	Date
ID4003_Vyvgart_Response-to-clarification-questions_[redacted]	1.0	No	24 March 2023

Section A: Clarification on effectiveness data

Systematic literature review

A1. The 694 publications excluded from the January 2023 update of the clinical effectiveness systematic literature review (SLR) have not been listed in the CS, but we note CS, Appendix D, section D.3.2.2, states that these are documented in an Excel spreadsheet. Please provide the Excel spreadsheet of these 694 excluded publications. Additionally, please provide a list of the 32 further publications excluded at full-text screening stage of the review, which are referred to in CS Appendix D, section D.2.2.

The Excel documenting the 694 studies excluded from the January 2023 update of the clinical effectiveness SLR is provided separately. Table 1 shows the 32 further publications excluded at full-text screening stage.

Table 1: List of studies excluded at full-text review for the January 2023 update of the clinical SLR

No.	Title	Citation
1	Quality of Life in Myasthenia Gravis and Correlation of MG-QOL15 With Other Functional Scales	Porras L., Homedes Pedret C., Vélez Santamaria V., Alberti M., Casasnovas Pons C. Journal of Neuromuscular Diseases (2022) 9 Supplement 1 (S197). Date of Publication: 2022.45:10.3233/JND-229001.43:-.
2	Involvement of Ocular Muscles in Patients with Myasthenia Gravis with Non-ocular Onset	Lei L., Fan Z., Su S., Xu M., Chen H., Zhu W., Luan Q., Da Y. Journal of Neuro-Ophthalmology (2022) 42:1 (E260-E266). Date of Publication: 1 Mar 2022.45:10.1097/WNO.0000000000001325.43:34369469.
3	Efgartigimod: A novel FcRN antagonist in the treatment of autoimmune diseases	De Haard H., Parys W., Ulrichts P., Rocca F., Guglietta A., Beauchamp J. Haematologica (2022) 107:SUPPL 1 (94-95). Date of Publication: 1 Mar 2022.45:-.43:-.
4	Prognostic predictors of remission in ocular myasthenia gravis	Çelebisoy N., Orujov A., Balayeva F., Özdemir H.N., Ak A.K., Gökçay F. Acta Neurologica Belgica (2022). Date of Publication: 2022.45:10.1007/s13760-022-02151-4.43:-.
5	Physician-Reported Perspectives on Myasthenia Gravis in the United States: A Real-World Survey	Mahic M., Bozorg A.M., DeCourcy J.J., Golden K.J., Gibson G.A., Taylor C.F., Ting A., Story T.J., Scowcroft A. Neurology and Therapy (2022) 11:4 (1535-1551). Date of Publication: 1 Dec 2022.45:10.1007/s40120-022-00383-3.43.
6	Zilucoplan in Myasthenia Gravis: Safety and Tolerability Results From the Phase 3 Randomised RAISE Study	Leite M., Vu T., Hussain Y., Kaminski H., Utsugisawa K., Genge A., Mantegazza R., Brock M., Boroojerdi B., Vanderkelen M., De La Borderie G., Duda P., Howard J. Journal of Neuromuscular Diseases (2022) 9 Supplement 1 (S241-S242). Date of Publication: 2022.45:10.3233/JND-229001.43.
7	Zilucoplan prevented functional impairment induced by AChR+ myasthenia gravis patient sera in an in vitro NMJ model	Shin B., Wang M., Wang J., Yim J., Girouard M., Mac George S., Poppe B., Miao D., Magdesian M., Sayegh C., Vadysirisack D. European Journal of Neurology (2022) 29 Supplement 1 (224). Date of Publication: 1 Jul 2022.45:10.1111/ene.15464.43.
8	035 Humanized anti-Desmoglein-3 antibodies as tools for research on	Zakrzewicz A., Würth C., Beckert B., Feldhoff S., Verheesen P., Vanderheyden K., Stoykov I., Hertl M., Bobkov V., Tikkanen R.035. Journal of Investigative Dermatology (2021) 141:10

	the role of the neonatal Fc receptor in pemphigus vulgaris	Supplement (S154). Date of Publication: 1 Oct 2021.45:10.1016/j.jid.2021.08.036.43.
9	ANA 2021 Abstracts	ANA 2021 Abstracts. Annals of Neurology (2021) 90:SUPPL 27. Date of Publication: 1 Oct 2021.45.43.
10	Current and emerging therapies: What comes next?	Rodolico C. European Journal of Neurology (2021) 28:SUPPL 1 (45). Date of Publication: 1 Jun 2021.45.43:(Rodolico C.) Messina, Italy.
11	Different Monoclonal Antibodies in Myasthenia Gravis: A Bayesian Network Meta-Analysis	Song Z., Zhang J., Meng J., Jiang G., Yan Z., Yang Y., Chen Z., You W., Wang Z., Chen G. Frontiers in Pharmacology (2021) 12 Article Number: 790834. Date of Publication: 18 Jan 2022.45:10.3389/fphar.2021.790834.43.
12	Efgartigimod in chronic inflammatory demyelinating polyneuropathy (CIDP): Interim baseline characteristics of the phase 2 ADHERE trial	Allen J., Lewis R., Merkies I., Parys W., Vangeneugden T., Tse A., Hofman E., Van Doorn P. Journal of the Peripheral Nervous System (2021) 26:3 (383). Date of Publication: 1 Sep 2021.45.43.
13	LB773 Treating pemphigus vulgaris (PV) and foliaceus (PF) by inhibiting the neonatal Fc receptor: Phase 2 multicentre open-label trial with efgartigimod	Goebeler M., Bata-Csörgo Z., de Simone C., Didona B., Remenyik E., Reznichenko N., Schmidt E., Stoevesandt J., Ward E., Parys W., de Haard H., Dupuy P., Verheesen P., Joly P. Journal of Investigative Dermatology (2021) 141:9 (B16). Date of Publication: 1 Sep 2021.45.43.
14	SY4.3. Therapeutic considerations in myasthenia gravis	Imai T.SY4.3. Clinical Neurophysiology (2021) 132:8 (e45). Date of Publication: 1 Aug 2021.45.43:(Imai T.) Sapporo Medical University, Sapporo, Japan.
15	Quantitative evaluation of drug efficacy in the treatment of myasthenia gravis	Chen R, Zhang N, Gao L, Zhong Y, Xu L, Liu H, Zheng Q, Li L. Expert Opin Investig Drugs. 2021 Dec;30(12):1231-1240. doi: 10.1080/13543784.2021.2010704. Epub 2021 Dec 6.45:34821184.43:Chen R.
16	Efgartigimod in myasthenia gravis: Phase 3 trial design	Howard J.F., De Haard H., Parys W., Ulrichts P., Guglietta A., Mantegazza R.E. European Journal of Neurology (2020) 27 Supplement 1 (353). Date of Publication: 1 May 2020.45.43.
17	Efgartigimod improves muscle weakness in a mouse model for muscle-specific kinase myasthenia gravis	Huijbers M.G., Plomp J.J., van Es I.E., Fillié-Grijpma Y.E., Kamar-Al Majidi S., Ulrichts P., de Haard H., Hofman E., van der Maarel S.M., Verschuuren J.J. Experimental Neurology (2019) 317 (133-143). Date of Publication: 1 Jul 2019.45:10.1016/j.expneurol.2019.03.001.43:30851266.
18	Quality of Life in Myasthenia Gravis and Correlation of MG-QOL15 with Other Functional Scales	Porras L.D., Homedes C., Alberti M.A., Santamaria V.V., Casasnovas C. Journal of Clinical Medicine (2022) 11:8 Article Number: 2189. Date of Publication: 1 Apr 2022.45:10.3390/jcm11082189.43.
19	Physical and mental fatigue in myasthenia gravis and its correlation with other symptoms	Akkan Suzan A., Kahraman Koytak P., Uluc K., Tanridag T. Acta Neurologica Belgica (2022) 122:4 (915-923). Date of Publication: 1 Aug 2022.45:10.1007/s13760-022-01919-y.43:35334084.
20	Myasthenia gravis-treatment and severity in nationwide cohort	Sobieszczuk E, Napiórkowski Ł, Szczudlik P, Kostera-Pruszczyk A. Acta Neurol Scand. 2022 Apr;145(4):471-478. doi: 10.1111/ane.13576. Epub 2022 Jan 4..45:34981830.43.
21	Long-term outcome in patients with myasthenia gravis: one decade longitudinal study	Bozovic I., Ilic Zivojinovic J., Peric S., Kostic M., Ivanovic V., Lavrnic D., Basta I. Journal of Neurology (2022) 269:4 (2039-2045). Date of Publication: 1 Apr 2022.45:10.1007/s00415-021-10759-4.43:34480608.
22	Diversity of Neurologic Disorders at a Free Neurology Community Health Clinic	Deliz J., Tong Jia D., Attarian H., Curran Y., Cherayil N.R., Carroll K. Annals of Neurology (2022) 92 Supplement 29 (S99). Date of Publication: 1 Oct 2022.45:10.1002/ana.26484.43.
23	Causes of symptom dissatisfaction in patients with generalized myasthenia gravis	Andersen L.K., Jakobsson A.S., Revsbech K.L., Vissing J.. Journal of Neurology (2022) 269:6 (3086-3093). Date of Publication: 1 Jun 2022.45:10.1007/s00415-021-10902-1.43:34806129.
24	Burden of disease in myasthenia gravis: taking the patient's perspective	Lehnerer S., Jacobi J., Schilling R., Grittner U., Marbin D., Gerischer L., Stascheit F., Krause M., Hoffmann S., Meisel A. Journal of Neurology (2022) 269:6 (3050-3063). Date of Publication: 1 Jun 2022.45:10.1007/s00415-021-10891-1.43:34800167.
25	Are There Racial Differences in Inpatient Outcomes and Treatment Utilization following Hospitalization	Syed M.J., Khawaja A., Lisak R.P. Neuroepidemiology (2022) 56:5 (380-387). Date of Publication: 1 Nov 2022.45:10.1159/000524733.43:35816997.

	for Myasthenia Gravis Exacerbation?	
26	Analysis of length of stay and treatment emergent complications in hospitalized myasthenia gravis patients with exacerbation	Ramsaroop T, Gelinas D, Kang SA, Govindarajan R. BMC Neurol. 2023 Jan 12;23(1):12. doi: 10.1186/s12883-022-02922-9..45:36631752.43.
27	A population-based follow-up study of maximal muscle strength and mobility in patients with myasthenia gravis	Thomsen J.L.S., Vinge L., Harbo T., Andersen H. Neuromuscular Disorders (2022) 32:4 (305-312). Date of Publication: 1 Apr 2022.45:10.1016/j.nmd.2022.02.007.43:35279342.
28	Identifying a patient-centered outcome measure for a comparative effectiveness treatment trial in myasthenia gravis	Narayanaswami P., Sanders D.B., Bibeau K., Krueger A., Venitz J., Guptill J.T. Muscle and Nerve (2022) 65:1 (75-81). Date of Publication: 1 Jan 2022.45:10.1002/mus.27443.43:34687458.
29	Japan MG registry: Chronological surveys over 10 years	Suzuki S., Masuda M., Uzawa A., Nagane Y., Konno S., Suzuki Y., Kubota T., Sugimoto T., Samukawa M., Watanabe G., Ishizuchi K., Akamine H., Onishi Y., Yoshizumi K., Uchi T., Amino I., Ueta Y., Minami N., Kawaguchi N., Kimura T., Takahashi M.P., Murai H., Utsugisawa K. Clinical and Experimental Neuroimmunology (2022). Date of Publication: 2022.45:10.1111/cen3.12731.43.
30	Emerging Therapies and Controversies in MG	Dimachkie M. Journal of Neuromuscular Diseases (2022) 9 Supplement 1 (S53-S54). Date of Publication: 2022.45:-.43:(Dimachkie M.) University of Kansas Medical Center, Kansas City, United States.
31	PROMISE-MG: A Multicenter Prospective Observational Comparative Effectiveness Study of Myasthenia Gravis Treatments	Narayanaswami P., Sanders D., Guptill J., Li F., Desai R., Liu B., Venitz J., Krueger A., Bibeau K. Neurology (2022) 98:18 SUPPL. Date of Publication: 1 May 2022.45:-.43.
32	Real-world utilization patterns of intravenous immunoglobulin in adults with generalized myasthenia gravis in the United States	Qi C.Z., Hughes T., Gelinas D., Li Y., Goyal A., Brauer E., Bhuwalka A., Sato M., Jadhav S., Phillips G. Journal of the Neurological Sciences (2022) 443 Article Number: 120480. Date of Publication: 15 Dec 2022.45:10.1016/j.jns.2022.120480.43:36347174.

A2. Details of the data extraction and critical appraisal processes for the clinical effectiveness SLR are not reported. Please describe the processes used, such as the number of reviewers carry out each of these tasks and their roles.

Data for the efgartigimod clinical evidence used in this appraisal were extracted directly into the NICE STA submission template. All extracted data were verified against the source paper by a second researcher.

Two independent researchers performed the quality assessment. If there was disagreement about quality, consensus was reached through a discussion between the two researchers.

A3. The ADAPT+ longitudinal single cohort extension study has been quality assessed using a checklist designed for randomised controlled trials (RCTs) (CS, Appendix D, section D.5). Single cohort observational studies are subject to different elements of bias to RCTs. Please provide a quality assessment of this study using a more appropriate tool. We suggest using the quality assessment aspects for non-randomised and non-controlled evidence available in NICE's 'Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template'. Additionally, we suggest providing commentary on how the ADAPT+ study meets each of the recommendations for judging the quality of open-label extension studies detailed in Bowers et al. (Bowers, M., Pickering, R.M., Weatherall, M. (2012). Design, objectives, execution and reporting of published open-label extension studies. *Journal of Evaluation in Clinical Practice*, *18(2)*, 209-215).

Quality assessment of the ADAPT+ study based on criteria relevant to non-randomised and non-controlled evidence is provided in Table 2.

Table 2: Results of quality assessment of non-randomised and non-controlled studies

	ADAPT+[1]
Was the cohort recruited in an acceptable way?	**Yes.** Participants were recruited from the prior randomised, double-blind, placebo-controlled ARGX-113-1704 (ADAPT) trial, provided they completed the study or they required retreatment that could not be completed during a TC in that study. Inclusion criteria for ADAPT included; adult, diagnosis of MG with generalized muscle weakness (meeting criteria for MGFA class II, III, IVa and IVb) confirmed by one of 3 clinical tests, an MG-ADL total score ≥ 5 at screening and baseline with >50% due to non-ocular symptoms and on a stable dose of SOC.
Was the exposure accurately measured to minimise bias?	**Yes.** Patients all received efgartigimod (IV 10mg/kg). Outcomes were measured at set timepoints throughout the study period. The number of participants who received efgartigimod in each cycle, the number of infusions received overall and the cycle duration was collected and summarised for participants who had previously received efgartigimod, those who had previously received placebo, the overall population and those who were AChR-Ab seropositive and seronegative.

	ADAPT+[1]
Was the outcome accurately measured to minimise bias?	**Yes.** Outcomes were measured as follows: • Disease severity: measured using MG-ADL +/- QMG (standardized assessments used to evaluate MG symptoms in adults in clinical studies). Serial measurements of these assessments over time while receiving treatment provided information on the efficacy of efgartigimod. • Safety measurements included assessment of TEAEs (assessed, documented, and reported following ICH GCP guidelines), clinical laboratory evaluations, vital signs, physical examinations, ECGs, and the suicidal ideation assessment derived from the PHQ-9 (part A only). • Pharmacodynamic assessments (Part A only) were done by measuring levels of total IgG and IgG subtypes (IgG1, IgG2, IgG3, and IgG4) from blood samples collected at set time points using validated methods. AChR-Ab in participants who are AChR-Ab seropositive and MuSK-Ab in participants who are MuSK-Ab seropositive were also measured. Analyses were performed by AChR-Ab status and overall. • Immunogenicity assessments include analyses of ADA and NAb raised against efgartigimod. Analyses were performed in the AChR-Ab seropositive and overall populations.
Have the authors identified all important confounding factors?	**Not clear.** No confounding factors are mentioned except the exclusion of participants with clinical evidence of other significant disease or who underwent a recent major surgery, or had clinical evidence of bacterial, viral, or fungal disease or any other significant disease that could confound the study results or put the patient at undue risk.
Have the authors taken account of the confounding factors in the design or analysis, or both?	**Not applicable**. The efficacy and safety results are presented descriptively.
Was the follow-up of patients complete?	**Yes**. This study is ongoing but follow up for part A is 1 year and part B is ≤ 2 years. Missing safety or efficacy data were not imputed. All available data collected from participants who dropped out of the study were included in the analyses.
How precise are the results? For example, in terms of confidence intervals and p values	**Not applicable**. The efficacy and safety results are presented descriptively.

Responses for each question could be: yes, no, not clear or not applicable.
Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; ADA, antidrug antibodies; ECG, Electrocardiogram; IgG, immunoglobulin gamma IV, intravenous; MG, Myasthenia Gravis; MG-ADL, myasthenia gravis activities of daily living scale; MGFA; Myasthenia Gravis Foundation of America; MuSK-Ab, anti–muscle-specific-kinase antibody; Nab, neutralizing antibody; PHQ-9, Patient Health Questionnaire item 9; TEAEs, Treatment Emergency Adverse Events; QMG, Quantitative Myasthenia Gravis score.

In response to the EAG's request to assess the ADAPT+ study against the recommendations in Megan *et al*,[2] this follows below:

Table 3: Results of quality assessment of non-randomised and non-controlled studies

	ADAPT+[1]
Explicitly stated aims, to minimize the possibility of Type I error?	**Yes.** The purpose of the study is clearly stated: 'to evaluate the long-term safety and tolerability of efgartigimod administered in participants with gMG'. There was no pre-specified hypothesis.
A well-characterized sample representative of the target population in whom the medication will be used?	**Yes.** The study population is described in detail. Participants were recruited from the ADAPT trial (randomized, double-blinded, placebo-controlled, multicentre, phase 3 study), provided they completed the study or they required retreatment that could not be completed during a TC in that study. Of 167 patients from the RCT, 151 rolled over into the ADAPT+ and 145 received at least 1 dose (or part of a dose) of open-label efgartigimod. 111 (76.5%) were AChR-Ab seropositive and 34 (23.5%) were AChR-Ab seronegative – in real-world settings approximately 90% of patients have IgG autoantibodies with the most common against AChR.
Outcome assessment is masked to treatment received where possible?	**Yes.** All patients in ADAPT+ received open label efgartigimod; outcome assessment masking to treatment was therefore not possible.
A low rate of sample slippage in relation to the numbers randomized in the preceding RCT, but the length of follow-up should be considered in making this assessment?	**Yes.** After rolling over from ADAPT, 145 participants in ADAPT+ had received ≥1 dose (or part of a dose) of efgartigimod by the interim data cut-off date (31st January 2022). The mean (SD) duration of treatment combined with follow-up in the total efgartigimod group was 548.0 (231.79) days, which results in 217.55 patient-years of observation. 35 (24.1%) patients discontinued efgartigimod. Primary reasons for discontinuation of efgartigimod (n=35) during the ADAPT+ study were "Withdrawal by participant" (11 [7.6%] participants), "Treatment failure" and "AEs" (8 [5.5%] participants each). A total of 56 (38.6%) patients rolled over to the ARGX-113-2002 study to continue efgartigimod treatment with PH20 SC dosing.
Objectives, design, conduct, analysis and results are adequately described?	**Yes.** The objectives of the study are clearly stated, as is the overall study design and plan, including detailed inclusion and exclusion criteria, details for why patients would be discontinued for the trial study and methods for analysis. Efficacy and safety evaluations are reported in detail, and a synopsis is provided.
Limitations of the specific study design used and its execution should be discussed?	**Unclear.** Limitations of the study design are not discussed.

Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; CSR, Clinical Study Report; gMG, generalised Myasthenia Gravis; SC, subcutaneous.

MyRealWorld MG study

A4. The company-led MyRealWorld MG study provides data for background information on the condition and informs the economic model analyses in the CS. Please provide a critical appraisal (risk of bias assessment) for this study.

Quality assessment of the MyRealWorld MG study based on criteria relevant to non-randomised and non-controlled evidence is provided in Table 4. The study is subject to the typical risk of bias associated with a prospective, observational, longitudinal, real-world, PRO study.

Table 4: Results of quality assessment of non-randomised and non-controlled studies

	MyRealWorld MG[3,4]
Was the cohort recruited in an acceptable way?	**Yes.** Recruitment was conducted primarily through Patient Advocacy Groups, social media and via treating neurologists. While there is some potential for selection bias towards more proactive patients – who may be more likely to engage with PAGs and social media and those who can access/use the internet and have a phone and/or tablet – the company believes that the population recruited is generalisable to UK patients with gMG.
Was the exposure accurately measured to minimise bias?	**Yes**. Participants were followed up as follows. • Participants initially asked to complete a profile to collect data about themselves (e.g. demographics, diagnosis, past treatments). If any of these changed then they can be updated by the participant. • Participants asked to complete a monthly tracker to document any MG-related events for that month e.g. time off work, hospital appointments. • Every 1 to 6 months (depending on the instrument) participants asked to complete PRO instruments to assess QoL, specific symptoms and function.
Was the outcome accurately measured to minimise bias?	**Yes.** Either core PRO instruments (to be completed by all participants) or optional PRO instruments (for participants who opt-in). • Core: EQ-5D-5L, EQ-5D-5L bolt on items, MG-ADL, MG-QOL 15R, HADS, HUI3, COVID-19 survey • Optional: PROMIS, FACIT-Fatigue, PROMIS sleep disturbance short form 6a While the PRO instruments were not originally developed to be administered via an app, the Company took expert advice on the selection of tools based on which we deemed to be transferable to an app. The sample size and composition of patients will likely vary for each instrument used and each time it is filled in. This will also make comparison with results

	MyRealWorld MG[3,4]
	from other literature difficult/limited. Additionally, due to the remote nature of the data collection patient eligibility and accuracy of the data could not be verified.
Have the authors identified all important confounding factors?	**Not clear**. None are mentioned
Have the authors taken account of the confounding factors in the design or analysis, or both?	**Not applicable**. As an exploratory observational study, causation is not explored regarding differences and patterns in the data. Analyses will be descriptive, and no hypotheses will be tested.
Was the follow-up of patients complete?	**Not applicable.** Study is ongoing, but patients will be followed up for 2 years.
How precise are the results? For example, in terms of confidence intervals and p values	Generally, this is **not applicable** as the results are descriptive. Confidence intervals are given for continuous variables, but otherwise results are distributions, means, SD, quartile ranges, proportions. A regression analysis on the utility complement (1 -utility value) and the different items of the MG-ADL instrument was estimated to establish which items had the largest impact on utility values (used a normal distribution and an identity link) - the confidence intervals for these are quite broad.

Responses for each question could be: yes, no, not clear or not applicable.
Abbreviations: EQ-5D-5L, EuroQol 5 Dimension 5 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HADS, hospital anxiety and depression scale; HUI3, Health Utilities Index III; MG, Myasthenia Gravis; MG-ADL, myasthenia gravis activities of daily living scale; MG-QOL 15r, Myasthenia Gravis Quality Of Life 15-item revised scale; PAG, Patient Advisory Group; PRO, Patient-Reported Outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, Quality of Life; SD, standard deviation.

Proposed use of efgartigimod in the treatment pathway

A5. Priority question: CS, section B.1.3.3.7, states that it is anticipated that efgartigimod will be used as an add-on to standard therapy in the treatment of adults with generalised myasthenia gravis who are AChR-Ab+. However, CS Figure 10 shows that efgartigimod is expected to be used either as an add-on to or as a replacement of pyridostigimine and corticosteroids, azathrioprine, ciclosporin or methotrexate or mycophenolate mofetil or tacrolimus. CS Figure 10 also shows efgartigimod is expected to replace rituximab/IVIg. Please clarify why it is expected that efgartigimod may be used as a replacement option for each of these drugs.

The Company is happy to clarify Figure 10 (Section B.1.3.3.7 Proposed place of efgartigimod in the current treatment pathway). While the current treatment schema suggests a stepwise approach through the treatment pathway, in practice, conventional therapies (pyridostigmine, corticosteroids or NSISTs) are selected according to patient characteristics, comorbidities and severity of symptoms. Importantly, these treatments may be used alone or in combination. As gMG disease progresses and becomes inadequately controlled, conventional therapies are typically escalated and used in combination. For example, the addition of NSISTs to the treatment regimen for a patient already receiving pyridostigmine and/or corticosteroids to improve disease control; furthermore, adding NSISTs may enable tapering the dose – or perhaps even discontinuing – pyridostigmine and/or corticosteroids.

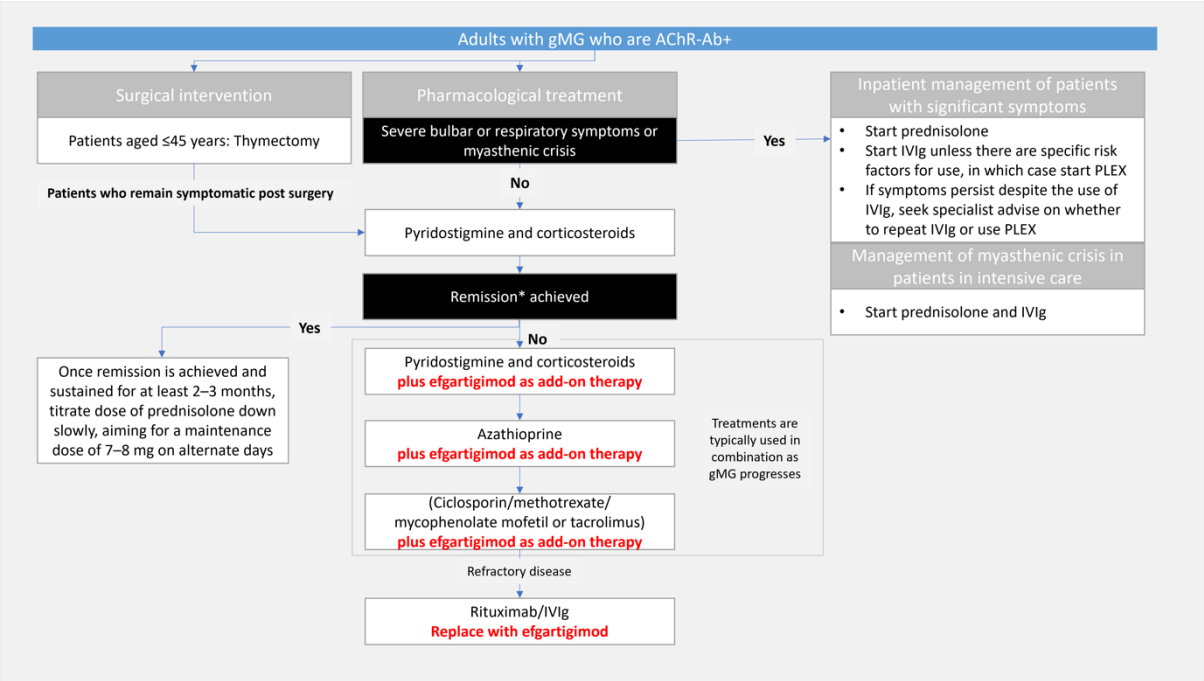
With an indication “as an add-on to standard therapy for the treatment of adult gMG patients who are AChR-Ab+”, efgartigimod addresses the unmet need for an effective, well-tolerated therapy that can be used to treat gMG patients whose symptoms remain uncontrolled despite receiving established clinical management.

For simplicity we have updated Figure 10 to reflect that efgartigimod will primarily be used as an add-on to established clinical management (see Figure 1 below). We have removed ‘replace’ from the pyridostigmine, corticosteroid and NSIST boxes. However, we anticipate that the addition of efgartigimod to such established clinical

management may enable gradual dose tapering of these concomitant agents. In line with the anticipated licence indication, efgartigimod has not been studied as a monotherapy.

In gMG patients with refractory disease, efgartigimod may be considered in combination with established clinical management as an alternative to rituximab or IVIg. Treatment with efgartigimod would make addition of rituximab or IVIg unnecessary.

Figure 1 Proposed place of efgartigimod in the current treatment pathway



Treatments may be used individually or in combination; where efgartigimod is used as add-on therapy, this may enable tapering – and in some cases discontinuation – of other therapies, e.g., corticosteroids.
*Remission of gMG on corticosteroid therapy is defined as the absence of symptoms or signs after pyridostigmine withdrawal.
Abbreviations: AChR-Ab+, acetylcholinesterase inhibitor antibody positive; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; PLEX, plasma exchange

A6. Priority question: CS, section B.1.3.3.7, Figure 10, suggests that the company is positioning efgartigimod for patients with generalised myasthenia gravis who are AChR-Ab+ and who do not achieve remission on pyridostigmine and corticosteroids. Please clarify why efgartigimod is being positioned for this sub-set of patients. For example, why is efgartigimod not being positioned as an initial pharmacological treatment for all patients with generalised myasthenia gravis who are AChR-Ab+?

Efgartigimod is not being positioned as an initial pharmacological treatment for all patients with gMG who are AChR-Ab+ to ensure alignment with the ADAPT study design, and approved licence indication i.e. as an add-on to standard therapy for the treatment of adult gMG patients who are AChR-Ab+. To be eligible for inclusion in ADAPT, patients were required to be on a stable dose of ≥1 therapy for gMG, that could include AChEis, steroids, and NSISTs, alone or in combination, prior to screening. Therefore ADAPT does not provide data on the use of efgartigimod as initial treatment for gMG.

A7. Is it expected that there will be any limit on the number of efgartigimod treatment cycles patients will be able to receive in clinical practice?

The posology for efgartigimod is a recommended dose of 10 mg/kg as a 1-hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks. Subsequent treatment cycles are administered according to clinical evaluation depending on patient response. The frequency of treatment cycles may vary by patient; in the clinical development program, the earliest time to initiate a subsequent treatment cycle was 7 weeks from the initial infusion of the previous cycle. There is no mandatory limit on the number of efgartigimod treatment cycles patients might receive in clinical practice.

Methodology of the included studies

A8. Please clarify if any centres or participants based in the UK were involved in the ADAPT, ADAPT+ and ADAPT-SC studies. If UK centres or participants were involved, how many participated in each study?

No UK sites participated in the ADAPT, ADAPT+ or ADAPT-SC studies. UK sites were initially selected for the ADAPT study; however, UK approval timelines meant that they were not able to open before recruitment started. ADAPT data were collected as 56 neuromuscular academic and community centres across Japan and 14 countries in Europe and North America; care pathways and available therapies in these countries is similar to that for the UK.

A9. CS, section B.2.3.1, Table 11, states that in the ADAPT trial randomisation was stratified based on whether or not participants were taking nonsteroidal immunosuppressive therapies (NSISTs) and Japanese nationality (yes versus no), as well as AChR-Ab status. What was the rationale for the stratifying according to use of NSISTs and Japanese nationality?

The Japanese regulatory authority – PMDA (Pharmaceuticals and Medical Devices Agency) – requires a minimum number of Japanese patients to be included in studies. Japanese nationality was therefore included as a stratification factor to ensure an even distribution of patients between treatment arms. There were 11 AChR-Ab seropositive patients in the Japanese/Asian population in study ARGX-113-1704 and Japan-specific analyses were prepared for the Japanese Marketing Authorization Application.

Use of concomitant NSIST at study entry was defined as a stratification factor as there had been an imbalance in this baseline characteristic in the Phase 2 study (25% placebo group receiving NSIST vs. 75% efgartigimod) and the aim was to avoid this in the Phase 3 study. As a higher proportion of patients with gMG are typically receiving AChEi and steroids, than NSIST, it was considered most important

to balance NSIST use between the treatment arms. Table 5 shows that concomitant exposure to MG treatment classes was well balanced in the ADAPT study.

Table 5: gMG therapy at baseline in ADAPT for the AChR-Ab+ patient population

	Efgartigimod (n=65)	Placebo (n=64)
gMG therapy at baseline, n (%)		
Any steroid	46 (70.8)	51 (79.7)
Any NSIST	40 (61.5)	37 (57.8)
Steroid + NSIST	34 (52.3)	31 (48.4)
No steroid or NSIST	13 (20.0)	6 (9.4)

Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; gMG, generalised myasthenia gravis; NSIST, nonsteroidal immunosuppressive therapy
Sources: Howard et al, 2021[5]; argenx, 2020.[6]

A10. Priority question: CS, section B.2.2, states that the systematic literature review identified data from an interim data analysis of the ADAPT+ study that had a data cut-off of January 2022. Is this the most recent analysis of the results of this study or has a further, planned interim analysis been undertaken? If more up-to-date clinical effectiveness results are available from the ADAPT+ study, please provide these.

The Company submission dated 14 February 2023 included the latest ADAPT+ data cut available, namely interim analysis 4 (IA4; cut-off date 31st January 2022). A manuscript based on IA4 is expected to be published by the end of July 2023.

The final analysis (cut-off date 14 Dec 2022) and associated clinical study report is due to be finalised in April 2023; data have been submitted and accepted for presentation at the American Academy of Neurology (AAN) annual conference in April 2023, and the European Academy of Neurology annual conference in July 2023.

Comparison of the IA4 data with the Final Analysis for treatment duration and number of treatment cycles is shown in Table 6. Minimal differences are observed between IA4 and the Final Analysis in terms of exposure and observation period.

Table 6: Treatment exposure in the ADAPT study at IA4 and Final Analysis

	IA4 (cut-off date: 31 Jan 2022)	Final analysis (cut-off date: 14 Dec 2022)
Mean (SD) duration of treatment combined with follow-up	548.0 (231.79) days 217.55 patient-years of observation	576.7 (253.32) days 228.94 patient-years of observation
Median (min, max) study duration	588.0 (40, 924) days	602.0 (50, 1074) days
Max number of cycles	17	19

Abbreviations: IA4, interim analysis 4; SD, standard deviation.

The data and conclusions from IA4 and the Final Analysis dataset are concordant. No new safety observations were identified in the Final Analysis set vs. IA4, and the Final Analysis showed consistent and repeatable improvements in MG-ADL and QMG scores over repeated cycles, similar to the IA4 results.

Study outcomes

A11. Priority question: We note that number and percentage of MG-ADL responders was a secondary endpoint in the ADAPT-SC study (CS, section B.2.12, Table 22). How were MG-ADL responders defined in this study?

MG-ADL responders were defined as having ≥2 point reduction (improvement) from baseline on the MG-ADL total score for ≥4 consecutive weeks, with the first reduction occurring at the latest 1 week after the last efgartigimod administration. The definition of MG-ADL responses in ADAPT-SC was the same as in the ADAPT study.

A12. Priority question: CS, section B.2.3.1, Table 11, suggests that the outcome 'hospitalisations' was measured in the ADAPT study, but results for this outcome do not appear to have been reported in the CS. Was this outcome measured? If so, please provide the results and information about how this outcome was defined.

While hospitalisation was not a prespecified endpoint in ADAPT, hospital stays for patients with gMG were captured as a component of the safety analysis i.e. from the serious adverse event (SAE) reporting listings. A *post hoc* analysis of this hospitalisation data has since been reported.[7] In this analysis, the observed number of all-cause and MG-related hospitalizations during ADAPT were combined with the patient follow up time to calculate an incidence rate of hospitalisations per treatment arm.

A total of 14 hospitalisation events were observed during ADAPT (n=4 for patients in the efgartigimod treatment arm, and n=10 in the conventional therapy arm). Among these, four hospitalizations were related to MG (n=1 for patients in the efgartigimod treatment arm, and n=3 in the conventional therapy arm). Patients receiving efgartigimod had a 60% lower rate of all-cause hospitalization (11.4 vs. 28.3 per 100 patient-year [PY]) and 67% lower rate of MG-related hospitalization (2.8 vs. 8.5 per 100 PY) than patients who received conventional therapy alone (p-value not significant). The congress poster providing further details of this analysis has been provided separately.[7]

Treatment discontinuation in ADAPT+ study

A13. CS, section B.2.4.2.2, provides some of the reasons why participants discontinued treatment during the ADAPT+ study (accounting for 72 of the 91 participants who discontinued). Please provide a full list of the reasons, along with a breakdown of the number and proportion of participants in the AChR-Ab+ and overall populations discontinuing for each reason.

We would like to clarify that of the 91 participants who discontinued from the ADAPT+ study, 56 (38.6%) of those elected to continue receiving efgartigimod in the ADAPT-SC study (ARGX-113-2002) and 35 (24.1%) discontinued efgartigimod. Reasons for discontinuation of efgartigimod (n=35) during the ADAPT+ study are shown in Table 7. Of the 24.1% of patients who discontinued efgartigimod, the primary reasons for discontinuation were “Withdrawal by participant” (11 [7.6%] participants), “Treatment failure” and “AEs” (8 [5.5%] participants each).

The AChR-Ab seropositive and AChR-Ab seronegative subpopulations were defined based on the stratification factor as randomized in the antecedent study ADAPT. The demography of the AChR-Ab seropositive population was similar to that of the overall population. Disease characteristics at baseline were similar among the AChR-Ab seropositive, AChR-Ab seronegative, and the overall populations.

Table 7 Reasons for discontinuation of efgartigimod in ADAPT+

Reason for discontinuation	AChR-Ab+ (n = 111)	All Patients (N = 145)
Withdrawal by participant	8 (7.2%)	11 (7.6%)
Treatment Failure	6 (5.4%)	8 (5.5%)
Adverse Events	7 (6.3%)	8 (5.5%)
Death	3 (2.7%)	4 (2.8%)
Prohibited medication	2 (1.8%)	2 (1.4%)
Rescue Therapy	1 (0.9%)	1 (0.7%)
Sponsor decision	1 (0.9%)	1 (0.7%)

Other

A14. Please summarise what known prognostic factors influence patient outcomes in generalised myasthenia gravis.

The literature reporting on possible prognostic factors that influence outcomes in gMG is variable, and often conflicting. A 2022 observational retrospective cross-sectional multicentre study based on data from 990 patients with MG included in the Spanish MG Registry (NMD-ES) provides data on clinical characteristics of patients who are drug refractory.[8] In their analysis, Cortes-Vincente and colleagues found that drug-refractory patients were more frequently women ($p < 0.0001$), younger at onset ($p < 0.0001$), and anti-MuSK positive ($p = 0.037$).

Other studies present conflicting views of the impact of patient age and/or age of onset. For example, de Meel and colleagues found the late-onset MG and the presence of additional autoimmune diseases were associated with a higher risk of exacerbations of MG and the necessity of emergency treatments,[9] while a retrospective chart review by Andersen and colleagues found that patients with late-onset MG had a higher frequency of optimal outcomes than patients with early-onset disease.[10]

Overall, the literature suggests that MG is a disease with no clear identified prognostic factors for response to treatment, beyond antibody status, and high variability in proposed prognostic factors for general disease outcomes.

In its analysis of the ADAPT and ADAPT+ study data, the Company did not identify any predictors of disease response, and there was good internal consistency within the ADAPT dataset. As shown in Appendix E of the CS (Appendix Figure 6, p56), efgartigimod demonstrated efficacy regardless of prior thymectomy status, and prior NSIST therapy.[11] Analyses of patient subgroups by baseline MG-ADL score showed consistent improvement across disease activity levels in MG-ADL and QMG scores in AChR-Ab+ patients treated with efgartigimod.[11] Overall, post *hoc* subgroup analyses demonstrated that efgartigimod was effective in a broad population of

patients, with improvements over placebo that were consistent regardless of concomitant therapy, baseline disease activity, or prior NSIST exposure.[12]

A15. Did the company conduct a review to try to identify real world sources of patient outcomes with established clinical management which could have been used in an indirect treatment comparison (ITC) of efgartigimod versus established clinical management? If so, please summarise the results and explain why, in each case, identified studies were not suitable (e.g. the Spanish Registry of Neuromuscular Diseases, NMD-ES).

The Company has conducted a review of potential real-world data sources in gMG, but not for the purposes of conducting an ITC of efgartigimod vs established clinical management. This research was a feasibility assessment to identify appropriate data sources that could be used to conduct a historical control arm study to assess and compare patient- and clinician-reported outcomes for efgartigimod-untreated seronegative gMG patients (from RWD) vs. efgartigimod-treated seronegative gMG patients (from Phase 3 efgartigimod trials) and also for the purposes of potential comparator data sets for the EMA post-approval safety study commitment. There are existing data sources, however the data collected is highly variable and most are not able or willing to provide data.

While the Company appreciates the benefits of using real-world data as a complement to randomised clinical trial data, it was considered unnecessary to use such data in the submission due to the existence of the Phase 3 ADAPT study. ADAPT is a randomised, double-blind, placebo-controlled, multicentre, 26-week, Phase 3 trial to evaluate the efficacy, safety, and tolerability of efgartigimod as add-on to established clinical management compared with established clinical management alone in adults with gMG.[5] This comparative RCT of efgartigimod vs established clinical management provides robust, randomised evidence of comparative effectiveness, without relying on identification of real-world data sources (which may themselves be subject to bias and uncertainty). The clinical trial included 167 patients from 56 clinical sites in 15 countries, representing a large and broad

population of patients, especially considering the low prevalence of gMG, which is an orphan disease.[5] The patient population enrolled in the study is representative of the gMG patient population in terms of age, gender, and prior and ongoing use of gMG therapies.

To address the fact that patients enrolled in ADAPT could not receive rituximab or IVIg – both considered part of established clinical management in the UK – (as described in Section B.2.3.1 in the CS), the Company conducted a review of randomised and non-randomised clinical trials to explore the potential conduct an ITC. As stated in Section B.2.10 of the CS the published evidence base for clinical trials of therapies for the management of gMG is limited, and recommendations are often based on established clinical practice rather than RCTs.[13–15] In the cases of rituximab and IVIg, evidence of clinical benefit is particularly limited. Section B.1.3.3.4 in the CS describes a Cochrane review for IVIg that concluded there is insufficient evidence from trials to determine whether IVIg is efficacious as a maintenance treatment in chronic gMG.[16] For rituximab, both the BeatMG and RINOMAX studies failed to demonstrate a statistically significant clinical benefit for rituximab vs. placebo.[17,18] Given the insufficient level of evidence available a reliable indirect treatment comparison was considered not feasible. The Company did not anticipate that real-world data would provide more robust estimates of the efficacy of rituximab and IVIg – in a format deemed appropriate for an ITC – than the published literature.

Section B: Clarification on cost-effectiveness data

Clinical parameters

B1. CS, section B.3.3.1, states MyRealWorld MG provided the data for baseline patient characteristics in the model, but the population in England and Wales in this study is a small sample (n=25). Please provide this demographic data for the AChR+ EU population in MyRealWorld MG who fulfilled the ADAPT inclusion criteria.

MyRealWorld MG includes patients from some EU countries (Denmark, France, Germany, Italy and Spain) and the United Kingdom (UK). Table summarizes by country the number of patients included in the MyRealWord MG study that meet the ADAPT criteria.

Table 8. Number of patients in MyRealWord MG study meeting the ADAPT criteria

Country	Number of patients meeting the ADAPT criteria (%)
Denmark	5 (1.43)
France	23 (6.57)
Germany	46 (13.14)
Italy	172 (49.14)
Spain	79 (22.57)
UK	25 (7.14)
EU + UK patients	350 (100)

Abbreviations: EU, European Union; UK, United Kingdom

While the Company acknowledges that the UK population in this study is relatively small (n=25, 7.14%), analysis of baseline characteristics and demographics suggests that the population is well matched in terms of age and gender to the ADAPT study population (45.2 and 80%, respectively for patients from UK, and 45.8 and 78% for patients from EU + UK). Therefore, the age and gender distribution for UK patients from the MyRealWord MG study was considered robust to populate the model. Baseline characteristics of the overall EU+UK population included in MyRealWorld MG, including characteristics that were not used for the model, are presented in Table 9.

Table 9. Baseline characteristic of patients in MyRealWorld MG study meeting the ADAPT criteria in EU + UK subset

Country	EU + UK patients
Age (years)	45.8
% females	77.7
Disease duration (years since diagnosed)	8.5
MG-ADL <5	0%
MG-ADL 5-7	46.9% (164/350)
MG-ADL 8-9	22.6% (79/350)
MG-ADL ≥10	30.6% (107/350)
Class I	0%
Class II	20.6% (72/350)
Class III	50.0% (175/350)
Class IV	29.4% (103/350)
Class V	0%
MG-QoL-15r total score	15.9
Employment status	74.0% (250/338)
Working or studying	1.8% (6/338)
Choose not to work/study	13.9% (47/338)
Cannot work/study or retired early due to MG disability	6.8% (23/338)
Retired (not because of MG)	3.6% (12/338)
Other	74.0% (250/338)
Of those working/studying, how many with sick days in past month	50.4% (126/250)

Abbreviations: EU, European Union; UK, United Kingdom.

B2. Priority question: Please clarify and justify the assumptions required for pooling the transition matrices for ADAPT and ADAPT+. Please provide separate transition matrices for ADAPT and ADAPT+ data showing the numbers of patients not percentages (i.e. disaggregating the data for these two studies as reported in tab 'Trans matrix efga' in the economic model).

In the base case of the submitted model, the Company used observations from the pooled ADAPT and ADAPT+ studies to calculate the transition probabilities in the efgartigimod arm while patients are on treatment. The company believes that this approach is the most appropriate for two reasons:

1. This approach maximises the sample size, thereby adding more precision in terms of transition probabilities calculations and, in some cases, improving the face validity of transitions in the model. As an example, if transition probabilities were based on ADAPT observations alone, in cycle 2 all patients in MG-ADL 5-7 will transition to MG-ADL<5 (see Table 11 below). By contrast, using ADAPT+ observations alone, in cycle 2 all patients in MG-ADL >7 will transit to MG-ADL<5 (see Table 13 below).

2. This approach better captures the comprehensive and long-term effect of efgartigimod therapy. For example, using the ADAPT+ transitions alone would potentially ignore the effects of initial treatment cycles for efgartigimod, as it would only consider data after patients had moved to the ADAPT extension study. Given that a high proportion of patients moved from ADAPT to ADAPT+, using ADAPT+ data alone would exclude earlier treatment outcomes data for some patients.

Table 10, Table 11, Table 12, Table 13 and Table 14 below provide data from both studies in terms of patient numbers who are transitioning between the health states for each cycle up to cycle 3 of treatment. Beyond treatment cycle 3 there are only observations from ADAPT+.

Table 10. Number of patients transitioning between the health states in ADAPT study in the first cycle of treatment

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10
MG-ADL <5	0	0	0	0
MG-ADL 5–7	9	1	0	0
MG-ADL 8–9	16	4	1	0
MG-ADL ≥10	9	6	3	2

Table 11. Number of patients transitioning between the health states in ADAPT study in the second cycle of treatment

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10
MG-ADL <5	0	0	0	0
MG-ADL 5–7	6	0	0	0
MG-ADL 8–9	7	2	0	0
MG-ADL ≥10	12	4	2	3

Table 12. Number of patients transitioning between the health states in ADAPT study in the third cycle of treatment

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10
MG-ADL <5	0	0	0	0
MG-ADL 5–7	1	0	0	0
MG-ADL 8–9	1	0	0	0
MG-ADL ≥10	2	1	1	0

Table 13. Number of patients transitioning between the health states in ADAPT+ study in the second cycle of treatment

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10
MG-ADL <5	0	0	0	0
MG-ADL 5–7	3	1	0	0
MG-ADL 8–9	2	0	0	0
MG-ADL ≥10	4	0	0	0

Table 14. Number of patients transitioning between the health states in ADAPT+ study in the third cycle of treatment

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10
MG-ADL <5	0	0	0	0
MG-ADL 5–7	7	0	0	0
MG-ADL 8–9	4	0	0	0
MG-ADL ≥10	12	6	4	2

In the updated model the disaggregated data for ADAPT and ADAPT+ have been added in the sheet 'Trans matrix efga'. Please note that observations from ADAPT are for a maximum of 3 cycles, while from ADAPT+ there are observations between cycles 2 and 19. Please note also that, given the lower sample size and relatively fewer observations beyond cycle 13 in ADAPT+ (i.e. there are only 10 patients in cycle 14, and fewer in the following cycles), only the average of the transitions observed between cycles 2 to 13 (i.e. not including the transitions observed in cycles 14 to 19) were considered for calculation of transition probabilities in the efgartigimod arm on treatment in cycle 2 onwards.

B3. Priority question: Please explain why, when selecting 'ADAPT' for the efgartigimod extrapolation (switch in the Results! Tab of the model), only cycle 2 data are used in the trans matrix for the MG-ADL>=5 patients in the efgartigimod group (from the Trans matrix efga! Tab of the model), and not cycle 3 as well.

In the CS the Company included a scenario in which transition probabilities were informed by patients from ADAPT only. For clarity, this meant that the scenario considered the cycle 1 observations from ADAPT (as only ADAPT provides cycle 1 data) and the cycle 2 observations from both ADAPT and ADAPT+ pooled (as both ADAPT and ADAPT+ provide cycle 2 data [though noting that the majority of these observations are from ADAPT]).

The table reporting the number of patients transitioning between health states in cycle 3, included in the in 'Trans matrix efga' tab in the model submitted to NICE on 15th February 2023, includes observations from both ADAPT (with just 6 observations) and ADAPT+ (with 35 observations). Although the cycle 3 counting table does include 6 patients from the ADAPT study, it was considered that this number of observations was too small to provide robust transition probabilities for cycle 3. Therefore, for the cycle 3 the Company pooled ADAPT and ADAPT+ to provide more robust transition estimates for the base case analysis.

B4. Priority question: CS, sections B.3.3.4.5 and 3.3.4.4: please explain why the transition probabilities during the efgartigimod off-treatment model cycle use changes in MG-ADL from week 4 to week 8 in the first treatment cycle in the placebo arm in ADAPT. Might the transition probabilities for patients previously treated with efgartigimod differ from the transition probabilities for patients in the placebo arm (e.g. due to residual treatment benefit)?

The Company is not aware of any proof of the existence of a residual treatment effect. In determining an appropriate and robust approach for incorporating transition probabilities in the model, the Company was concerned that the low number of observations may lead to uncertainty in the transition probabilities, such that each individual patient would exert a potentially significant impact in shifting transition probabilities. In other words, because of the small patient numbers, only one observation in the opposite direction compared to the other treatment arm could have a considerable impact on the difference in transition probabilities between the two arms. To address these potential uncertainties – which could affect the respective arms of the model in opposite directions – the Company choose to source transition probabilities for patients not receiving efgartigimod in both arms from the same set of data, derived from the placebo arm of the ADAPT trial. This means that transition probabilities in efgartigimod arm, while patients remain off treatment, are informed by the same data that are used to estimate transitions in the SoC arm. The Company's approach ensures that any bias introduced by the low number of observations impacts both treatment arms equally.

B5. Please define 'acute exacerbation' as used in the economic model (CS, section B.3.2.2, page 85).

For economic model purposes, 'acute exacerbation' reflects the serious treatment-emergent adverse event that was reported as 'myasthenia gravis' in Table 43 of the ADAPT CSR, in which it was categorized as a nervous system disorder. According

to the ADAPT protocol, an adverse event is considered 'serious' if at least one of the following criteria apply:

- Results in death
- Is life-threatening (the patient is at a risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization. However, a planned hospitalization related to the administration of the investigational product, is not considered a serious AE.
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect.
- Other: Medically significant events, which do not meet any of the criteria above, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in inpatient hospitalization

Health-related quality of life

B6. Priority question: Uncertainty over the differences in utility estimates between the treatment arms from the mixed model regression of ADAPT data (CS, Table 40) is explored in a scenario analysis using data from MyRealWorld MG (CS, Table 41) (CS, section B.3.4.2). Please provide further detail about the data and methods used in the MyRealWorld MG utility analysis. Please also run a scenario of the ADAPT utility analysis, omitting the treatment co-variate.

In the scenario highlighted by the EAG, the utility values assigned to the MG-ADL <5, MG-ADL 5-7, MG-ADL 8-9 and MG-ADL ≥10 health states were estimated by regressing the corresponding EQ-5D-5L utilities in each health state using observations from the MyRealWorld MG dataset. In MyRealWorld MG, EQ-5D-5L data were collected at one-monthly intervals. The UK EQ-5D-5L value sets were

applied to obtain utility values applicable to the population in England.[19] Data were mapped to EQ-5D-3L to derive utility values according to the mapping function developed by the Decision Support Unit, using the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) dataset.[19]

The regression was implemented using a mixed model with fixed and random effects. The mixed model is an extension of the linear model and is used to analyse longitudinal data from several patients. With longitudinal data, the EQ-5D observations of the same patient have a higher correlation. For this reason, the results of a linear model may be biased because they may represent a trend that would only be observable with aggregated data, but different from what would be observed when considering data from a single patient. The mixed model solves this problem by taking into account that the longitudinal EQ-5D observations of each patient may show different trends. Thus, the parameters of the model, which refer to the whole population and not to a specific patient, are subject to a certain degree of uncertainty and vary randomly within a certain range. A fixed term and a random term are introduced into the model for each parameter assumed to differ between patients. The fixed term represents the expected value of the parameter in the whole sample, while the random term represents its variability.

In the analysis, a random term is introduced for the intercept, which means that the average EQ-5D utility of the entire sample is assumed to vary between patients. The corresponding fixed term represents the expected EQ-5D utility value. The EQ-5D utility in health state MG-ADL <5 is used as a reference (model intercept). All other values per health state are coefficients representing the difference in EQ-5D utility from the reference value.

The mixed model was based on the following equation:

$$HRQoL = \beta_0 + r_0 + \beta_{MG-ADL\,5-7} \times HS_{MG-ADL\,5-7} + \beta_{MG-ADL\,8-9} \times HS_{MG-ADL\,8-9} + \beta_{MG-ADL\geq 10} \times HS_{MG-ADL\geq 10} + \varepsilon$$

- β_0 is the fixed term, which represents the expected value of quality of life;
- r_0 is the random term, which represents the variability in quality of life;
- $\beta_{MG-ADL\,5-7}$, $\beta_{MG-ADL\,8-9}$ and $\beta_{MG-ADL\geq 10}$ are the coefficients representing the impact of health states on quality of life;

- $HS_{MG-ADL\,5-7}$, $HS_{MG-ADL\,8-9}$ and $HS_{MG-ADL\geq 10}$ are dummy variables that have a value of 1 when the observation corresponds to the health state and a value of 0 otherwise;
- ε is the residual.

Table 15 and Table 16 present the coefficients and the covariance matrix for the mixed model of MyRealWorld MG utility values respectively. Table 17 presents the utility values used in the model in the scenario analysis that uses the MyRealWorld MG utility values.

Table 15. Mixed model coefficients on MyRealWorld MG population used to estimate utility values associated with health states - EQ-5D-3L UK tariff

Parameter	Coefficient	SE	P-value
Intercept	[redacted]	0.0074	0
MG-ADL 5-7	[redacted]	0.0092	4.6253×10^{-46}
MG-ADL 8-9	[redacted]	0.0114	4.7061×10^{-73}
MG-ADL ≥10	[redacted]	0.0116	1.7441×10^{-155}

Table 16. Covariance matrix of the mixed model on MyRealWorld MG population

Parameter	Intercept	MG-ADL 5-7	MG-ADL 8-9	MG-ADL ≥10
Intercept	0.0000554	-0.0000375	-0.0000440	-0.0000483
MG-ADL 5-7	-0.0000375	0.0000844	0.0000513	0.0000462
MG-ADL 8-9	-0.0000440	0.0000513	0.0001296	0.0000675
MG-ADL ≥10	-0.0000483	0.0000462	0.0000675	0.0001354

Table 17. Utility values used in the model when considering MyRealWorld MG utility data in scenario analysis

Parameter	Mean	SE
MG-ADL <5	[redacted]	0.0074
MG-ADL 5-7	[redacted]	0.0081
MG-ADL 8-9	[redacted]	0.0099
MG-ADL ≥10	[redacted]	0.0097

Following the request from the EAG, an alternative scenario has also been conducted, which applies the ADAPT utility data and removes the covariate for the treatment arm. Table 18, Table 19 and Table 20 present the mixed model coefficients, the covariance matrix of the mixed model and utility values used in the model when considering ADAPT utility data in a mixed model without treatment as covariate, respectively.

Table 18. Mixed model coefficients on ADAPT population used to estimate utility values associated with health states - EQ-5D-3L UK tariff

Parameter	Coefficient	SE	P-value
Intercept	[redacted]	0.0138	<0.0001
MG-ADL 5-7	[redacted]	0.0065	<0.0001
MG-ADL 8-9	[redacted]	0.0081	<0.0001
MG-ADL ≥10	[redacted]	0.0088	<0.0001

Table 19. Covariance matrix of the mixed model on ADAPT population

Parameter	Intercept	MG-ADL 5-7	MG-ADL 8-9	MG-ADL ≥10
Intercept	[redacted]	-0.0000241	-0.0000281	-0.0000313
MG-ADL 5-7	[redacted]	0.0000427	0.0000287	0.0000274
MG-ADL 8-9	[redacted]	0.0000287	0.0000651	0.0000366
MG-ADL ≥10	[redacted]	0.0000274	0.0000366	0.0000768

Table 20. Utility values used in the model when considering ADAPT utility data in scenario analysis without treatment effect

Parameter	Mean	SE
MG-ADL <5	[redacted]	0.0138
MG-ADL 5-7	[redacted]	0.0136
MG-ADL 8-9	[redacted]	0.0141
MG-ADL ≥10	[redacted]	0.0143

Results indicate a limited impact on the ICER results (from £ 28,702/QALY [updated base case following corrections discussed in questions B10, B12 and B13] to £31,588/QALY).

However, the results of this scenario analysis should be interpreted with caution. The Company accepts that, from a theoretical point of view, health states in a Markov model should fully capture discrete disease stages, including their associated QoL utility, and therefore a treatment effect is generally not considered appropriate. However, in a context of limited data, as common with orphan diseases, more nuances should be taken into account. As described in sections B.3.2.2 and B.3.4.2 of Company's submission, MG-ADL was considered the best option to define model's health states for gMG, but at the same time it is recognised that MG-ADL is not fully capturing the effect of efgartigimod for gMG patients. In the current case, the treatment effect is a statistically significant variable in the regression analysis for EQ-

5D. Patients receiving efgartigimod experienced an additional improvement of [redacted] ($p = 0.00004$) in utility for the same MG-ADL score. Therefore, if the treatment effect were to be neglected, and utilities estimated only based on health-state effect, the benefit of efgartigimod would likely be underestimated.

For these reasons we believe that it is appropriate to consider a treatment effect in the calculation of QALYs, as removing the treatment effect from the utilities that were derived from ADAPT would introduce bias against efgartigimod.

If the view of the EAG is that it is not acceptable to include a treatment effect on utilities, the Company considers it more appropriate to base utilities used for the cost-effectiveness model on those observed in MyRealWorld MG, where the bias of a specific treatment was not present. However, the approach of using treatment-specific utility values has been accepted in previous appraisals by NICE,[20,21] and is therefore considered an appropriate approach by the Company.

B7. Priority question: Please provide evidence to show that generalised myasthenia gravis is associated with a substantial effect on carers' health-related quality of life (CS, section B.3.4.5.3), as per the NICE health technology evaluations manual (2022) paragraph 4.3.17.

While there are limited data published on caregiver burden in gMG, the patient burden of gMG is relatively well characterised. Within these studies, which are presented in the CS (Section B.1.3.2.2), the substantial caregiver impact of gMG arises from the physically and mentally disabling symptoms of the condition. For example, muscle weakness experienced by gMG patients severely impacts their day-to-day functioning, which can lead to difficulties with swallowing, vision, speech, breathing, and mobility, as well as extreme fatigue.[22] Consequently, patients may require help with eating or mobility, both of which a regular caregiver would be required to support. It has been estimated that about one-third of patients require regular care from their partner.

This requirement for support is similar to that of other neurodegenerative diseases, including MS, which has been used as a proxy for gMG in the economic model. In a

2020 review of caregiver burden in MS,[23] aspects of impaired caregiver QoL included pathologic anxiety and depression, stress, substantial time commitment required for caregiving, reducing or stopping work (and associated negative economic impact), and challenges in juggling the competing demands of the patient with gMG alongside parenting duties. Indeed, regarding impact on ability to work, a poster has recently been presented based on data from the MyRealWorld MG study, which shows a significant loss in productivity for both patients and caregivers of patients with MG.[24]

Moreover, while the physical symptoms of gMG have a relatively obvious and predictable consequence in terms of the support patients need, there is also an impact of patient mental health on caregiver wellbeing. In a 2022 cross-sectional study surveying 1,399 patients on symptoms of depression, anxiety, HRQoL (MG Quality of Life scale; MG-QoL15), and also caregiver burden (using the Burden Scale for Family Caregivers; BSFC), showed that caregiver burden was significantly associated to MG disease severity (estimated marginal means for severe vs. mild MG severity = 0.16 [0.13; 0,19); $p \leq 0.001$) and also negatively influenced by symptoms of depression (estimated marginal means = 0.12 [0.09; 0.15]).[25] The study therefore shows the significant impact on caregivers of the less physically disabling symptoms of gMG.

When this impact is considered alongside the substantial need for physical and day-to-day support that gMG patients need, the Company believes that this represents a substantial effect on carers' health-related quality of life (CS, section B.3.4.5.3), as outlined in the NICE health technology evaluations manual (2022)

Previous NICE appraisals in similar neurodegenerative diseases, including MS (used as a proxy condition fog MG as described in B8 below), have included the impact on carer's quality of life in the cost-effectiveness analysis,[26–29] and the Company therefore considers it appropriate to incorporate caregiver disutilities in the base case cost-effectiveness analysis. As no published caregiver disutilities for gMG patients are available, the values used in the model are based on the literature values available for a proxy disease, multiple sclerosis (MS), as discussed in Question B8.

B8. Priority question: Please provide further justification for the use of caregiver disutilities based on the proxy condition of multiple sclerosis (MS) (CS, section B.3.4.5.3). Please report what other conditions were considered and why MS was chosen, and justify the mapping from Patient Determined Disease Steps (PDDS) stage to MG-ADL health states (CS, Table 45).

No studies were identified reporting caregiver disutility in gMG. A search was conducted to identify caregiver disutility in conditions characterized by progressive disability (disease worsening), with stages of severity that could be linked to the gMG disease activity scale (MG-ADL) used in the current analysis.

As stated in section B.1.3.1 of the CS, gMG is a complex neuromuscular disease. Other neuromuscular diseases that could be considered comparable in terms of need for caregivers – selected on the basis that they are associated with similar manifestations of muscular impairment – included:[30]

- Amyotrophic lateral sclerosis (ALS);
- Charcot-Marie-Tooth disease;
- Multiple sclerosis;
- Muscular dystrophy;
- Myopathy;
- Myositis, including polymyositis and dermatomyositis;
- Peripheral neuropathy;
- Spinal muscular atrophy.

The Company selected MS as a proxy condition for gMG because these two neuromuscular diseases are both characterized by progressive muscle weakening and a wide array of serious multisystem complications, including respiratory muscle dysfunction. In addition, both diseases:

- Impose an HRQoL burden attributable separately to both chronic (i.e., ongoing disease burden) and acute effects (i.e., attack-related); and
- Can be staged by disease severity.

Caregiver disutility at different disability stages of MS was therefore used as a proxy for caregiver disutility in the different gMG health states in the conventional therapy

arm, based on caregiver HRQoL data reported in the MS study by Acaster *et al*. 2013 as follows:[31]

- MG-ADL<5: Assumed equal to caregiver disutility in PDDS Stage 0-1 in MS: mild disability;
- MG-ADL 5-7: Assumed equal to caregiver disutility in PDDS Stage 2-3 in MS: moderate disability;
- MG-ADL 8-9: Assumed equal to caregiver disutility in PDDS Stage 4 in MS: initial walking difficulty;
- MG-ADL≥10: Assumed equal to caregiver disutility in PDDS Stage 5 in MS: important walking difficulty;
- Crisis: Assumed equal to caregiver disutility in PDDS Stage 6 in MS.

Resource use and costs

B9. Priority question: CS, section B.3.5.1.1, Figure 28: please clarify why a piecewise approach is used to model time on treatment (ToT), rather than a parametric curve for the whole time horizon. Please report the numbers of patients at risk for the ToT KM curve over time and justify the robustness of extrapolating from month 33.

A piecewise approach was used to model ToT whereby the Kaplan-Meier (KM) curve from ADAPT was used until 33 months (the latest available KM data), and the exponential curve was used to extrapolate for the remaining duration of the model. Figure 2 presents the Kaplan-Meier curve for time on treatment with efgartigimod, including the number of patients at risk.

The Company's position is that a piecewise approach is appropriate in situations where there is uncertainty regarding how long patients are likely to remain on treatment in routine clinical practice. In such cases the Company prefers to use observed data where it is available, and then extrapolating from the point that observed data are no longer available. This approach could be considered more robust and to be superior to extrapolating over the full model horizon because they better represent the observed data from the trial. Consequently, the piecewise

approach would provide a more accurate representation of discontinuation during the study period and therefore would reduce overall uncertainty. A similar approach has been requested and accepted by NICE previously.[32]

The base case analysis extrapolates time on treatment from month 33 because that it is the last time point where observed data are available. As an alternative, the Company would consider it reasonable to start extrapolation from the point where fewer than 5 patients (approximately 10%) remain on treatment. However, given that there are no discontinuations from 33.3 months to the end of follow-up, the Company believes that there is limited value in taking this approach, and that it would be preferable and reasonable to directly use the Kaplan-Meier data where available.

Figure 2: Kaplan-Meier curve of time on treatment with efgartigimod in ADAPT and ADAPT+, including number of patients at risk

B10. Why does the model use two different unit costs for PLEX? £827 (Non-elective inpatient short stay from PSSRU 2021; HCRU&Costs data! D67) and £779 (SA44A National Schedule of NHS Reference Costs 2020/1; HCRU&Costs data! D106).

This was a typographical error and we would like to apologize for any confusion. The unit cost that should be considered for PLEX is £779 (SA44A National Schedule of NHS Reference Costs 2020/1). Please note that this update together with the amendments incorporated based on the Company's responses to questions B12 and B13 changes the base case ICER to £28,702/QALY.

B11. CS, section B.3.5.1.4, Table 53, corticosteroid costs: please explain how the three data sources (Voorham et al, 2019; Janson et al, 2018; Bexelius et al, 2013) were pooled.

The corticosteroid costs were based on the three data sources; Voorham et al, 2019; Janson et al, 2018; Bexelius et al, 2013. In the model, the relevant data source(s) are selected, depending on the threshold for corticosteroid use that is selected by the user.

In the base case analysis, the definition of the threshold for 'high dose' is 10 mg/day. In that case the data source selected Bexelius et al, 2013, with costs inflated to current prices, because they assumed a high-dose threshold of 7.5 mg/day.

In the scenario analysis that assumes a high-dose threshold of 5 mg/day, corticosteroid costs are based on an average cost, inflated to current prices, from by Voorham et al, 2019 and Janson et al, 2018 as both publications assumed a high-dose threshold of 5 mg/day.

B12. CS, section B.3.5.3: please clarify the source for the end of life care costs. PSSRU 2021 lists £382 for 'Inpatient, specialist palliative care (adults only), average cost per bed day' (page 83). PSSRU 2021, section 8.2, Table 1, estimates an average cost of £12,149 of care services used per decedent in the last twelve months of life.

The Company agrees that the average cost of health and care services used in the last year of life, i.e., £12,149 from the PSSRU 2021 source, is the more appropriate figure to use in the model. The revised model submitted with the Company's response to clarification questions incorporates this change.

B13. Please clarify the sources for the cost data used in the model below.

Name of cost and location in model	Model undiscounted unit cost and source	EAG comment
Consultant-led outpatient follow-up (WF01A) HRCU&Cost data! Row 64	£143; 2021/2 National Tariff Workbook	This is listed as £134 in National Tariff Workbook (Outpatients tab, 303 clinical haematology). NHS National Schedule of NHS costs = £214.56 (Consultant-led tab, 303 Clinical haematology).
Non-consultant-led outpatient follow-up (WF01A) HRCU&Cost data! Row 65	£78; 2021/2 National Tariff Workbook	The tariff workbook only lists costs for consultant-led attendances (Outpatients tab). NHS National Schedule of NHS costs = £153.70 (Non-consultant-led tab, non-admitted follow-up, 303 clinical haematology) and as £93.03 (Outpatient procedures, non-admitted follow-up, 303 clinical haematology)
Tacrolimus capsules HRCU&Cost data! Row 22	60 units per pack	BNF says 50 capsules per pack @ £56 (if using the Adoport product) not 60 capsules. Which product is costed in the model?
GP visit HCRU&Cost data! C53	£33; Unit Costs of Health & Social Care 2021. See Ch10 pp110-6	PSSRU lists a surgery consultation as £39 (PSSRU 2021 table 10.3b).

Specialist visit, hospital HCRU&Cost data! C54	£197; NHS National tariff workbook (2022/23). Assumed as General Internal Medicine Service (HRG Code:300). First attendance	Is this WF01B (consultant-led)? This is listed as £202 in the workbook.
Physician visit HCRU&Cost data! D87	GP unit cost - £115, including direct care; NHS- Unit costs of health and social care 2021 (last version)	PSSRU costs are £255 per hour of patient contact (incl. direct care and with qualification costs), or £217 per hour without qual costs (Table 10.3b). Why is the cost per consultation (£39) not used here?

The Company thanks the EAG for reviewing the model cost inputs. The Company's response to each issue is provided in the table below. The economic model has been updated per the responses below, and the revised model (redacted and unredacted) have been included in the supporting documents related to the response to clarification questions.

Name of cost and location in model	Model undiscounted unit cost and source	EAG comment	Company response
Consultant-led outpatient follow-up (WF01A) HRCU&Cost data! Row 64	£143; 2021/2 National Tariff Workbook	This is listed as £134 in National Tariff Workbook (Outpatients tab, 303 clinical haematology). NHS National Schedule of NHS costs = £214.56 (Consultant-led tab, 303 Clinical haematology).	The Company agrees that the appropriate value should be £134
Non-consultant-led outpatient follow-up (WF01A) HRCU&Cost data! Row 65	£78; 2021/2 National Tariff Workbook	The tariff workbook only lists costs for consultant-led attendances (Outpatients tab). NHS National Schedule of NHS costs = £153.70 (Non-consultant-led tab, non-admitted follow-up, 303 clinical haematology) and as £93.03	The Company agrees that the appropriate value should be £93.03

		(Outpatient procedures, non-admitted follow-up, 303 clinical haematology)	
Tacrolimus capsules HRCU&Cost data! Row 22	60 units per pack	BNF says 50 capsules per pack @ £56 (if using the Adoport product) not 60 capsules. Which product is costed in the model?	Adoport 1mg capsules is the reference point. The Company confirms that NHS indicative price of £55.69 for 50 capsules has been used in the updated model
GP visit HCRU&Cost data! C53	£33; Unit Costs of Health & Social Care 2021. See Ch10 pp110-6	PSSRU lists a surgery consultation as £39 (PSSRU 2021 table 10.3b).	The Company agrees that £39 is the appropriate value
Specialist visit, hospital HCRU&Cost data! C54	£197; NHS National tariff workbook (2022/23). Assumed as General Internal Medicine Service (HRG Code:300). First attendance	Is this WF01B (consultant-led)? This is listed as £202 in the workbook.	The Company agrees that £202 is the appropriate value
Physician visit HCRU&Cost data! D87	GP unit cost - £115, including direct care; NHS-Unit costs of health and social care 2021 (last version)	PSSRU costs are £255 per hour of patient contact (incl. direct care and with qualification costs), or £217 per hour without qual costs (Table 10.3b). Why is the cost per consultation (£39) not used here?	The Company agrees that £39 is the appropriate value

Probabilistic analysis

B14. Priority question: Please comment on the discrepancy between the deterministic and probabilistic ICERs shown in the table below. The difference is large and appears to be robust to increasing iterations. Can you explain this based on sources of non-linearity in the model, rather than potential errors in the PSA parameter distributions and calculations?

Run	ICER (£/QALY)
Deterministic	28,066
PSA 1000 iterations 1	22,514
PSA 1000 iterations 2	22,396
PSA 2000 iterations	24,249
PSA 5000 iterations	22,958
PSA 10000 iterations	23,427

The transition probabilities are the parameters causing non-linearity in the model when running the probabilistic sensitivity analysis. This is because some theoretically possible transitions – for example transitioning directly from MG-ADL<5 to MG-ADL>10 – have not been observed in the trial. To account for this, the model includes a prior distribution assigning each transition an equal probability of occurring in addition to the observed transitions.

In the submitted model these priors were set to 0.01 for all transitions, causing the probabilistic ICER to be consistently lower than the deterministic one. In the updated model we have now set the priors to 0.05, results in probabilistic ICERs very similar to the base case ICER (see Table 21).

Table 21: Comparison of deterministic and probabilistic ICERs

Run	ICER (£/QALY)
Deterministic	28,702
PSA 1000 iterations 1	31,525
PSA 1000 iterations 2	29,455
PSA 2000 iterations	28,988
PSA 5000 iterations	29,652
PSA 10000 iterations	30,462

Section C: Textual clarification and additional points

Marketing authorisation

C1. In CS, Appendix C, Section C.1.1, a copy of the draft Summary of Product Characteristics (SmPC) has been provided; however, this appears to be only a picture of the first page. Please provide a full copy of the draft SmPC or the final SmPC, if the latter is now available.

A copy of the final SmPC is provided separately.

C2. CS, section B.1.2, Table 2, states that efgartigimod is presently being reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) and that the marketing authorisation is expected in Q1 2023. Is a decision still pending or has the MHRA now issued a marketing authorisation for efgartigimod? If the marketing authorisation has been issued, please supply a copy of the final SmPC.

Marketing authorisation for efgartigimod was granted by the MHRA on 15th March 2023. A copy of the final SmPC is provided separately.

C3. CS, Appendix C, section C.1.2, states that the UK public assessment report was not available at the time of submission and that it will be provided when available. Has this now become available? If so, please supply a copy of this.

Efgartigimod was approved by the MHRA based on the European Commission Decision Reliance Procedure (ECDRP). Consequently, the Company does not expect to receive a UK PAR from the MHRA. The MHRA approval refers to the

EPAR, which was included in the reference package submitted to NICE on 15th February 2023.

Reference requests

C4. Please provide the study protocols and statistical analysis plans for the ADAPT, ADAPT+ and ADAPT-SC studies (these do not appear to have been included with the CS).

The study protocols and statistical analysis plans for the ADAPT, ADAPT+ and ADAPT-SC studies have been uploaded separately.

C5. CS, section B.3.2.2, page 85, explains that a clustering analysis was used to identify appropriate categorical groupings based on the MG-ADL score and health-related quality of life (HRQoL) data from ADAPT. Please provide a full report of the methods and results of this analysis.

The methodology and results of the analysis are discussed here.

Objective

There is no clear definition of gMG-related health states available from previous models or literature. In the ADAPT and ADAPT+ trials a score of 5 on the MG-ADL scale is used as criterium for re-treatment. For this reason this threshold is used in the cost-effectiveness model (CEM) to define the most preferable health state. Then the question remains how to further classify the remaining patients in clinically meaningful distinct health states.

The objective of this analysis is to define cut-offs for MG-ADL scores to allow for the definition of health states for the CEM.

Methods

Unsupervised clustering techniques allow to identify clusters in the data when a given categorical classification is missing. One of these techniques is the K-means method,[33] which is a simple and transparent unsupervised machine learning algorithm. This technique was implemented in the current analysis.

The algorithm takes the following steps:

1. Choose a number of random values that matches the number of clusters that are aimed to identify. In this case, the aim is to identify two clusters of the data (apart from the MG-ADL<5 ‘cluster’), so two random numbers are chosen (A and B), which lay between the maximum and minimum observed values;

2. Each observation is assigned to cluster A or cluster B depending on its distance from the respective random numbers. All observation closer to random number A are clustered in cluster A and all observation closer to random number B are clustered in cluster B;

3. The respective averages of clusters A and B are calculated and the process is repeated again, but using the two averages as numbers A and B respectively;

4. The full process is reiterated until there is a convergence of the cluster averages, i.e., the average of each cluster does not change any further by adding further iterations.

5. Testing the quality of the clustering using the ‘silhouette method’.[34] This method assigns a value between -1 and 1 to each cluster. The closer the value is to 0, the more similar the observations in one cluster are to the observations in the other clusters, meaning that the quality of the clustering is poor. A value close to 1 or -1 means that the observations in one cluster are well differentiated from those of the other clusters.

The algorithm can be also used in multiple dimensions, basing it on multiple variables at the same time. This approach has been taken for the current analysis, basing the analysis on the following variables: “MG-ADL” and “EQ-5D-based utility score”.

Results

Figure 3 presents the results of the clustering analysis taking into account both the EQ-5D and the MG-ADL score of patients in ADAPT. Two clear clusters are identified; one with a higher MG-ADL and lower utility (presented in red) and one with lower MG-ADL and higher utility (presented in blue). Table 22 shows that the two clusters have a mean MG-ADL of 11.02 and 6.94. Based on these analyses, a cut-off between the clusters of an MG-ADL score of 10 was selected to define the most severe health state for the cost-effectiveness model.

The silhouette method resulted in values of 0.32 and 0.46 for the respective clusters.

Figure 3: Clusters identified in the ADAPT data

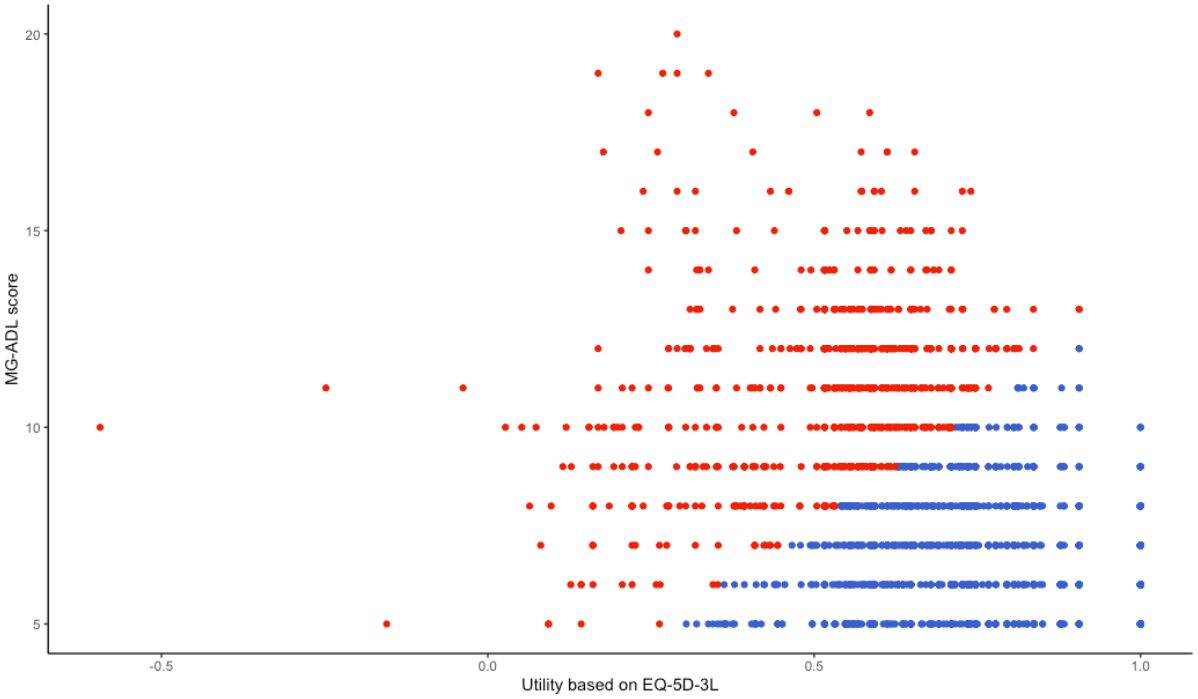


Table 22: Results of the clustering analysis

Cluster	N	MG-ADL			EQ-5D		
		Mean	SD	SE		SD	SE
1	834	11.02	2.28	0.08	0.522	0.165	0.006
2	1316	6.94	1.46	0.04	0.734	0.141	0.004

C6. Priority question: The CS refers to a source of data called 'argenx, MyRealWorldMG data on file' and this study is used to inform the economic model analyses. Please supply a copy of this source or a reference reporting the methodology and results of this study. (We have located the statistical analyses plan supplied with the CS for this study, but have not identified any other references reporting it.)

No formal report of the study has been developed. The source of data referred to in the EAG's clarification question refers to *ad hoc* analyses conducted solely for the purpose of developing the economic model, and were conducted using patient-level data from the study. Publicly available references for the study were included in the CS dated 15th February 2023, and the study is ongoing.

C7. The meaning of the following sentence in CS, section B.1.3.3.3, is not fully clear to us: "Treatments may be used individually or in combination, with some treatments starting before others – e.g., corticosteroids – are tapered". Please clarify the meaning.

The sentence should read "Treatments may be used individually or in combination; where efgartigimod is used as add-on therapy, this may enable tapering – and in some cases discontinuation – of other therapies, e.g., corticosteroids."

Further details on the positioning, and expected use of efgartigimod as add-on to established clinical management, are provided in the Company's response to EAG Clarification Question B2 above.

Other

C8. CS, section B.2.12, provides the expected date for the approval of the subcutaneous (SC) formulation of efgartigimod in the UK – should this be

marked as commercial-in-confidence, in line with the confidentiality marking in CS, section B.1.2, Table 2?

Yes, the EAG is correct that the expected approval date should be marked as commercial-in-confidence. Thank you.

References

1. argenx. Efgartigimod (ARGX-113-1705) Clinical Study Report (Interim Analysis 4): A Long-term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Study of ARGX 113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT+). 2022;1–165.

2. Megan B, Pickering RM, Weatherall M. Design, objectives, execution and reporting of published open-label extension studies. J Eval Clin Pract. 2012 Apr;18(2):209–15.

3. Berrih-Aknin S, Claeys KG, Law N, Mantegazza R, Murai H, Saccà F, et al. Patient-reportedimpact of myasthenia gravis in the real world: protocol for a digital observational study (MyRealWorld MG). BMJ Open. 2021 Jul 20;11(7):e048198.

4. Dewilde S, Kousoulakou H, Janssen M, Claeys K, Friconneau M, Jacob S, et al. Digital data collection to measure the impact of myasthenia gravis on patients' quality of life in the real world: report at baseline [Presented at the Virtual International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2021 conference, 30 November - 3 December 2021]. Value Health. 2022 Nov 30;25(1 Suppl):S246.

5. Howard JF Jr, Bril V, Vu T, Karam C, Peric S, Margania T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2021/06/20 ed. 2021 Jul;20(7):526–36.

6. argenx. Efgartigimod (ARGX-113-1704) Clinical Study Report: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT). 2020.

7. Qi CDSGDBEPG, Author A, Argenx IBMAU, States, She VBRBB, Full Record Entry D. CO135 Hospitalization and Exacerbation Estimates of Efgartigimod Vs. Conventional Therapy in Generalized Myasthenia Gravis Patients: A Post-Hoc Analysis of the Phase 3 ADAPT Study. Value Health. 1AD;25(7 Supplement):S329.

8. Cortes-Vicente E, Alvarez-Velasco R, Segovia S, Paradas C, Casasnovas C, Guerrero-Sola A, et al. Clinical and therapeutic features of myasthenia gravis in adults based on age at onset. Neurology. 2020/02/20 ed. 2020 Mar 17;94(11):e1171–80.

9. de Meel RHP, Lipka AF, van Zwet EW, Niks EH, Verschuuren JJGM. Prognostic factors for exacerbations and emergency treatments in myasthenia gravis. J Neuroimmunol. 2015 May 15;282:123–5.

10. Andersen LK, Jakobsson AS, Revsbech KL, Vissing J. Causes of symptom dissatisfaction in patients with generalized myasthenia gravis. J Neurol. 2022 Jun 1;269(6):3086–93.

11. argenx. Efgartigimod (ARGX-113-1704) Clinical Study Report: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT). 2020;1–171.

12. Takahashi M, Howard JF Jr, Bril V, Vu T, Karam C, Imai T, et al. Efgartigimod demonstrates consistent improvements in myasthenia gravis across patient populations. In: Japanese Society of Neurology Annual Meeting. 2022.

13. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology. 2016/07/01 ed. 2016 Jul 26;87(4):419–25.

14. Narayanaswami P, Sanders DB, Wolfe G, Benatar M, Cea G, Evoli A, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. Neurology. 2020/11/05 ed. 2021 Jan 19;96(3):114–22.

15. Skeie GO, Apostolski S, Evoli A, Gilhus NE, Illa I, Harms L, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol. 2010/04/21 ed. 2010 Jul;17(7):893–902.

16. Gajdos PCSTK, Author A, Raymond Poincaré Hospital APHP c o, Intensive Care Unit boulevard RPGI de, France F, Correspondence A, et al. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev. (2006)(2):CD002277.

17. Nowak RJ, Coffey CS, Goldstein JM, Dimachkie MM, Benatar M, Kissel JT, et al. Phase 2 trial of rituximab in acetylcholine receptor antibody-positive generalized myasthenia gravis: The BeatMG Study. Neurology. 2021/12/04 ed. 2022 Dec 2;98(4):e376.

18. Piehl F, Eriksson-Dufva A, Budzianowska A, Feresiadou A, Hansson W, Hietala MA, et al. Efficacy and safety of rituximab for new-onset generalized myasthenia gravis: The RINOMAX randomized clinical trial. JAMA Neurol. 20220919th ed. 2022 Sep 19;e222887.

19. Hernandez Alava M, Wailoo A, Grimm S, Pudney S, Gomes M, Sadique Z, et al. EQ-5D-5L versus EQ-5D-3L: the impact on cost effectiveness in the United Kingdom. Value Health. 2018/01/07 ed. 2018 Jan;21(1):49–56.

20. NICE. Patisiran for treating hereditary transthyretin amyloidosis (HST10). Published 14 August 2019. Available at: https://www.nice.org.uk/guidance/hst10 (last accessed 17 March 2023). [Internet]. NICE; 2019 [cited 2023 Mar 17]. Available from: https://www.nice.org.uk/guidance/hst10

21. NICE. Ravulizumab for treating paroxysmal nocturnal haemoglobinuria (TA698). Published 19 Mat 2021. Available at: https://www.nice.org.uk/guidance/ta698

(last accessed 17 March 2023). [Internet]. NICE; 2021 [cited 2023 Mar 17]. Available from: https://www.nice.org.uk/guidance/ta698

22. Ruiter AM, Verschuuren J, Tannemaat MR. Prevalence and associated factors of fatigue in autoimmune myasthenia gravis. Neuromuscul Disord. 2021/05/27 ed. 2021 Apr 24;31(7):612–21.

23. Maguire R, Maguire P. Caregiver Burden in Multiple Sclerosis: Recent Trends and Future Directions. Curr Neurol Neurosci Rep. 2020;20(7):18.

24. Jacob S, DeWilde S, Qi C, Saccà F, Meisel A, Palace J, et al. Productivity Losses for Generalized Myasthenia Gravis Patients and their Caregivers: Association with Disease Severity. Journal of Neuromuscular Diseases. J Neuromuscul Dis. 2022;9(Supplement 1):S245–6.

25. Marbin D, Piper SK, Lehnerer S, Harms U, Meisel A. Mental health in myasthenia gravis patients and its impact on caregiver burden. Sci Rep. 2022 Nov 11;12(1):19275.

26. NICE. Ocrelizumab for treating relapsing–remitting multiple sclerosis (TA533). Available at: https://www.nice.org.uk/guidance/ta533 (last accessed 22 March 2023).

27. NICE. Ofatumumab for treating relapsing multiple sclerosis (TA699). Available at: https://www.nice.org.uk/guidance/ta699/ (last accessed 22 March 2023).

28. NICE. Beta interferons and glatiramer acetate for treating multiple sclerosis (TA527). Available at: https://www.nice.org.uk/guidance/ta527 (last accessed 22 March 2023).

29. NICE. Cladribine tablets for treating relapsing–remitting multiple sclerosis (TA 493). Available at: https://www.nice.org.uk/guidance/ta493 (last accessed 22 March 2023).

30. Neuromuscular Disorders | Cedars-Sinai [Internet]. [cited 2023 Mar 17]. Available from: https://www.cedars-sinai.org/health-library/diseases-and-conditions/n/neuromuscular-disorders.html

31. Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. BMC Health Serv Res. 20130909th ed. 2013 Sep 9;13:346.

32. NICE. Givosiran for treating acute hepatic porphyria (HST16). Published 24 November 2021. Available at: https://www.nice.org.uk/guidance/hst16/ (last accessed 17 March 2023).

33. Hartigan JA, Wong MA. Algorithm AS 136: A K-Means Clustering Algorithm. J R Stat Soc Ser C Appl Stat. 1979;28(1):100–8.

34. Rousseeuw PJ. Silhouettes: A graphical aid to the interpretation and validation of cluster analysis. J Comput Appl Math. 1987 Nov 1;20:53–65.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted] and [redacted]
2. Name of organisation	Myaware and Muscular Dystrophy UK
3. Job title or position	[redacted] and [redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	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. 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. 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	Myaware has not received any such funding in the past 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.**	MDUK have received the following funding from possible comparator companies: - £5,000 sponsorship from Roche for the MDUK Neuromuscular Physiotherapist Conference 2022 - £3,000 sponsorship from Novartis for the MDUK Neuromuscular Physiotherapist Conference 2022
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. - A patient survey for those currently being treated with Efgartigimod focused on their experiences. We had 7 respondents.

NICE National Institute for Health and Care Excellence

Living with the condition

Patient organisation submission
Efgartigimod for treating generalised myasthenia gravis [ID4003]

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: **Physical Impact** 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 and increased feelings of anxiety, with one respondent telling us: *"I've had myasthenia for 60 years and I thought I could manage it very well. What I have found is I have become very suspicious of people. I didn't go out beforehand. So many letters from the NHS made me feel extremely vulnerable and now when I go shopping I look at which is the shortest queue and I'm quite suspicious of people. And that is so unlike me. But now I want to withdraw from people."* 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. I have a supportive employer, so I don't dare change jobs in case I end up somewhere where my employer doesn't understand. I was headhunted while I was being diagnosed but had to turn down a lucrative and exciting prospect. It's accepting the fact that I won't be looking for a change of employer of job for a long time. Career progression has slowed down massively, so myasthenia will affect my finances at some point.""*

	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.

NICE National Institute for Health and Care Excellence

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-to-day 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.

NICE National Institute for Health and Care Excellence

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Efgartigimod alfa is a new and developing form of treatment for patients with autoimmune disease. Efgartigimod is an engineered antibody fragment that binds to the neonatal Fc receptor (FcRn), thereby preventing the FcRn from recycling serum immunoglobulins and so extending their effective lifetime. By preventing this interaction, the drug allows an increase in the degradation of the circulating immunoglobulin. Myasthenia gravis is an autoimmune disease caused by autoantibodies to components of the neuromuscular junction. Antibodies to the acetylcholine receptor are found in over 80% of patients, with a smaller number of other patients having detectable antibodies to other neuromuscular proteins such as MuSK. Myasthenia is a difficult to control chronic disease. Many patients may have myasthenic crisis brought on by infection, stress, and other causes both known and unknown. There is no cure, but the symptoms of a proportion of patients can be controlled using a range of drugs including steroid and steroid replacement drugs. Some patients can have their symptoms controlled by these drugs, however the symptoms in a significant proportion of patients are hard to control, and these patients face a prolonged period on steroids with the danger of the many known medical side effects of long-time steroid usage and are prone to “myasthenic crisis”, when their condition may suddenly become severe and life threatening. When asked to what extent they agreed or disagreed that Efgartigimod will be preferable treatment option for managing their MG-related symptoms, 72% of respondents strongly agreed, 14% somewhat agreed, and the remaining 14% didn’t know. Patients with myasthenia, do not like taking steroids. 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 in their symptoms and an increase possibility of myasthenic crisis. One respondent to our Efgartigimod experience survey spoke on their negative experience of taking steroids and the impact Efgartigimod has had: “*Over the past 3 years I have tried everything to get control of my MG and all options have failed. I was diagnosed in 2006 and had a full thymectomy, was on prednisolone for several years, pyridostigmine and azathioprine. The azathioprine was the main medication and it worked very well for 14 years before it's efficacy started to fail and my body no longer responded to it. When this happened I went back on steroids, increased pyridostigmine and started Mycophenolate on a variety of different doses all the way up to the maximum. I tried this for nearly 2 years with no positive effect at all. Since starting Efgartigimod I have felt better than I have in a very long time. I am still on prednisolone but feel that if I can reduce this right down to around 5mg or even remove it completely then Efgartigimod will look after my MG 100%.”*

	As Efgartigimod alfa works by reducing IgG levels, this drug should work in all antibody-positive patients, which may be up to 90% of people with MG. Additionally, there is a school of thought that the remaining 10% "antibody-negative" patients do in fact have autoantibodies, but we are currently unable to detect them, but obviously that is still hypothetical. Efgartigimod have been shown to be effective in clinical trials in patients with MG, as well as in other autoimmune diseases such as thrombocytopenia, and appear to have a good clinical safety record and may offer a new drug that could manage the patient's symptoms without the serious and troublesome side effects of steroids. It will be especially useful in patients with hard to control MG who do not know, day to day, what their condition will be like, a chance of a stable lifestyle. Many of our members spend their life fearing a myasthenic crisis that could warrant a hospital stay or worse. In a significant minority of patients with myasthenia the symptoms are not well controlled, and these patients are continuously seriously and chronically unwell. This new treatment may certainly offer the possibility of a superior prognosis in patients in which current treatments are ineffective or partially effective. One respondent stated that treatment with Efgartigimod has provided them with real confidence in their MG management: "*It is the best thing to have happened to me and my MG since diagnosis in 2006. I feel very confident in the medication, it is easy to tolerate, is quick & pain free to administer, no negative side effects and it really works. It feels like it is just targeting the things that are wrong inside my body rather than flooding me with chemicals that damage the good parts of my body too. It feels clean, safe and so much more modern than many of the other medications that I have to take. I have real confidence in it*." The drug is likely to be administered by an intravenous infusion once weekly for 4 weeks as one treatment cycle. This regime may be restrictive but thought of by many of our members as an advantage over multiple daily tablets. Our members complain that taking so many immunosuppressive drugs take a lot of organisation both 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) or as a disadvantage if the travel is difficult. Because of the cost, Efgartigimod, cannot be used as a front-line drug, but selective usage in patients with severe, refractory, hard to treat MG, could be a lifesaving and life changing addition to the pharmaceutical arsenal in

	selective patients. Those who have had a positive response have felt a significant impact on their quality of life, with 85% of responses stating Efgartigimod will improve their ability to engage in family and social life, plan activities with more certainty, and have greater confidence in managing their MG. No respondents thought Efgartigimod would have no impact on their quality of life. When asked to further explain how Efgartigimod will impact their quality of life, respondents replied with the following: "*I have been able to go for daily walks, to dress/wash myself, to meet up with family. I'm less reliant on my husband for many daily tasks and I have started helping with housework again. It has improved my strength levels to such an extent that I expect to take part in family activities that I previously could not*." "*When you no longer feel so weak and able to have the strength to wash and dress myself, this new drug gives me HOPE, for my future and I pray that I will one day have some quality of my life*." "*So far I have had one course of treatment, once a week for 4 consecutive weeks. I feel stronger, my muscles all have more strength and I am able to focus on doing other things rather than just thinking about my MG. Since having the treatment I have been able to engage in my work again for the first time in about 2 years. I am also thinking about doing new things such as starting a Masters Degree in September 2023, not something I could have even contemplated doing before the Efgartigimod treatment*."

NICE National Institute for Health and Care Excellence

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The most likely clinical disadvantage of this drug (and other related monoclonal-engineered drugs) is its non-selective mode of action. Blocking the neonatal Fc receptor will result in an increase in the degradation of all circulating antibodies, good as well as bad. In certain cases, it may lay the patient open to infection. However, this is true of other forms of immunosuppressive drugs too, and so the patient will need to be monitored and be aware of this possibility. The drug will require intravenous administration, which will require hospital/GP visits. A visit to the hospital or GP surgery for an intravenous injection rather than by oral tablet, may be seen as a serious disadvantage, but of course is dependent on how effective the treatment is in an individual patient, and how difficult travel to the centre maybe. Respondents to our Efgartigimod experience survey have commented on the inconvenience of attending hospital, but the majority have said this is outweighed by the positive response they have had to the treatment. A few respondents have also been able to have their infusions at home, for which they are grateful and have had good experiences so far. 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. Many of our respondents listed the side effects that present in Efgartigimod treatment as negative aspects of the therapy. The majority of these list headache and tiredness as the main side effects experienced. One respondent experienced incorrect infusion of Efgartigimod and this has concerned them: "*My first round of infusions were not done correctly, which has been concerning me ever since I found out, and nobody has been able to tell me why, or exactly what was done, and what I was given. The infusion should be 125ml of Efgartigimod and saline, infused at a rate of 125ml/per hour. My first week, I was given 80ml total, and infused at a rate of 90ml/per hour. I have also experienced quite unpleasant side effects in terms of headaches and back/neck pain*." The other significant disadvantage is the cost of the drug, which will be very high. Our members appreciate the cost is higher than the day-to-day cost of tablets, 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 stated previously, Efgartigimod should work in alleviating symptoms for all 'antibody-positive' presenting patients. There has been historical concern that the more prevalent ACh receptor-positive antibody expressing patients would primarily benefit from recently developed medications. The clinical mode-of-action offered by Efgartigimod suggests that it will also be able to help MUSK antibody and LRP4 antibody-presenting patients.

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.

NICE National Institute for Health and Care Excellence

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. The significance of associated health implications is highlighted by the fact that two in five survey respondents were admitted to hospital within the first year of their diagnosis. • MG has a wide-ranging impact on the lives of people living with the condition and their families. Survey data showed that MG not only affects individuals physically, but also impacts them emotionally, socially and financially. • Currently, people with MG take a range of different treatments to manage their symptoms. This presents several challenges. 1) Lots of people with MG take steroids, such as prednisolone, to increase muscle strength and reduce inflammation. Some patients can have their symptoms controlled by these drugs. However, a significant proportion of patients find their symptoms are hard to control, and they therefore face a prolonged period on steroids. For people living with hard to control MG, 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 prolonged use 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. 2) To manage the symptoms of MG as well as possible requires consistent medication intake and therefore a stringent treatment schedule. The research found that this resulted in frustration at how the need for such a medical intake routine 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. • As Efgartigimod alfa works by reducing IgG levels, this drug should work in all antibody-positive patients, which is the vast majority (up to 90%) of people with MG. Efgartigimod has been shown to be effective in clinical trials in patients with MG, as well as in other autoimmune diseases such as thrombocytopenia, and appears to have a good clinical safety record. • Whilst Efgartigimod cannot be used as a front-line drug due to costs, it could be a lifesaving and life changing pharmaceutical option if used in a targeted manner for those living with severe, refractory, hard to treat MG, that causes them to be seriously and chronically unwell. This is due to the possibility of Efgartigimod replacing the need for steroids, and therefore steroid related side-effects, as well as offering

	a superior prognosis for people who find that current treatments are ineffective/partially effective. This is supported by qualitative feedback from people living with MG who have received Efgartigimod, which indicates they view it as a preferable treatment for their MG. Having reported that receiving Efgartigimod can result in improvements in their symptoms, they consider it to have enhanced their overall quality of life.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

CONFIDENTIAL UNTIL PUBLISHED

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

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Fay Chinnery, Research Fellow, Health Economics, SHTAC Lois Woods, Senior Research Assistant, Evidence Synthesis and Information Specialist, SHTAC Keith Cooper, Senior Research Fellow, Health Economics, SHTAC Bogdan Grigore, Research Fellow, University of Exeter David Alexander Scott, Principal Research Fellow, Statistics, SHTAC Joanna Picot, Senior Research Fellow, Evidence Synthesis, SHTAC
Correspondence to	Dr. J. Picot, Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	26/04/2023

Source of Funding: This report was commissioned by the National Institute for Health Research (NIHR) Evidence Synthesis Programme as project number NIHR135824.

Acknowledgements

We are grateful for clinical advice and comments on a draft of the report provided by Dr Pablo Garcia-Reitboeck, Consultant Neurologist, St George's University Hospitals NHS Foundation Trust, & Honorary Senior Lecturer, St George's University of London. We also thank Karen Pickett, SHTAC for initial project management and drafting some of the clarification questions and Geoff Frampton, SHTAC, and Jo Lord, SHTAC, for providing a quality assurance review of the draft EAG report.

Declared competing interests of the authors and advisors

- The authors declare none
- Dr Pablo Garcia-Reitboeck declares none

Rider on responsibility for report

The view 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:

Chinnery, F.; Woods, L.; Cooper, K.; Grigore, B.; Scott, D.A.; Picot, J. Efgartigimod for treating generalised myasthenia gravis: A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2023.

Contributions of authors

Fay Chinnery critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Lois Woods critically appraised the company searches, critically appraised the clinical effectiveness systematic review, and drafted the report; Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Bogdan Grigore critically appraised the economic evaluation, and drafted the report; David Scott critically appraised the clinical effectiveness systematic review, and drafted the report Joanna Picot critically

appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

Confidential information

Content in this report highlighted in [redacted] is ‘academic in confidence’. Content [redacted] is ‘commercial in confidence’.

Table of Contents

LIST OF TABLES

LIST of FIGURES

LIST of APPENDICES

LIST OF ABBREVIATIONS

ABN	Association of British Neurologists
ACh	Acetylcholine
AChEis	Acetylcholinesterase inhibitors
AChR	Acetylcholine receptor
AChR-Ab+	Acetylcholine receptor antibody positive
AE	Adverse event
AESIs	Adverse events of special interest
AIC	Academic in confidence
AUC	Area under the curve
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CMI	Clinically meaningful improvement
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DSU	Decision Support Unit
EAG	External Assessment Group
ECM	Established clinical management
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
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
FcRn	Neonatal Fc receptor
gMG	Generalised myasthenia gravis
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IgG	Immunoglobulin G

IPD	Individual patient level data
ITT	Intent to treat
IV	Intravenous
IVIg	Intravenous immunoglobulin
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living scale
MGC	Myasthenia Gravis Composite scale
MG-QOL15r	Myasthenia Gravis Quality of Live 15-item scale (revised)
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intent to treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMJ	Neuromuscular junction
NR	Not reported
NSIST	Nonsteroidal immunosuppressive therapy
PAS	Patient access scheme
PLEX	Plasma exchange
PRO	Patient-reported outcome
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
RR	Relative risk/risk ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
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 1.5 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

Issue number	Summary of issue	Report sections
1	Exclusion of maintenance intravenous immunoglobulin (IVIg)	4.2.8.1
2	Extrapolation of time on treatment (ToT) curve	4.2.6.3.1
3	Permanent treatment discontinuation transition probabilities	4.2.6.1.3
4	Caregiver disutilities	4.2.7.6
5	Disutilities associated with corticosteroid use	4.2.7.5
6	Costs of complications associated with corticosteroid use	4.2.8.4

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are listed in Table 1 and are discussed in section 1.5.

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.

Following their response to the clarification questions, the company updated their model. The company's updated base case deterministic cost-effectiveness results for efgartigimod compared with established clinical management are shown in Table 2. Efgartigimod provides an increase of [redacted] QALYs at an additional cost [redacted] compared with established clinical management.

Table 2 Company updated base case results for efgartigimod, including PAS

Treatments	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£ per QALY)
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£28,702
ECM	[redacted]	[redacted]	-	-	-

ECM, Established clinical management; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Source: Updated company base case model results

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

No key issues were identified with respect to the decision problem. Although the company exclude plasma exchange as a comparator, clinical advice to the EAG is that the proportion of patients who would receive plasma exchange outside an acute need is certainly less than 10%. There may be variability between treatment centres.

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

No key issues were identified with respect to the clinical effectiveness evidence.

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

Issue 1 Exclusion of maintenance IVIg

Report section	4.2.8.1
Description of issue and why the EAG has identified it as important	The company included IVIg as a maintenance treatment for those with generalised myasthenia gravis (gMG), particularly for those with more severe disease. Clinical advice to the EAG was that IVIg is no longer used regularly as a maintenance treatment for patients with gMG due to a shortage of IVIg and that this practice is unlikely to change. However, there is some uncertainty due to the limited expert opinion available to the EAG and the difference between clinical advice to the EAG and clinical advice provided to the company in December 2022 which indicated that IVIg maintenance is used to treat a proportion of UK patients. As IVIg is an expensive treatment, which in the company base case is used more often for patients in the established clinical management (ECM) arm than those in the efgartigimod arm, this has a large effect on the ICER.
What alternative approach has the EAG suggested?	As advised by our clinical expert, we have excluded maintenance IVIg in the EAG's preferred assumption.
What is the expected effect on the cost-effectiveness estimates?	Excluding maintenance IVIg treatment increases the ICER from £28,702 to £169,590 per QALY for efgartigimod vs ECM using the company's revised model.
What additional evidence or analyses might help to resolve this key issue?	Further clinical advice on whether maintenance IVIg is currently available for this population or whether it may be available again in the future.

Issue 2 Extrapolation of time on treatment (ToT) curve

Report section	4.2.6.3.1
Description of issue and why the EAG has identified it as important	The company uses time on treatment data from the ADAPT and ADAPT+ studies to estimate treatment discontinuation of efgartigimod. The company uses pooled Kaplan-Meier data, and then uses the exponential distribution for extrapolation beyond the end of the ADAPT+ study data (33 months onwards). The company prefers to use this approach as it uses all observed data.
What alternative approach has the EAG suggested?	The EAG prefers to use the exponential distribution for the time horizon of the model. We note that the exponential distribution provides a good fit to the observed data so there is no reason not to use this for the whole time horizon. We disagree with starting the extrapolated parametric tail at the end of the study data at 33 months, because there are no patients at risk at this timepoint, causing high uncertainty in the KM curve. In this case, there is a large drop in the proportion of patients on treatment between 30 and 33 months. The EAG considers starting the tail when there are more patients at risk (typically about 20%) to be a better approach. We conduct a scenario where the extrapolated tail starts at 24 months.
What is the expected effect on the cost-effectiveness estimates?	Using the exponential distribution for the whole time period increases the ICER from £28,702 to £47,996 per QALY for efgartigimod vs ECM using the company revised model.
What additional evidence or analyses might help to resolve this key issue?	Clinical advice on how the probability of discontinuation of treatment may change over time. The EAG has completed scenarios for alternative parametric distributions.

Issue 3 Permanent treatment discontinuation transition probabilities

Report section	4.2.6.1.3
Description of issue and why the EAG has identified it as important	The company submission (CS) states that all patients who discontinue treatment are assumed to gradually return to the initial baseline health state distribution over 6 months. The EAG considers that the transition probabilities for those patients who have permanent treatment discontinuation have been underestimated. This results in patients in the efgartigimod arm having less severe disease, on average, than those in the ECM arm even after all patients have discontinued efgartigimod.
What alternative approach has the EAG suggested?	The EAG calculates the correct transition probabilities so that all patients who have discontinued treatment have returned to the initial baseline health state distribution after 6 months. Using these transition probabilities results in the severity of disease of discontinued patients in the efgartigimod arm worsening in line with that of the ECM arm.
What is the expected effect on the cost-effectiveness estimates?	Using the EAG's preferred permanent treatment discontinuation transition probabilities increases the ICER from £28,702 to £212,983 per QALY for efgartigimod vs ECM using the company revised model.
What additional evidence or analyses might help to resolve this key issue?	In their response to clarification question B4, the company states they are "*not aware of any proof of the existence of a residual treatment effect*". However, further evidence or expert clinical opinion on this may resolve the issue.

Issue 4 Caregiver disutilities

Report section	4.2.7.6
Description of issue and why the EAG has identified it as important	In the company base case it is assumed that there is a caregiver disutility applied to patients with gMG. The NICE manual requires evidence showing that a condition is associated with a substantial effect on carer's health-related quality of life (NICE manual section 4.3.17). The CS states there is limited data published on caregiver burden in gMG, and so the company uses the Patient Determined Disease Steps (PDDS) scale for multiple sclerosis (MS) as a proxy for mapping caregiver disutility in the different gMG health states. However, there is a lack of evidence for the validity of mapping from PDDS to MG-ADL. The impact on the health-related quality of life of caregivers is likely to differ between MS and gMG due to difference in the symptoms of the diseases. Consequently, there is large uncertainty around the caregiver disutilities used in the model.
What alternative approach has the EAG suggested?	Clinical advice to the EAG is that the majority of gMG patients would be independent and not require a caregiver. In addition, the typical symptoms for gMG patients are not similar to those for MS patients, so the disutility values estimated are not likely to be representative. The EAG's view is that the CS has not provided evidence to show that gMG has a substantial effect on carers.
What is the expected effect on the cost-effectiveness estimates?	Removing caregiver disutilities increases the ICER from £28,702 to £39,425 per QALY for efgartigimod vs ECM using the company revised model.
What additional evidence or analyses might help to resolve this key issue?	Confirmation from other clinical experts and patient experts on whether patients with gMG would typically need caregivers whose health-related quality of life would adversely affected.

Issue 5 Disutilities associated with corticosteroid use

Report section	4.2.7.5
Description of issue and why the EAG has identified it as important	Utilities are taken from patients in the ADAPT trial. Patients in the efgartigimod and ECM arms were using corticosteroids in the trial so the utility estimates from the trial already captured the effect of corticosteroid use.
What alternative approach has the EAG suggested?	The EAG has not included disutilities for corticosteroid use.
What is the expected effect on the cost-effectiveness estimates?	Removing the disutilities associated with corticosteroid use increases the ICER from £28,702 to £36,302 per QALY for efgartigimod vs ECM using the company revised model.
What additional evidence or analyses might help to resolve this key issue?	No further evidence or analyses are required. We have presented results of our scenarios excluding corticosteroid disutilities from the company base case (Table 24), and including corticosteroid disutilities in the EAG base case (Table 28) for completeness.

Issue 6 Costs of complications associated with corticosteroid use

Report section	4.2.8.4
Description of issue and why the EAG has identified it as important	The company conducted a systematic literature review to identify sources for the costs of the complications associated with corticosteroid use. The review found three studies Voorham et al.,[1] Janson et al.[2] and Bexelius et al.[3] The company uses the study by Bexelius et al. The EAG disagrees with the source used by the company for corticosteroid complication costs.
What alternative approach has the EAG suggested?	The EAG considers the study by Voorham et al. to be a better source as there are considerably more patients in each arm in this study and it appears to be more representative of the costs associated with corticosteroid use in the UK.
What is the expected effect on the cost-effectiveness estimates?	Using the EAG's preferred source of corticosteroid complication costs increases the ICER from £28,702 to £41,080 per QALY for efgartigimod vs ECM using the company revised model.
What additional evidence or analyses might help to resolve this key issue?	Clinical advice on the likely costs associated with managing corticosteroid complications.

1.6 Other issues: summary of the EAG's view

The following issues identified by the EAG in the cost effectiveness evidence are not considered to be key issues as they have a negligible impact on the model results and so are not included in the EAG base case:

- End of life costs (EAG section 4.2.8.7): our preferred source for end-of-life costs is Georghiou and Bardsley,[4] who calculate the cost of the last three months of life as £6,146, when adjusted for inflation to 2021.
- Calculation of adverse event costs (EAG report section 4.2.6.6): the EAG prefers to use a weighted average across all NHS reference cost categories,[5] rather than a single point cost estimate, for each adverse event.
- Intravenous drug administration costs (EAG report section 4.2.8.2): we prefer to use the NHS reference cost SB13Z 'Deliver more complex parenteral chemotherapy at first attendance' (£258.56),[5] rather than the outpatient IV administration tariff.[5]
- All costs: the company base case uses costs inflated to 2022 using the Consumer Price Index inflation indices. The EAG prefers to use the HCHS Pay & Prices from PSSRU, which is the standard source for inflation in economic analyses. The latest versions available for the NHS reference costs and the PSSRU costs are for 2021, so we consider this the best price year to use and not inflate costs to 2022.

1.7 Summary of the EAG's preferred assumptions and resulting ICERs

Based on the EAG's critique of the company's model (discussed in section 4.2), we have identified several aspects of the company base case with which we disagree. Our preferred model assumptions are:

1. Removing costs for maintenance IVIg (EAG report section 4.2.8.1)
2. Using the exponential function to model efgartigimod time-on-treatment (EAG report section (4.2.6.3.1)
3. Using our preferred permanent treatment discontinuation transition probabilities for the efgartigimod arm (EAG report section 4.2.6.1.3)
4. Removing caregiver disutilities (EAG report section 4.2.7.6)
5. Removing disutilities associated with chronic corticosteroid use (EAG report section 4.2.7.5)
6. Using alternative source of costs from Voorham et al.[1] to model costs for high and low-dose corticosteroid use (EAG report section 4.2.8.4)

The EAG's preferred assumptions increased the ICER for efgartigimod compared with established clinical management to £623,135 per QALY (Table 3).

Table 3 Cumulative change from the company base case with the EAG's preferred model assumptions for efgartigimod versus established clinical management

Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)
Company base-case	[redacted]	[redacted]	£28,702
Exponential function to model efgartigimod ToT	[redacted]	[redacted]	£47,996
Caregiver disutilities removed	[redacted]	[redacted]	£65,655
Disutilities associated with chronic corticosteroid use	[redacted]	[redacted]	£91,358
Using alternative cost data from Voorham et al.[1] for complications costs from corticosteroid use	[redacted]	[redacted]	£114,505
Costs for maintenance IVIg removed	[redacted]	[redacted]	£381,550
EAG's preferred permanent treatment discontinuation transition probabilities for the efgartigimod arm (shown in Table *14*)	[redacted]	[redacted]	£628,135
EAG base case	[redacted]	[redacted]	**£628,135**

ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; QALYs, quality-adjusted life years; ToT, time on treatment

The EAG did not identify any technical calculation errors in the company's economic model. For further details of the exploratory and sensitivity analyses undertaken by the EAG, 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 argenx on the clinical effectiveness and cost effectiveness of efgartigimod (Vyvgart®) for treating generalised myasthenia gravis (gMG). It identifies the strengths and weaknesses of the CS. A clinical expert was 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 9th March 2023. A response from the company via NICE was received by the EAG on 24th March 2023 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

Myasthenia gravis (MG) is a rare long term autoimmune condition that causes muscle weakness and fatigue. There are two main forms of MG, ocular MG and generalised MG (gMG). The focus of this technology appraisal is gMG.

2.2.1 Background information on generalised myasthenia gravis

The CS provides an overview of gMG (CS section B.1.3) including descriptions of this condition and its cause, diagnosis and classification, the patient-report outcomes that are used to assess disease activity and severity, epidemiology and the burden of gMG both clinically and to the patient. The key facts of relevance to this appraisal from the CS are summarised below, supplemented with additional information where appropriate.

CS section B.1.3.1 gives an accurate overview of gMG, a rare and chronic autoimmune disorder that affects the neuromuscular junction (NMJ) impairing communication between nerves and muscles (neuromuscular transmission) and causing muscle weakness and fatigue.[6; 7] Normally when acetylcholine (ACh) is released into the space between a neuron and a muscle at the NMJ it binds to the acetylcholine receptor (AChR) as shown in the left-hand panel of CS Figure 2 initiating events that ultimately result in muscle contraction. gMG is caused by immunoglobulin G (IgG) autoantibodies that affect the function of the NMJ with three autoantibodies being well established as being involved in gMG: autoantibodies against i) the AChR, ii) muscle-specific kinase (MUSK) and iii) liproprotein-related protein 4 (LRP4).[7] The most common IgG autoantibody, detected in 80% of gMG patients, binds to AChRs[7] which means the receptors are not free to bind to ACh. Furthermore, IgG autoantibodies binding to AChRs accelerates the cellular mechanisms that internalise and

degrade AChRs and activates the complement system and these two events result in a lower density of functional AChRs and structural damage to the NMJ as shown in the right-hand panel of CS Figure 2. Patients with gMG who are AChR antibody positive are the population of interest in this appraisal, patients with gMG caused by other autoantibodies (i.e. they are AChR antibody negative) are not included in this appraisal.

2.2.1.1 Diagnosis and disease classification

The main symptom of gMG is muscle weakness but the muscle weakness is heterogenous between subtypes of gMG (depending on the type of autoantibody involved) and between individuals with gMG and at different times for the same individual with gMG.[6-8] In more severe disease more critical muscle groups are involved e.g. muscles affecting breathing. For people presenting with symptoms of gMG the main diagnostic test is serum anti-AChR antibody testing, followed by testing for other autoantibodies involved in gMG if the anti-AChR antibody test is negative. The CS (section B.1.3.1.1) describes other tests that may be required to help establish a diagnosis of gMG, particularly for patients with negative serology and neurophysiology tests, and the need for patients to have a CT scan or MRI of the thymus to detect thymoma.

In most patients with gMG it is not possible to identify why they have developed autoantibodies. It is believed that genetic factors combined with environmental factors may precipitate its development and it can also be caused by thymoma (a type of thymus cancer) or thymic dysplasia.[6; 8]

The Myasthenia Gravis Foundation of America (MGFA) designed a classification system to help identify different subgroups of MG patients[9] and this is presented in CS Table 3. It ranges from MG class I (characterised by any ocular muscle weakness; may have weakness of eye closure; all other muscle strength is normal) to class V (defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management). Ocular MG (class I) is not included in this appraisal, only classes II to V are relevant to gMG and Class V would be considered myasthenic crisis.

2.2.1.2 Assessment of disease activity and severity gMG

Assessment of disease activity and severity in gMG is achieved using patient-reported outcome (PRO) instruments several of which have been validated: the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale, the revised MG quality of life 15 (MG-QOL15r), the quantitative MG (QMG) scale and the MG composite (MGC) scale. These are described in

CS Table 4. Our clinical expert confirmed that the MG-ADL is commonly used in clinical practice in England to assess improvement in gMG, and that his clinic uses both the MG-ADL and MGC noting that the MG-ADL can be completed by patients remotely.

2.2.1.3 Epidemiology of gMG

The CS states that MG affects about 15 in every 100,000 people but it is unclear where this value comes from because an incorrect reference appears to have been cited. We have identified a 1998 population based epidemiological study that surveyed a population of 684,000 in Cambridgeshire which reports a prevalence of 15 per 100,000 population[10] but a more recent analysis of the prevalence of neuromuscular conditions in the UK between 2000 and 2019[11] reported a prevalence estimate for MG of 34 per 100,000 in 2019. If this more recent prevalence value is correct that would be equivalent to 19,222 patients living with MG in England (based on the 2021 population estimate for England of 56,536,000) but the number who have gMG that is AChR antibody positive would be lower than this (potentially between 11,000 and 12,000 patients based on 80% of prevalent MG patients developing gMG and 77.2% of these having AChR antibody positive disease as stated in CS section B.1.3.1.3).

MG can affect anyone. In women, incidence rates may have two peaks, one at around the age of 30 years (although this has not been observed in all studies[12]) and a second peak at around 50 years. In men the incidence increases steadily with age.

2.2.2 Background information on efgartigimod

Efgartigimod is a human IgG antibody fragment that has been engineered to have increased affinity for the neonatal Fc receptor (FcRn). The role of the FcRn in the pathogenesis of MG is described in detail in CS section B.1.3.1. The therapeutic approach of efgartigimod is to block the FcRn which results in the reduction of IgG levels, including reducing the IgG autoantibodies that cause MG. Other types of immunoglobulins that are not recycled by FcRn are unaffected, so FcRn blocking does not lead to widespread immunosuppression.

Efgartigimod for intravenous use in the treatment of gMG gained its marketing authorisation with the Medicines and Healthcare products Regulatory Agency (MHRA) on 15th March 2023 (company response to clarification question C2). The company also have a subcutaneous formulation of efgartigimod which does not have a marketing authorisation yet, but this has been applied for in the EU and the company intends to apply for a UK Marketing authorisation for the subcutaneous formulation (as described in CS Table 2).

The indication for efgartigimod for intravenous use in the UK is the same as the EU indication which is as an add-on to standard therapy for the treatment of adult patients with generalised myasthenia gravis who are anti-acetylcholine receptor antibody positive. Efgartigimod is given as a 1-hour intravenous infusion at a dose of 10mg/kg with a treatment cycle comprising once weekly infusions for 4 weeks. Subsequent treatment cycles are stated to be "*according to clinical evaluation*" (CS Table 2). The Summary of Product Characteristics (SmPC)[13] states that "the earliest time to initiate a subsequent treatment cycle was 7 weeks from the initial infusion of the previous cycle. The safety of initiating subsequent cycles sooner than 7 weeks from the start of the previous treatment cycle has not been established."

2.2.3 The position of efgartigimod in the treatment pathway

The company states that there is no single universally accepted treatment pathway for gMG and provides a list of six practice statements and consensus guidelines (CS Table 9). Of these, the guidelines of the Association of British Neurologists (ABN) from 2015[14] (ABN 2015) are the focus in the CS, although the company acknowledges that they do not include all the current NHS commissioned treatments for gMG (the CS states these guidelines are due to be updated in 2023) and consequently the information from the ABN 2015 guideline has been supplemented with more recent commissioning information on rituximab[15; 16] and immunoglobulin.[17]

The CS presents the UK treatment pathway (reproduced below as Figure 1). The ABN 2015 guidelines state that they "could be followed to the letter or used flexibly" and also that because individuals with MG vary, it is assumed that clinicians will select therapy accordingly.[14] Nevertheless, the outpatient treatment plan presented for MG in the ABN 2015 guidelines does broadly follow a sequential process that begins with pyridostigmine (an acetylcholinesterase inhibitor) therapy and consideration of thymectomy for those who are AChR antibody positive and aged under 45 years, adds prednisolone if patients are symptomatic despite pyridostigmine and provides criteria for starting immunosuppression (describing azathioprine as a first-line immunosuppressive agent with other immunosuppressive agents i.e. mycophenolate mofetil, methotrexate, ciclosporin, or rituximab considered if azathioprine has failed or the patient cannot tolerate it). This sequence of treatments (acetylcholinesterase inhibitor, corticosteroids, and immunosuppressive therapy) is also described as conventional therapy. Inpatient management for severe symptoms includes the use of intravenous immunoglobulin, plasma

exchange and prednisolone. Details for each of the current UK treatment options for gMG are provided in CS section 1.3.3.4.

The clinical expert we consulted stated that most patients in the UK who require a nonsteroidal immunosuppressive therapy would receive azathioprine with mycophenolate mofetil being the second most commonly used nonsteroidal immunosuppressive therapy (methotrexate is rarely used). The clinical expert acknowledged that although IVIg and plasma exchange can be used in practice in treating refractory disease this use varies by treatment centre and IVIg is usually used as an acute treatment.

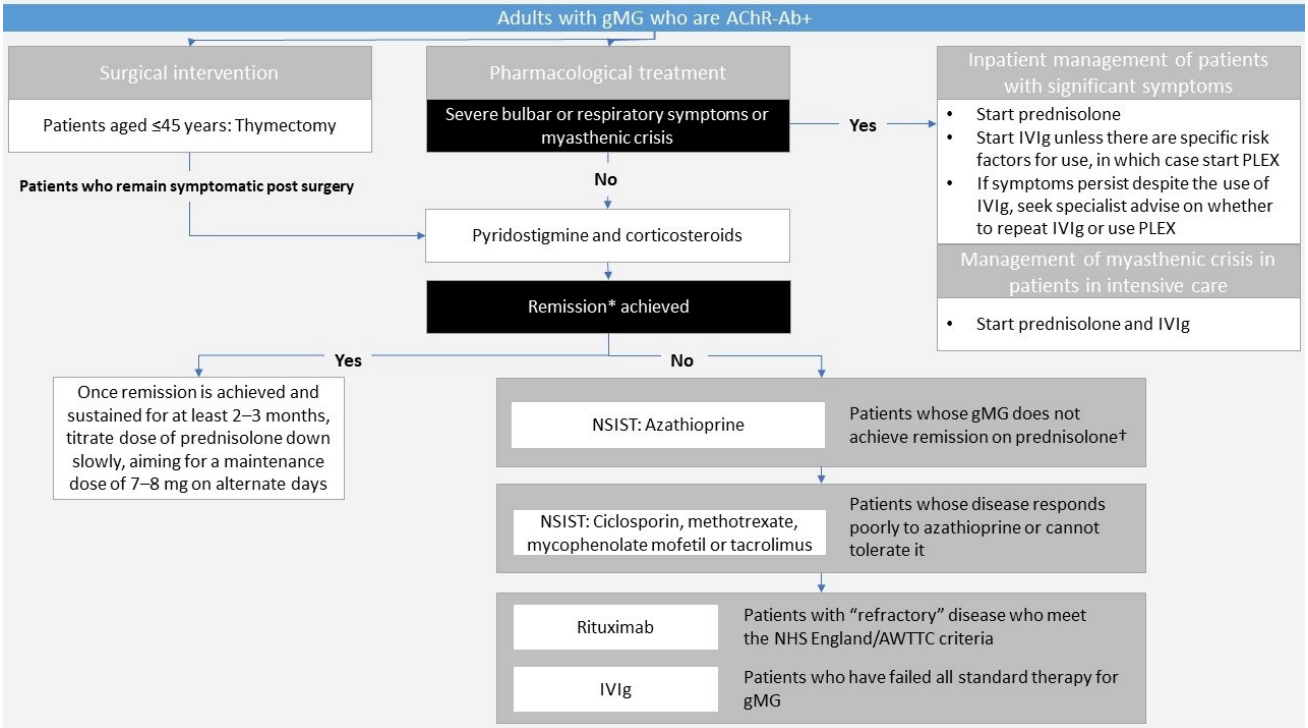


Figure 1 UK treatment pathway for gMG based on ABN guidelines and national commissioning policies

Source: Reproduction of CS Figure 7 (CS sources cited for this figure are Sussman 2015,[14] NHS England 2018,[17] AWTTC 2021,[15] NHS England 2021[16])
*Remission of gMG on corticosteroid therapy is defined as the absence of symptoms or signs after pyridostigmine withdrawal.
†A corticosteroid dose above15–20 mg on alternate days is unacceptable for long-term use and is considered an indication to introduce alternative immunosuppression.
Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; NSIST, nonsteroidal immunosuppressive therapy; PLEX, plasma exchange

Evidence from the MyRealWorld MG study (see section 3.5 of this report for more information on this study) on the MG treatments patients had taken in the previous year indicates that a high proportion (around 80%) of patients received an acetylcholinesterase inhibitor (such as pyridostigmine) and approximately 65% received corticosteroids, with a

wide range of other treatments (including NSISTs) also used (CS Figure 9). This suggests that for many patients an acetylcholinesterase inhibitor is not sufficient to control MG symptoms.

The company proposes that efgartigimod will be used as an add-on to established clinical management (as shown in Figure 2), with the anticipation that the addition of efgartigimod may enable the gradual dose tapering of whichever concomitant agent(s) it has been combined with. As part of their response to clarification question A5 the company confirms that efgartigimod has not been studied as a monotherapy and that the licensed indication is as an add-on therapy. The company's response to clarification question A5 also states that for patients with gMG refractory disease efgartigimod treatment would make the addition of rituximab or IVIg unnecessary and thus, efgartigimod in combination with established clinical management would be an alternative to rituximab or IVIg for this group of patients.

The company shows plasma exchange (PLEX) on the right-hand side of their current treatment pathway figure (Figure 2). Plasma exchange is usually used as an acute inpatient treatment (for a gMG exacerbation or crisis) but clinical advice to the EAG is that plasma exchange is used outside the management of acute episodes in a minority of patients (about 5%). However, the clinical expert acknowledged that this mode of use may be variable between different treatment centres.

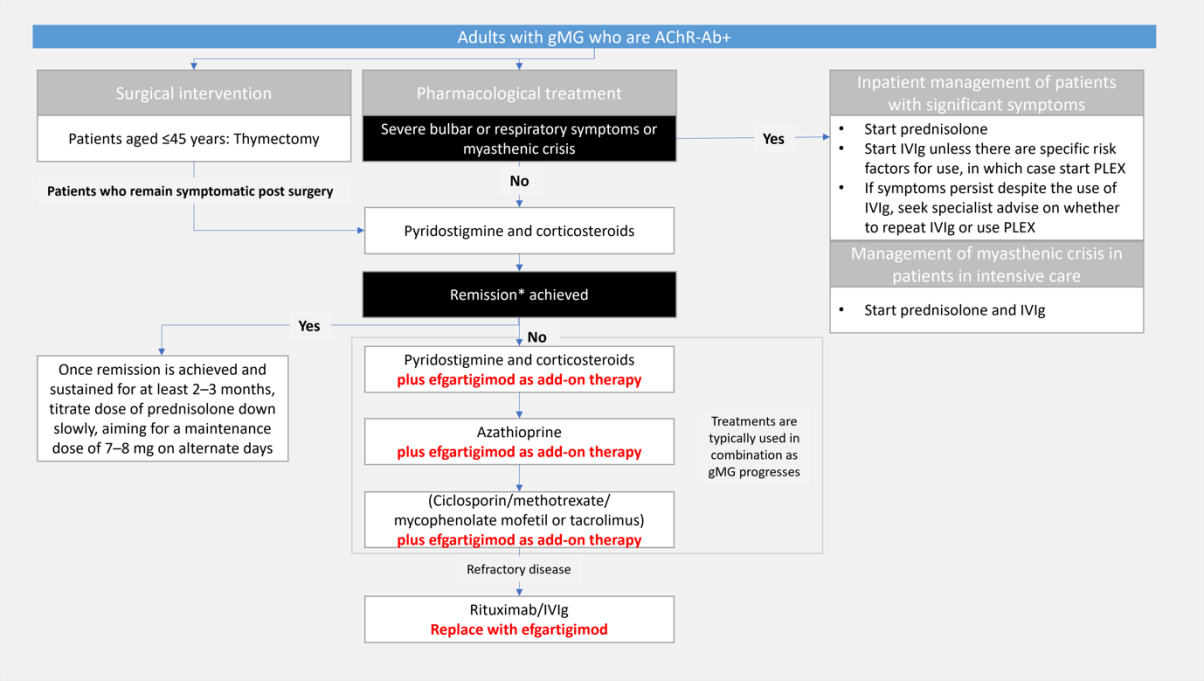


Figure 2 Proposed place of efgartigimod in the current treatment pathway

Source: Company response to clarification question A5, Figure 1
Treatments may be used individually or in combination; where efgartigimod is used as add-on therapy, this may enable tapering – and in some cases discontinuation – of other therapies, e.g., corticosteroids.
*Remission of gMG on corticosteroid therapy is defined as the absence of symptoms or signs after pyridostigmine withdrawal.
Abbreviations: AChR-Ab+, acetylcholinesterase receptor antibody positive; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; NSIST, nonsteroidal immunosuppressive therapy; PLEX, plasma exchange

EAG conclusion

The background information provided by the company accurately describes the diagnosis and classification of gMG, the assessment of gMG disease activity and severity, gMG epidemiology, and efgartigimod's mode of action and intended use within the treatment pathway for patients with gMG.

2.3 Critique of the company's definition of the decision problem

Table 4 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.

Table 4 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 myasthenia gravis (gMG) who are acetylcholine receptor antibody positive.	As per scope, the company submission is in adults with generalised myasthenia gravis who are acetylcholine receptor antibody positive.	Not applicable	The EAG notes that neither the NICE scope, company's decision problem, nor the SmPC for efgartigimod specify whether the patients are receiving treatment for day-to-day symptom control, for a gMG exacerbation or for a myasthenic crisis. However, the company's RCT did not enrol patients with myasthenic crisis. The SmPC states that treatment with efgartigimod has not been studied in patients with myasthenic crisis, adding that the sequence of therapy initiation between established therapies for myasthenia gravis crisis and efgartigimod, and their potential interactions should be considered.

Intervention	Efgartigimod	Efgartigimod	Not applicable	Consistent with the NICE scope. The EAG notes that the current submission is for the intravenous infusion of efgartigimod (MHRA marketing authorisation granted 15th March 2023) but a subcutaneous formulation has been developed (EMA marketing authorisation decision expected [redacted] with an MHRA licensing application expected thereafter).
Comparators	Established clinical management without efgartigimod including corticosteroids and immunosuppressive therapies, with or without intravenous immunoglobulin (IVIg) or plasma exchange (PLEX)	Similar to the NICE scope the company submission compares established clinical management without efgartigimod including corticosteroids and immunosuppressive therapies, with or without intravenous immunoglobulin vs. efgartigimod added to established clinical management including corticosteroids and immunosuppressive therapies, with or without intravenous immunoglobulin. Plasma exchange is not included as a comparator.	The company does not consider that plasma exchange should be included as a comparator for management of gMG for this decision problem as a result of the lack of clinical data that describes its use outside the management of acute episodes (exacerbations or myasthenic crisis).	The company excludes plasma exchange as a comparator. Clinical advice to the EAG is that whilst plasma exchange is usually used as an acute treatment (for gMG exacerbations or crisis) there are certain circumstances where plasma exchange is used outside the management of acute episodes e.g. when patients have been using corticosteroids for a long time or have significant symptoms from steroids but are waiting for other slow acting treatments to take effect. However, the clinical expert acknowledges that this use of plasma exchange

				varies by treatment centre. The clinical expert estimates the proportion of patients who would receive plasma exchange outside an acute need is about 5% (and certainly less than 10%).
Outcomes	The outcome measures to be considered include: • Improvement in myasthenia gravis • Time to clinically meaningful improvement • Mortality • Hospitalisations • Adverse effects of treatment Health-related quality of life	As per scope, the company submission considers the following outcomes: • Improvement in myasthenia gravis (MG-ADL responder) • Time to clinically meaningful improvement • Mortality • Hospitalisations • Adverse effects of treatment Health-related quality of life	Not applicable	Consistent with the NICE scope.

Source: CS Table1 with some abbreviations expanded for improved readability and EAG comments added
Abbreviations: EAG, External Assessment Group, EMA, European Medicines Agency; gMG, generalised myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; MHRA, Medicines and Healthcare products Regulatory Agency; RCT, randomised controlled trial

3 CLINICAL EFFECTIVENESS

In this chapter we summarise and critique the key clinical effectiveness evidence identified by the company's systematic literature review (SLR).

The health economic model uses some data from the MyRealWorld MG study (baseline cohort characteristics, EQ-5D-5L data) and uses this study to help estimate health state resources for patient-monitoring. Therefore, although effectiveness data from this study is not reported in section B.2 (Clinical effectiveness) of the CS, we critique the MyRealWorld MG study in section 3.5 of this report.

3.1 Critique of the methods of review(s)

The company carried out a clinical SLR to identify RCTs on the treatment of gMG with the first searches performed in April 2022 and update searches performed in January 2023. After review of the CS and clarification responses A.1 to A.4, the EAG considers that overall the SLR methodology was robust, at low risk of bias, and that there are not likely to be any missing studies. The EAG critique of the SLRs is in Appendix 1 of this report. The company did not search prior to January 2012 and no justification for this date was provided. However, there is not likely to be efgartigimod evidence prior to 2012 and as we considered an ITC is not necessary then there is also no need to identify further comparator evidence.

The company's SLR identified 3,900 records. After title and abstract screening by two independent reviewers, using the inclusion and exclusion criteria specified in CS Appendix Table 10, 393 full texts were obtained assessed for eligibility using the same methods. Of these, 92 full texts were assessed as relevant to the NICE scope but from the data presented in CS Appendix tables 12 and 13 it is difficult to ascertain the total number of separate studies identified for each of the treatments included. The company focuses on three efgartigimod studies in CS section B.2.2 and present these in CS Table 10: the pivotal ADAPT phase 3 RCT,[18; 19] the open label extension study ADAPT+[20; 21] which followed on from ADAPT and the ADAPT-SC RCT[22; 23] which compares subcutaneous (SC) to IV administration of efgartigimod. However, the company does not describe how they selected these three efgartigimod studies. The EAG notes that the SLR identified publications for a Phase II study of efgartigimod which is not otherwise mentioned in the CS.[24] Although the SLR identified records for the Phase III ADAPT-SC study in both the April 2022 and January 2023 searches it was excluded, however the study is included in the CS and the references cited in CS Table 10 for ADAPT-SC do not appear in either CS Appendix Table 12 or Table

13. The EAG concludes there is a lack of transparency in the company's approach to study selection for the CS.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

In this section we critique the key clinical effectiveness evidence from the pivotal ADAPT phase 3 RCT and the single-arm open label extension study ADAPT+ which followed on from ADAPT (Table 5). We do not critique the ADAPT-SC RCT which provides supporting evidence in the CS (CS section B.2.12) because the primary objective of the study was to demonstrate that the pharmacodynamic effect of subcutaneous injections of efgartigimod was noninferior to that of IV infusions of efgartigimod. Furthermore, approximately 50% ([redacted]) of the participants enrolled in ADAPT-SC had previously taken part in ADAPT and ADAPT+. For completeness, we do include the safety results from ADAPT-SC (section 3.3.9.3 of this report).

We summarise the key features of the ADAPT RCT and its extension ADAPT+ in sections 3.2.1 to 3.5.1.

Table 5 Clinical effectiveness evidence

Study	**ADAPT[18; 19] (ARGX-113-1704; NCT03669588)**	**ADAPT+[20; 21] (ARGX-113-1705; NCT03770403)**
Study design	Phase 3, randomised, double-blind, placebo-controlled, multicentre	Phase 3, long-term, single-arm, open-label, multicentre
Population	Adults with gMG	Adults with gMG
Intervention(s)	Efgartigimod 10 mg/kg (IV formulation)	Efgartigimod 10 mg/kg (IV formulation)
Comparator(s)	Placebo	Placebo
Supports marketing authorisation application?	Yes	Yes
Study used economic model?	Yes	Yes

Study	ADAPT[18; 19] (ARGX-113-1704; NCT03669588)	ADAPT+[20; 21] (ARGX-113-1705; NCT03770403)
Reported outcomes specified in the decision problem	• Improvement in MG • Time to clinically meaningful improvement • Mortality • Hospitalisations • AEs of treatment • HRQoL	• AEs of treatment • Improvement in MG (MG-ADL and QMG score changes)

Source: CS Table 10 edited by the EAG
Abbreviations: gMG, generalised myasthenia gravis; HRQoL, health-related quality of life; IgG, immunoglobulin G; IV, intravenous; MG, myasthenia gravis; MG-ADL, MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite; MG-QOL15r, 15-item revised version of the Myasthenia Gravis Quality of Life questionnaire; SC, subcutaneous

3.2.1 ADAPT RCT: Study characteristics

The ADAPT study[18; 19] is an international company-sponsored, randomised, double-blind, placebo-controlled, multicentre Phase 3 trial that evaluated the efficacy, safety and tolerability of efgartigimod given to adults with gMG by IV infusion in addition to established clinical management. This 26-week study is complete. The CS summarises features of the ADAPT study design and methodology in CS section B.2.3.1, CS Figure 11 and CS Table 11. Evidence for ADAPT in the CS comes predominantly from a journal publication[18] and the clinical study report (CSR).[19]

- Enrolled participants (n=167, of whom 129 were AChR antibody positive) had to meet the following entry requirements:
    - MG-ADL total score of ≥5 points with >50% of the total score attributed to non-ocular symptoms
    - On a stable dose of gMG treatment (could include acetylcholinesterase inhibitors [AChEis], steroids and NSISTs alone or in combination)
    - Could be AChR antibody positive or negative (but only the 129 AChR antibody positive patients are included in this appraisal)
- Patients with only ocular weakness or myasthenic crisis were not eligible to be enrolled. Full ADAPT trial inclusion criteria have been published.[18]
- Randomisation was stratified by AChR antibody status (positive or negative) current treatment with NSISTs (taking or not taking) and Japanese nationality (yes or no) and participants were randomised in a 1:1 ratio.
- After a 2-week screening period, participants received either efgartigimod in addition to their stable concomitant therapy or placebo in addition to their stable concomitant therapy for a 26-week treatment period.

- Intervention arm participants received efgartigimod (10mg/kg) in cycles consisting of four IV infusions (one infusion per week) to a maximum of three cycles. A ≥ 5-week follow-up occurred after each cycle. All patients received an initial cycle and the initiation of subsequent cycles was dependent on individual clinical response (i.e. the timing of second and third cycles varied between patients).
- Placebo arm participants received a matching placebo by IV infusion.
- Participants in both arms continued to receive stable doses of concomitant therapy for gMG that was limited to AChEis, steroids and NSISTs (either singly or in combination). No changes in types or doses of concomitant medication was permitted for any reason.
- Pre-planned subgroup analyses for the primary outcome were specified but these were for the whole trial population (i.e. AChR antibody positive and negative participants) whereas only the AChR antibody positive participants are relevant to this submission. Post-hoc analyses for the AChR antibody positive population were performed by prior thymectomy (yes or no), baseline MG-ADL score (MG-ADL score 5-7, 8-9, ≥ 10) concomitant gMG treatment (AChEi only, Any steroid, Any nonsteroidal immunosuppressive therapy).
- No UK centres were involved in the study.

3.2.2 ADAPT+ open label extension: study characteristics

The ADAPT+ study[20; 21] is an ongoing international company-sponsored, single-arm, open-label, multicentre 3-year extension of ADAPT evaluating the long-term safety, tolerability and efficacy, of efgartigimod as a treatment for adults with gMG. The CS summarises features of the ADAPT+ study design and methodology in CS section B.2.3.2, and CS Table 13. Evidence for ADAPT in the CS comes from a data cut-off of 31 Jan 2022.[20]

- Enrolled participants had to meet the following entry requirements:
    - Had completed ADAPT (either the efgartigimod or placebo arm)
    - Had met the criteria to initiate a treatment cycle that could not be completed within the timeframe of ADAPT
    - Were on a stable dose of concomitant gMG treatment (i.e. any AChEis, steroids and NSISTs) prior to study entry.
- 151 patients (of the 167 originally enrolled) from ADAPT rolled over into ADAPT+. Of these 145 received at least one dose of efgartigimod and 111 were AChR antibody positive.
- Receipt of efgartigimod followed the same dosing regimen as in ADAPT: in cycles consisting of four IV infusions (one infusion per week) with subsequent treatment

cycles initiated according to individual clinical response but with an interval from the last infusion of the previous cycle of at least 4 weeks.

3.2.3 Participants characteristics for ADAPT and ADAPT+

Baseline characteristics participants in the ADAPT and ADAPT+ studies are described in CS sections B.2.4.1.4 and B.2.4.2.2 respectively with summary data presented in CS Table 14 and CS Table 15 respectively. For ease of comparison the EAG has provided a composite table (Table 6). The EAG observes that baseline characteristics are mainly balanced between the efgartigimod and placebo arms of the ADAPT RCT with some exceptions. We note that there is a lower proportion of participants aged 65 years or over in the efgartigimod arm: 12.3% compared to 20.3% in the placebo arm and higher proportion with previous thymectomy in the efgartigimod arm (69.2% compared to 46.9% in the placebo arm). Our clinical expert felt the increased proportion of thymectomy in the efgartigimod arm might be due to the higher proportion of younger patients and that the increased proportion of thymectomy could make a difference to trial outcomes. However, we acknowledge that the company did a subgroup analysis on this and stated that the higher prevalence of thymectomy in the efgartigimod treatment group did not appear to favour efgartigimod (see CS Appendix E1). In the efgartigimod arm there is also a slightly higher proportion of females (70.8% compared to 62.5% in the placebo arm) and a higher proportion with no steroid or NSIST (20% versus 9.4% in the placebo arm). Our clinical expert did not raise any concerns over these differences and confirmed that the patients in the ADAPT RCT are representative of those seen in clinical practice in England.

Table 6 ADAPT and ADAPT+ baseline demographics and clinical characteristics of the AChR antibody positive patient population

Characteristic	ADAPT		ADAPT+ (n=111)
	Efgartigimod (n=65)	Placebo (n=64)	
Mean age (SD), years	44.7 (15)	49.2 (15.5)	47.1 (15.5)
Age category, n (%)			
18 to <65 years	57 (87.7)	51 (79.7)	93 (83.8)
≥65 years	8 (12.3)	13 (20.3)	18 (16.2)
Sex, n (%)			
Female	46 (70.8)	40 (62.5)	75 (67.6)
Male	19 (29.2)	24 (37.5)	36 (32.4)
Race, n (%)			
Asian	7 (10.8)	4 (6.3)	8 (7.2)
Black or African American	1 (1.5)	3 (4.7)	3 (2.7)
White	54 (83.1)	56 (87.5)	97 (87.4)
Other*	3 (4.6)	1 (1.6)	3 (2.7)
Mean time since diagnosis, years (SD)	9.7 (8.3)	8.9 (8.2)	9.7 (7.9)
Previous thymectomy, n (%)	45 (69.2)	30 (46.9)	NR
MGFA class at screening, n (%)			
II	28 (43.1)	25 (39.1)	NR
III	35 (53.8)	36 (56.3)	NR
IV	2 (3.1)	3 (4.7)	NR
Total MG-ADL score, mean (SD)	9.0 (2.5)	8.6 (2.1)	9.5 (3.1)
Total QMG score, mean (SD)	16.0 (5.1)	15.2 (4.4)	15.3 (5.7)
Total MGC score, mean (SD)	18.6 (6.1)	18.1 (5.2)	NR
Total MG-QOL15r score, mean (SD)	15.7 (6.3)	16.6 (5.5)	NR
At least one previous NSIST, n (%)	47 (72.3)	43 (67.2)	NR
gMG therapy at baseline (ADAPT) or concomitant gMG treatment (ADAPT+), n (%)			
Any steroid	46 (70.8)	51 (79.7)	NR
Any NSIST	40 (61.5)	37 (57.8)	67 (60.4)
No NSISTs	NR	NR	44 (39.6)
Steroid + NSIST	34 (52.3)	31 (48.4)	NR
No steroid or NSIST	13 (20.0)	6 (9.4)	NR

Source: CS Table 14 and CS Table 15 merged by EAG.
Ranges of the clinical outcome assessments are as follows: MG-ADL total score 0–24, QMG score 0–39, MGC 0–50, and MG-QOL15r 0–30; for each instrument, higher scores are indicative of more active disease
*Includes American Indian or Alaska Native, multiple reported, or not reported
Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; gMG, generalised myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite scale; MGFA, Myasthenia Gravis Foundation of America; MG-QOL15r, Myasthenia Gravis Quality of Life revised; NSIST, nonsteroidal immunosuppressive therapy; QMG, Quantitative Myasthenia Gravis; SD, standard deviation

EAG conclusion on the design, methodology and participant characteristics of the included studies

The CS includes one RCT (ADAPT) comparing efgartigimod + established clinical management against placebo + established clinical management and the single-arm extension (efgartigimod + established clinical management) to this trial (ADAPT+).

The EAG identified no concerns about the design or methodology of the ADAPT RCT and clinical advice to the EAG is that the participants in the trial are representative of those seen in clinical practice.

3.2.4 Risk of bias assessment

The company initially carried out quality assessments of ADAPT (CS section B.2.5.1 Table 16) and ADAPT+ (CS Appendix D.5 Table 15) using the NICE-recommended CRD checklist for RCTs.[25]

ADAPT+ is an observational cohort study without a comparator arm and should be assessed with a tool appropriate to its study design. In response to Clarification question A3, the company supplied two revised quality assessments of ADAPT+ using the NICE-recommended checklist for non-randomised and non-controlled evidence and the criteria in Bowers et al. 2012 aimed at judging the quality of open-label extension studies.[26]

The company does not make a statement about the potential for risk of bias in either of the ADAPT studies.

3.2.4.1 EAG risk of bias assessment for ADAPT

The EAG critique and interpretation of risk of bias for the ADAPT RCT is in Appendix 2 of this report. The company assessed the overall trial population in relation to differences between groups and we additionally assessed the AChR antibody positive population in relation to these criteria, and our responses concluded the same. Handling of missing data is clearly reported for all outcomes. A sensitivity analysis for the primary outcome using imputed data for non-response shows consistent results, however the extent of missing data for the other outcomes is unclear although we believe appropriate handling mitigates this. Generally, we agree with the assessment made by the company and believe that the ADAPT RCT is at low risk of bias for the primary outcome and probably at low risk of bias for the other outcomes.

3.2.4.2 EAG risk of bias assessment for ADAPT+

The EAG critique and interpretation of risk of bias for the ADAPT+ study is in Appendix 3 of this report. We agree with most of the company's updated assessments, however, we consider that the study design and the extent of sample slippage pose a high risk of bias in this study. The open-label design and lack of a control arm means there is inherently a risk of bias in favour of the treatment arm. In terms of sample slippage in relation to the number

randomised in the original ADAPT RCT 90% (151/167, 68 of whom had received placebo) were enrolled in ADAPT+ with 87% (145/167) receiving efgartigimod during ADAPT+. However, 54% (91/167) discontinued efgartigimod treatment during ADAPT+, with [redacted] discontinuing from ADAPT+ so they could enrol in ADAPT-SC (all reasons for discontinuations from ADAPT+ are shown in CS Appendix Figure 4). The proportion of sample slippage in relation to the number randomised in the original RCT is substantially more than the 20% discontinuation threshold suggested by Schulz et al. and supported by Bowers et al. that would lead to validity concerns.[26; 27] Although participant flow and reasons for discontinuation are reported on a cycle-by-cycle basis (ADAPT+ CSR Interim 4, Table 8), it is not clear whether the length of follow-up has mitigated the effects of losing over [redacted] of the population sample over the course of the study.

EAG conclusion on risk of bias in the included studies

The ADAPT trial is at low risk of bias. However, ADAPT+ is at high risk of bias.

3.2.5 Outcomes assessment

Key outcomes of the ADAPT trial are summarised in CS Table 12 and for the extension study ADAPT+ in CS Table 13. Here we focus on key efficacy outcomes that inform the economic model:

- MG-ADL, which is used in the model to provide the probabilities of patients transitioning between different health states defined by MG-ADL score ranges (full description of transition states for economic modelling in CS section B.3.3.2 to B.3.3.5 and EAG critique in section 4.2.6 of this report)
- gMG exacerbations and adverse events of grade 3 or higher (safety results section 3.3.9 of this report)
- EQ-5D-5L data used to inform HRQoL in the model (full description of their use in the economic model in CS section B.3.4 and EAG critique in section 4.2.7.2 of this report)

We also include data on treatment duration here, which although not a clinical efficacy outcome, is important for interpreting adverse events (because the overall exposure to efgartigimod differed between ADAPT and ADAPT+) and because pooled individual patient data from ADAPT and ADAPT+ for time on treatment informed the economic model.

- Time on treatment (see discontinuation of efgartigimod treatment section 4.2.6.3.1 of this report)

3.2.5.1 Clinical efficacy outcomes

The company used disease-specific PRO/HRQoL measures commonly used in clinical trials for myasthenia gravis.[28] Each measure is accurately described and justified in CS section B.1.3.1.2 and CS section B.2.5.2. In ADAPT, all measures were assessed weekly for eight weeks after the initiation of each cycle and then every two weeks until the end of the study at 26 weeks (CS section B.2.3.1.1). In ADAPT+, measures were [redacted] (ADAPT+ CSR Interim 4 section 9.5.1).

MG-ADL

The Myasthenia Gravis Activities of Daily Living (MG-ADL) profile was developed in the late 1990s.[29] It comprises eight items that cover different activities or symptoms (talking, chewing, swallowing, breathing, brushing teeth/combing hair, arising from a chair, double vision, eyelid droop) which are scored from Grade 0 (normal/no impairment) to Grade 3 (the most severe e.g. for breathing grade 3 is ventilator dependence). The total score range on the MG-ADL is therefore from 0-24.

The company used the MG-ADL score for the primary outcome in ADAPT and for some secondary and exploratory outcomes. The company used a validated clinically meaningful improvement (CMI) threshold of a ≥2-point reduction in MG-ADL score to indicate response.[30] The EAG's clinical expert confirmed that a ≥2-point improvement in MG-ADL score is deemed clinically meaningful in practice. They also confirmed that the MG-ADL is used in clinical practice in England and at their centre it is used in conjunction with the Myasthenia Gravis Composite (MGC) score.

The ADAPT trial primary outcome was MG-ADL responders in cycle 1, defined as the proportion of patients with a ≥2-point improvement in MG-ADL score for ≥4 consecutive weeks with first improvement occurring by week 4 of the cycle (one week after the fourth infusion) (CS section Table 11). This would indicate a clinically meaningful improvement effective within one cycle of treatment.

Further secondary outcomes using the MG-ADL score in ADAPT cover variations of time to clinically meaningful improvement and duration of effect, as listed below:

- Proportion of time with a CMI in MG-ADL (until day 126) (secondary outcome) was defined as having ≥2-point improvement in total MG-ADL score compared with baseline.

- Time to qualify for retreatment (time to no CMI) was defined as the time from day 28 (end of a cycle of treatment) to no CMI as indicated by a <2-point reduction in the MG-ADL total score and MG-ADL total score of ≥5 points with >50% of the total score attributed to non-ocular symptoms, compared with baseline of the first cycle (secondary outcome). Eligibility for retreatment therefore uses a validated CMI threshold and a MG-ADL total score that indicates generalised myasthenia gravis.
- MG-ADL early responders in cycle 1 (secondary outcome) the same definition as for responders except that the first improvement is no later than week 2 of the first treatment cycle which is two weeks earlier than required for the primary outcome.

The extension study ADAPT+ assessed mean MG-ADL change from week 1 to week 3 for cycles 1-14 as a secondary outcome.

QMG, MGC, and MG-QOL15r

The ADAPT trial used the Quantitative Myasthenia Gravis (QMG) score for secondary and exploratory outcomes, and the Myasthenia Gravis Composite (MGC) score and the revised Myasthenia Gravis Quality of Life, 15-item (MG-QOL15r) questionnaire for exploratory outcomes only. They are not used in the economic model. As noted in section 2.2.1.2 above these are validated outcome measures accurately described in CS section B.1.3.1.2, and the company uses validated CMI thresholds where applicable.[31-33] CS section B.2.6.3.1 states that including the QMG measure aims to indicate where there is consistent improvement across the different scales that measure the manifestations of gMG, and which presumably applies to the other outcome measures (MGC and MG-QOL15r) as well.

The QMG secondary outcome, QMG responders in cycle 1, is reported below in section 3.3.2. It was defined as a ≥3-point improvement in QMG score for ≥4 consecutive weeks (with first improvement no later than 1 week after last infusion) (CS Table 12). This would indicate a conservative clinically meaningful improvement,[31] effective within one cycle of treatment. The QMG, MGC and MG-QOL15r exploratory outcomes are reported in CS section B.2.6.4.

The extension study ADAPT+ assessed mean QMG change from week 1 to week 3 for cycles 1-7 as a tertiary outcome. ADAPT+ does not assess MGC or MG-QOL15r.

3.2.5.2 HRQoL outcomes

The company used EQ-5D-5L and MG-QOL15r to measure HRQoL in ADAPT RCT participants. Here we consider the EQ-5D-5L which was used in the model. The MG-QOL15r was not used in the model and is noted as an exploratory outcome above in section 3.2.5.1.

EQ-5D-5L

EQ-5D-5L data from ADAPT was mapped to EQ-5D-3L and informs utility values for the MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states used in the economic model.

HRQoL outcomes were not assessed in ADAPT+.

3.2.5.3 Safety outcomes

Adverse events

The ADAPT, ADAPT+ and ADAPT-SC studies all reported treatment-emergent adverse events and serious adverse events. The economic model uses the number of grade ≥3 adverse events from both efgartigimod and placebo arms of the ADAPT trial only (CS section B.3.3.8). The EAG considers all studies (ADAPT, ADAPT+ and ADAPT-SC) in the safety results section 3.3.9 below.

Pre-defined adverse events of special interest (AESIs) were infections because efgartigimod causes a transient reduction in IgG levels. Therefore, all adverse events in the system organ class 'infections and infestations' are reported.

Hospitalisation

Hospitalisation data from the ADAPT trial informs the economic model (see section 4.2.6.4 of this report), however hospitalisation is not a prespecified outcome in the trial and is therefore not reported in the efficacy or safety results of the CS or CSR. However, in a post-hoc analysis,[34] the observed number of all-cause and MG-related hospitalisations during the study were captured from the serious adverse event listings and combined with patient follow-up time to calculate an incidence rate of hospitalisations per treatment arm (Clarification response A12).

Hospitalisation and gMG exacerbations: the CS defines gMG exacerbations as acute events requiring in-hospital care for the purposes of cost-effectiveness analysis (CS section B.3.3.6). However, the EAG's clinical expert said that patients are not likely to be admitted to

hospital with gMG unless they have swallowing or breathing problems, i.e. they are in myasthenic crisis, whereas an exacerbation is worsening which has not reached the extent of a crisis. The ABN 2015 guidelines state that a patient should be managed in hospital for significant bulbar symptoms, low vital capacity, respiratory symptoms or progressive deterioration.[14] The EAG's clinical expert believes there is generally a consensus around which patients require hospital admission for myasthenic crisis and noted that the British treatment guidelines are currently being updated.

Mortality

Mortality data from the ADAPT, ADAPT+ and ADAPT-SC studies are reported in the CS but not used in the economic model. The studies are relatively short (26 weeks, ongoing, or 10 weeks respectively) and not long enough to assess mortality in people with myasthenia gravis as most patients have a normal lifespan.[35] Mortality data used in the model are discussed in section 4.2.6.7 of this report.

The EAG presents the hospitalisation and mortality results from the included studies in the safety results section of this report (section 3.3.9).

3.2.5.4 Treatment duration

ADAPT treatment duration

As noted above (in study characteristics section 3.2.1 and 3.2.2), time on treatment varied between patients as they were only re-treated with the study treatment if they met specified non-response criteria, and in ADAPT there was a maximum of three cycles of treatment. The CS reports treatment duration for the overall study population only (CS section B.2.6.1) whereas [redacted] for the AChR antibody positive population is reported in the CSR (CSR section 12.1 and CSR Table 14.1.2.11.1): presented below in Table 7.

Table 7 Treatment duration and exposure (ADAPT)

Treatment duration / exposure	ADAPT AChR-Ab+ population		ADAPT Overall study population	
	Efgartigimod N=65	Placebo N=64	Efgartigimod N=84	Placebo N=83
Duration in the study, days, mean (SD)	[redacted]	[redacted]	151.5 (22.4)	151.7 (29.6)
Cumulative duration of treatment exposure, patient-years	[redacted]	[redacted]	34.9	34.5
Time to the second treatment cycle, weeks, mean (SD)	[redacted]	[redacted]	13 (5.5)	NR
Patients receiving, **1 cycle of treatment,** n (%) **2 cycles of treatment,** n (%) **3 cycles of treatment,** n (%)	[redacted]	[redacted]	21 (25) 56 (66.7) 7 (8.3)	26 (31.3) 54 (65.1) 3 (3.6)

Sources: CS section B.2.6.1 and CSR Table 14.1.2.11.1.
AChR-Ab+: AChR antibody positive; SD: standard deviation.
[a] derived from CSR Table 14.1.2.11.1 and calculated by the reviewer.

ADAPT+ treatment duration

Similar to ADAPT, treatment duration is reported for the overall study population (n=145) in CS section B.2.7.1, and [redacted] are provided for the AChR antibody positive population (n=111) in the CSR (ADAPT+ CSR Interim 4 Table 27).

Data is presented from Interim analysis 4 (data cut off 31 January 2022): the mean duration of treatment for the overall study population was 548.0 days (SD: 231.79) and the cumulative duration of treatment exposure was 217.55 patient-years, during which patients received up to [redacted] treatment cycles (CS section B.2.7.1).

EAG conclusion on outcomes assessment

We consider the company uses the MG-ADL score appropriately for the clinical efficacy evidence and for the economic model. Other efficacy outcome measures are relevant and provide supporting data. Relevant HRQoL and adverse event outcomes from the main study ADAPT are used in the economic model. The post-hoc analysis of serious adverse event data was necessary to provide hospitalisation outcome data for the model as hospitalisation was not a pre-specified outcome in any of the studies.

3.2.6 Statistical methods of the included studies

Statistical analysis plans (SAPs) for the ADAPT and ADAPT+ studies were provided with clarification response C4. Summary information is provided in the CS and clinical study reports. Analyses reported here are relevant to outcomes reported for the AChR antibody positive population in each study unless stated otherwise.

3.2.6.1 Statistical methods in ADAPT

The analysis populations are appropriate: the efficacy analyses used a modified intention-to-treat population (mITT), i.e. all randomised patients with a valid baseline MG-ADL assessment and at least one post-baseline MG-ADL assessment; and safety analyses included all patients who received at least one dose or part-dose of study treatment (CS section B.2.4.1.1).

The sample size appears adequate and is justified: a sample size of 150 was calculated which provided 96% power in the population of AChR antibody positive patients to detect a difference of 35% in the proportion of responders with 120 patients; thus it allowed for 10% attrition and enrolment of up to 20% AChR antibody negative patients (CS section B.2.4.1.2).

Methods to account for multiplicity to reduce type I error are appropriate: the primary and secondary outcomes were tested in hierarchical order with each one required to meet a significance at the 5% two-sided alpha level before testing the next outcome in the hierarchy (CS section B.2.4.1.2; hierarchical order reported in ADAPT CSR 9.7.1.3.1).

Outcome analyses appear appropriate: the primary outcome (and other outcomes involving binary variables) was tested using a two-sided exact test using logistic regression at the two-sided 5% significance level, and the treatment effect was presented as an odds ratio which if more than 1 represented a higher response rate for efgartigimod than placebo (CS section B.2.4.1.2; ADAPT CSR 9.7.1.2.2). The primary outcome was also analysed using a [redacted] (CSR Table 14.2.1.3). [redacted] (ADAPT CSR 9.7.1.3.2). An analysis of covariance (ANCOVA) model was used to analyse percentage of time patients had CMI, with randomised treatment group and stratification variables (race, concomitant gMG treatment, and AChR antibody status) included as factors and baseline total MG-ADL score included as a covariate (CS section B.2.4.1.2). Time not having a CMI was estimated using Kaplan-Meier time-to-event analysis and compared using stratified log-rank test, stratified for the stratification variables. Additional outcomes were analysed descriptively.

The handling of missing data for the primary outcome [redacted] (ADAPT CSR 11.4.2.2). The EAG considers this method is conservative in approach. [redacted] (ADAPT CSR Table 14.2.1.4.1 and the efficacy results section 3.3.1 of this report). [redacted] (ADAPT SAP 4.1.2.2 and 4.1.2.3). PROs are associated with high rates of missing data and poor compliance rates,[36] and although many outcomes in ADAPT incorporate the patient reported MG-ADL score, it is unclear how much missing data there was.

3.2.6.2 Statistical methods in ADAPT+

As the long-term safety extension study of ADAPT, from which 151 patients rolled over (111 of whom were AChR antibody positive), all analyses in ADAPT+ were performed on the

safety analysis set, i.e., all patients who received at least one dose or part-dose of study treatment, which the EAG finds appropriate (CS section B.2.4.2.1; ADAPT+ CSR Interim 4, section 9.7.1.1). However, [redacted] of the enrolled patients exited the study to enter ADAPT-SC (CS section B.2.4.2.2) which has substantially decreased the sample size.

For efficacy outcomes, [redacted] (ADAPT+ CSR interim 4, section 9.7.1.2). For safety outcomes, [redacted] (ADAPT+ CSR Interim 4, section 9.7.1.3). [redacted] (ADAPT+ SAP section 2.3.1), however, the amount of missing data and how it is reported is unclear. No statistical testing is performed in this study.

EAG conclusion on study statistical methods

The majority of results are reported descriptively and as summary statistics. Where statistical testing is performed standard methods are used appropriately. In ADAPT, missing data were handled appropriately although it is unclear how much missing data there was. In ADAPT+, [redacted] and the amount of missing data is unclear.

3.3 Clinical efficacy results of the intervention studies

Here we present results for the pivotal ADAPT RCT, focussing on key clinical efficacy outcomes and outcomes that inform the economic model (see outcomes assessment section 3.2.7 of this report). Supporting results from the non-comparative extension study ADAPT+ are also presented for illustrative purposes. All results presented in this section are for the AChR antibody positive population unless otherwise stated.

3.3.1 ADAPT RCT primary outcome: MG-ADL responders in cycle 1 (AChR antibody positive population)

A clinically meaningful improvement of ≥2-points in MG-ADL score for ≥4 consecutive weeks with first improvement occurring by week 4 of the cycle was achieved by 68% (44/65) of patients in the efgartigimod arm compared to 30% (19/64) in the placebo arm (CS Figure 12). The difference of effect was statistically significant (OR 4.95; 95% CI 2.21 to 11.53; p<0.0001).

Prespecified sensitivity analyses [redacted] (CSR Tables 14.2.1.3 and 14.2.1.4.1): [redacted].

3.3.2 ADAPT secondary outcomes

Results of the secondary outcomes support the favourable efficacy result for efgartigimod in the primary outcome: there were statistically significantly more QMG responders in cycle 1 in the efgartigimod group than in the placebo group and a statistically significant greater amount of time was spent with a CMI in the efgartigimod group than in the placebo group. Time from day 28 (1 week after the last infusion of cycle 1) to qualifying for retreatment was longer in the efgartigimod group, but not statistically significant. There were proportionally more MG-ADL early responders in cycle 1 in the efgartigimod group than in the placebo group. Results of the secondary outcomes are reported in CS section B.2.6.3 and summarised in Table 8 below.

Table 8 Summary of results for secondary outcomes in ADAPT (AChR antibody positive population)

Outcome	Efgartigimod N=65	Placebo N=64	Difference of effect
QMG Responder in cycle 1, n/N (%)	41/65 (63)	9/64 (14)	OR 10.84 [95% CI 4.18 to 31.20]; p<0.0001
Mean % time with CMI in MG-ADL (until day 126), % (95% CI)	48.7% (36.5 to 60.9)	26.6% (14.1 to 39.2)	p=0.0001
Time from Day 28 to no CMI (full study), days, median (IQR)	35 (18-71)	8 (1-57)	p=0.26
MG-ADL Early responder in cycle 1, n/N (%)	37/65 (57)	16/64 (25)	Not tested[a]

Source: adapted from CS Table 17 and supplemented with data from CS section B.2.6.3.2.
CMI: clinically meaningful improvement; IQR: inter quartile range; MG-ADL: Myasthenia Gravis Activities of Daily Living scale; OR: odds ratio; QMG: Quantitative Myasthenia Gravis scale.
[a] not tested for significance because a statistically significant difference between the efgartigimod and placebo groups was not attained in the previous endpoint (time to no CMI) in the hierarchy outlined in the ADAPT CSR section 11.4.1.

3.3.3 ADAPT exploratory outcomes

The results of the exploratory analyses reported in CS section B.2.6.4 also support the efficacy of efgartigimod that was demonstrated in the primary and secondary outcomes. Some of these reported outcomes explore the timings of onset and duration of response for

responders in the efgartigimod arm only, so there is no comparator arm data. These results should be viewed as illustrative only.

3.3.4 ADAPT tertiary outcomes

The results of the tertiary outcomes for pharmacodynamic analyses on IgG levels and anti-AChR antibodies are not in the scope of this appraisal but they are reported in CS section B.2.6.5 and do not raise any concerns.

3.3.5 ADAPT post-hoc analyses

As noted above (in study characteristics section 3.2.1 and 3.2.2) patients received subsequent treatment cycles only when they met pre-specified retreatment criteria. Therefore patients received different numbers of treatment cycles and had different lengths of time between cycles during the study. An area under the curve (AUC) analysis was carried out for change in total MG-ADL, QMG and MG-QOL15r scores from baseline to the end of the study (baseline to week 26) to compare efficacy over the whole study period instead of per cycle. This post-hoc analysis is reported in CS section B.2.6.7 where the mean differences in the AUC from baseline to week 26 are reported as [redacted] for all three scales.

3.3.6 ADAPT HRQoL results

EQ-5D-5L

The EQ-5D-5L UK utility outcome (with UK value sets applied) informs the economic model after mapping to UK EQ-5D-3L values (see section 4.2.7.2 of this report for the EAG's critique of this). A statistically significant difference between trial arms was seen for the mean change from baseline of the EQ-5D-5L UK utility score at week 4 of cycle 1, favouring efgartigimod. The statistically significant difference was sustained from week 1 to week 8 of cycle 1 (CS Figure 22) but lost by week 10. Mean EQ-5D-5L utility scores are not provided for either of the subsequent treatment cycles.

The maximum mean change in EQ-5D-5L visual analogue scale (VAS) score was seen in the efgartigimod group week 4 of cycle 1. A statistically significant difference between the efgartigimod and placebo trial arms was sustained from week 1 to week 6 of cycle 1 (CS Figure 21).

The CS reports EQ-5D-5L domain responses for treatment cycles one and two in section B.2.6.6.3 and Figure 23 which shows numerical improvements at 4 weeks for the efgartigimod arm for both cycle 1 and cycle 2 but not the placebo arm of the trial.

3.3.7 Subgroup analyses in ADAPT

The NICE scope does not specify any subgroups. The ADAPT trial had pre-planned subgroup analyses in the overall study population (i.e. AChR antibody positive and AChR antibody negative patients grouped together) for the percentages of MG-ADL responders by race, concomitant gMG treatment, MG-ADL total score at baseline category, and the number of administered cycles (CS Table 11) but the results are not reported in the CS.

The CS reports a post-hoc analysis of the responder rates (MG-ADL responders for cycle 1 and QMG responders for cycle 1) for the following subgroups in the ADAPT trial AChR antibody positive population who are relevant to this appraisal: concomitant or prior gMG therapies (AChEi only; any steroid; any nonsteroidal immunosuppressive therapy; prior thymectomy; no prior thymectomy); prior nonsteroidal immunosuppressive therapy exposure; and baseline MG-ADL score. Results show there were consistently higher proportions of MG-ADL and QMG responders among efgartigimod treated participants in comparison to placebo treated participants in all subgroups (CS Appendix E). The level of certainty around these results is low, limited by the small sample sizes of each subgroup (range n=6 to n=51) and wide 95% confidence intervals (CS Appendix E).

3.3.8 ADAPT+ single arm extension study

The primary outcome of ADAPT+ was safety and tolerability of efgartigimod in AChR antibody positive participants (CS Table 13) and these safety results are presented in section 3.3.9.2 of this report. Efficacy outcomes relevant to this appraisal are MG-ADL total score and QMG score which are provided as supporting information.

3.3.8.1 ADAPT+ secondary outcomes

MG-ADL total score

The mean change from baseline in the MG-ADL total score was measured at week 3 of each cycle (the ADAPT study measured this outcome at week 4) due to timing of scheduled visits. CS Figure 24 shows that clinically meaningful improvements were made in each of cycles 1 to 14. For all cycles, [redacted] AChR antibody positive patients had a clinically meaningful improvement of ≥2 points in the MG-ADL total score (CS section B.2.7.2).

QMG score

The mean change from baseline in QMG score was also measured at week 3, but for cycles 1 to 7 only as prespecified for part A of the study. CS Figure 25 shows that clinically meaningful improvements were made in each cycle (CS section B.2.7.3). It is not reported what proportion of (AChR antibody positive) patients achieved the clinically meaningful improvement of ≥3 points in QMG total score.

3.3.9 Safety results

3.3.9.1 Safety results in ADAPT

The CS reports adverse events and serious adverse events for the overall study population (CS section B.2.11.1) with a cumulative duration of treatment exposure of 34.9 and 34.5 patient-years in the efgartigimod and placebo arms respectively (full details on treatment exposure are provided in section 3.2.5.4). A high proportion of participants in both trial arms experienced a treatment-emergent adverse event (efgartigimod group 77%, placebo group 84%). The most common treatment-emergent adverse events in the efgartigimod group were headache (29%, vs 28% in the placebo group), nasopharyngitis (12%, vs 18% in the placebo group), upper respiratory tract infections (11%, vs 5% in the placebo group), urinary tract infections (10%, vs 5% in the placebo group), nausea (8%, vs 11% in the placebo group), and diarrhoea (7%, vs 11% in the placebo group).

Results for the overall system organ class 'infections and infestations' show the greatest difference between the efgartigimod and placebo groups (46% vs 37% respectively). This is to be expected as infections were an adverse event of special interest because efgartigimod causes a transient reduction in IgG levels. There were no discontinuations due to an infectious event.

There were slightly fewer serious adverse events in the efgartigimod group than in the placebo group (5% vs 8% respectively). The serious adverse events in the efgartigimod group were thrombocytosis, rectal adenocarcinoma, MG worsening, and depression; all except depression led to treatment discontinuation.

Hospitalisation

The CS does not report the total number of gMG exacerbations during the ADAPT RCT, only the three gMG exacerbations defined as acute events requiring in-hospital care, two of these occurred in the placebo group and one in the efgartigimod group (CS section B.3.3.6). However, the company reports a post hoc analysis of hospitalisation data as a component of

the safety analysis in clarification response A12. There were fewer hospitalisation events in the efgartigimod group than in the placebo group (n=4 vs n=10 respectively), and fewer of those hospitalisation events were related to myasthenia gravis in the efgartigimod group than in the placebo group (n=1 vs n=3 respectively). The efgartigimod group had a 60% lower rate of all-cause hospitalisation and a 67% lower rate of MG-related hospitalisation; however, the difference between the rates is not statistically significant and the EAG notes that with a small number of events in a 26 week RCT these rates may not be robust. The conference poster by Qi et al. 2022 reports hospitalisations in the AChR antibody positive population that are consistent with the overall population and also reports the overall number of exacerbations in the AChR antibody positive population (17/65 in the efgartigimod arm and 27/61 in the placebo arm).[34]

Mortality

There were no deaths during the study in either arm (CS section B.2.11.1).

[redacted] (ADAPT CSR Tables 14.3.1.1.1 and 14.3.1.2.1).

3.3.9.2 Safety results in ADAPT+

The CS reports adverse events and serious adverse events for the overall safety population in ADAPT+ (n=145, CS section B.2.11.2), however no results are available for the AChR antibody positive subgroup (n=111) despite "safety and tolerability in the AChR-Ab+ population" being the primary outcome of the study (CS Table 13). The cumulative duration of treatment exposure was 217.55 patient-years. The most common treatment-emergent adverse events are similar to those in ADAPT: headache (25%), nasopharyngitis (14%), COVID-19 (12%), diarrhoea (10%), and urinary tract infection (9%) (CS Table 21). Infections were also an adverse event of special interest in this study:

[redacted] (ADAPT+ CSR Interim 4 section 12.2.1), however the incidence rate of AESIs did not increase with subsequent efgartigimod cycles (CS section B.2.11).

Serious adverse events were observed in 34 (23%) of patients, however only one Grade 1 infusion-related reaction was considered probably related to efgartigimod treatment.

Hospitalisation

Neither hospitalisation nor exacerbations requiring hospitalisation were reported for the ADAPT+ study.

Mortality

There were five deaths during the study none of which were considered related to efgartigimod treatment.

3.3.9.3 Safety results in ADAPT-SC

Results are for the safety analysis set ([redacted]), there is no subgroup analysis for AChR antibody positive patients and the EAG has not been able to find information on the duration of treatment exposure for this study. The CS reports that the safety profile of efgartigimod is consistent with the ADAPT study and that most adverse events were mild to moderate in severity (CS section B.2.12.2). Data in the CSR [redacted] (ADAPT-SC CSR section 11.2.1.1. Table 19). The most commonly reported serious adverse event was [redacted] (ADAPT-SC CSR section 11.2.1.6).

Hospitalisation

Hospitalisations reported during the study are not provided in the CS and the relevant section of the CSR was not present in the version provided to the EAG.

Mortality

[redacted] (ADAPT-SC CSR section 11.2.1.5).

3.3.9.4 Neoplasms

The European Public Assessment Report (EPAR) for Vyvgart, based on pooled data from ADAPT and ADAPT+, noted an imbalance in neoplasms between patients treated with efgartigimod (11 events in eight patients) and placebo (one event) with six of these neoplasms (in five efgartigimod treated patients) events considered serious.[37] After investigation, the EPAR concluded that although there is no evidence for a correlation between IgG reduction and an increased risk of developing cancer the difference in the number of events between study arms is noteworthy and malignancies are included as an important potential risk in their risk management plan.[37]

EAG conclusion on safety results

The results of all the studies indicate that efgartigimod is well tolerated, that infections are generally the most common adverse event and mostly not serious, and that it is advisable to monitor the occurrence of neoplasms in the current ongoing studies as a precaution.

3.3.10 Pairwise meta-analysis of intervention studies

The efficacy evidence is drawn from the ADAPT RCT so no meta-analysis is not included in the CS.

3.4 Critique of studies included in the indirect comparison and/or multiple treatment comparison

3.4.1 Rationale for ITC

The company did not conduct an indirect treatment comparison (ITC) since the ADAPT trial control arm consisted of established clinical management without efgartigimod (which is the comparator for this appraisal). The company considered the control arm of ADAPT "*representative of the gMG patient population in terms of age, gender, and prior and ongoing use of gMG therapies*" (clarification response A15). Hence the direct within-trial comparison was used to estimate comparative effectiveness. The EAG's clinical expert agreed the ADAPT control arm was representative of the gMG population in England and Wales. The EAG queried whether larger studies or databases such as the Spanish Registry of Neuromuscular Diseases, NMD-ES) might have been explored as a suitable candidate for population matching (clarification question A15) in an ITC but the company did not comment on this in their response.

The company noted ADAPT trial participants were not permitted to receive rituximab and IVIg despite these being used in the UK. In addition, the EAG's expert observed that the proportion of patients receiving a steroid + nonsteroidal immunosuppressive therapy would be higher, and mycophenolate use would also be higher in UK clinical practice than that observed in ADAPT. The company searched for trials of rituximab and IVIg for potential use in an ITC. A 2012 Cochrane review[38] on IVIg concluded "there is insufficient evidence from RCTs to determine whether IVIg is efficacious" but it is unclear whether any of the included trials could have been used in an ITC or if there is anything more recent. Two recent trials of rituximab (BeatMG,[39] RINOMAX[40]) "*failed to demonstrate a statistically significant clinical benefit for rituximab vs placebo*" (Company response to clarification question A15). This

should not per se rule out an ITC but both studies are small (BeatMG N=52 and RINOMAX N=47) and the EAG's clinical expert agreed these different therapies were unlikely to translate into differences in clinical efficacy. Therefore, the EAG agrees the choice of ADAPT control arm as representative of established clinical management to be appropriate.

3.5 Critique of the MyRealWorld MG study

Effectiveness data from the MyRealWorld MG study were not included in section B.2 (clinical effectiveness) of the CS but data from this study are used in the health economic model in the following ways:

- Providing the baseline cohort characteristics for age and gender (section 4.2.3 of this report)
- EQ-5D-5L data from the MyRealWorld MG study is used to inform utility values generally and also specifically for the crisis health state in the economic model because no patient had a crisis during the ADAPT study (section 4.2.7.2 of this report)
- To help estimate health state resources for patient-monitoring (section 4.2.8.3)

Consequently, we include our critique of this study here.

3.5.1 MyRealWorld MG: study and participant characteristics

3.5.1.1 Study characteristics

The MyRealWorld MG study[41; 42] is an international prospective observational study designed to capture the impact of MG from the patient perspective. The study is sponsored by the company working with patient organisations from 10 countries (US, Japan, Germany, UK, France, Italy, Spain, Canada, Belgium and Denmark). Patients can be invited to participate by their neurologist, via communications from patient organisations or by word of mouth. Adults diagnosed with MG can download the MyRealWorld study app and self-enrol. The inclusion criteria are broader than for this appraisal, for example, the study includes patients with ocular MG, and there is no identifiable AChR antibody positive subgroup. Participants can self-report monthly information about their well-being, treatments and healthcare visits through the use of regular questionnaires and surveys about diagnosis, symptoms, treatments, activities and quality of life.[43] These include generic and disease-specific patient-reported outcome measures, for example, EQ-5D-5L, MG-ADL, and MG-QOL15r. A 2023 publication on baseline results from this study[41] states that participants enter data over a period of approximately 2 years. The study is ongoing.

3.5.1.2 Patients' baseline characteristics

In response to clarification question B1 the company provided baseline characteristics for 350 patients in the MyRealWorld MG study from the EU and the UK (25 patients from the UK) who met the ADAPT trial entry criteria and these are shown in Table 9. Our clinical expert thought that in comparison to his clinical experience, a greater proportion of those participating in MyRealWorld MG had severe disease (the EAG notes that 29.4% have class IV disease whereas in the two arms of ADAPT just 3.1% and 4.7% have class IV disease).

Table 9 Baseline characteristics of patients from the MyRealWorld MG study meeting the ADAPT trial criteria, EU+UK subset.

Characteristic	EU + UK patients n=350	UK patients only (n=25)
Age (years)	45.8	[redacted]
% females	77.7	[redacted]
Disease duration (years since diagnosed)	8.5	Not reported
MG-ADL <5	0%	Not reported
MG-ADL 5-7	46.9% (164/350)	Not reported
MG-ADL 8-9	22.6% (79/350)	Not reported
MG-ADL ≥10	30.6% (107/350)	Not reported
Class I	0%	Not reported
Class II	20.6% (72/350)	Not reported
Class III	50.0% (175/350)	Not reported
Class IV	29.4% (103/350)	Not reported
Class V	0%	Not reported
MG-QoL-15r total score	15.9	Not reported

Source: Part reproduction of Table 9 in the company response to clarification questions supplemented with data from CS Table 26.
Abbreviations: EU, European Union; UK, United Kingdom.

3.5.2 Risk of bias assessment for MyRealWorld MG

We requested that the company provide a quality assessment of the company-led MyRealWorld MG study. This was carried out using the NICE-recommended checklist for non-randomised and non-controlled evidence (Clarification response A4).

The EAG critique and interpretation of risk of bias for the MyRealWorld MG study is in Appendix 4 of this report. The information in the company assessment is accurate, however, our interpretation finds this study at high risk of bias. There is a high risk of selection bias due to the recruitment and enrolment methods which promotes self-selection of motivated patients and potentially patients with more severe disease with access to the Internet/use of

a smartphone, and the remote self-enrolment is not verified.[41; 43] There is a high risk of bias related to measuring and reporting the outcomes due to complete reliance on patient reporting of patient reported outcome measures via an unmediated smartphone application (although response options are limited to promote data quality), and some of the patient reported outcome measures are optional to avoid overburdening participants.[41; 43]

3.5.3 Statistical methods in MyRealWorld MG

The statistical methods of the MyRealWorld MG prospective observational study can be found in the study SAP,[44] which was included with the CS, the published protocol,[43] and the recently published analysis of baseline results.[41]

The analysis population is defined as participants who have completed at least one patient reported outcome survey and the necessary elements of their participant profile, and there will be planned subgroup analyses, including by country, however data from the subgroup analyses will not be tested for differences.[44]

The SAP indicates that,

[redacted].

This study is ongoing and only the baseline results have been published.[41] Data informing the economic model is taken from ad hoc analyses carried out specifically for this appraisal using patient level data (clarification response C6).

EAG conclusion on the MyRealWorld MG study

The MyRealWorld MG observational study collects self-reported data from participants who have self-enrolled in this study. Consequently, the study is at a high risk of bias, particularly selection bias and therefore data from this study should be viewed cautiously. The CS uses data from a subgroup of participants who met the ADAPT trial entry criteria, but a greater proportion have severe disease than in ADAPT. Ad hoc analyses have been conducted to provide data to inform the economic model.

3.6 Conclusions on the clinical effectiveness evidence

The company identified one RCT, the ADAPT trial, that directly compares efgartigimod + established clinical management to placebo + established clinical management in adults with gMG. The single-arm extension study, ADAPT+, which followed on from ADAPT was also included in the CS. The ADAPT RCT adequately reflects the population, intervention, established clinical management comparator and outcomes specified in the company's decision problem and NICE scope. The company have not included plasma exchange as a comparator but the EAG's clinical advisor confirmed that plasma exchange is usually used as a treatment for gMG exacerbations or crises (i.e. as an acute treatment) and estimated that the proportion of patients who receive plasma exchange outside an acute need is small (about 5% and certainly less than 10%). Consequently, we do not raise this as a key issue. We judged that the ADAPT RCT was at a low risk of bias whereas the single-arm extension study ADAPT+ was at a high risk of bias. Our clinical expert confirmed that the ADAPT RCT participants are representative of those seen in clinical practice in England and was not concerned about the few differences we identified between the trial arms in some baseline characteristics.

The primary outcome of ADAPT showed there was a statistically significant effect in favour of efgartigimod in terms of the proportion of AChR antibody positive participants who achieved a response on the MG-ADL in cycle 1 (68% versus 30% in the placebo arm, OR 4.95; 95% CI 2.21 to 11.53; $p<0.0001$). Secondary outcomes were also in favour of efgartigimod. Clinically meaningful improvements in the total MG-ADL score and the QMG score were observed in the single arm ADAPT+ extension study.

In ADAPT, the mean change from baseline in health-related quality of life among AChR antibody positive participants (measured by the EQ-5D-5L in cycle 1) was greater in the efgartigimod arm than in the placebo arm and the difference between arms was statistically significant.

Efgartigimod appears to be well tolerated and there were few serious adverse events in the ADAPT overall study population (efgartigimod 5%; placebo 8%). The greatest difference in adverse events was for those events categorised by the system organ class 'infections and infestations' with 46% of these events in the efgartigimod arm versus 37% in the placebo arm but none of these events led to a discontinuation from the trial. It is difficult to draw conclusions on hospitalisation because of the small number of events over the 26-week RCT and there were no deaths during the study. The safety results reported from ADAPT+ and ADAPT-SC are similar to those in ADAPT.

A real-word evidence study MyRealWorld-MG contributes baseline cohort characteristics and EQ-5D-5L data to the health economic model but no clinical effectiveness data are reported in CS section B.2 (clinical effectiveness).

The EAG have not identified any aspects of the clinical efficacy evidence that we believe should be raised as a key issue.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted two systematic literature reviews. The main review was completed on 7-9th April 2022 to identify evidence published from 1st January 2012 for cost-effectiveness models and costs (section 4.1), quality of life data (section 4.2.7) and resource use (section 4.2.8) for patients with gMG. A separate systematic review sought evidence on the quality of life and cost burden associated with chronic corticosteroid use in patients with gMG (discussed in sections 4.2.7.5 and 4.2.8.4).

The main review was updated on 19-21st January 2023, with a search strategy more closely aligned with the final scope of the current appraisal and was limited to studies published in 2022 and 2023 only. The initial April 2022 review included a broad range of appropriate sources (both for databases and grey literature). The January 2023 update only included searches in MEDLINE, the Cochrane Database of Systematic Reviews and for conference abstracts (using Embase.com and hand searching). Publications were limited to those in English at the screening stage. The search strategy is described in CS Appendix G1.1 and eligibility criteria given in CS Appendix G Tables 24 and 25 (CS Appendix G.1.3).

The original review of cost-effectiveness studies in April 2022 identified five unique studies: one study reported costs and a cost utility analysis for rituximab,[45] but no other economic evaluations in gMG were identified. The January 2023 update identified a further two publications (relating to one study) and were included in the review.[46; 47]

Tice et al. (2022)[47] is the only published economic evaluation of the cost-effectiveness of efgartigimod as an add-on to established clinical management of gMG. The model had four health states based on the QMG scoring system. The study estimated the cost effectiveness of efgartigimod to be US $2,076,000 per QALY.

The CS states that this model has several limitations for informing the current appraisal, including:

- Taking a US healthcare system perspective,
- Using a two-year time horizon,
- The health states are defined using the QMG score, which the company considers to be overly simplistic,
- Assuming continuous dosing, rather than a treatment plan personalised to the patient.

Consequently, the company developed a de novo economic model to assess the cost-effectiveness of efgartigimod plus established clinical management versus established clinical management without efgartigimod for people with AChR antibody positive gMG.

EAG conclusion

Overall, the EAG has no major concerns regarding the main systematic literature review for cost-effectiveness, quality of life data and resource use studies. The searches are up to date, but the company do not give a justification for the 2012 start date limit. However, we consider it unlikely that any key cost-effectiveness studies have been missed.

The EAG agrees that the Tice et al.[47] model is not directly applicable to this appraisal. The two-year time horizon is not appropriate for modelling a chronic disease like gMG. Our clinical expert advised us that efgartigimod retreatment would be given on an individual patient basis. Further, clinicians would avoid treating patients unnecessarily, and would instead observe a patient's response to treatment, then administer another cycle of treatment if the patient's condition deteriorated. The timing of when a patient's disease gets worse tends to be predictable, so scheduling the next infusion before their health state worsens is feasible. Therefore, we do not believe that efgartigimod would be given continually in UK practice as assumed in the study by Tice et al. [47]

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The company's economic model fulfils the requirements of NICE's reference case (Table 10).

Table 10 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment. Company model meets reference case?
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
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, maximum age 100 years
Synthesis of evidence on health effects	Based on systematic review	Yes
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, EQ-5D-5L data from ADAPT trial

Element of health technology assessment	Reference case	EAG comment. Company model meets reference case?
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, EQ-5D-5L data mapped to the UK 3L value set with the Hernández-Alava et al. 2020 method[48]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes, the NICE decision modifier for severity is not applied (see section 7 below).
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

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company developed a de novo cost-effectiveness state transition model in Microsoft Excel with a lifetime horizon. The model structure has six health states to show different disease severities, based on the MG-ADL scale. The model structure is shown in Figure 3 (CS Figure 26). We note that the model structure diagram shows that patients can move from the crisis health state to other health states (not MG-ADL < 5), whereas these patients in the model only move to the MG-ADL ≥10 health state. The model features are shown in CS Table 24. The model uses a 28-day cycle length. A half-cycle correction is applied.

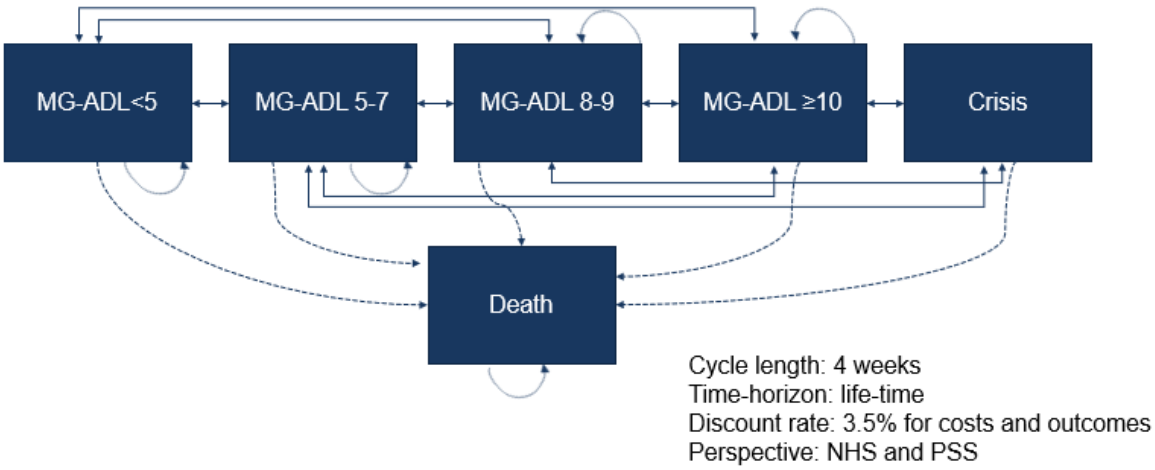


Figure 3 Model structure

Reproduced from CS Figure 26
MG-ADL, Myasthenia Gravis Activities of Daily Living scale

The company comments that the model structure was selected as:

- The structure is consistent with the primary outcome (MG-ADL) and eligibility criteria (MG-ADL ≥5) in the ADAPT trial
- The model captures the highly variable nature of gMG, including fluctuating symptoms and the rapid transition between health states as patients experience disease exacerbations or myasthenic crises

Patients start in the model in the 'MG-ADL 5–7', 'MG-ADL 8–9', or 'MG-ADL ≥10' health states, according to the proportion of patients in these categories in the ADAPT trial, shown in Table 12 below. Patients may transition to other health states over the time-horizon, according to the model transition probabilities, which were derived from the ADAPT trial and ADAPT+ study. Patients may also transition to crisis or death. Crisis is a transitional health state where patients stay for one model cycle.

The model also includes gMG exacerbations that require hospitalisation. These are treated as events in the model, rather than a health state, with patients remaining in their current health state and maintaining ongoing treatment. When an exacerbation occurs, the corresponding costs and utility reduction are applied in the model. The EAG was unclear how acute exacerbations differ from crisis. The company provided a definition of 'acute exacerbation' in response to clarification question B5. Acute exacerbations are assumed to require an inpatient hospitalisation or prolongation of an existing hospitalisation, and result in a persistent or significant disability or incapacity. However, this definition does not specify the differences between the acute exacerbation and crisis. The resources required for acute

exacerbation and crisis are shown in CS Table 57. We note that the differences in resources appear to be related to invasive ventilation support and tracheostomy, which are higher for crisis than for acute exacerbation.

Patients in the efgartigimod arm receive weekly treatments of efgartigimod during the first four-week model cycle, followed by no treatment with efgartigimod for the subsequent four-week cycle. The subsequent treatments with efgartigimod are based upon the individualised treatment criteria used in the ADAPT trial, shown in CS Figure 11. This consists of at least eight weeks since initiation of the previous cycle of treatment and a MG-AGL score of at least five.

Patients discontinue efgartigimod over time, with the probability of discontinuation based on time on treatment discontinuation data from ADAPT and ADAPT+ data (discussed in section 4.2.6.3.1). The model assumes that the health state of patients permanently discontinuing efgartigimod will deteriorate towards the baseline health state distribution (Table 12). This deterioration is assumed to occur gradually over six months after discontinuation. Patients in the ECM arm are assumed to revert to their baseline health state in the fifth cycle and remain in the same health state unless crisis or death occurs.

All patients transition from the crisis health state to the MG-AGL ≥10 health state, regardless of their health state before entering the crisis health state. The company comments that patients could require in-hospital treatments and rehabilitation programmes to achieve full recovery. When in the crisis health state, ongoing treatments for gMG are suspended. Rescue therapy is administered and ongoing gMG treatments are not resumed until patients transition out of the crisis health state.

The summary of the key model assumptions for the company's economic model are shown in CS Table 64.

EAG conclusions on model structure

Clinical advice to the EAG suggested that the MG-ADL scoring system is commonly used in UK clinical practice and that the model structure was appropriate for this condition. The EAG considers that the model structure and the key model assumptions are reasonable.

4.2.3 Population

The population considered in the company model is adult patients with AChR antibody positive gMG and a MG-ADL score of at least five. The population is aligned with the NICE scope, the SmPC and the licensed population for efgartigimod. The ADAPT trial included patients with AChR antibody positive gMG and AChR antibody negative disease, but only the data from the subgroup of patients with AChR antibody positive gMG has been used for this appraisal.

The baseline cohort characteristics for age and gender were taken from UK patients who fulfilled the ADAPT inclusion criteria and provided data to the MyRealWorld MG study (n=25), shown in Table 11 (CS Table 26). Data were not available for body weight for these patients, so the company uses data from the EU population of the ADAPT trial.

The ADAPT trial data for age and gender are shown in Table 11. These data are for all AChR antibody positive participants, because data specifically for the ADAPT AChR antibody positive EU population were not available to the EAG. Of the 129 AChR antibody positive participants in ADAPT, 25 (19.4%) were recruited outside of the EU. As a result, the ADAPT age and gender data may not be representative of the EU population.

The EAG notes the company model uses a higher proportion of females and a lower average initial age in the base case compared with the ADAPT trial data. We have some concerns on the external validity of the MyRealWorld MG, given that they are from a self-selected motivated population of digital mobile device users (section 3.5). Despite the ADAPT AChR antibody positive population not being solely from the EU, we explore using the patient characteristics from ADAPT in a scenario (section 6.1). For the company base case, this increases the ICER from £28,702 to £33,167 per QALY.

Table 11 Baseline model cohort characteristics

Characteristic	Model input	ADAPT trial
Initial age, years	[redacted]	46.9
Female, %	[redacted]	67.0
Weight, kg	[redacted]	-
Cohort with weight >80kg, %	[redacted]	-
Cohort with weight 80-90kg, %	[redacted]	-

Sources: MyRealWorld MG data on file; company, data derived from ADAPT; CS Table 26

The starting distribution for patients among the MG-ADL health states in the model is shown in Table 12 (CS Table 27). It is based on the baseline MG-ADL of the AChR antibody positive gMG population in the ADAPT trial**.**

Table 12 Health-state distribution of the cohort at model entry

Health-state	Model input
MG-ADL <5, %	[redacted]
MG-ADL 5–7, %	[redacted]
MG-ADL 8–9, %	[redacted]
MG-ADL ≥10, %	[redacted]
Crisis, %	[redacted]

Source: argenx, data derived from ADAPT; CS Table 27
MG-ADL, Myasthenia Gravis Activities of Daily Living scale

EAG conclusions on model population

The population used in the economic model aligns with the NICE scope and the marketing authorisation for efgartigimod.

4.2.4 Interventions and comparators

The economic model compares efgartigimod with established clinical management (ECM) to ECM without efgartigimod. Efgartigimod is administered as an IV infusion once a week for four weeks. Subsequent treatment cycles are administered according to the criteria used in the ADAPT trial. This consists of more than eight weeks since initiation of the previous cycle of treatment and a MG-AGL score of greater than five. The CS notes that a subcutaneous formulation of efgartigimod has been developed (EMA marketing authorisation decision expected in [redacted]). The company conducts sensitivity analyses using the subcutaneous formulation of efgartigimod in CS table 71.

ECM consists of corticosteroids and immunosuppressive therapies with or without intravenous immunoglobulin (IVIg) or plasma exchange. More details of the intervention and comparator treatments are given in section 4.2.8.1. Clinical advice to the EAG was that patients would no longer receive IVIg for elective maintenance treatment due to a shortage of IVIg. We do not include IVIg for maintenance treatment in the EAG base case (section 6.2). Ravulizumab is not included in the NICE scope. It is currently being appraised by NICE for this indication.

EAG conclusion on intervention and comparators

The intervention and comparators in the economic model are consistent with the NICE scope. Clinical advice to the EAG stated that patients would no longer receive IVIg for elective maintenance treatment.

4.2.5 Perspective, time horizon and discounting

The perspective of the analysis is that of the NHS and Personal Social Services (PSS). Costs and QALYs are discounted at 3.5% per year in the base case, as per the NICE reference case.[49] In the company base case, the model has a lifetime horizon of 55 years. The CS comments that the horizon is considered long enough to capture the lifetime of patients in this setting, given the baseline characteristics of the UK population in the MyRealWorld MG study.

The EAG notes that after 20 years in the model, all patients have permanently discontinued from efgartigimod treatment. We consider that after this time there is unlikely to be any further differences between the treatment arms. We discovered that the benefits of efgartigimod were continuing after discontinuation of treatment. We corrected the post permanent treatment discontinuation transition probabilities to correct this (section 4.2.6.1.3).

EAG conclusion on perspective, time horizon and discounting

The company adopt the recommended perspective and discounting rates and an appropriate time horizon, which are all in line with NICE guidelines.[49] We agree that the most appropriate time horizon is a lifetime horizon.

4.2.6 Treatment effectiveness and extrapolation

The treatment effect is modelled as changes in MG-ADL score. Reduced MG-ADL score is associated with lower morbidity including: lower probability of myasthenic crises and exacerbation, lower corticosteroid use, and better quality of life. The treatment effect for efgartigimod is modelled through the transition probabilities of transitioning between health states. The transition probabilities for the efgartigimod arm are taken from the ADAPT and ADAPT+ studies. The transition probabilities for the ECM arm are taken from the ADAPT trial only. Non-responders to efgartigimod are not included in the population used to estimate the transition probabilities (see section 4.2.6.1 below for more detail on non-responders).

The following transition probabilities are described in turn below:

Efgartigimod arm

- On-treatment first and subsequent cycles
- Off-treatment MG-ADL ≥5
- Off-treatment MG-ADL <5, cycles 1, 2, 3 and 4+
- Post permanent treatment discontinuation

ECM

- Cycles 1, 2, 3 and 4
- Cycle 5 return to baseline health state distribution
- Cycle 6+ no further transitions (identity matrix)

4.2.6.1 Transition probabilities

4.2.6.1.1 Efgartigimod treatment on-treatment

For patients in the efgartigimod arm, separate transition probabilities are applied to patients when they are on or off treatment. The transition probabilities for the first cycle on treatment with efgartigimod are taken from the transitions between health states that occurred by week 4 in the efgartigimod arm of the ADAPT trial (i.e. in the first treatment cycle) and are shown in CS Table 28. The on-treatment transition probabilities in the model after treatment cycle 1 were estimated by averaging the observed health state transitions between the start and end of each subsequent treatment cycle combining the data from all treatment cycles in ADAPT and ADAPT+. The transition probabilities after the first treatment cycle are shown in CS Table 29.

4.2.6.1.2 Efgartigimod off treatment cycles

At the end of a treatment cycle, patients will have at least one model cycle (four weeks) with no efgartigimod treatment. The transition probabilities, for health states with MG-ADL > 5 during the off-treatment model cycle, were informed by MG-ADL changes in the placebo arm in ADAPT during the second cycle (i.e. from weeks 4-8). CS Table 31 shows the resulting transition probabilities used for off-treatment cycles. The EAG was unclear why the company has used placebo arm data for this transition and not used transitions from the off-treatment phases in the efgartigimod arm of ADAPT and ADAPT+ studies. We conducted an EAG scenario using the same transition probability matrix as for post-permanent discontinuation. This change had minimal effect on model results.

Patients with a MG-ADL score of less than five do not receive efgartigimod treatment. Tunnel states for these patients were created in the model. Transition probabilities were taken from the first 20 weeks of the placebo arm of the ADAPT trial. The CS comments that

the number of observations beyond 20 weeks was too low to be informative. CS Table 30 shows the transition probabilities for the health state with MG-ADL score less than five.

4.2.6.1.3 Efgartigimod post permanent treatment discontinuation

The cycle transition matrix for patients who have permanently discontinued efgartigimod treatment is shown in Table 13. This transition matrix is used for all subsequent model cycles for the those who have discontinued treatment. The company states that patients are assumed to gradually return to the initial baseline health state distribution over 6 months. The CS does not state the basis of this assumption, however clinical advice to the EAG suggested that this was reasonable. The CS does not comment on how these transition probabilities have been calculated.

The EAG notes that the transition probabilities of transitioning to the MG-ADL > 5 health states have been estimated using the formulas:

$$Transition\ probability\ to\ health\ state\ (MG-ADL\ ) = 1-(1-dist(init\ ))\text{^}(\frac{1}{Number\ of\ cycles\ in\ 6\ months})$$

where dist(init) is the initial distribution of patients in each of the health states MG-ADL > 5.

However, the EAG notes that, using these transition probabilities, there will be a large proportion of patients still in the MG-ADL <5 health state after six months (~30%).

Table 13 Transition matrix used for post permanent treatment discontinuation, company preferred values

From / To	MG-ADL <5	MG-ADL 5-7	MG-ADL 8-9	MG-ADL ≥10	Total
MG-ADL <5	[redacted]	[redacted]	[redacted]	[redacted]	1
MG-ADL 5-7	[redacted]	[redacted]	[redacted]	[redacted]	1
MG-ADL 8-9	[redacted]	[redacted]	[redacted]	[redacted]	1
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1

Source: Company economic model.

Therefore, the EAG considers that the transition probabilities should be changed so that patients move out of the MG-ADL <5 health state more quickly. We calculated the transition probability for remaining in the MG-ADL < 5 health state using a similar formula to that shown above, assuming that 1% of patients remain in this health state after six months. Probabilities for the other health states were calculated using the initial distribution of patients in each health state. The transition matrix is shown in Table 14. Using this transition

matrix, 1% of patients remain in the MG-ADL <5 health state after six months and the proportions in the other health states are similar to the initial distribution shown in Table 12. We use these transition probabilities in the EAG base case analyses in section 6.2 and raise this as a key issue in section 1.5. We also conduct a scenario varying these transition probabilities.

Table 14 Transition matrix used for post permanent treatment discontinuation, EAG preferred values

From / To	MG-ADL <5	MG-ADL 5-7	MG-ADL 8-9	MG-ADL ≥10	Total
MG-ADL <5	[redacted]	[redacted]	[redacted]	[redacted]	1
MG-ADL 5-7	[redacted]	[redacted]	[redacted]	[redacted]	1
MG-ADL 8-9	[redacted]	[redacted]	[redacted]	[redacted]	1
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1

4.2.6.2 Established clinical management

The transition probabilities in the ECM arm are taken from the placebo arm of the ADAPT trial. The first four cycles use transition probabilities from the corresponding cycle in ADAPT (CS Tables 32-35). In the fifth cycle, patients are assumed to revert to their baseline health state and remain in the same health state unless a crisis or death occurs (CS Table 36). The CS comments that this assumption is based upon clinical advice and that the distribution between health states in the ECM arm is representative of the expected population-level distribution in gMG patients with a MG-ADL score of more than five. CS Table 32-36 shows the transition probabilities in the ECM arm in the first six cycles of the model.

4.2.6.3 Non-responder and treatment discontinuation

Patients are considered non-responders if they do not have a clinically meaningful response, (see section 3.2.5.1 for more details on the definition of response in the ADAPT trial). They are assumed to have two cycles of treatment with efgartigimod and are then treated as patients receiving ECM thereafter. The CS assumes that [redacted] of the efgartigimod cohort are classified as non-responders, based on the proportion of patients who did not respond to two consecutive treatment cycles. The non-responder cohort is excluded from the efgartigimod cohort (who are eligible for further treatment) at the start of the simulation and the costs of two cycles of efgartigimod are included. Thereafter they incur costs, effects of the HRQoL of the ECM arm.

4.2.6.3.1 Discontinuation of efgartigimod treatment

Data from the ADAPT trial and ADAPT+ study were pooled to provide time on treatment data for patients receiving efgartigimod treatment (CS Figure 28). The company fitted parametric curves to the time on treatment KM curves. The exponential function was selected as the best fitting curve based on Akaike Information Criterion / Bayesian Information Criterion (AIC/BIC) values (CS Table 49). In the company's base case, the time on treatment Kaplan Meier data were used up to 33 months, and the exponential function was used to extrapolate over the remaining time horizon.

In response to clarification question B9, the company justified their decision to use the KM data directly by stating that their preference is to use observed data where possible, and then extrapolate from the point where observed data are no longer available. They consider this approach to be more robust and superior to extrapolating over the full model horizon as it best represents the observed data from the trial.

The EAG notes that the company start the extrapolated parametric tail at 33 months, i.e. at the end of the KM data. We disagree with this approach as at this timepoint there are no patients at risk which causes high uncertainty in the KM curve and in this case, there is a large drop in the proportion of patients on treatment between 30 and 33 months. A better approach would be to start the tail when there are more patients at risk. Typically, the tail would start when there is 20% of patients still at risk. We conduct a scenario where the extrapolated tail starts at 24 months (section 6.3)

Our preference is to use the exponential function for the model's whole time horizon, so that there is a constant rate of discontinuation. As noted above, the EAG disagrees with the company's approach to fix the parametric extrapolation at the end of the observed data. We consider the exponential provides a good fit to the time on treatment data. However, the lognormal, Weibull and log-logistic also provide a good fit to the observed data. It is unclear whether patients' probability of discontinuation will lessen over time (i.e. like in the lognormal, Weibull and log-logistic distributions) or remain constant (like in the exponential distribution). We explore other functions in scenario analyses in section 6.2, including using the KM data with an extrapolated parametric tail starting at 24 months.

4.2.6.4 gMG exacerbations

The model only includes gMG exacerbations that require hospitalisation because those are the ones that have a significant cost and quality of life impact. The CS states that

exacerbations not requiring hospitalisation are likely to have minimal impact on costs and quality of life. Exacerbations are included in the model as acute events with no change to the patients' health states. The rate of exacerbations was obtained from the ADAPT trial using the mITT population. In ADAPT, only two patients in the placebo arm and one in the efgartigimod arm had a gMG exacerbation. The resulting probability of exacerbation per model cycle is [redacted] and [redacted] for the ECM and efgartigimod arms, respectively.

4.2.6.5 Myasthenic crisis

The probability of a myasthenic crisis was taken from a registry study by Ramos-Fransi et al.,[50] which analysed 648 gMG patients in Spain. For the model, the probability of transitioning to crisis was assumed to be 0.09% per model cycle for health states with MG-ADL > 5 for both treatment arms. Patients are all assumed to spend one model cycle in gMG crisis and then all patients transition to the MG-ADL ≥10 health state. The CS notes that after an ICU stay, patients require specific in-hospital treatments and rehabilitations programs, which may include mechanical ventilation, to achieve recovery.

4.2.6.6 Adverse reactions

The model only considers the costs of managing adverse reactions to treatment. Based on the incidence of grade ≥3 AEs reported in the ADAPT trial, the adverse reactions for both arms are included in the model, with the probability per cycle shown in CS Table 37.

The company uses a mid-point cost estimate for each adverse reaction, rather than a weighted average across all critical care categories. For example, the cost for 'infection' in the model is taken from the NHS reference cost DZ22P 'Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 5-8; Total Unit Cost'. The EAG prefers to use a weighted average of codes DZ22K – DZ22Q, using data from all the critical care categories.[5] We note that changes to these costs have a minor impact on the model results and so have not included this in the EAG base case. We raise this as a minor issue in section 1.6.

4.2.6.7 Mortality

The model assumes that the mortality for gMG is the same as for the general population, except for the additional mortality associated with gMG crisis. The model assumes a 12% probability of death during myasthenic crisis, estimated from seven studies that the company found in their targeted literature review.[51-57]

EAG conclusions on treatment effectiveness and extrapolation

In general, the company's approach to deriving transition probabilities for the economic model is reasonable. The transition probabilities are taken from the ADAPT and ADAPT+ studies. The EAG notes that some of these transition probabilities are based upon small numbers, which increases the uncertainty. For some of the probabilities, the company has pooled data from different cycles and the EAG considers that this is reasonable. We believe that some of the transition probabilities relating to post permanent treatment discontinuation have been underestimated which leads to the persistence of efgartigimod effects beyond the company assumptions of six months, which is favourable to efgartigimod compared with ECM. This is discussed in more detail in the model validation section (section 5.2.2). We suggest alternative transition probabilities for this group (Table 14).

The EAG has concerns over how the company has modelled time on treatment. The company start the extrapolated parametric tail at the end of the KM data. We disagree with this approach. A better approach would be to start the tail when there are more patients at risk (e.g. 20%). Our preference is to use the exponential function for the whole time period, so that there is a constant rate of discontinuation.

There are additional uncertainties due to sparsity of data on exacerbation, crisis and mortality rates, but the model is not sensitive to these parameters.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company's main systematic literature review included searches for HRQoL studies in adult patients with gMG. The methodology is described in CS Appendix G1.1. The searches were completed on 7-9th April 2022 and updated on 19-21st January 2023. The eligibility criteria are given in CS Appendix H Table 29.

The review, completed in April 2022, identified five unique publications, of which two reported utility data[58; 59] (CS Appendix H Table 32). Barnett et al.[58] calculated mean health utilities for Canadian patients with MG for each of the Myasthenia Gravis Foundation of America (MGFA) classification severity classes, using the EQ-5D-5L and SF-6D utility instruments. The MyRealWorld MG longitudinal study[59] collected HRQoL data (including EQ-5D-5L) using a smartphone/tablet application from 617 patients with gMG in Belgium, Canada, Germany, Italy, Japan, Spain, the UK and USA.

The January 2023 review update identified a further 21 records (CS Appendix H Table 33). Three studies included EQ-5D derived utility values, two presenting trial data from ADAPT[60; 61] and one describing utilities from the MyRealWorld MG study.[62] Dewilde et al. (2023)[60] report results for the whole trial population in ADAPT, which differs from the population of interest in this appraisal (i.e. participants who are AChR antibody positive). Sacca et al.[61] report the health state utility values from the same patient population as the company (ADAPT AChR antibody positive participants), but their results have not been mapped to the UK EQ-5D-3L values. Dewilde et al. (2022)[62] present utility values for patients data from MyRealWorld MG. These are adult patients with gMG from seven countries (USA, Japan, Germany, UK, Italy, Spain and Canada), and not limited to UK population who fulfilled the ADAPT inclusion criteria as the company use.

In addition to the studies reporting primary utilities, the company's searches also identified two cost-effectiveness analyses that included utility data.[45; 47] Peres 2017[45] assessed clinical data, quality of life and economic costs in patients with gMG before and after treatment with rituximab. The economic model by Tice et al. 2022[47] evaluated the cost-effectiveness of efgartigimod plus conventional therapy vs conventional therapy alone in patients with gMG, including those with or without anti-AChR antibodies. Utilities were determined using the EQ-5D-5L health states and the US-based societal value set developed by Pickard et al.[63] Utility scores were calculated using the estimated association between QMG and EQ-5D-5L by using a univariate linear regression model.

4.2.7.2 Study-based health related quality of life

The company base case uses health state utility values collected from the AChR antibody positive participants in the ADAPT trial. EQ-5D-5L data were collected in ADAPT at 1-week intervals for patients on treatment and at 2-week intervals for patients not on treatment. EQ-5D-5L data were mapped to UK EQ-5D-3L values using the study by Hernandez et al. (2020).[48]

The utility values were estimated for the different health states using a mixed effect model. The CS comments that the mixed model is an extension of the linear model and is used to analyse longitudinal data for multiple patients. The mixed effect model also included a treatment effect coefficient. The CS states that the treatment effect is a statistically significant variable in the regression analysis for EQ-5D, indicating that MG-ADL is not fully capturing the effect of efgartigimod on gMG patients. In addition, the company notes a

recent study by Dewilde (2023)[60] where MG-ADL is treated as a continuous variable and this confirmed the existence of a treatment effect (CS Figure 27).

Table 15 shows the utility values for the two arms of the ADAPT study. Patients in the ECM arm have consistently lower utility values than those in the efgartigimod arm. The company explores removing the treatment effect in a scenario, which increases the ICER from £28,702 per QALY to £31,588 per QALY (company response to clarification B6 and EAG report Table 20).

The HRQoL systematic review identified the MyRealWorld MG study as another source of EQ-5D data for the population of interest, which collected patient data using a smartphone/tablet app. The company provided further detail about the data and methods used in this utility analysis in response to clarification question B6. The company explored using these utilities (Table 15) in a scenario analysis (CS Table 71).

Table 15 Utility values by health state derived from mixed model regression on ADAPT and MyRealWorld MG data

Health state	ADAPT - efgartigimod	ADAPT - ECM	MyRealWorld MG
MG-ADL <5	[redacted]	[redacted]	[redacted]
MG-ADL 5–7	[redacted]	[redacted]	[redacted]
MG-ADL 8–9	[redacted]	[redacted]	[redacted]
MG-ADL ≥10	[redacted]	[redacted]	[redacted]

Source: Adapted from CS B.3.4.2 Tables 40 and 42
ECM, established clinical management; MG-ADL, Myasthenia Gravis Activities of Daily Living scale

No patients experienced a myasthenic crisis during the ADAPT trial, so the company uses data from the MyRealWorld MG study to inform the utility value in the crisis health state, using the average utility of the MGFA Class V of [redacted]. The EAG considers this value to be suitable, because MGFA Class V is defined as "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."[9]

The EAG considers that the methods used to derive utilities from the ADAPT trial are reasonable. We agree that there appears to be a treatment effect for efgartigimod whereby patients receiving efgartigimod treatment have better quality of life than those in the same health state in the ECM arm. However, we consider that some of the differences in utility

may be due to differences in corticosteroid use between the two arms. For example, patients in the ECM arm use more corticosteroids, on average. The EAG received clinical advice, which explained that the complications and side effects of corticosteroid use have a significant detrimental impact on patients' quality of life. The between-arm difference in utilities is unlikely to be caused by serious adverse events, because there was a similar number of grade 3 or higher adverse events in both arms of the ADAPT trial: 21 in the placebo arm and 24 in the efgartigimod arm.

4.2.7.3 Disutilities due to adverse events

The model assumes the effects of adverse events on HRQoL are captured within the health-state utilities.

4.2.7.4 Disutilities due to exacerbations

The company uses severe allergic rhinitis[64] as a proxy to derive the disutility for a gMG exacerbation, because both conditions require the use of high-dose corticosteroids and hospitalisation. The disutility of -0.16 is applied for 20.73 days, which the company calculates as the average duration of hospitalisation for gMG exacerbations reported in four studies (CS B.3.4.5.1 Table 43).

The company provided a definition of 'acute exacerbation' in response to clarification question B5. Only acute exacerbations that require an inpatient hospitalisation or prolongation of an existing hospitalisation, and result in a persistent or significant disability or incapacity are considered in the model. The clinical advisor to the EAG commented that not all patients with an exacerbation would be hospitalised. This indicates that the definition in clinical practice may vary and may differ from that used in the ADAPT trial.

The EAG is unclear how representative the disutilities used for acute exacerbation are, as the disutilities have been taken from an unrelated condition. However, as the disutilities are only applied for a short time period, using alternative disutility values does not have a significant impact on model results.

4.2.7.5 Disutilities due to corticosteroid use

In addition to their main systematic literature review, the company also conducted a systematic literature review concerning the impact of systemic corticosteroids on HRQoL in patients with gMG. No studies were found, but the CS discusses two studies that reported utility values, by corticosteroid dose, in other chronic diseases (CS section B.3.4.5.2; CS

Appendix O). Bexelius et al.[3] evaluated the impact of corticosteroid use on HRQoL and costs in Swedish patients with systemic lupus erythematosus. Sullivan et al.[65] explored the impact of systemic corticosteroid use on HRQoL in a range of chronic conditions in a cohort of patients in the US and UK.

Based on clinical advice, the company considers ≥10mg/day of corticosteroids to be a high dose and ≤10mg/day to be a low dose. The company base case uses utility decrements estimated by averaging the difference in disutilities between no corticosteroid use and high use (≥10mg/day) reported in the Bexelius et al.[3] and Sullivan et al. studies[65] (CS section B.3.4.5.2, CS Table 44), and the company explores setting the corticosteroid high-dose threshold at 5mg/day in a scenario analysis.

The EAG notes that patients in the ADAPT trial would have received corticosteroids and therefore their effects are captured within the trial measure of HRQoL. We therefore do not consider that corticosteroid disutility should be included in the model. We do not include corticosteroid disutility in the EAG base case (section 6.2) and raise this as a key issue (section 1.5).

4.2.7.6 Caregiver disutilities

The company's main systematic review did not identify any studies reporting caregiver disutility in gMG. The company performed an ad hoc search and identified a study by Acaster et al. (2013),[66] which reported HRQoL data for caregivers of patients with multiple sclerosis (MS). The company uses the Patient Determined Disease Steps (PDDS) scale as a proxy for caregiver disutility in the different gMG health states, mapping the PDSS to MG-ADL categories (CS section B3.4.5.3, CS Table 45). In response to clarification question B8, the company added that they selected MS as a proxy condition for gMG because these two neuromuscular diseases are both characterized by progressive muscle weakening and a wide array of serious multisystem complications, including respiratory muscle dysfunction.

The company justifies including caregiver disutilities in their response to clarification question B7. The company explains that the physically and mentally disabling symptoms of gMG are detrimental to caregivers' health related quality of life, because muscle weakness caused by the disease can cause patients with gMG to have difficulties with swallowing, vision, speech, breathing, and mobility, as well as extreme fatigue. As a result, patients may require help with eating or mobility. The company suggests a regular caregiver would be needed to support these activities, and adds that it has been estimated that about one-third of patients

with gMG require regular care from their partner (no source provided). In addition to assisting patients manage the physical symptoms of gMG, the company provides evidence that caregiver burden is also increased if patients experience depression.[67] NICE appraisals in other neurodegenerative diseases have included the impact on caregivers' quality of life in the cost-effectiveness analysis.[68-70] Consequently, the company considers it appropriate to incorporate caregiver disutilities in their base case analysis.

Clinical advice to the EAG is that the majority of gMG patients would be independent and not require a caregiver. In addition, the typical symptoms for gMG patients are not similar to those for MS patients, so the disutility values estimated are not likely to be representative. The NICE methods guide requires that evidence is provided to show that the condition is associated with a substantial effect on carer's health related quality of life. The EAG's view is that the CS has not provided sufficient evidence to show that gMG has a substantial effect on carers. Therefore, the EAG does not consider that caregiver disutility should be included in the economic model and we have not included it in our base case (section 6.2); we raise this as a key issue (section 1.5).

EAG conclusions on HRQoL

The EAG has no concerns with the company's HRQoL searches, other than they do not give a justification for the 2012 start date limit. We do not believe this will have caused any key HRQoL publications to be missed. The January 2023 review update was limited to MEDLINE, Embase and Cochrane Database of Systematic Reviews, which is appropriate. EQ-5D data are derived directly from the ADAPT trial patient data, as per the NICE reference case,[49] except for utility values for patients in crisis.

The EAG considers that the methods to derive utilities from the ADAPT trial are reasonable and agree that there appears to be a treatment effect for efgartigimod whereby patients receiving efgartigimod treatment have better quality of life than those in the same health state in the ECM arm. The EAG does not agree with the inclusion of disutility values for corticosteroid use or for caregivers and we have removed these in our base case analysis.

4.2.8 Resources and costs

The company's main systematic literature review also aimed to identify sources of costs and resource use (CS Appendix I), using the methodology as described in CS Appendix G1.1.

The searches were completed on 7-9th April 2022 and updated on 19-21st January 2023; eligibility criteria are given in CS Appendix G Table 24 and CS Appendix I Table 36.

The searches conducted in April 2022 identified 5 studies, of which one publication reported costs and a cost-utility analysis for rituximab[45] (CS Appendix I Table 38). Fifteen studies were assessed for cost and resource use following the January 2023 searches (CS Appendix I Table 40); three publications have a UK setting. Sacca et al.[61] conducted a post-hoc analysis on ADAPT trial data to identify the economic burden of gMG in terms of productivity losses. Resource use data were not reported. Harris et al.[71] reported the clinical burden of gMG in England, but costs were not collected, calculated or reported in the analysis. Jacob et al.[72] undertook a retrospective observational cohort study using Hospital Episode Statistics (HES) between June 2014 and June 2021. This poster abstract reports cumulative costs for admission only. The CS does not comment on whether any of these studies informed their costing in the economic model.

The CS includes the following healthcare resource use and costs:

- Drug acquisition and administration
- Patient monitoring
- Management of complications associated with the chronic use of corticosteroids
- Rescue treatments
- Management of treatment-emergent AEs
- End-of-life care

4.2.8.1 Drug acquisition

Table 16 presents the drug acquisition costs for efgartigimod and conventional therapy. The recommended dosage for a single infusion of efgartigimod is 10 mg/kg and is dispensed in single-dose vials of 400 mg (20 mL). Patients weighing ≤80kg require two vials, and patients weighing ≥90kg need three vials. The company estimated the average number of vials needed per infusion based on the weight distribution of the EU AChR antibody positive patient population in ADAPT (n=52), and the base case assumes [redacted] vials are required per administration in the simulated cohort.

The list price per vial of efgartigimod is £6,569.73, reduced to [redacted] after applying the PAS discount of [redacted]. Data from ADAPT+ show that [redacted] administrations are delivered out of a planned four during a treatment cycle, so the company base case assigns a relative dose intensity of [redacted] to efgartigimod.

A proportion of patients who receive established clinical management receive recurrent treatment with immunoglobulin therapy and rituximab. The proportion of patients who receive these treatments are based upon the ADAPT trial and clinical advice. Immunoglobulin therapy is administered as an intravenous infusion (IVIg) in the UK. It is administered once every four weeks (i.e. once per model cycle). It comes in two formulations of 2.5 mg / 25ml and 10mg / 100 ml respectively (with 100mg per 1mL). Each dose is 1000 mg / kg. The average adult weight from the ADAPT trial was [redacted] kg. Rituximab is administered as an intravenous infusion every six months at a dose of 2000 mg (i.e. four vials). Drug costs and dosages are taken from the British National Formulary.[73]

Clinical advice to the EAG was that patients would no longer receive IVIg for elective maintenance treatment due to the IVIg shortage and this shortage is likely to continue. We do not include IVIg for maintenance treatment in the EAG base case and raise this as a key issue (section 1.5) acknowledging that the real-world usage of IVIg in the UK for patients with gMG inadequately controlled with standard treatments is uncertain.

Table 16 Established clinical management therapy cost per cycle

Drug	Vials per cycle	Mg per unit	Drug cost per unit (£)	Drug cost per admin (£)	Drug cost per cycle (£)
Efgartigimod[a]	4.00*[redacted]	400	[redacted]	[redacted]	[redacted]
IVIg (2.5mg/25mL)	1.00	2500	172.50	690.00	5,520
IVIg (10mg/100mL)	1.00	10,000	690.00	4,830.00	
Rituximab	0.15	500	785.84	3,143.36	481.90

Source: Adapted from CS B.3.5.1 Tables 47 and 48
Admin, administration; IVIg, intravenous immunoglobulin
[a] Applies to on-treatment sub-state of the model
[b] Relative dose intensity = [redacted]
[c] List price with PAS applied
[d] Corticosteroids, acetylcholinesterase inhibitors and nonsteroidal immunosuppressive therapy

Patients in both arms of the model are assumed to receive conventional therapy (corticosteroids, acetylcholinesterase inhibitors (AChEi), and nonsteroidal immunosuppressive therapy). Conventional therapy was assumed to be administered continuously unless patients transitioned to the crisis health state where they would receive

rescue therapy. Clinical advice to the EAG is that one advantage of efgartigimod is that patients would, on average, receive lower doses of corticosteroids.

The proportion of patients who receive these treatments were based upon the ADAPT trial and clinical advice. Clinical advice to the EAG suggested that within clinical practice, most patients would receive azathioprine and the second most common nonsteroidal immunosuppressive therapy is mycophenolate. The EAG notes that more patients in the model receive ciclosporin than mycophenolate. The cost per cycle for conventional therapy is £98.93 per patient.

4.2.8.2 Drug administration

Drug administration costs include the cost of intravenous infusions. The cost of administration for efgartigimod and rituximab was taken from the outpatient IV administration tariff[5] (£145.80). The EAG prefers to use the NHS reference cost SB13Z 'Deliver more complex parenteral chemotherapy at first attendance' (£258.56),[5] for this cost, which is typically used in NICE appraisals and we raise this as a minor issue in section 1.6.

Administration costs for IVIg also included a short-stay hospitalisation for observation (£1717.92). The model assumes that oral treatments used for conventional therapy do not have an administration cost.

4.2.8.3 Monitoring costs

Health state resources for patient-monitoring were estimated from the company's sponsored MyRealWorld MG study and a survey of clinicians in the UK. The average annual frequency of monitoring visits by health state is shown in CS Table 50. The health care resource unit costs were taken from NHS reference costs, PSSRU and the NHS Tariff Workbook[74] and are shown in CS Table 51. The monitoring cost per cycle by health state are shown in Table 17 and CS Table 52. In response to clarification question B13, the company corrected and updated some of the costs in the economic model. The updated costs are shown in the clarification response document.

Table 17 Patient monitoring cost by health state, per cycle in revised economic model

Health state	Cost per cycle, £
MG-ADL <5	£79.93
MG-ADL 5–7	£104.22
MG-ADL 8–9	£189.31
MG-ADL ≥10	£258.76

Source: Revised costs in company's updated model
MG-ADL, Myasthenia Gravis Activities of Daily Living scale;

We note that the costs used in the economic model have been inflated to 2022 costs using Consumer Price Index inflation indices. However, the standard source to use for inflation in economic analyses is HCHS Pay & Prices from PSSRU. As the latest versions available for the NHS reference costs and the PSSRU costs are for 2021, we consider this the best price year to use (i.e. there is no need to inflate costs to 2022). However, we have only inflated prices using the HCHS Pay & Prices and have used costs from 2021 in the EAG scenarios as these have little impact on the model results (scenario 13, Table 24).

4.2.8.4 Management of complications associated with the chronic use of corticosteroids

In addition to their main systematic literature review, the company also conducted a systematic literature review seeking evidence on the burden of chronic corticosteroid use (CS Appendix O). The company identified three studies from the UK and Sweden that report the economic burden of corticosteroid use (Table 18). The costs in the studies by Voorham et al.,[1] Janson et al.[2] and Bexelius et al.[3] were applied to low and high dose corticosteroid use. None of the studies were for patients with gMG. The study by Bexelius et al. included patients with systemic lupus erythematosus, which is an autoimmune disease like gMG, while both Voorham et al. and Janson et al. included patients with asthma, which may be less comparable to gMG.

In the company base case, the company assumes a high dose threshold of 10mg/day, i.e. all doses higher than the threshold are defined as high-dose corticosteroid use. The costs from the study by Bexelius et al. are used. The cost per cycle is £934.95 for high-dose and £440.51 for low-dose corticosteroid use (CS Table 53). The EAG notes the weekly costs for managing corticosteroid complications in the Bexelius et al.[3] study are far higher compared with the other two studies (Table 18), and were for a different disease area. The company conducted a scenario where the high-dose threshold was set to 5mg/day. In this case, the

costs from Voorham et al.[1] and Janson et al.[2] are averaged and the cost per cycle is £252.11 for high-dose and £64.96 for low-dose corticosteroid use.

Voorham et al. report mean annual all-cause adverse outcome associated costs for 9,413 patients in the UK who were using over a range of daily doses of corticosteroids. This study appears to be more representative of the costs associated with corticosteroid use in the UK. Consequently, the EAG considers the Voorham et al.[1] study alone should be used to provide the cost data of managing complications associated with chronic corticosteroid use. The EAG prefers to use a high dose threshold of 7.5mg/day (raised as a key issue in section 1.5). We calculated weighted average costs for patients in Voorham et al. for the low dose (all patients taking <7.5mg/day) and the high dose (all patients taking ≥7.5mg/day). The resulting costs are £6.16 per week for low dose and £43.99 per week for high dose, i.e. £24.69 and £175.94 per treatment cycle, respectively. Table 18 shows the high dose thresholds used and costs for the three studies, with the EAG's preferred source and high dose threshold shown in bold. We use the costs from Voorham et al. in the EAG base case analysis (section 6.2).

Table 18 Sources of costs for corticosteroid-related chronic complications

Authors, year and country	Disease area	Patients providing data on CS use (n)	High dose thresholds	Cost per week	
				High dose	Low dose
Voorham et al.[1] UK	Asthma	9,413	5mg/day	£54.59	£13.45
Janson et al.[2] Sweden	Asthma	223	5mg/day	£71.46	£19.03
Bexelius et al.[3] Sweden	Lupus	190	7.5mg/day	£233.74	£110.13
Voorham et al.[1] UK	**Asthma**	**9,413**	**7.5mg/day**	**£43.99**	**£6.16**

CS, corticosteroids

4.2.8.5 Rescue treatments

Myasthenia gravis crises and acute exacerbations requiring hospitalisation need additional rescue treatment. Health care resources were estimated from the company's survey of clinicians and are shown in CS Table 57. The drugs used for rescue treatment are shown in CS Table 54. The unit costs of the health care resources are shown in CS Table 56. The total costs of acute exacerbation are £15,930.62 per event, and the total costs for gMG crisis

are £34,726.62 per cycle (Table 58). These costs are presented this way, because crisis is modelled as a transitional health state where patients stay for one model cycle, whereas acute exacerbations are modelled as discrete events within the MG-ADL health states that last 21 days.

4.2.8.6 Management of treatment-emergent AEs

The CS presents the costs related to managing treatment-emergent grade 3 adverse events (CS Table 59), which are modelled according to the proportion of adverse events per treatment arm. The costs of the adverse events were based on the National Schedule of NHS costs (2020-2021).[5]

We note that the adverse event costs were estimated by choosing a specific NHS reference cost associated with the adverse event, rather than taking a weighted average of all relevant codes. For example, for infection, the code used is DZ22P, rather than taking a weighted average of codes DZ22M – DZ22Q. The EAG has not changed these costs as they are unlikely to make a significant difference to the model results.

4.2.8.7 End-of-life care

The company gives end-of-life care costs as £382 for 'end of life (inpatient)'. However, the Personal Social Services Research Unit (PSSRU),[75] list this cost for 'Inpatient, specialist palliative care (adults only), average cost per bed day'. In response to clarification question B12, the company agrees that that the average cost of health and care services used in the last year of life, i.e. £12,149 from the PSSRU 2021 source, is the more appropriate figure to use in the model and uses this value in their revised model submitted with the company's response to clarification questions.

The EAG preferred source for end-of-life costs is Georghiou and Bardsley.[4] Here the cost of the last three months of life is £5,381 (Table 9 of the reference) which, when adjusted for inflation to 2021, is £6,146. We raise this as a minor issue in section 1.6 and conduct a scenario using our preferred cost in section 6.3.

EAG conclusions on resources and costs

Clinical advice to the EAG was that patients would no longer receive IVIg for elective treatment due to the IVIg shortage. We therefore do not include IVIg for maintenance treatment for gMG patients.

We consider that the costs used for treating corticosteroid use complications is an overestimate. We prefer the costs from Voorham et al.,[1] as we consider this source to be more representative for UK practice and have used this source in the EAG base case.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company reports their base case cost-effectiveness analysis results for efgartigimod versus established clinical management in CS Table 65, using the PAS discount price for efgartigimod and list prices for all other treatments.

Following their response to the clarification questions, the company updated their model to include:

- A new scenario analysis using the ADAPT utility analysis, but omitting the treatment co-variate i.e. setting the health state utility values to be the same for both arms, rather than the different values used in the base case (Table 15). The EAG requested this scenario, because the between-arm difference in health state utilities is substantial and it is not clear what is causing the difference
- Minor cost corrections, as described in the company's response to clarification questions B10, B12 and B13
- Adjusting the prior distributions that assign each transition between health states an equal probability of occurring
    - In their response to clarification question B14, the company explains that some theoretically possible transitions were not observed in the ADAPT trial (transitioning directly from MG-ADL<5 to MG-ADL>10, for example). To account for this, the model includes a prior distribution assigning each transition an equal probability of occurring in addition to the observed transitions.

      In their original model, the company set these priors to 0.01 for all transitions, causing the probabilistic ICER to be consistently lower than the deterministic one. In their updated model, the company have set the priors to 0.05, resulting in probabilistic ICERs more similar to the deterministic base case ICER (see Table 22).

The company's changes to the model increase the company base case ICER from £28,066 per QALY to £28,702 per QALY, with a QALY gain of [redacted] and an additional cost of [redacted] versus ECM. Table 19 below shows the company's updated deterministic base case analysis. The results using the PAS discounts for all treatments have been produced by the EAG in a separate confidential addendum.

Table 19 Company base case results for efgartigimod, including PAS

Treatments	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£ per QALY)
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£28,702
ECM	[redacted]	[redacted]	-	-	-

Source: Updated company base case model results
ECM, Established clinical management; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

5.1.1 Deterministic sensitivity analyses

The company considers 107 parameters in their one-way sensitivity analyses (OWSA), listed in CS Table 68. Variations in input parameters are based on 95% confidence intervals, calculated using the standard error. If the standard error was not reported, the company uses an assumed standard error of 10% of the base case value.

Table 70 in CS section B.3.11.2 shows the 10 variables with the most influence on the ICER. The model is most sensitive to varying the discount rates for costs. Reducing the proportion of patients using IVIg in the MG-ADL ≥10 in the ECM group also had a significant effect on the ICER, increasing it to £47,088 per QALY. In the remaining sensitivity analyses, the ICERs ranged from £20,123 per QALY when increasing the proportion of the ECM cohort in the MG-ADL 8-9 health state receiving immunoglobulin, to £37,212 per QALY when increasing the initial age of the cohort to 49.59 years.

5.1.2 Scenario analyses

The CS includes six scenario analyses, reproduced below in Table 20. In response to clarification question B6, the company ran a scenario using the ADAPT utility values without the treatment co-variate (Table 20; scenario 7). This increased the ICER to £31,588 per QALY. The company discusses their rationale for not using these utility values in their base case in their response to clarification question B6. We do not include them in our base case either, but we explore using these utilities in a scenario analysis (section 6.3).

Using health-state utility values obtained from the MyRealWorld MG study reduces the ICER to £26,572 per QALY due to a greater gain in QALYs. The EAG's clinical expert's view was that, provided the company paid for the nurses, all patients receiving administration of efgartigimod at home after receiving their initial dose in hospital (scenario 6) was feasible, which reduces the ICER to £26,857 per QALY.

Defining high-dose systemic corticosteroid use as >5mg/day (rather than >10mg/day as in the company base case; scenario 5) had the most effect on the ICER, increasing it to £38,043 per QALY (Table 20). The company is using different costs for corticosteroid-related chronic complications for the two different thresholds, which causes the increase in the ICER. For more details, please see section 4.2.8.4.

Table 20 Scenario analyses for efgartigimod vs ECM, including the PAS discount

	Scenario description	Efgartigimod vs ECM		
		Incr Cost, £	Incr QALYs	ICER £/QALY
0	Base case	[redacted]	[redacted]	28,702
1	IVIg only in MG-ADL 8-9 and MG-ADL>10 health states	[redacted]	[redacted]	32,920
2	Updated distribution of treatments in established clinical management MG-ADL>10 (the other health states remain the same): IVIG: 90% PLEX: 10%	[redacted]	[redacted]	32,699
3	Transition matrices in efgartigimod arm based on ADAPT only (i.e., not ADAPT +)	[redacted]	[redacted]	35,139
4	Utilities by health-state based on MyRealWorld MG	[redacted]	[redacted]	26,572
5	Definition of high-dose corticosteroid in systemic use: >5mg/day	[redacted]	[redacted]	38,043
6	From year 2 onwards it is assumed that 100% of patients receive administration of efgartigimod at home at no cost (supported by the company)	[redacted]	[redacted]	26,857
7	ADAPT utility values without treatment as a covariate	[redacted]	[redacted]	31,588

Source: CS Section B.3.11.3 Table 71, and response to clarification question B6 (scenario 7)
ECM, Established clinical management; Incr, incremental; ICER, incremental cost-effectiveness ratio; IV, intravenous; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; PLEX, plasma exchange; UK, United Kingdom; QALY, quality-adjusted life-years

5.1.3 Probabilistic sensitivity analysis

CS Section B.3.11.1 describes the company's probabilistic sensitivity analysis using a Monte Carlo approach with 1,000 simulations. The results from the company's updated base case are shown in Table 21.

Table 21 Comparison of the base case and PSA results, including PAS

	Cost, £			QALYs			ICER (£/QALY)
	Efgartigimod	ECM	Incr.	Efgartigimod	ECM	Incr.	
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,766
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,525

Source: Adapted from CS section B.3.11.1 Table 67
ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life-year

The model parameters in the probabilistic sensitivity analyses were varied by random sampling from probability distributions. The company reports the distributions used for each variable in CS Table 63. The EAG considers the company's choice of parameter distributions to be suitable. Relevant parameters are included in the probabilistic sensitivity analyses, but the company could also have varied patient characteristics such as age and weight.

Figure 4 shows the cost-effectiveness scatterplot for efgartigimod versus ECM and Figure 5 presents the cost-effectiveness acceptability curve for the company's updated base case. Efgartigimod has a [redacted] and [redacted] probability of being cost-effective versus ECM at the £20,000 and £30,000 willingness to pay (WTP) thresholds, respectively.

[redacted]

Figure 4 Incremental cost and QALY cloud in the cost-effectiveness plane, updated company base case with PAS discount

Source: CS Figure 29

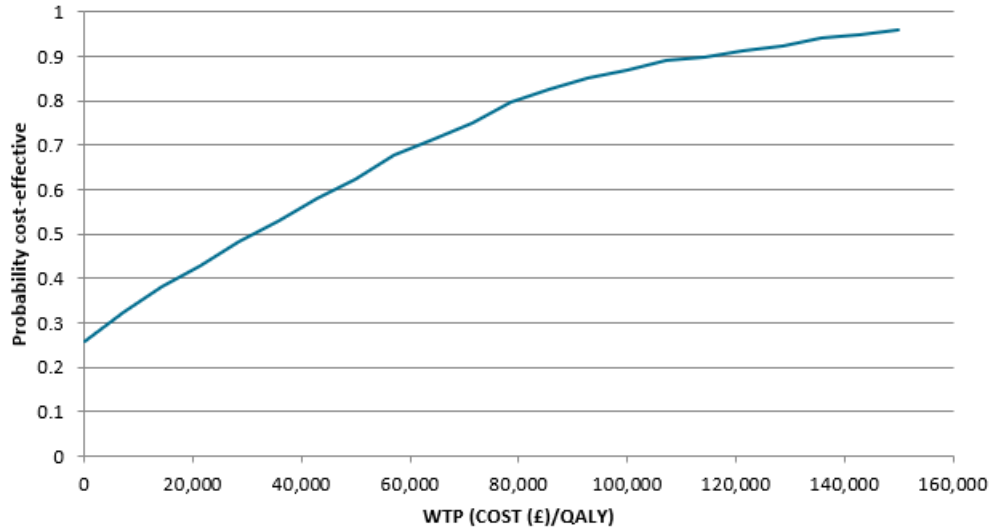


Figure 5 Cost-effectiveness acceptability curve

Source: CS Figure 30

5.2 Model validation and face validity check

5.2.1 Company model validation

The company's approach to validating their model is described in CS section B.3.14. The company surveyed UK clinical experts in gMG to determine healthcare resource use for managing gMG. One clinical expert was involved in validating the model, who agreed that the conceptual model is appropriate and the comparator, patient population characteristics, key assumptions behind the model structure, extrapolation of effects and health-care resource use reflect disease management in the UK.

The CS states that the economic model was thoroughly assessed by an experienced health economist using the transparency and validation checklist from Eddy et al. (2012).[76] The results of this technical validation are presented in CS Table 72. The EAG notes that the Eddy et al. 2012 report[76] is not a formal checklist, but describes best practices for achieving transparency and validation of health care models, which the company has followed regarding internal validation.

EAG conclusion

The company completed a detailed internal validity check and it was helpful to see the model technical validation checklist presented in the CS. The CS does not mention the number, location or affiliation of the experts who contributed their opinion, so uncertainty remains around the validation completed by the company.

5.2.2 EAG model validation

The EAG conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses
- Checking the individual equations within the model ('white box' checks)
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks)

We also checked the stability of the probabilistic results of the updated base case against the company's reported results (Table 22). There was little change in the ICER when increasing the number of iterations above 1000; running the PSA with 10,000 iterations resulted in an ICER of £29,750 per QALY. However, the 95% credible intervals for the PSA results are extremely wide, even using 10,000 iterations: -£52,738 per QALY and £168,990 per QALY for the lower and upper confidence intervals, respectively.

Table 22 Company comparison of deterministic and probabilistic ICERs, updated company base case

Run	ICER (£/QALY)
Deterministic	28,702
PSA 1000 iterations 1	31,525
PSA 1000 iterations 2	29,455
PSA 2000 iterations	28,988
PSA 5000 iterations	29,652
PSA 10000 iterations	30,462

Source: Company response to clarification question B14

5.2.2.1 Comparison of model results with the ADAPT+ study

The EAG also compared the mean change from baseline in the MG-ADL total score for cycles 1 to 14 using the model transition matrix for efgartigimod with the results for ADAPT+

given in the CS (CS Figure 27, reproduced in Figure 6 below). The cycle changes in the model follow those in ADAPT+ reasonably closely. Differences are likely caused by:

- Using a different patient group. CS Figure 27 presents results for all AChR antibody positive patients in ADAPT+, whereas the model uses pooled data for AChR antibody positive patients from ADAPT and ADAPT+. The efgartigimod matrix includes AChR antibody positive patients, but excludes people who did not respond to two consecutive cycles of treatment and were permanently discontinued.
- The EAG calculated an average MG-ADL score for each health state using data from the US Myasthenia Gravis Patient Registry (Cutter et al.),[77] because we do not have access to data from ADAPT+.

A

B

Figure 6 (A) ADAPT+, mean change from cycle baseline to Week 3 of cycle in MG-ADL total score in AChR Ab+ patients. (B) Mean change from baseline to cycle MG-ADL total score in ACh Ab+ patients (model efgartigimod transition matrix).

Source: (A) CS section B.2.7.2 Figure 24; (B) Company cost-effectiveness model
Blue line at -2 represents the CMI threshold (≥2-point improvement in total MG-ADL score)
Abbreviations: AChR-Ab+, acetylcholine receptor autoantibody-positive; CMI, clinically meaningful improvement; MG-ADL, Myasthenia Gravis Activities of Daily Living scale.

5.2.2.2 Transition probability for permanent treatment discontinuation

The company states that patients are assumed to gradually return to the initial baseline health state distribution over six months, and the model assumes that all patients have discontinued efgartigimod treatment after about 20 years. Consequently, we would not expect patients to receive a treatment benefit after 20 years and have a MG-ADL score <5 as seen in Figure 7. The EAG considers that the model is overestimating the benefit of efgartigimod. We have adjusted the permanent treatment discontinuation transition probabilities to correct the model so that all patients have discontinued treatment have a MG-ADL score > 5 after six months, as shown in Figure 8.

Figure 7 Distribution of treatment cohorts by health-state over the time-horizon of the analysis, company base case with company transition probabilities

MG-ADL, Myasthenia Gravis—Activities of Daily Living
Source: Company cost-effectiveness model

Figure 8 Distribution of treatment cohorts by health-state over the time-horizon of the analysis, company base case with EAG transition probabilities

MG-ADL, Myasthenia Gravis—Activities of Daily Living
Source: Company cost-effectiveness model

5.2.3 Company corrections to the model

As mentioned in section 5.1, the company's updated base case includes:

- Minor cost corrections, as described in the company's response to clarification questions B10, B12 and B13
- Adjusted prior distributions within the model, which assign each transition between health states an equal probability of occurring

5.2.4 EAG corrections to the company model

The EAG did not find any technical calculation errors in the company's economic model.

5.2.5 EAG summary of key issues and additional analyses

The EAG's observations on key aspects of the company base case are presented below (Table 23). We investigate these uncertainties through additional scenario analyses described in section 6.1.

Table 23 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG base case
Population characteristics	CS Section B.3.3.1 and Table 26. Based on UK patient population included in the MyRealWorld	Very small sample size.	No change. We test using the ADAPT trial participant

	MG study who fulfilled the ADAPT inclusion criteria (n=25).		characteristics in a scenario analysis
Transition probabilities	CS Section B.3.3.4.3 and Table 28	We disagree with the transition probabilities used for post permanent treatment discontinuation – the health state distribution over time in the efgartigimod group lacks face validity	We have used alternative transition probabilities shown in Table 14. The effect of these alternative probabilities is shown in Figure 8.
Time-on-treatment	CS Section B.3.5.1.1 and Figure 28 and response to clarification question B9. Piecewise approach: available K-M data are used to define the probability of treatment discontinuation, after which the best-fitting parametric model (exponential) is used.	We disagree – there is potential bias from using the ADAPT+ data up to 33 months, and then using a parametric curve thereafter, due to the small number of patients remaining at risk between 30 and 33 months.	Exponential function gives a good fit to data prior to month 30; we explore using other functions as well as fitting the exponential curve after 24 months in scenario analyses
Utilities			
Health state utilities	CS Section B.3.4.2 and Table 40 From ADAPT trial, UK tariffs based on Hernandez et al.[78] value sets	We agree	No change
AE disutility (exacerbations)	CS Section B.3.4.5 and Table 43	We agree	No change
Age-related disutility	Indirectly modelled by adjusting for the general population utility	We agree	No change
Chronic corticosteroid disutility	CS Section B.3.4.5.2 and Table 44 The company base case includes utility decrements related to corticosteroid use, differentiated by dose.	We disagree - these decrements will have been captured in the MG-ADL health state utilities	Disutilities associated with chronic corticosteroid use removed
Caregiver disutility	CS Section B.3.4.5.3 and Table 45 and response to	We disagree. There is large uncertainty around the caregiver disutilities in the model as these are from patients with MS. The	Caregiver disutilities removed

	clarification questions B7 and B8.	impact on the health of caregivers is likely to differ between MS and gMG. Clinical advice to the EAG suggested that most patients with gMG would be independent and so would not need caregivers. The company has not provided evidence for the need for caregiver utility in these patients.	
Resource use and costs			
All costs	Inflated to 2022 using the Consumer Price Index	We prefer to use the HCHS Pay & Prices from PSSRU (standard source for inflation in economic analyses). Current versions of the NHS reference costs and the PSSRU costs are for 2021; we consider this the best price year to use.	No change. We explore using costs that are not inflated to 2022, and inflation indices from the PSSRU in a scenario
Administration costs	CS Section B.3.5.1	We prefer to use the NHS reference cost SB13Z 'Deliver more complex parenteral chemotherapy at first attendance' (£258.56),[5] rather than the outpatient IV administration tariff.[5] But, we have not changed this in our base case as this has minimal effect on ICER.	No change
Subsequent therapy	CS Section B.3.5.1.1 Discontinued cohort is assumed to be the same as established clinical management cohort and receives ECM	We agree	No change
AE costs	CS Section B.3.5.2 and Table 59	We prefer to use a weighted average across all NHS reference cost categories,[5] rather than a single point cost estimate, for each adverse event, but have not changed this in our base case as this has minimal effect on ICER.	No change
Costs for complications from corticosteroid use	CS Section B.3.5.1.4 and Table 53 and response to clarification question B9	We disagree – we do not consider the references used for the costs to be appropriate	We use cost data from Voorham et al.,[1] with a high dose threshold of 7.5mg/day
Resource use	CS Section B.3.5.3 £382, PSSRU; updated to £12,149 in response to clarification question B12.	We prefer to use a different source by Georghiou and Bardsley,[4] but have not changed this in our base case as this has minimal effect on ICER.	No change

Treatment costs	CS Section B.3.5.1 and Table 47 IVIg therapy	We disagree with including maintenance IVIg therapy as our clinical expert advised that IVIg are not commissioned for maintenance treatment. However, we acknowledge that there is uncertainty about the real-world usage of IVIg in the UK for gMG patients inadequately controlled with standard treatments.	Maintenance treatment costs for IVIg removed; we explore reduced maintenance IVIg use in scenario analyses

AE, adverse event; ECM, established clinical management; IVIg, intravenous immunoglobulin; K-M, Kaplan-Meier; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; PSSRU, Personal Social Services Research Unit

6 EAG'S ADDITIONAL ANALYSES

6.1 Additional EAG scenario analyses

The EAG conducted additional scenario analyses on the company base case to explore the key issues described in section 5.2.5 and to investigate other areas of uncertainty not included in the company's scenario analyses (Table 24):

Table 24 EAG scenario results, using the company base case model

No.	Scenario description	ICER (£/QALY)
Company base case		£28,702
1	Using the exponential function for ToT	£47,996
2	Fitting the exponential function for ToT after 24 months	£46,043
3	Using the lognormal function for ToT	£121,642
4	Using the Weibull function for ToT	£66,976
5	Using the loglogistic function for ToT	£105,230
6	Removing utility decrements for caregivers	£39,425
7	Removing utility decrements related to chronic corticosteroid use	£36,302
8	Using cost data from Voorham et al. and a high dose threshold of 7.5mg/day to model costs for complications from corticosteroid use	£41,080
9	No IVIg use in health states outside of crisis	£169,590
10	Maintenance IVIg costs reduced by 50% from company base case	£99,146
11	Maintenance IVIg costs reduced by 75% from company base case	£134,368

No.	Scenario description	ICER (£/QALY)
12	Using ADAPT trial data for participant initial age and % females in the cohort, rather than My RealWorld MG	£33,167
13	Using PSSRU inflation indices and 2021 costing year	£31,260
14	EAG's preferred permanent treatment discontinuation transition probabilities for the efgartigimod arm (shown in Table 14); 1% of patients remain in the MG-ADL <5 health state after 6 months	£212,983
15	Alternative permanent treatment discontinuation transition probabilities for the efgartigimod arm (shown in Table 25); 5% of patients remain in MG-ADL <5 health state after 6 months	£148,469

AE, adverse events; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life-year; ToT, time on treatment

Table 25 shows the alternative transition matrix used for the permanent treatment discontinuation transition probabilities in scenario 15.

Table 25 Alternative transition matrix used for post permanent treatment discontinuation, EAG scenario: 5% of patients in the efgartigimod arm remain in the MG-ADL <5 health state at 6 months

From / To	MG-ADL <5	MG-ADL 5-7	MG-ADL 8-9	MG-ADL ≥10	Total
MG-ADL <5	[redacted]	[redacted]	[redacted]	[redacted]	1
MG-ADL 5-7	[redacted]	[redacted]	[redacted]	[redacted]	1
MG-ADL 8-9	[redacted]	[redacted]	[redacted]	[redacted]	1
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]	1

6.2 EAG's preferred assumptions

Based on the EAG's critique of the company's model (discussed in section 5.2.5) and the scenarios described in section 6.1, we have identified several aspects of the company base case with which we disagree. Our preferred model assumptions are:

- Removing costs for maintenance IVIg (section 4.2.8.1)
- Using the exponential function to model efgartigimod time-on-treatment (section (4.2.6.3.1)
- Using our preferred permanent treatment discontinuation transition probabilities for the efgartigimod arm (section 4.2.6.1.3)
- Removing caregiver disutilities (section 4.2.7.6)
- Removing disutilities associated with chronic corticosteroid use (section 4.2.7.5)
- Using alternative costs from to model costs for high and low-dose corticosteroid use (Voorham et al.)[1] (section 4.2.8.4).

Table 26 shows the cumulative effect of each of these changes. The EAG's preferred assumptions increase the ICER for efgartigimod compared with established clinical management to £628,135 per QALY.

Table 26 Cumulative change from the company base case with the EAG's preferred model assumptions

Assumption	Incr. costs (£)	Incr. QALYs	Cumulative ICER £/QALY
Company base-case	[redacted]	[redacted]	£28,702
Exponential function to model efgartigimod ToT	[redacted]	[redacted]	£47,996
Caregiver disutilities removed	[redacted]	[redacted]	£65,655
Disutilities associated with chronic corticosteroid use	[redacted]	[redacted]	£91,358
Using alternative cost data from Voorham et al.[1] for complications costs for corticosteroid use	[redacted]	[redacted]	£114,505
Costs for maintenance IVIg removed	[redacted]	[redacted]	£381,550
EAG's preferred permanent treatment discontinuation transition probabilities for the efgartigimod arm (shown in Table 14)	[redacted]	[redacted]	£628,135
EAG base case	[redacted]	[redacted]	**£628,135**

ICER, incremental cost-effectiveness ratio; Incr., incremental; IVIg, intravenous immunoglobulin; QALYs, quality-adjusted life years; ToT, time on treatment

6.2.1 Probabilistic sensitivity analyses

The results for the PSA using the EAG preferred assumptions are shown in Table 27. The mean probabilistic ICER is similar to the deterministic result, however there is considerable variability in the PSA results, as shown by the incremental cost and QALYs scatterplot (Figure 9).

Table 27 Deterministic and probabilistic results for efgartigimod compared with ECM, EAG base case

Analysis	Treatments	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£ per QALY)
Deterministic	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£628,135
	ECM	[redacted]	[redacted]	-	-	-
PSA	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£627,128

	ECM	[redacted]	[redacted]	-	-	-

ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Incr., incremental; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 9 Incremental cost and QALYs scatterplot, EAG base case

6.3 Scenario analyses conducted on the EAG's preferred assumptions

The EAG ran scenario analyses using our base case assumptions (Table 28). The greatest change in the ICER was caused by using health state utilities based on ADAPT but omitting the treatment covariate (scenario 18), increasing the ICER to £991,114 per QALY. Using utilities from MyRealWorld MG, rather than the ADAPT trial (scenario 17) also substantially increased the ICER, to £697,284 per QALY.

The greatest reductions in the ICER were caused by setting the permanent treatment discontinuation transition probabilities for the efgartigimod arm to the company base case (scenario 9), decreasing the ICER to £381,550 per QALY and including IVIg as maintenance therapy (scenario 6), which decreases the ICER to £391,182 per QALY. Including caregiver disutilities (scenario 11) and disutilities associated with chronic corticosteroid use included (scenario 12) also significantly reduced the ICER, to £441,214 and £478,048 per QALY, respectively.

Table 28 Scenario results for efgartigimod versus established clinical management, using the EAG base case model

No.	Scenario description	ICER (£/QALY)
EAG base case		£628,135

No.	Scenario description	ICER (£/QALY)
1	ToT modelled using company base case piecewise curve	£627,720
2	Fitting the exponential function for ToT after 24 months	£627,909
3	Using the lognormal function for ToT	£632,192
4	Using the Weibull function for ToT	£629,268
5	Using the loglogistic function for ToT	£631,500
6	Maintenance IVIg frequency as per the company base case	£391,182
7	Maintenance IVIg frequency reduced by 50% from company base case	£509,659
8	Maintenance IVIg frequency reduced by 75% from company base case	£568,897
9	Permanent treatment discontinuation transition probabilities for the efgartigimod arm set to company base case	£381,550
10	Alternate permanent treatment discontinuation transition probabilities for the efgartigimod arm (Table 25 shows the alternative transition matrix used for the permanent treatment discontinuation transition probabilities in scenario 15)	£551,894
11	Caregiver disutilities included	£441,214
12	Disutilities associated with chronic corticosteroid use included	£478,048
13	Using company's choice for the source of costs for complication costs for corticosteroids.	£609,572
14	Use PSSRU inflation indices and 2021 costing year	£627,904
15	Using ADAPT trial data for participant initial age and % females in the cohort, rather than My RealWorld MG	£625,902
16	Transition matrices in efgartigimod arm based on ADAPT only (i.e., no ADAPT +)	£649,697
17	Health state utilities based on MyRealWorld MG	£697,284
18	Health state utilities based on ADAPT without treatment covariate	£991,114
19	From year 2 onwards, assume that 100% of patients receive administration of efgartigimod at home at no cost (supported by argenx)	£621,581

6.4 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost effectiveness of efgartigimod plus ECM compared with ECM alone. The EAG considers the structure of the model to be reasonable and appropriate. The model uses treatment effectiveness data from the ADAPT

and ADAPT+ studies. The company base case produced a revised ICER of £28,702 per QALY for efgartigimod plus ECM compared with ECM alone. The company base case includes a PAS discount for efgartigimod.

The EAG did not identify any significant technical calculation errors in the company's model. The company made some minor changes to the model inputs in response to clarification questions.

The EAG disagrees with several of the assumptions in the company's model. Our preferred assumptions include:

- IVIg not used for maintenance treatment,
- Using the exponential function to model efgartigimod time-on-treatment
- Using alternative transition probabilities for permanent treatment discontinuation for the efgartigimod arm,
- Not including caregiver disutilities,
- Not including disutilities associated with chronic corticosteroid use,
- Using alternative cost source for corticosteroid complication costs (Voorham et al.)[1]

The EAG preferred assumptions increase the ICER to £628,135 per QALY for the deterministic analysis and £627,128 per QALY for the probabilistic analysis (Table 27). The model results most are most sensitive to changing the permanent treatment discontinuation transition probabilities for the efgartigimod arm, whether the costs for maintenance IVIg are included, and whether the disutilities for caregivers and corticosteroids are included. We also disagree with some other issues, for example with costing, however these issues have only a minor impact on model results.

7 SEVERITY

The 2022 NICE Health Technology Evaluations Manual specifies criteria for QALY weightings for severity based on the proportional and absolute QALY shortfall for the population with the condition, in comparison with the general population with the same age and sex distribution. The company estimates QALYs for the general population using appropriate sources and uses the sex distribution (80% female) and starting age (45.2 years) from the UK patient population included in the MyRealWorld MG study who fulfilled the ADAPT trial inclusion criteria (n=25). The absolute QALY shortfall for efgartigimod in the company base case is below 12 and the proportional QALY shortfall is less than 85%, so the company did not apply a multiplier for disease severity (Table 29).[49]

The absolute and proportional QALY shortfall do not meet the thresholds for severity in the EAG base case (Table 29), so we do not apply a multiplier for disease severity either. We are unsure why the expected total discounted QALYs for the general population are different between the two models. The EAG analysis uses the default reference case in the Scharr QALY shortfall calculator (https://r4scharr.shinyapps.io/shortfall/), none of the alternative value sets give an expected total discounted QALYs for the general population of 16.09.

Table 29: Summary of QALY shortfall analysis

Analysis	Expected total discounted QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
Company base case	16.09	[redacted]	[redacted]	[redacted]
EAG base case	17.39	[redacted]	[redacted]	[redacted]

Source: Adapted from CS section B.3.6 Table 62

EAG conclusion

The EAG agrees with the company's analysis; a greater QALY weighting is not appropriate, because none of these treatment comparisons meet the criteria for severity.

8 References

1. Voorham J, Xu X, Price DB, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy* 2019;74(2):273-83. doi: 10.1111/all.13556
2. Janson C, Lisspers K, Stallberg B, et al. Health care resource utilization and cost for asthma patients regularly treated with oral corticosteroids - a Swedish observational cohort study (PACEHR). *Respir Res* 2018;19(1):168. doi: 10.1186/s12931-018-0855-3
3. Bexelius C, Wachtmeister K, Skare P, et al. Drivers of cost and health-related quality of life in patients with systemic lupus erythematosus (SLE): a Swedish nationwide study based on patient reports. *Lupus* 2013;22(8):793-801. doi: 10.1177/0961203313491849
4. Georghiou T, Bardsley M. Exploring the cost of care at the end of life: Research report 2014 [Available from: www.nuffieldtrust.org.uk/files/2017-01/end-of-life-care-web-final.pdf.
5. NHS England. National Schedule of NHS Costs Year : 2020-21 - All NHS trusts and NHS foundation trusts - HRG Data. 2021
6. Dresser L, Wlodarski R, Rezania K, et al. Myasthenia gravis: epidemiology, pathophysiology and clinical manifestations. *Journal of Clinical Medicine* 2021;10(11) doi: 10.3390/jcm10112235
7. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. *The Lancet Neurology* 2015;14(10):1023-36. doi: 10.1016/s1474-4422(15)00145-3 [published Online First: 2015/09/18]
8. Bubuioc A-M, Kudebayeva A, Turuspekova S, et al. The epidemiology of myasthenia gravis. *Journal of Medicine and Life* 2021;14(1):7-16.
9. Jaretzki A, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology* 2000;55(1):16-23. doi: 10.1212/wnl.55.1.16
10. Robertson NP, Deans J, Compston DA. Myasthenia gravis: a population based epidemiological study in Cambridgeshire, England. *Journal of Neurology, Neurosurgery, and Psychiatry* 1998;65(4):492-6. doi: 10.1136/jnnp.65.4.492 [published Online First: 1998/10/15]
11. Carey IM, Banchoff E, Nirmalananthan N, et al. Prevalence and incidence of neuromuscular conditions in the UK between 2000 and 2019: A retrospective study using primary care data. *PLoS One* 2021;16(12):e0261983. doi: 10.1371/journal.pone.0261983
12. Carr AS, Cardwell CR, McCarron PO, et al. A systematic review of population based epidemiological studies in Myasthenia Gravis. *BMC Neurol* 2010;10:46. doi: 10.1186/1471-2377-10-46 [published Online First: 2010/06/23]
13. Efgartigimod (Vyvgart 20 mg/mL concentrate for solution for infusion) Summary of Product Characteristics (UK). 2023
14. Sussman J, Farrugia ME, Maddison P, et al. Myasthenia gravis: Association of British Neurologists' management guidelines. *Pract Neurol* 2015;15(3):199-206. doi: 10.1136/practneurol-2015-001126
15. All Wales T, Toxicology C. OW12: Rituximab for myasthenia gravis.
16. NHS England. Clinical commissioning policy statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults).
17. NHS England. Updated Commissioning Guidance for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England December 2018. 2018
18. Howard JF, Jr., Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised,

placebo-controlled, phase 3 trial. *The Lancet Neurology* 2021;20(7):526-36. doi: 10.1016/S1474-4422(21)00159-9
19. argenx. Efgartigimod (ARGX-113-1704) Clinical Study Report: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT). 2020:1-171.
20. argenx. Efgartigimod (ARGX-113-1705) Clinical Study Report (Interim Analysis 4): A Long-term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Study of ARGX 113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT+). 2022:1-165.
21. #108: Long-term safety, tolerability, and efficacy of efgartigimod in patients with generalized myasthenia gravis. Presented at the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) annual meeting; 2022 2022.
22. argenx. Efgartigimod (ARGX-113-2001) Clinical Study Report: A Phase 3, Randomized, Open-label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of Efgartigimod PH20 SC With Multiple Intravenous Infusions of Efgartigimod in Patients With Generalized Myasthenia Gravis (ADAPTSC). 2022:1-122.
23. ClinicalTrials.gov. Evaluating the Pharmacodynamic Noninferiority of Efgartigimod PH20 SC Administered Subcutaneously as Compared to Efgartigimod Administered Intravenously in Patients With Generalized Myasthenia Gravis (ADAPTsc), 2022.
24. Howard JF, Jr., Bril V, Burns TM, et al. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. *Neurology* 2019;92(23):e2661-e73. doi: 10.1212/wnl.0000000000007600 [published Online First: 2019/05/24]
25. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. 2009
26. Bowers M, Pickering RM, Weatherall M. Design, objectives, execution and reporting of published open-label extension studies. *Journal of Evaluation in Clinical Practice* 2012;18(2):209-15. doi: 10.1111/j.1365-2753.2010.01553.x [published Online First: 2010/11/03]
27. Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *Lancet* 2002;359(9308):781-5. doi: 10.1016/s0140-6736(02)07882-0 [published Online First: 2002/03/13]
28. Thomsen JLS, Andersen H. Outcome measures in clinical trials of patients with myasthenia gravis. *Frontiers in Neurology* 2020;11:596382. doi: 10.3389/fneur.2020.596382
29. Wolfe GI, Herbelin L, Nations SP, et al. Myasthenia gravis activities of daily living profile. *Neurology* 1999;52(7):1487-9. doi: 10.1212/wnl.52.7.1487 [published Online First: 1999/05/05]
30. Muppidi S, Wolfe GI, Conaway M, et al. MG-ADL: still a relevant outcome measure. *Muscle & Nerve* 2011;44(5):727-31. doi: 10.1002/mus.22140
31. Katzberg HD, Barnett C, Merkies IS, et al. Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial. *Muscle & Nerve* 2014;49(5):661-5. doi: 10.1002/mus.23988
32. Burns TM, Conaway M, Sanders DB, et al. The MG Composite: a valid and reliable outcome measure for myasthenia gravis. *Neurology* 2010;74(18):1434-40. doi: 10.1212/WNL.0b013e3181dc1b1e
33. Barnett C, Herbelin L, Dimachkie MM, et al. Measuring clinical treatment response in myasthenia gravis. *Neurologic Clinics* 2018;36(2):339-53. doi: 10.1016/j.ncl.2018.01.006
34. Qi C, DeWilde S, Gelinas D, et al. ISPOR 2022: Hospitalization and Exacerbation Estimates of Efgartigimod Vs. Conventional Therapy in Generalized Myasthenia Gravis Patients: A Post-Hoc Analysis of the Phase 3 ADAPT Study. *Value in Health* 2022;25(7 Supplement S329)

35. Editorial Team (Myasthenia-Gravis.com). The outlook for someone with myasthenia gravis: Myasthenia-Gravis.com: a Health Union Community; 2021 (last updated August 2022) [Available from: https://myasthenia-gravis.com/life-expectancy accessed 17 April 2023.
36. Mercieca-Bebber R, Palmer MJ, Brundage M, et al. Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome (PRO) data: a systematic review. *BMJ Open* 2016;6(6):e010938. doi: 10.1136/bmjopen-2015-010938
37. European Medicines Agency (EMA). Assessment report: Vyvgart, 2022.
38. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. *Cochrane Database Syst Rev* 2012;12(12):CD002277. doi: 10.1002/14651858.CD002277.pub4
39. Nowak RJ, Coffey CS, Goldstein JM, et al. Phase 2 trial of rituximab in acetylcholine receptor antibody-positive generalized myasthenia gravis: The BeatMG Study. *Neurology* 2022;98(4):e376. doi: 10.1212/WNL.0000000000013121
40. Piehl F, Eriksson-Dufva A, Budzianowska A, et al. Efficacy and safety of rituximab for new-onset generalized myasthenia gravis: The RINOMAX randomized clinical trial. *JAMA Neurology* 2022:e222887. doi: 10.1001/jamaneurol.2022.2887
41. Dewilde S, Philips G, Paci S, et al. Patient-reported burden of myasthenia gravis: baseline results of the international prospective, observational, longitudinal real-world digital study MyRealWorld-MG. *BMJ Open* 2023;13(1):e066445. doi: 10.1136/bmjopen-2022-066445
42. Vitaccess Ltd. MyRealWorld website 2023 [Available from: https://myrealworld.com/uk/en/myasthenia-gravis/ accessed 30 March 2023 2023.
43. Berrih-Aknin S, Claeys KG, Law N, et al. Patient-reported impact of myasthenia gravis in the real world: protocol for a digital observational study (MyRealWorld MG). *BMJ Open* 2021;11(7):e048198. doi: 10.1136/bmjopen-2020-048198
44. argenx. MyRealWorld® MG: an international, prospective,observational,digital study of the impact of myasthenia gravis in the real world - Statistical Analyses Plan v3.0. 2020
45. Peres J, Martins R, Alves JD, et al. Rituximab in generalized myasthenia gravis: Clinical, quality of life and cost-utility analysis. *Porto Biomedical Journal* 2017;2(3):81-85. doi: 10.1016/j.pbj.2017.02.002
46. Lien PW, Agboola F, Joshi M, et al. Eculizumab and Efgartigimod for the Treatment of generalized Myasthenia Gravis. *Neurology* 2022;98(18 Suppl.)
47. Tice JA, Touchette DR, Lien P-W, et al. The effectiveness and value of eculizumab and efgartigimod for generalized myasthenia gravis. *Journal of Managed Care and Specialty Pharmacy* 2022;28(1):119-24. doi: 10.18553/jmcp.2022.28.1.119
48. Hernandez Alava M, Wailoo A, Pudney S, et al. Mapping clinical outcomes to generic preference-based outcome measures: development and comparison of methods. *Health Technology Assessment* 2020;24(34):1-68. doi: 10.3310/hta24340
49. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. 2022
50. Ramos-Fransi A, Rojas-García R, Segovia S, et al. Myasthenia gravis: descriptive analysis of life-threatening events in a recent nationwide registry. *Eur J Neurol* 2015;22(7):1056-61. doi: 10.1111/ene.12703
51. Alshekhlee A, Miles JD, Katirji B, et al. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. *Neurology* 2009;72(18):1548-54. doi: 10.1212/WNL.0b013e3181a41211
52. Liu C, Wang Q, Qiu Z, et al. Analysis of mortality and related factors in 2195 adult myasthenia gravis patients in a 10-year follow-up study. *Neurol India* 2017;65(3):518-24. doi: 10.4103/neuroindia.NI_804_16
53. Liu F, Wang Q, Chen X. Myasthenic crisis treated in a Chinese neurological intensive care unit: clinical features, mortality, outcomes, and predictors of survival. *BMC Neurology* 2019;19(1):172. doi: 10.1186/s12883-019-1384-5

54. Mandawat A, Kaminski HJ, Cutter G, et al. Comparative analysis of therapeutic options used for myasthenia gravis. *Ann Neurol* 2010;68(6):797-805. doi: 10.1002/ana.22139
55. Neumann B, Angstwurm K, Mergenthaler P, et al. Myasthenic crisis demanding mechanical ventilation: a multicenter analysis of 250 cases. *Neurology* 2020;94(3):e299-e313. doi: 10.1212/WNL.0000000000008688
56. Soleimani A, Moayyeri A, Akhondzadeh S, et al. Frequency of myasthenic crisis in relation to thymectomy in generalized myasthenia gravis: a 17-year experience. *BMC Neurology* 2004;4:12. doi: 10.1186/1471-2377-4-12
57. Spillane J, Hirsch NP, Kullmann DM, et al. Myasthenia gravis--treatment of acute severe exacerbations in the intensive care unit results in a favourable long-term prognosis. *Eur J Neurol* 2014;21(1):171-3. doi: 10.1111/ene.12115
58. Barnett C, Bril V, Bayoumi AM. EQ-5D-5L and SF-6D health utility index scores in patients with myasthenia gravis. *Eur J Neurol* 2019;26(3):452-59. doi: 10.1111/ene.13836
59. Dewilde S, Kousoulakou H, Janssen M, et al. Digital data collection to measure the impact of myasthenia gravis on patients' quality of life in the real world: report at baseline [Presented at the Virtual International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2021 conference, 30 November - 3 December 2021]. *Value in Health* 2022;25(1 Suppl):S246.
60. Dewilde S, Qi C, Philips G, et al. Association Between Myasthenia Gravis-Activities of Daily Living (MG-ADL) and EQ-5D-5L Utility Values: The Additional Effect of Efgartigimod on Utilities. *Advances in Therapy* 2023
61. Saccà F, Barnett C, Vu T, et al. Efgartigimod improved health-related quality of life in generalized myasthenia gravis: results from a randomized, double-blind, placebo-controlled, phase 3 study (ADAPT). *Journal of Neurology* 2023 doi: 10.1007/s00415-022-11517-w
62. Dewilde S, Paci S, Kousoulakou H, et al. PCR84 Myasthenia Gravis Patients Have Lower Eq-5D-5L and HUI3 Utility Values Than a Matched Sample of the General Population: Analysis of Digitally Collected Observational Data from 8 Countries. *Value in Health* 2022;25(12):S406. doi: 10.1016/j.jval.2022.09.2019
63. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value Health* 2019;22(8):931-41. doi: 10.1016/j.jval.2019.02.009 [published Online First: 2019/08/21]
64. Van Wilder L, Rammant E, Clays E, et al. A comprehensive catalogue of EQ-5D scores in chronic disease: results of a systematic review. *Quality of Life Research* 2019;28(12):3153-61. doi: 10.1007/s11136-019-02300-y
65. Sullivan PW, Ghushchyan VH, Globe G, et al. Health-related quality of life associated with systemic corticosteroids. *Quality of Life Research* 2017;26(4):1037-58. doi: 10.1007/s11136-016-1435-y
66. Acaster S, Perard R, Chauhan D, et al. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. *BMC Health Serv Res* 2013;13:346. doi: 10.1186/1472-6963-13-346
67. Marbin D, Piper SK, Lehnerer S, et al. Mental health in myasthenia gravis patients and its impact on caregiver burden. *Scientific Reports* 2022;12(1):19275. doi: 10.1038/s41598-022-22078-3
68. National Institute for Health and Care Excellence (NICE). Ocrelizumab for treating relapsing–remitting multiple sclerosis 2018 [Available from: https://www.nice.org.uk/guidance/ta533 accessed 22 March 2023.
69. National Institute for Health and Care Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis (TA527) 2018 [accessed 22 March 2023.
70. National Institute for Health and Care Excellence (NICE). Ofatumumab for treating relapsing multiple sclerosis (TA699) 2021 [Available from: https://www.nice.org.uk/guidance/ta699/ accessed 22 March 2023.

71. Harris L, Graham S, MacLachlan S, et al. A retrospective longitudinal cohort study of the clinical burden in myasthenia gravis. *BMC Neurology* 2022;22(1):172. doi: 10.1186/s12883-022-02692-4
72. Jacob S, Betts A, Hosnijeh FS, et al. RWD17 A Retrospective Observational Study on the Healthcare Resource Use of Patients With Myasthenia Gravis in Secondary Care in England Using Hospital Episodes Statistics. *Value in Health* 2022;25(12 Supplement):S451.
73. British National Formulary. 2022
74. NHS England. 2022/23 National Tariff Payment System: Annex A - National tariff workbook. 2022
75. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2022 Manual 2022 [Available from: https://www.pssru.ac.uk/unitcostsreport/.
76. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. *Value Health* 2012;15(6):843-50. doi: 10.1016/j.jval.2012.04.012 [published Online First: 2012/09/25]
77. Cutter G, Xin H, Aban I, et al. Cross-sectional analysis of the Myasthenia Gravis Patient Registry: disability and treatment. *Muscle & Nerve* 2019;60(6):707-15. doi: 10.1002/mus.26695
78. Hernandez Alava M, Wailoo A, Grimm S, et al. EQ-5D-5L versus EQ-5D-3L: the impact on cost effectiveness in the United Kingdom. *Value in Health* 2018;21(1):49-56. doi: 10.1016/j.jval.2017.09.004

9 Appendices

Appendix 1 EAG appraisal of the company's methods for the systematic review of clinical effectiveness

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The eligibility criteria in the two PICOS tables (CS Appendix D.1.2, Tables 10 and 11) match the aim, stated in CS section B.2.1, to identify randomised clinical studies for efgartigimod and comparator treatments for the management of gMG. There are fewer interventions in the eligibility criteria for the January 2023 clinical SLR update than in the original April 2022 clinical SLR which is appropriate because the omitted interventions are not currently reimbursed by NICE.
Were appropriate sources of literature searched?	Yes	Overall, both April 2022 and January 2023 SLRs searched a broad range of sources including core medical databases, relevant websites, and reference lists of included studies. The handsearching of recent conferences was particularly comprehensive (CS Appendix D.1.1).
Was the time period of the searches appropriate?	Yes	The CS states the April 2022 searches sought studies published from January 1, 2012 to 7 April 2022 and the update search covered January 2022 to January 2023; the start date limit 2012 is not justified (CS Appendix D.1). However, there is not likely to be efgartigimod evidence prior to 2012 and as we consider an ITC is not necessary then there is also no need to identify further comparator evidence.
Were appropriate search terms used and combined correctly?	Yes	The search terms used for the April 2022 SLR are fewer whereas the search terms used for the January 2023 SLR are much more comprehensive. However, both SLRs perform sensitive searches using both index terms and free-text terms combined correctly (CS Appendix D.1.1.3-4).

Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	As above, there are fewer interventions in the eligibility criteria for the January 2023 clinical SLR update than in the original April 2022 clinical SLR (CS Appendix D.1.2, Tables 10 and 11), justified as aligning the update SLR more closely with the scope of this appraisal (CS Appendix D.1). This is appropriate because the omitted interventions are not currently reimbursed by NICE.
Were study selection criteria applied by two or more reviewers independently?	Yes	References and articles were independently reviewed by two reviewers, with any uncertainty checked by a senior reviewer (CS Appendix D.1.2). Lists of excluded studies from the 2023 update search were missing from the CS but reported in clarification response A1.
Was data extraction performed by two or more reviewers independently?	Yes	Data was extracted directly into the NICE submission template, and all extracted data were verified against the source paper by a second researcher (Clarification response A.2).
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The company initially assessed ADAPT, ADAPT+ and ADAPT-SC using the quality assessment checklist for RCTs from the NICE Single Technology Assessment: User Guide for Company Evidence Submission template, adapted from Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care (CS section B.2.5.1, Table 16; CS Appendix D.5, Table 15). Subsequently, ADAPT+ was assessed using both the relevant criteria for non-randomised and non-controlled evidence suggested in NICE's 'Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template' and using criteria from Bowers et al. 2012 (Clarification response A3).[26] The MyRealWorld MG study was assessed using the relevant criteria for non-randomised and non-controlled evidence suggested in NICE's 'Single technology appraisal and highly

		specialised technologies evaluation: User guide for company evidence submission template' (Clarification response A4).
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Yes	Two independent researchers performed the quality assessment, and any disagreements were resolved via discussion (Clarification response A2).
Is sufficient detail on the individual studies presented?	Yes	CSRs and study publications were provided with the CS. Protocols and SAPs were provided subsequently (Clarification response C4).
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Not applicable	No statistical evidence synthesis undertaken.
CSRs: clinical study reports; gMG: generalised myasthenia gravis; ITC: indirect treatment comparison: NMA: network meta-analysis: PICOS/PICOD: population, intervention, comparator, outcomes, study design/design of study; RCTs: randomised controlled trials: SAPs: statistical analysis plans; SLR: systematic literature review.		

Appendix 2 Company and EAG critical appraisal the ADAPT study

	Company		EAG
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Response and interpretation of risk of bias**
Was the randomisation	Yes	Central randomisation was conducted using voice and web interactive response	**Agree.** Randomisation methods would have ensured unbiased randomisation to either efgartigimod or placebo arm.

	Company		EAG
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Response and interpretation of risk of bias**
method adequate?		technology. Three stratification factors were applied: acetylcholine receptor antibody status (positive vs negative), NSISTs (taking vs not taking), and Japanese nationality (yes vs no). Randomisation was done across centres rather than within centres.	**Low risk of bias**
Was the allocation adequately concealed?	Yes	Central randomisation was conducted using voice and web interactive response technology.	**Agree.** Allocation was concealed at randomisation due to the technologies used. **Low risk of bias**
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline disease characteristics were balanced between groups, including duration of MG, median MG-ADL total score, and median QMG total score. There were no imbalances in prior or concomitant gMG treatments, except for the proportion of patients who had undergone thymectomy for gMG (efgartigimod: 70%; placebo: 43%).* *Upon further analysis, efgartigimod was found to be efficacious regardless of prior	**Agree.** CS Table 14 shows that the baseline patient characteristics for the AChR antibody positive patients – population of interest for this appraisal – in the efgartigimod and placebo groups were similar, except for the proportion of patients who had undergone thymectomy (efgartigimod: 69%; placebo: 47%). Also, see the company note on subgroup analysis in the cell on the left. **Low risk of bias**

	Company		EAG
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Response and interpretation of risk of bias**
		thymectomy status; thus, the higher prevalence of thymectomy in the efgartigimod treatment group did not appear to favour efgartigimod (see Appendix E1).	
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Investigators, patients, study personnel, clinic staff, and funders were masked to treatment conditions for the duration of the study. Placebo was matched to efgartigimod in appearance and supplied in identical containers.	**Agree.** The CSR [redacted] **Low risk of bias**
Were there any unexpected imbalances in	Yes and yes	Overall treatment discontinuation was numerically higher in the placebo group	**Agree, but the EAG uses the data reported for the AChR antibody positive population relevant to this appraisal (not reported in CS).**

	Company		EAG
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Response and interpretation of risk of bias**
dropouts between groups? If so, were they explained or adjusted for?		(n=10) than the efgartigimod group (n=5). The primary reason for discontinuation from treatment was the occurrence of an AE, which was reported in six patients overall: 3 patients in the efgartigimod group and three patients in the placebo group. Withdrawal due to participant's decision was reported for three patients in the placebo group (none in the efgartigimod group). Administration of rescue therapy resulted in the discontinuation of treatment in three patients overall: 1 patient in the efgartigimod group and two patients in the placebo group. Additional discontinuations were due to prohibited medication use (n=1, placebo); protocol deviation (n=1, efgartigimod); and sponsor decision (n=1, placebo).	CSR Table 14.1.1.6.1 [redacted] **Low risk of bias**

	Company		EAG
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Response and interpretation of risk of bias**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes were reported in the Clinical Study Report.	**Unlikely.** The study protocol was not supplied with the CS so it is not possible to compare it with the outcomes reported in the CSR. However, within the CSR, the schedule of assessments does not suggest any more outcomes were measured than were reported. **Low risk of bias**
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 and yes	Efficacy was analysed on a mITT basis (patients with a valid baseline MG-ADL assessment and at least one post-baseline MG-ADL assessment). Safety analysis included all patients who received at least one dose or part of a dose. Rules for handling missing data were clearly described in an a priori statistical analysis plan. A sensitivity analysis was performed to assess the imputation impact for missing values.	**Agree – mITT analysis.** Information in the CS and CSR indicate the efficacy analyses were as reported by the company and CSR Table 13 [redacted]. The study SAP was not supplied with the CS but was provided in response to Clarification question C4. For the primary outcome, [redacted] (CSR 11.4.2.2), and overall this is a conservative measure that does not favour efgartigimod. [redacted] (CSR Table 14.2.1.4.1). **Low risk of bias for primary outcome**

	Company		EAG
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Response and interpretation of risk of bias**
			For the secondary and tertiary endpoints, the extent of missing data is unclear, but the methods to handle missing data are reported in the SAP (sections 4.1.2.2 and 4.1.2.3 respectively) [redacted] **Low risk of bias for other outcomes**
Did the authors of the study publication declare any conflicts of interest?	Yes	Several interests have been declared, including individual author support from various manufacturers conducting MG research. The study itself was sponsored by argenx.	ADAPT is the company sponsored pivotal trial.
Source: CS Table 16; with added EAG comments. AChR-Ab+: Acetylcholine receptor antibody positive; AE: adverse event; CSR: clinical study report; MG: myasthenia gravis; MG-ADL: Myasthenia Gravis Activities of Daily Living scale; mITT: modified intention-to-treat; SAP: statistical analysis plan.			

Appendix 3 Critical appraisal of the ADAPT+ study

Study question	Company response	EAG response and interpretation of risk of bias
Criteria relevant to non-randomised and non-controlled evidence		
Was the cohort recruited in an acceptable way?	**Yes.** Participants were recruited from the prior randomised, double-blind, placebo-controlled ARGX-113-1704 (ADAPT) trial, provided they completed the study or they	**Agree** Participants were recruited from both efgartigimod and placebo arms of the prior ADAPT RCT where they met the eligibility criteria to be representative of people with gMG who would be treated with the licensed indication of efgartigimod. In relation to the number randomised in the original ADAPT RCT 90% (151/167) entered the

	required retreatment that could not be completed during a TC in that study. Inclusion criteria for ADAPT included; adult, diagnosis of MG with generalized muscle weakness (meeting criteria for MGFA class II, III, IVa and IVb) confirmed by one of 3 clinical tests, a MG-ADL total score ≥ 5 at screening and baseline with >50% due to non-ocular symptoms and on a stable dose of SOC.	extension study, this represented all but one (151/152) of the population in ADAPT who completed treatment. However, lack of a control arm in ADAPT+ leads to a high risk of bias. **High risk of bias**
Was the exposure accurately measured to minimise bias?	**Yes.** Patients all received efgartigimod (IV 10mg/kg). Outcomes were measured at set timepoints throughout the study period. The number of participants who received efgartigimod in each cycle, the number of infusions received overall and the cycle duration was collected and summarised for participants who had previously received efgartigimod, those who had previously received placebo, the overall population and those who were AChR-Ab seropositive and seronegative.	**Agree** with the company assessment. **Low risk of bias**
Was the outcome accurately measured to minimise bias?	**Yes.** Outcomes were measured as follows: • Disease severity: measured using MG-ADL +/- QMG (standardized assessments used to evaluate MG symptoms in adults in clinical studies). Serial measurements of these assessments over time while receiving treatment provided information on the efficacy of efgartigimod.	**Agree** with the company assessment. **Low risk of bias**

	• Safety measurements included assessment of TEAEs (assessed, documented, and reported following ICH GCP guidelines), clinical laboratory evaluations, vital signs, physical examinations, ECGs, and the suicidal ideation assessment derived from the PHQ-9 (part A only). • Pharmacodynamic assessments (Part A only) were done by measuring levels of total IgG and IgG subtypes (IgG1, IgG2, IgG3, and IgG4) from blood samples collected at set time points using validated methods. AChR-Ab in participants who are AChR-Ab seropositive and MuSK-Ab in participants who are MuSK-Ab seropositive were also measured. Analyses were performed by AChR-Ab status and overall. Immunogenicity assessments include analyses of ADA and NAb raised against efgartigimod. Analyses were performed in the AChR-Ab seropositive and overall populations.	
Have the authors identified all important confounding factors?	**Not clear.** No confounding factors are mentioned except the exclusion of participants with clinical evidence of other significant disease or who underwent a recent major surgery, or had clinical evidence of bacterial, viral, or fungal	**Agree unclear** **Unclear risk of bias**

	disease or any other significant disease that could confound the study results or put the patient at undue risk.	
Have the authors taken account of the confounding factors in the design or analysis, or both?	**Not applicable**. The efficacy and safety results are presented descriptively.	**Agree, not applicable** No statistical analyses were performed on the results
Was the follow-up of patients complete?	**Yes**. This study is ongoing but follow up for part A is 1 year and part B is ≤ 2 years. Missing safety or efficacy data were not imputed. All available data collected from participants who dropped out of the study were included in the analyses.	**Agree** The study is ongoing and the latest CSR (Interim 4 for the data cut of January 2022) was provided. **Low risk of bias**
How precise are the results? For example, in terms of confidence intervals and p values	**Not applicable**. The efficacy and safety results are presented descriptively.	**Disagree, applicable** The results are presented descriptively. Although statistical significance cannot be inferred from the results this aspect is not likely to cause a risk of bias. **Low risk of bias**
Criteria from Bowers et al. 2012[26]		
Explicitly stated aims, to minimize the possibility of Type I error?	**Yes.** The purpose of the study is clearly stated: 'to evaluate the long-term safety and tolerability of efgartigimod administered in participants with gMG'. There was no pre-specified hypothesis.	**Not applicable** Without a pre-specified hypothesis there was no indication to consider multiplicity in the results.
A well-characterized sample representative of	**Yes.** The study population is described in detail. Participants were recruited from the ADAPT trial (randomized, double-blinded, placebo-controlled, multicentre, phase 3	**Agree** The sample is representative of the population in the licensed indication for efgartigimod. This aspect is not likely to cause a risk of bias. **Low risk of bias**

the target population in whom the medication will be used?	study), provided they completed the study or they required retreatment that could not be completed during a TC in that study. Of 167 patients from the RCT, 151 rolled over into the ADAPT+ and 145 received at least 1 dose (or part of a dose) of open-label efgartigimod. 111 (76.5%) were AChR-Ab seropositive and 34 (23.5%) were AChR-Ab seronegative – in real-world settings approximately 90% of patients have IgG autoantibodies with the most common against AChR.	
Outcome assessment is masked to treatment received where possible?	**Yes.** All patients in ADAPT+ received open label efgartigimod; outcome assessment masking to treatment was therefore not possible.	**Agree** that treatment masking was not carried out as this is an open-label trial (assume company 'Yes' is a typo as it does not align with their text.) **High risk of bias**
A low rate of sample slippage in relation to the numbers randomized in the preceding RCT, but the length of follow-up should be considered in making this assessment?	**Yes.** After rolling over from ADAPT, 145 participants in ADAPT+ had received ≥1 dose (or part of a dose) of efgartigimod by the interim data cut-off date (31st January 2022). The mean (SD) duration of treatment combined with follow-up in the total efgartigimod group was 548.0 (231.79) days, which results in 217.55 patient-years of observation. 35 (24.1%) patients discontinued efgartigimod. Primary reasons for discontinuation of efgartigimod (n=35) during the ADAPT+ study were "Withdrawal by participant" (11 [7.6%] participants), "Treatment failure" and "AEs" (8 [5.5%] participants each). A total of 56 (38.6%) patients rolled over to the ARGX-113-2002	**Disagree** Participant flow and reasons for discontinuation are reported in CSR (interim 4) section 10.1 and on a cycle-by-cycle basis in CSR (interim 4) Table 8. The most significant sample slippage is the number of patients who discontinued to enrol in ADAPT-SC: [redacted]. Schulz et al. 2002 suggests that loss of more than 20% of trial participants renders a trial unable to withstand challenges to validity.[27] It is not reported at what point these patients left the study, so it is unclear on whether the length of follow-up has mitigated any effects of this. **High risk of bias**

	study to continue efgartigimod treatment with PH20 SC dosing.	
Objectives, design, conduct, analysis and results are adequately described?	**Yes.** The objectives of the study are clearly stated, as is the overall study design and plan, including detailed inclusion and exclusion criteria, details for why patients would be discontinued for the trial study and methods for analysis. Efficacy and safety evaluations are reported in detail, and a synopsis is provided.	**Agree** with the company assessment. No impact on risk of bias.
Limitations of the specific study design used and its execution should be discussed?	**Unclear.** Limitations of the study design are not discussed.	**Disagree** The study design provides an inherent risk of bias: it is open-label and therefore at risk of performance bias from any prior expectations of the treatment; there is no control arm. **High risk of bias**
Sources: Clarification response A3, Tables 2 and 3; with added EAG comments. AChR-Ab: anti-acetylcholine receptor antibody; ADA: antidrug antibodies; AEs: adverse events; CSR: clinical study report; ECG: Electrocardiogram; gMG: generalised myasthenia gravis; ICH GCP: International Committee on Harmonization of Good Clinical Practice; IgG: immunoglobulin gamma; IV: intravenous; MG: Myasthenia Gravis; MG-ADL: myasthenia gravis activities of daily living scale; MGFA: Myasthenia Gravis Foundation of America; MuSK-Ab: anti–muscle-specific-kinase antibody; NAb: neutralizing antibody; PHQ-9: Patient Health Questionnaire item 9; QMG: Quantitative Myasthenia Gravis score; RCT: randomised controlled trial; SC: subcutaneous [injection]; SD: standard deviation; TEAEs: Treatment Emergency Adverse Events.		

Appendix 4 Critical appraisal of the MyRealWorld MG study

Study question	Company response	EAG response and interpretation of risk of bias
Was the cohort recruited in an acceptable way?	**Yes.** Recruitment was conducted primarily through Patient Advocacy Groups, social media and via treating neurologists. While there is some potential for selection bias towards more proactive patients – who may be more likely to engage with PAGs and social media and those who can access/use the internet and have a phone and/or tablet – the company believes that the population recruited is generalisable to UK patients with gMG.	**Disagree** The cohort is at risk of selection bias towards a population with access to/ability to use the Internet due to the smartphone application being the study platform and one that is already engaged with PAGs and social media. More severely affected patients may have been more likely to join the study as evidenced by the greater proportion with class IV disease in comparison to ADAPT. Study enrolment was by self-enrolment via the smartphone application and patient eligibility was not verified. **High risk of bias**
Was the exposure accurately measured to minimise bias?	**Yes**. Participants were followed up as follows. • Participants initially asked to complete a profile to collect data about themselves (e.g. demographics, diagnosis, past treatments). If any of these changed then they can be updated by the participant. • Participants asked to complete a monthly tracker to document any MG-related events for that month e.g. time off work, hospital appointments. Every 1 to 6 months (depending on the instrument) participants asked to complete PRO instruments to assess QoL, specific symptoms and function.	**Unclear** All data is patient-reported, including baseline characteristics (profile), monthly tracker, and completion of PRO instruments. Timing of assessments is dependent on the participants' reporting their responses. **Unclear risk of bias**
Was the outcome accurately measured to minimise bias?	**Yes.** Either core PRO instruments (to be completed by all participants) or optional PRO instruments (for participants who opt-in). • Core: EQ-5D-5L, EQ-5D-5L bolt on items, MG-ADL, MG-QOL 15R, HADS, HUI3, COVID-19 survey • Optional: PROMIS, FACIT-Fatigue, PROMIS sleep disturbance short form 6a	**Unclear** All data is patient-reported, including baseline characteristics (profile), monthly tracker, and completion of PRO instruments. Timing of assessments is dependent on the participants' reporting their responses. Due to the remote nature of the data collection, via the smartphone application, accuracy of the data could not be verified.

	While the PRO instruments were not originally developed to be administered via an app, the company took expert advice on the selection of tools based on which we deemed to be transferable to an app. The sample size and composition of patients will likely vary for each instrument used and each time it is filled in. This will also make comparison with results from other literature difficult/limited. Additionally, due to the remote nature of the data collection patient eligibility and accuracy of the data could not be verified.	**High risk of bias**
Have the authors identified all important confounding factors?	**Not clear**. None are mentioned	**Agree unclear** confounding factors are not discussed in the study publications, nor in the CS. However, auto-immune comorbidities are reported: diabetes and rheumatoid arthritis. **Unclear risk of bias**
Have the authors taken account of the confounding factors in the design or analysis, or both?	**Not applicable**. As an exploratory observational study, causation is not explored regarding differences and patterns in the data. Analyses will be descriptive, and no hypotheses will be tested.	**Agree** with company assessment, not applicable.
Was the follow-up of patients complete?	**Not applicable.** Study is ongoing, but patients will be followed up for 2 years.	**Disagree, unclear** The study is ongoing and only the baseline results have been recently published (DeWilde et al. 2023).[41] However, it is unclear what data cut or timepoint was used to obtain data for the ad hoc analyses for the economic model of this appraisal and clarification response B1. **Unclear risk of bias**
How precise are the results? For example, in terms of confidence intervals and p values	Generally, this is **not applicable** as the results are descriptive. Confidence intervals are given for continuous variables, but otherwise results are distributions, means, SD, quartile ranges, proportions. A regression analysis on the utility complement (1 -utility value) and the different items of the MG-ADL instrument was estimated to establish which items had the largest impact on utility values	**Disagree, applicable** The results are mainly descriptive and confidence intervals are only reported for continuous variables and a regression analysis on the utility component, therefore although statistical significance cannot be inferred from the results this aspect is not likely to cause a risk of bias. **Low risk of bias**

	(used a normal distribution and an identity link) - the confidence intervals for these are quite broad.	

Source: Clarification response A4, Table 4; with added EAG comments.
EQ-5D-5L, EuroQol 5 Dimension 5 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HADS, hospital anxiety and depression scale; HUI3, Health Utilities Index III; MG, Myasthenia Gravis; MG-ADL, myasthenia gravis activities of daily living scale; MG-QOL 15r, Myasthenia Gravis Quality of Life 15-item revised scale; PAG, Patient Advisory Group; PRO, Patient-Reported Outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, Quality of Life; SD, standard deviation.

Single Technology Appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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 Wednesday 10 May 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 '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Comment 1 Exclusion of maintenance intravenous immunoglobulin (IVIg) from established clinical management (ECM

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The company would like to thank the EAG for their fair and balanced critique of the CS for efgartigimod as an add-on to established clinical management in adults with acetylcholinesterase receptor antibody-positive generalised myasthenia gravis. In relation to the EAG's recommendation that maintenance IVIg use should be set to 0 in the economic model, however, the company posits that this is not a factually accurate representation of current practice. The EAG justifies this recommendation based on advice they received that "IVIg is no longer used regularly as a maintenance treatment for patients with gMG due to a shortage of IVIg and that this practice is unlikely to change." However, on pages 15 and 24 of the report, the EAG acknowledges that variation exists between clinical centres in the use of IVIg as maintenance treatment for gMG patients inadequately controlled with standard treatments, and uncertainty on their position arises from the limited expert opinion available to them at the time of their assessment of the CS. Consistent with the NICE scope, the CS includes corticosteroids, acetylcholinesterase inhibitors, non-steroidal immunosuppressive therapy, rituximab and maintenance IVIg in the ECM basket. This definition of ECM was developed in consultation with clinical experts working in England. Expert advice to the company in December 2022 –	On pages 15, 64, 78, 82, 94 and 96 of the EAG report, where the EAG have described clinical expert advice that IVIg is no longer used regularly as a maintenance treatment for patients with gMG, please can the text be amended to include the statement: "There remains uncertainty in the real-world usage of IVIg in the UK for patients inadequately controlled with standard treatments;	To correct a potential factual error that IVIg maintenance is not used in UK clinical practice in the target population most likely to receive efgartigimod.	We do not believe it is necessary to make the change the company suggests at every point in the report that the company has indicated. We have made the following changes (added text shown in bold type): Page 13: Clinical advice to the EAG was that IVIg is no longer used regularly as a maintenance treatment for patients with gMG due to a shortage of IVIg and that this practice is unlikely to change. However, there is some uncertainty due to the limited expert

which included three clinical experts from across the UK – indicated that there is current IVIg usage, in the circumstances specified in the CS (CS version 2.0, Section B.3.2.3, pages 88 and 89). Moreover, [redacted]. This usage pattern is consistent with previous discussions with NICE and NHS England in relation to the efgartigimod Budget Impact assessment. Here, NHS England has accepted that regular IVIg treatment is part of ECM for some patients, and the company believes that it would be appropriate to use the same assumption in the cost-effectiveness analysis. Overall, the company agrees with the EAG that there is uncertainty in the amount of current IVIg use in the UK and that this is a key topic for technical engagement. The company intends to provide further support for inclusion of IVIg maintenance as part of ECM during technical engagement, and would request the following amendments in the EAG report for clarity.	clinical advice provided to the company in December 2022 indicated that IVIg maintenance is used to treat a proportion of UK patients."		opinion available **to the EAG and the difference between clinical advice to the EAG and clinical advice provided to the company in December 2022 which indicated that IVIg maintenance is used to treat a proportion of UK patients.** Page 78: Clinical advice to the EAG was that patients would no longer receive IVIg for elective maintenance treatment due to the IVIg shortage and this shortage is likely to continue. We do not include IVIg for maintenance treatment in the EAG base case and raise this as a key issue (section **Error! Reference source not**

			found.) **acknowledging that the real-world usage of IVIg in the UK for patients with gMG inadequately controlled with standard treatments is uncertain**. Page 95 (end of Table 23): We disagree with including maintenance IVIg therapy as our clinical expert advised that IVIg are not commissioned for maintenance treatment. **However, we acknowledge that there is uncertainty about the real-world usage of IVIg in the UK for gMG patients inadequately controlled with standard treatments.**

Comment 2 Established clinical management (ECM) vs standard of care

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On pages 32, 35 and 55 the EAG report refers to “standard care” or “standard of care” in relation to the ADAPT study. The company is aware that the same term is used on pages 42 and 139 of the company submission (Document B). For consistency across the EAG report, and consistency with the economic model submitted, the company would suggest aligning wording to “established clinical management” throughout.	On pages 32, 35 and 55, replace “standard care” and “standard care” with established clinical management.	For consistency and clarity across clinical and economic sections of the report.	The EAG has amended the EAG report as suggested.

Comment 3 EAG base case cost per QALY

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The text reporting the EAG’s preferred assumptions for the base case reports the ICER for efgartigimod with established clinical management as £623,325 per QALY and referenced to Table 3 in the EAG report. However, Table 3 gives the ICER (£/QALY) for the EAG base case as £628,135	Please could the EAG confirm that the values in Table 3 are correct, and that the text should report the same base case ICER.	Correcting a potential typographical error.	This typographical error has been corrected as suggested.

Comment 4 Epidemiology of gMG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Thank you for identifying the referencing error for the prevalence rate of gMG in the CS (page 22). The rate of 15 in every 100,000 patients is taken from the NICE final scope document which was referenced to: "2. Patient, Myasthenia gravis. 2017. Accessed November 2021. 3. Muscular Dystrophy UK. Myasthenia gravis Overview. 2011. Accessed November 2021." The company would like to clarify that the epidemiology data used in the CS is aligned with the prevalence rate reported in the NICE final scope.	No amendment is required in the EAG report.	Not applicable	Agree no action required.

Comment 5 Caregiver disutilities

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 76 it is stated that it is "the EAG's view (..) that the CS has not provided evidence to show that gMG has a substantial effect on carer's health related quality of life". However, in response to clarification question B7, the	On page 76 could the statement that the Company have not provided evidence to show that gMG has a substantial	To ensure that the EAG report accurately captures the evidence submitted by the Company	The EAG report outlines the evidence provided by the company. In light of this comment, we have amended the wording in

Company has provided a reference to a poster by Jacob et al (2022) that reports that 32.4% of gMG patients require help from a caregiver, and that this proportion is increasing with MG-ADL score. The number of weekly hours of caregiver help needed is also substantial, as reported on this poster, and increases with MG-ADL score. This same poster also reports the proportion of caregivers who stop paid employment as well as the proportion who reduce their working hours, the sum of this is approximately 36% for all gMG patients combined. From this research it seems evident that there is an impact on the life of caregivers, and from that it can be reasonably concluded that there is also an impact on the caregivers' health-related quality of life. At the time of submission and responding to the clarification questions, the company did not have direct evidence on the magnitude of impact on the health-related quality of life of gMG caregivers. However, in response to the EAG raising this issue, the company is commissioning a qualitative survey of gMG caregivers designed to address this gap. The Company looks forward to the opportunity of sharing the results of this survey with NICE	effect on carer's health related quality of life be amended to say that the company has provided evidence to show there is an impact on carers health-related quality of life, albeit that the magnitude of this impact is uncertain		the report to: The EAG's view is that the CS has not provided **sufficient** evidence to show that gMG has a substantial effect on carers.

during the upcoming stages of the appraisal.			

Comment 6 Transition probabilities after treatment discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 4.2.6.1.3 the EAG noted that in the original analysis submitted a large proportion of patients remained in the MG-ADL <5 health state after permanent treatment discontinuation. The company acknowledges the incorrect implementation of the relevant transition probabilities, and recognises that the solution provided by the EAG is more appropriate. The EAG derived those transition probabilities assuming that just 1% of the patients who achieved MG-ADL <5 before discontinuation, were going to remain in the same health state. The EAG also explored a scenario, where this residual fraction of controlled patients is set to 5%. In support to their preferred assumption (1%) the EAG quoted the company response to clarification question B4, were they stated to be “not aware of any proof of the existence of a residual treatment effect”. This statement corresponds with the status of the information available at	No amendment is required in the EAG report.	Not applicable.	Agree no action required.

the time of making the submission and responding to the clarification questions. However, in response to the EAG raising this issue, the company will be exploring the ADAPT data further, and the company looks forward to the opportunity of sharing this updated information with NICE during the upcoming stages of the appraisal.			

Comment 7 Time on Treatment scenario

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The impact of considering a piecewise approach with Kaplan Meier data for up to and the exponential curve for the remaining time horizon was tested by the EAG in a scenario analysis (Table 24 on page 95 and Table 28 on page 98 of the EAG report). From the methodologic point of view, we consider that the transition from the Kaplan Meier data to the exponential curve should be done using the proportion of patients in the previous cycle multiplied by the probability of discontinuing the treatment in that cycle. Using that approach we can ensure to have a continuous and fluid curve that can better represents the	Change the ICER reported in Table 24, scenario # 2 from £46,720 to £46,043, and the ICER reported in Table 28, scenario 2 from £627,910 to £627,909	To correct the small methodological error.	The model has been amended as suggested by the company. The ICERs in Tables 24 and 28 have been corrected.

patients' discontinuation. The approach adopted by the EAG directly considers the extrapolated parametric curve after 24 months, which could result in a sudden drop or increase of the proportion of patients still on treatment. The impact of this methodological inaccuracy on the ICER results is small.			

Comment 8 Costs of corticosteroid complications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG considers that Voorham et al. provide a more representative cost of complications associated with corticosteroid use in the UK than Bexelius et al, which was used in the CS base case. Although the company disagrees with the choice of Voorham et al. as best reflective of gMG patients in the UK, which we look forward to discussing during technical exchange, we do kindly request the EAG to provide their calculations for the per week costs for patients in low (<7.5 mg/day) and high dose (≥7.5 mg/day) at £6.16 and £43.99 respectively. The company attempted to reproduce this calculation, but landed on slightly different	To provide a calculation for the per week costs of CS related complications based on Voorham et al. Reflect in the EAG report that the population on which the Bexelius et al. publication was based, had a disease more similar to gMG than those in Voorham et al and Janson et al.	To correct the inaccurate reporting of evidence submitted by the Company	We note that there are minor differences between the EAG's estimated costs from Voorham et al. and those suggested by the company in column 1 of this table. Further, the estimated costs before inflation are the same. Therefore, there appear to be minor differences in how the values have been inflated. The following text has

values. Considering a high dose threshold of 7.5mg/day, the low dose costs should be a weighted average of £1,209.53 (annual costs in 5,152 patients using 0 – 0.5 mg/day), £1,610.17 (annual costs in 3,497 patients using 0.5 – 2.5 mg/day), £2,427.65 (annual costs in 436 patients using 2.5 - 5 mg/day) and £3,116.72 (annual costs in 174 patients using 5 - 7.5 mg/day), which results in an average cost of £1,454.05 which, when adjusted for inflation to 2021 (using PSSRU inflation indices), is £1,609.05 and converting to a weekly cost would be £6.13 and not £6.16. Using a similar rationale to calculate the high dose CS use costs we achieve an average of £3,225.91 (considering an annual cost in 134 patients using 7.5 – 15 mg/day and 20 patients using ≥ 15 mg/day of £3,043.43 and £4,448.53, respectively), which, when adjusted for inflation to 2021, is £3,569.80 and converting in a weekly cost would be £43.71 and not £43.99. Furthermore, the EAG states on page 80 that “the weekly costs for managing corticosteroid complications in the Bexelius et al. study (…) were for a different disease area”. In fact, the			been added, as suggested: None of the studies were for patients with gMG. The study by Bexelius et al. included patients with systemic lupus erythematosus, which is an autoimmune disease like gMG, while both Voorham et al. and Janson et al. included patients with asthma, which may be less comparable to gMG.

costs presented in Bexelius et al. were in a population of patients with systemic lupus erythematous, which is an autoimmune disease, as is gMG, while both Voorham et al. and Janson et al. were measured in patients with asthma, which is less comparable to gMG.			

Comment 9 Disutilities due to exacerbations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 74 of the EAG report it is stated that "Acute exacerbations are assumed to require an inpatient hospitalisation or prolongation of an existing hospitalisation, and result in a persistent or significant disability or incapacity." However, in -ADAPT both exacerbation not requiring and exacerbation requiring hospitalisation were collected. In the model the company only included those requiring hospitalisation, as the others are likely to have very small impact in terms of costs and health-related quality of life. This means the company is not making the assumptions that all exacerbations require hospitalisation but	Amend the statement to "Only acute exacerbations that require an inpatient hospitalisation or prolongation of an existing hospitalisation, and result in a persistent or significant disability or incapacity are considered in the model."	To reflect the data used for the model	The text has amended as suggested by the company.

rather only considers those exacerbations that require hospitalisation			

Minor misalignment in wording

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 62 and 64; “This consists of more than eight weeks since initiation of the previous cycle of treatment and a MG-ADL score of greater than five” does not accurately reflect treatment criteria in ADAPT	Correct to “This consists of at least eight weeks since initiation of the previous cycle of treatment and a MG-ADL score of at least five”	To be in line with the ADAPT treatment criteria	The text has amended as suggested by the company.
Page 63; “The population considered in the company model is adult patients with AChR antibody positive gMG” is not entirely reflective of the population considered in the model and the submission.	Correct to “The population considered in the company model is adult patients with AChR antibody positive gMG and MG-ADL of at least 5”	To be in line with the population in scope of the appraisal	The text has amended to “The population considered in the company model is adult patients with AChR antibody positive gMG and a MG-ADL score of at least five.”

Minor typographic errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 11, Table 1; “probabilites” is mis-spelled	Correct to “probabilities”	Minor typographic error	Minor error corrected.
Page 32; “gGM” is mis-spelled	Correct to “gMG”	Minor typographic error	Minor error corrected.
Page 78, Table 16; “Rituxumab” is mis-spelled	Correct to “Rituximab”	Minor typographic error	Minor error corrected.

Incorrect marking

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG response</th></tr>
<tr>
<td>ID4003 efgartigimod EAG report 26042023 ACIC FAC, Page 35, Table 6. Table heading for the ADAPT+ column</td>
<td>The AIC marking of the cohort size of AChR Ab+ patients in ADAPT+ (n=111) no longer requires AIC marking and can be unredacted</td>
<td>Table 1 ADAPT and ADAPT+ baseline demographics and clinical characteristics of the AChR antibody positive patient population
<table>
<tr><th rowspan="2">Characteristic</th><th colspan="2">ADAPT</th><th rowspan="2">ADAPT+ (n=111)</th></tr>
<tr><th>Efgartigimod (n=65)</th><th>Placebo (n=64)</th></tr>
<tr><td>Mean age (SD), years</td><td>44.7 (15)</td><td>49.2 (15.5)</td><td>47.1 (15.5)</td></tr>
<tr><td colspan="4">Age category, n (%)</td></tr>
<tr><td>18 to <65 years</td><td>57 (87.7)</td><td>51 (79.7)</td><td>93 (83.8)</td></tr>
<tr><td>≥65 years</td><td>8 (12.3)</td><td>13 (20.3)</td><td>18 (16.2)</td></tr>
</table>
</td>
<td>AIC marking for the AChR Ab+ patient cohort size (n=111) has been removed throughout the report.</td>
</tr>
</table>

ID4003 efgartigimod EAG report 26042023 ACIC FAC, Page 37, Paragraph 1, Line 3.	The AIC marking applied to the proportion of patients discontinuing in ADAPT+ so that they could enrol in ADAPT-SC should also be applied to the absolute numbers (56/167), otherwise, the redacted value can be directly calculated.	However, 54% (91/167) discontinued efgartigimod treatment during ADAPT+, with [redacted] ([redacted]) discontinuing from ADAPT+	The AIC marking has been extended.
ID4003 efgartigimod EAG report 26042023 ACIC FAC, Page 42, Paragraph 1, Line 3.	The AIC marking of the cohort size of AChR Ab+ patients in ADAPT+ (n=111) no longer requires AIC marking and can be unredacted	Similar to ADAPT, treatment duration is reported for the overall study population (n=145) in CS section B.2.7.1, and [redacted] are provided for the AChR antibody positive population (n=111) in the CSR (ADAPT+ CSR Interim 4 Table 27).	AIC marking for the AChR Ab+ patient cohort size (n=111) has been removed throughout the report.
ID4003 efgartigimod EAG report 26042023 ACIC FAC, Page 44, Paragraph 3, Line 1.	The AIC marking of the cohort size of AChR Ab+ patients in ADAPT+ (n=111) no longer requires AIC marking and can be unredacted	As the long-term safety extension study of ADAPT, from which 151 patients rolled over (111 of whom were AChR antibody positive),	AIC marking for the AChR Ab+ patient cohort size (n=111) has been removed throughout the report.
ID4003 efgartigimod EAG report 26042023 ACIC FAC, Page 50, Paragraph 1, Line 3.	The AIC marking of the cohort size of AChR Ab+ patients in ADAPT+ (n=111) no longer requires AIC marking and can be unredacted	However no results are available for the AChR antibody positive subgroup (n=111) despite “safety and tolerability in the AChR-Ab+ population” being the primary outcome of the study	AIC marking for the AChR Ab+ patient cohort size (n=111) has been removed throughout the report.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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 **19 June 2023**. 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	Sergio Iannazzo
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	argenx 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.	Not applicable
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.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Exclusion of maintenance intravenous immunoglobulin (IVIg)	Yes	The Company disagrees with the EAG's recommendation that maintenance IVIg use should be set to 0 in the economic model, and does not agree that this represents current clinical practice. The EAG justifies this recommendation based on advice they received that "IVIg is no longer used regularly as a maintenance treatment for patients with gMG due to a shortage of IVIg and that this practice is unlikely to change." On page 13 of their report, however, the EAG acknowledges that there is uncertainty around the use of IVIg as maintenance treatment for gMG patients inadequately controlled with standard treatments, and uncertainty on their position arises from the limited expert opinion available to them at the time of their assessment of the CS. Consistent with the NICE scope, the Company submission includes corticosteroids, acetylcholinesterase inhibitors, non-steroidal immunosuppressive therapy, rituximab and maintenance IVIg in the established clinical management (ECM) basket. This definition of

		ECM was developed in consultation with clinical experts in England. Expert advice to the Company in December 2022 – which included three clinical experts from across the UK – indicated that regular or intermittent (i.e., maintenance) IVIg is used for patients with gMG in the circumstances specified in the CS (CS version 2.0, Section B.3.2.3, pages 88 and 89). During technical engagement, the Company has worked to provide new relevant data sources relating to regular or intermittent (i.e., maintenance) IVIg use in the UK and has also consulted again with UK clinicians to ensure that the Company submission and response to technical engagement is a true reflection of current clinical practice. The Company's revised base case assumes that [redacted]% of patients (i.e., 100% of patients with MG-ADL ≥ 10 and [redacted]% of patients with MG-ADL 8-9) receive with maintenance IVIg in clinical practice; supporting data are presented in a separate new evidence submission and are summarised below. **Real-world prior IVIg use for patients receiving efgartigimod in England** The Company proposes that data collected from the MHRA efgartigimod EAMS and subsequent EAMS+ programmes provide the most up-to-date view of maintenance IVIg utilitisation in England. [redacted]

		[redacted] It is the collective opinion of the clinical experts who provided data for this analysis, that this is a realistic illustration of maintenance IVIg utilisation in England, in the population of patients for whom efgartigimod is likely to be considered when used in routinely commissioned practice. The Company has provided separately a letter signed by the clinical expert who is coordinating the EAMS/EAMS+ data collection that confirms regular or intermittent (i.e. maintenance) IVIg use prior to starting efgartigimod treatment and attesting to the accuracy of the EAMS/EAMS+ data collected to date. For clarity, the Company would also like to note that prior or concomitant maintenance IVIg use is in no way a requirement for treatment with efgartigimod. **Publicly available IVIg utilisation data from the NHS** During technical engagement, the Company also identified data from the NHS Immunoglobulin Database (IGD), a real-world source that provides historical data on IVIg usage for NHS supply planning.[1] The latest report, published in January 2023, shows that between 2018 and 2021, there was only a slight reduction in the number of patients receiving IVIg – as either maintenance or acute therapy – in England:[1] • 2021/2022 – 666 patients taking 189,534g • 2020/2021 – 681 patients taking 197,283g • 2019/2020 – 733 patients taking 197,828g

		• 2018/2019 – 775 patients taking 215,355g Given this pattern of IVIg use – captured in an independent UK database – it is unlikely that maintenance IVIg use has dropped to zero since March 2022, thereby supporting the data from the efgartigimod EAMS/EAMS+. **Supplemental clinical expert opinion** In collecting further evidence of maintenance IVIg use in the UK, the Company also proactively sought clinical expert opinion to ensure that the Committee has a full and current picture of UK treatment practice. When consulting one of the UK's leading Consultant Neurologists, the Company heard that, while IVIg as a treatment has been subject to a number of supply interruptions and difficulties over recent years, this has been a constant feature as opposed to a new or emerging issue. Supply interruptions have been partly driven by increased international demand for the product and a drop in plasma donations due to COVID. In response, NHSE has provided clear commissioning guidance for the use of IVIg across numerous different conditions, including gMG (https://www.england.nhs.uk/wp-content/uploads/2021/12/cpag-policy-for-therapeutic-immunoglobulin-2021-update.pdf), and multiple brands are used to secure supply. Despite these issues, maintenance IVIg remains an important aspect of clinical management for gMG patients needing viable treatment options when first- and second-line medications have failed. Indeed, in 2021 the UK Government lifted its 20-year ban on manufacturing IVIg

		from UK-derived blood plasma,[2,3], with the expectation that this will further support alleviation of supply challenges in the future. **Reducing uncertainty for Committee decision making** The Company acknowledges that the amount of maintenance IVIg use in the UK is a key topic for the Committee to consider. The Company's preferred assumption uses the real-world data collected by clinicians in England for the efgartigimod EAMS/EAMS+ programme, which showed that [redacted]% of patients were previously treated with regular or intermittent IVIg. The Company assumes that all patients with MG-ADL ≥ 10, and [redacted]% of patients with MG-ADL 8-9, would receive maintenance IVIg. The percentage of [redacted]% was calculated using the baseline distribution of the patients over the health states so that the overall baseline population in the model reflects the proportion of EAMS/EAMS+ patients in England that are treated with regular or intermittent IVIg [redacted] The Company considers this assumption reasonable and supported by recent IVIg usage data for patients receiving efgartigimod collected in England.
Key Issue 2: Extrapolation of time on treatment (ToT) curve	No	The Company accepts the EAG's alternative approach of modelling extrapolation of ToT.

Key Issue 3: Permanent treatment discontinuation transition probabilities	Yes	The Company has incorporated the EAG's preferred methodology for calculating transition probabilities after permanent treatment discontinuation into the updated model. In Section 4.2.6.1.3 of their report, the EAG noted that in the original analysis submitted, a large proportion of patients remained in the Myasthenia Gravis Activities of Daily Living Scale (MG-ADL) <5 health state after permanent treatment discontinuation. Using their suggested methodology, the EAG derived new transition probabilities assuming that just 1% of the patients who achieved MG-ADL <5 before discontinuation would remain in the same health state. The EAG also explored a scenario where this residual fraction of controlled patients is 5%. Supporting their preferred assumption (1%), the EAG quoted the Company response to clarification question B4, where the Company stated it was "not aware of any proof of the existence of a residual treatment effect". This statement corresponded with the status of the information available at the time of initial submission and response to clarification questions. Subsequently, the Company has conducted further research to explore assumptions around the proportion of patients remaining in MG-ADL <5 after permanent discontinuation to support reducing uncertainty for the Committee. The Company has collated evidence around the existence of patients who are "long responders" to efgartigimod in a separate new evidence submission. While these data rely on small sample sizes, they point towards a

		residual treatment effect for efgartigimod; the evidence supporting this effect is summarised below. **Supplementary efgartigimod post-discontinuation data in gMG** When considering the ADAPT+ population, [redacted] patients received only one cycle of efgartigimod for the entire duration of the study (3 years), suggesting a long-lasting treatment effect after the first cycle of infusions.[4] Moreover, data from ADAPT and ADAPT+ demonstrate that [redacted] who had MG-ADL scores <5 at the time of treatment discontinuation maintained a residual efgartigimod effect for [redacted] after the last treatment exposure.[5] Moreover, real-world data from US patients who received efgartigimod in a Patient Support Programme demonstrates that [redacted]% of patients who had an MG-ADL score <5 at the time of permanent treatment discontinuation still had MG-ADL<5 at the time of their latest MG-ADL measure, which was on average [redacted] after their last infusion.[6] **Efgartigimod evidence in non-gMG indications** Finally, evidence from Phase II studies in other efgartigimod indications – namely Immune Thrombocytopenic Purpura (ITP) and Pemphigus Vulgaris/Pemphigus Foliaceus (PV/PF) showed sustained remission in several patients, even after treatment cessation.[7,8] In the Phase II study of efgartigimod in adult patients with ITP, while most patients who responded to efgartigimod had a transient increase in platelet counts, with counts returning to baseline levels in the treatment-free follow-up period, at least 3 of 26 (11.5%) efgartigimod treated

		patients (two newly diagnosed; one chronic) with ITP remained in remission throughout the follow-up period.[7] Separately, in the Phase II study of efgartigimod in PV/PF, autoreactive antibody levels remained low in several study participants after discontinuation of efgartigimod treatment (with a 10-week treatment-free follow-up). This suggests a sustained reduction in autoantibody levels during efgartigimod treatment and indicates potential disease modification in peripheral lymphocytes in some patients even after treatment cessation. The Company plans to explore these effects further in Phase III trials to, in part, help us understand if efgartigimod has the potential to modify disease course in certain patients. **Reducing uncertainty for Committee decision making** Based on the new evidence presented, the Company believes that assuming only 1% of patients remain at MG-ADL<5 after six months following the permanent discontinuation from efgartigimod underestimates the duration of clinical effect for efgartigimod. The updated base case therefore reflects the assumption that 15% of patients remain at MG-ADL<5 after six months following the permanent discontinuation from efgartigimod. The Company acknowledges that this is higher than was proposed in its submission dated 14 February 2023 when the additional data presented above were unavailable. Given that the additional discontinuation data indicate a potential for [redacted]% of patients to have residual treatment benefits, the Company proposes that 15% is a reasonable value for the base case presented below.

Key Issue 4: Caregiver disutilities	Yes/No	The Company disagrees with the clinical advice received by the EAG that there is little or no impact on caregivers due to people having gMG. We acknowledge that the literature on this topic is not extensive, hence why a proxy approach was deemed most appropriate to strengthen the Company submission further. ***Similarities between MG and Multiple Sclerosis*** The Company has conducted some comparative analysis to explore the appropriateness of Multiple Sclerosis (MS) caregiver burden as a proxy for gMG (in the absence of published utility data) (Table 1). gMG is a chronic, long-term, autoimmune disease caused by autoantibodies against the neuromuscular junction proteins, leading to chronic fatigue and potentially life-threatening muscular weakness.[9] MS is a chronic, lifelong, autoimmune demyelinating disease of the central nervous system with both inflammatory and neurodegenerative components.[10,11] Both diseases are chronic, autoimmune conditions that can disturb the neuromuscular system and affect mainly young women. Myasthenia Gravis has a bimodal age incidence.[12] In the younger age group (peak around 30 years), there is a higher frequency of females than in the older groups (peak around 50 years). In MS, the usual presentation is in young adults around 30 years, which more commonly affects women (female-to-male sex ratio of approximately 3:1).[11]

		gMG and MS have some similar symptoms, even though MS affects the central nervous system and can cause several clinical manifestations that vary among patients. Some gMG and MS common symptoms are muscle weakness, vision problems, chewing and difficulty swallowing, speech limitations, fatigue, mobility problems and psychological involvement (depression and anxiety).[13,14] The co-occurrence of MS and gMG has been described in the literature based on the hypothesis of a common immunological mechanism (cell-mediated and humoral immunity are involved in the pathogenesis of both diseases).[15] The presentation of gMG can occur before or after the development of MS, and the onset can vary from person to person.[16–19] However, the coexistence of both conditions could be undetected due to possible overlap of ocular and bulbar symptoms.[19] Currently, several treatments are available to treat both conditions. Corticosteroids, immunosuppressants and therapeutic plasma exchange are some common medications available as possible therapies for both conditions. However, specific treatment protocols and algorithms have been developed for each disease.[11,12] Regarding mortality, both conditions are rarely fatal, and deaths are associated with secondary complications.

Table 1: Comparison between multiple sclerosis and gMG

Disease	Multiple sclerosis (MS)	Myasthenia Gravis
Causes	Autoimmune disease	Autoimmune disease
Physiopathology	Cell-mediated and humoral immunity (Increased numbers of Th1 and Th17 cells and their related cytokines IL-1, IL-6, IL-17, interferons (IFN), and tumor necrosis factor (TNF) are found in MS and MG patients)	Cell-mediated and humoral immunity (Increased numbers of Th1 and Th17 cells and their related cytokines IL-1, IL-6, IL-17, interferons (IFN), and tumor necrosis factor (TNF) are found in MS and MG patients)
Time frame	Chronic disease (neurodegenerative disease, characterised by CNS inflammation and demyelination) Progressive disease	Chronic disease (neuromuscular junction)

		Symptoms	*fatigue *vision problems *numbness and tingling *muscle spasms, stiffness and weakness *mobility problems *pain *problems with thinking, learning and planning *depression and anxiety *sexual problems *bladder problems *bowel problems *speech and swallowing difficulties	*fatigue * generalised muscle weakness *weakness of the eye muscles *double vision *difficulty making facial expressions *problems chewing and difficulty swallowing *slurred speech *shortness of breath and occasionally serious breathing difficulties
		Treatment	Corticosteroids, therapeutic plasma exchange (relapses that do not respond to steroids). Immunosuppressants, biological medications, Monoclonal antibody infusions	Corticosteroids, Pyridostigmine, Immunosuppressants, PLEX, Immunoglobulin
		Prognosis	Lifelong condition that can cause serious disability, although it can occasionally be mild.	Rare long-term condition

Age of diagnosis	Commonly diagnosed in young adults, people in their 20s, 30s and 40s although it can develop at any age.	Most often found in women under 40 and men over 60
Population	More common in women than men. Ratio 3:1	Men are more often affected after age 50; this incidence appears to be rising. Women are more often affected at a younger age. The highest incidence for women is in the 20s and 30s.
Mortality	Rarely fatal, but complications may arise from severe MS, such as chest or bladder infections, or swallowing difficulties.	Although the mortality rate was previously high, resulting in the name myasthenia gravis, the current mortality rate in MG is reported as 0.06 to 0.89 deaths per million person years

Supplemental survey data on caregiver impact

In response to the EAG's critique of this part of our submission, the Company has initiated work to generate new direct evidence on caregiver burden in gMG. The Company has worked closely with Research Institute for Disabled Consumers Charity (RiDC) and MDUK to develop a survey to assess caregiver disutility.

The survey asks about different aspects of the deleterious impact on a carer's quality of life due to caring for someone with gMG. There are also questions on the severity of the disease experienced by the person with gMG, so there will be data that look at the burden related to

		severity. Neither the Company nor efgartigimod alfa will be mentioned during the recruitment for, or conduct of, the survey. The Company has engaged MDUK to support RiDC in the identification and recruitment of caregivers of people living with gMG, partly by using their extensive database and communication channels. RiDC will be responsible for performing the survey (approximately 20 caregivers) and will share the survey returns anonymously with the Company, which will then create a summary report for submission to NICE. We expect RiDC to share the anonymous survey responses with the Company by the end of June 2023.
Key Issue 5: Disutilities associated with corticosteroid use	No	The Company accepts the EAG's approach of not including disutilities associated with corticosteroid use.
Key Issue 6: Costs of complications associated with corticosteroid use	No	The EAG argues that in the base case cost-effectiveness analysis, the source of costs associated with complications from the chronic use of corticosteroids should be Voorham *et al.* (2019),[20] as this is based on a UK population, rather than Bexelius *et al.* (2013)[21] which reports data from a Swedish population and was used for the base case analysis of the model submitted by the Company. However, Voorham *et al.* undertook their study in patients with asthma, whereas Bexelius *et al.* included patients with systemic lupus erythematosus (SLE). SLE and gMG are both autoimmune disorders, making SLE a better comparator with gMG than asthma. Additionally, the socioeconomic status of the UK and Sweden are not significantly different, and therefore

		healthcare costs can be reasonably assumed to be comparable between the countries. Therefore, the Company's observation is that the estimate of costs in Bexelius *et al.* provides a better proxy for the costs associated with the chronic use of corticosteroids in gMG patients. If the Committee disagrees with the Company that gMG is more similar to SLE than asthma, the Company would suggest taking the average of the costs from both Voorham *et al.* and Bexelius *et al.*, as this would mean the costs of the management of complications of corticosteroid use are based on not only one but two proxy diseases.

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: Price for the efgartigimod subcutaneous formulation	Not applicable	Yes	Given the likely availability of the subcutaneous formulation within the timeframe for the efgartigimod NICE appraisal, the Company would like to provide an update on the proposed price and its impact on the efgartigimod ICER. The price for the SC formulation aligns with the overall treatment cost for the IV formulation. Consequently, the ICER for SC efgartigimod is lower than that of the IV formulation due to the more convenient administration route. However, the cost of treatment will remain aligned across the two formulations. The list price of the SC formulation is £15,307.47. The results of the ICER with the SC formulation are reported as a scenario analysis further down.

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)
Key Issue 1: Exclusion of maintenance intravenous immunoglobulin (IVIg)	Based on UK clinician feedback, it was assumed that 100% of patients with MG-ADL ≥ 10, 50% of patients with MG-ADL 8-9 and 12.5% of patients with MG-ADL 5-7 are treated with maintenance IVIg.	Based on EAMS/EAMS+ data from England, which showed that overall [redacted]% of patients were treated with regular or intermittent IVIg, it was assumed that 100% of patients with MG-ADL ≥ 10 and [redacted]% of patients with MG-ADL 8-9 are treated with maintenance IVIg. The percentage of [redacted]% was calculated using the baseline distribution of the patients over the health states so that the overall baseline population in the model reflects the proportion of EAMS/EAMS+ patients in England that are treated with maintenance IVIg [redacted]	£11,911 (-£16,791)

Key Issue 2: Extrapolation of time on treatment (ToT) curve	Kaplan-Meier data from ADAPT and ADAPT+ were used directly for as long as available, after which the time on treatment was extrapolated using the exponential curve	The Company accepts the EAG's standpoint to use the extrapolated exponential curve from the start of the model	£47,996 (+£19,294)
Key Issue 3: Permanent treatment discontinuation transition probabilities	In the Company submission, it was stated that the assumption was that all patients discontinuing treatment with efgartigimod gradually return to the initial baseline health state distribution. However, the transition probabilities for this return to baseline were underestimated, resulting in patients in the efgartigimod arm having less severe disease, on average, than those in the ECM arm, even after all patients have discontinued efgartigimod.	The Company accepts that the method used to calculate the transition probabilities after permanent treatment discontinuation in the Company submission is inappropriate and therefore accepts the methodology adopted by the EAG. This methodology required the assumption of a specific proportion of patients to remain in the MG-ADL <5 health state, which the EAG conservatively assumed to be 1%. Based on a *post hoc* analysis of data from ADAPT and ADAPT+, there appears to be residual benefit from treatment with efgartigimod for a significant proportion of discontinued patients. Therefore the revised Company base case assumes that 15% of these patients remain in the MG-ADL <5 health state.	£73,466 (+£44,764)

Key Issue 4: Caregiver disutilities	In the Company submission, it is assumed that a caregiver disutility is applied to patients with gMG.	The Company believes that caregivers' quality of life is significantly impacted and therefore has not changed its base case following this issue raised by the EAG.	N/A
Key Issue 5: Disutilities associated with corticosteroid use	The Company submission assumed a utility decrement for patients treated with corticosteroids.	The Company acknowledges the EAG's view that the utilities from the ADAPT trial already captured the effect of corticosteroid use, and therefore the revised Company base case does not consider the utility decrement for patients treated with corticosteroids	£36,302 (+£7,600)
Key Issue 6: Costs of complications associated with corticosteroid use	Based on a systematic literature review, the costs of complications associated with corticosteroid use were based on a publication from Bexelius *et al.*, which used data from patients with SLE.	The Company believes SLE is a better proxy disease for gMG than asthma, which is the disease of patients in the publication considered by the EAG (Voorham *et al.*). It has not updated its base case following this issue raised by the EAG.	N/A
Update of PAS discount	The Company submission considered a simple PAS discount of [redacted]	The PAS discount has been updated to [redacted]	Dominant
Company's base case following technical engagement (or revised base case), with updated PAS discount	Incremental costs: [redacted] Incremental QALYs: [redacted]	Incremental costs: [redacted] Incremental QALYs: [redacted]	£29,976 (+£1,274)

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to assess the robustness of the model to parameter uncertainty. In the PSA, 1,000 simulations were performed in which model parameters were varied simultaneously by sampling at random from hypothetical distributions. The distributions used for each variable in the PSA are reported in the model.

In the PSA, the iterations are spread amongst the North-East and South-East quadrants of the cost-effectiveness plane (i.e., positive incremental benefit and positive or negative incremental cost) (Figure 1). The base case ICER and the PSA mean ICER were similar, confirming the overall robustness of the model results (Table 2).

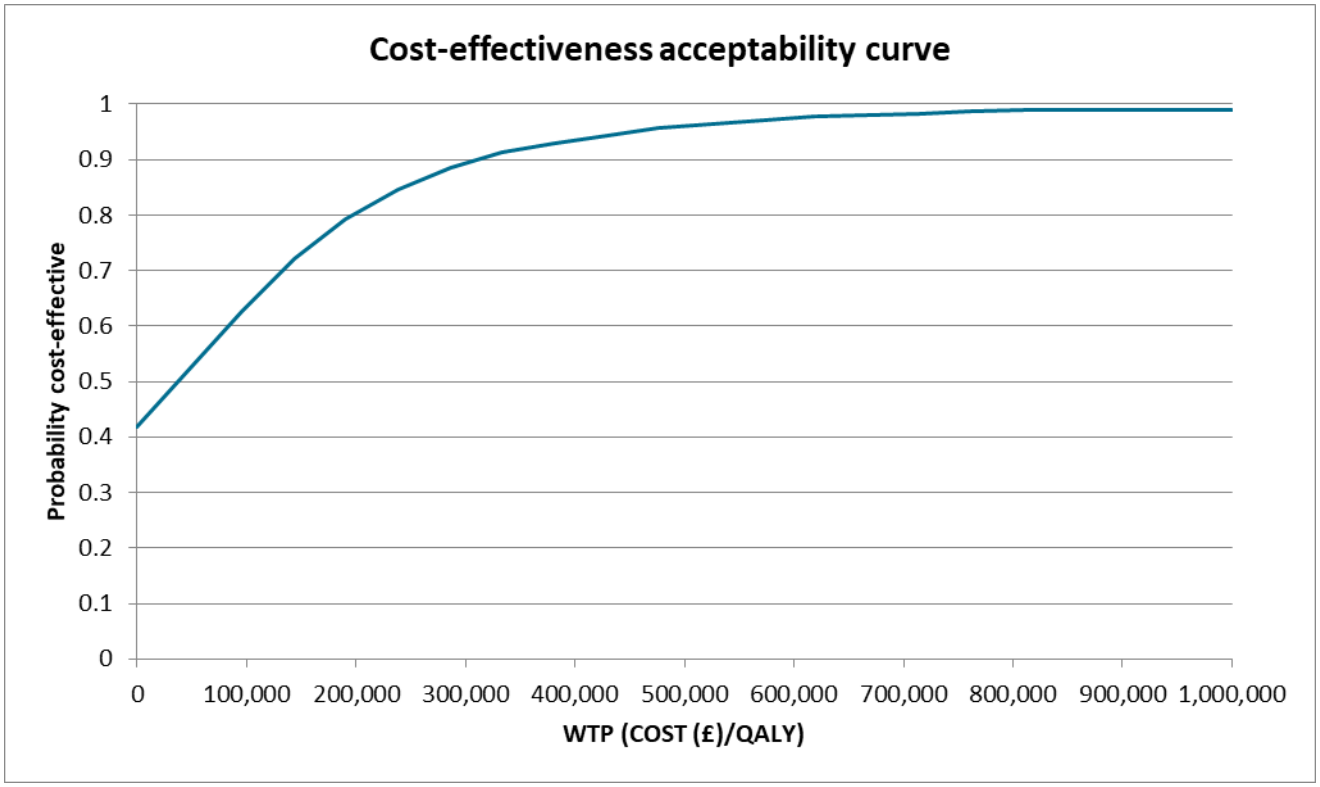
Figure 1: Incremental cost and QALY cloud in the cost-effectiveness plane (with updated PAS)

Table 2: Comparison of the deterministic and probabilistic base case results (with updated PAS)

	Cost, £			QALYs			ICER (£/QALY)
	Efgartigimod	ECM	Incremental	Efgartigimod	ECM	Incremental	
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,976
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,989
PSA 95% CI lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-163,013
PSA 95% CI upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	589,548

ICER, incremental cost-effectiveness ratio; ECM: established clinical management; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year

Figure 2: Cost-effectiveness acceptability curve (with updated PAS)



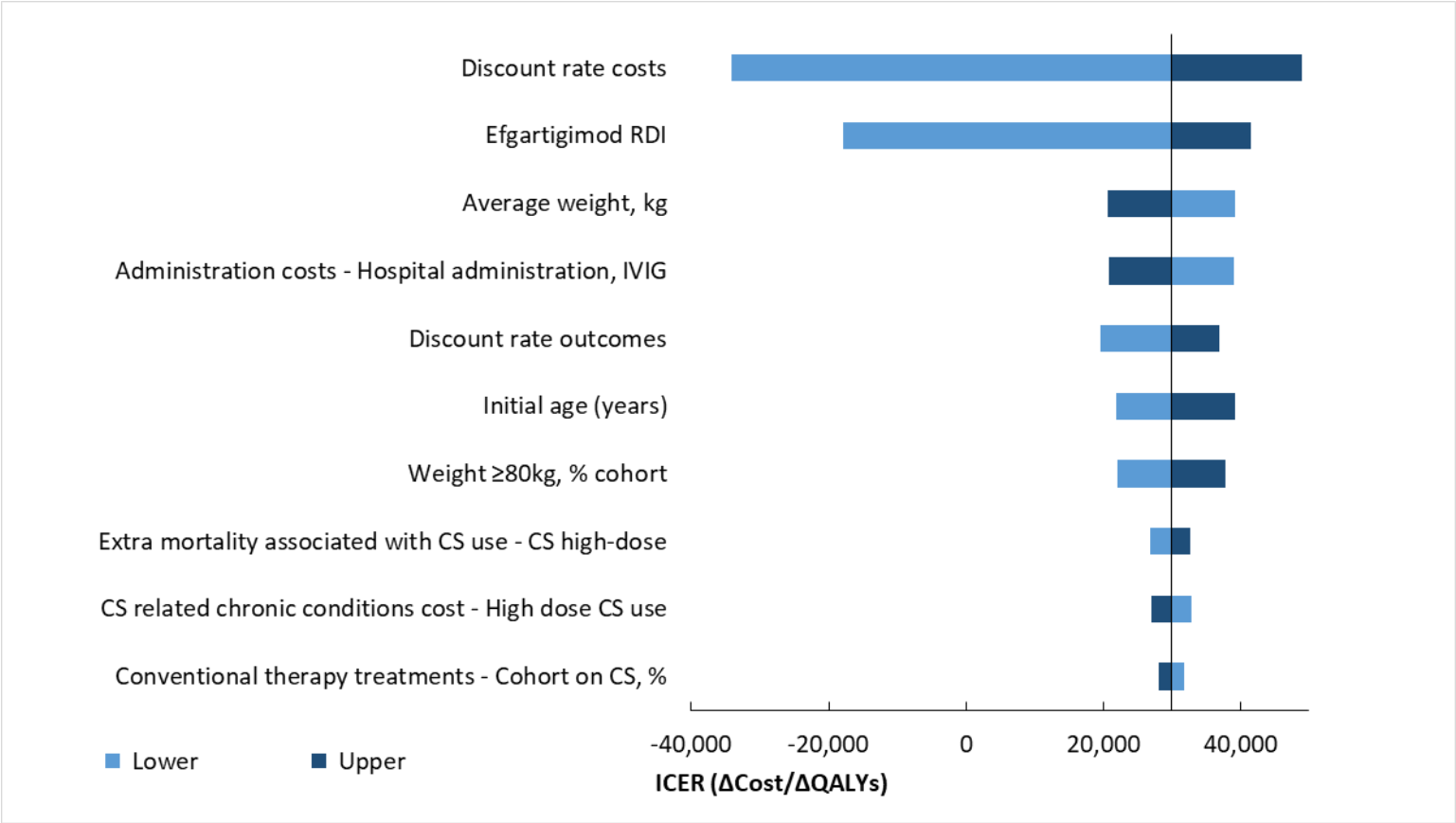
QALY, quality-adjusted life-year; WTP, willingness to pay

Deterministic sensitivity analysis

A series of one-way sensitivity analyses were performed to evaluate the sensitivity of model results to variations in input parameters. Key model parameters were varied one at a time around their base case values. When the SE was not reported, 10% of the base case value was used as a proxy for SE. Each parameter was varied to assess the impact on incremental LYs, QALYs, and costs.

In the one-way sensitivity analysis, the two main variables with the greatest influence on the ICER were the discount rate for costs and the efgartigimod RDI (Figure 3). Other influential variables were the average weight (kg), the hospital administration costs of IVIg, the discount rate for outcomes and the initial age (years). The remaining variables have percentage variations below 30% compared with the base case ICER.

Figure 3: Results of the one-way sensitivity analysis (with updated PAS)



ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QALY, quality-adjusted life-year; SoC, standard-of-care therapy

Table 3: Detailed results of the one-way sensitivity analysis (with updated PAS)

Parameter	ICER (£/QALY)	
	Lower	Upper
Discount rate costs	-34,165	49,021
Efgartigimod RDI	-17,955	41,499
Average weight, kg	39,271	20,639
Administration costs - Hospital administration, IVIg	39,051	20,901
Discount rate outcomes	19,577	36,999
Initial age (years)	21,842	39,238
Weight ≥80kg, % cohort	22,086	37,866
Extra mortality associated with CS use - CS high-dose	26,820	32,786
CS related chronic conditions cost - High-dose CS use	32,946	27,006
Conventional therapy treatments - Cohort on CS, %	31,908	28,049

ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; RDI, relative dose intensity; CS, corticosteroid; QALY, quality-adjusted life-year; ECM, established clinical management.

Scenario analyses

Table 4 provides the results of scenario analyses around the revised base case presented above. The numbers in the first column refer to the issue number in the EAG report, with multiple scenarios presented for each issue, except for Issue 5 (disutilities associated with corticosteroid use), for which no scenario analyses are presented.

One additional scenario (Scenario 7) has been presented, where it was assumed that all patients in the model are treated with the subcutaneous (SC) formulation of efgartigimod. This formulation will be available at a list price of £15,307.47, and the same PAS applies here as to the IV formulation. One vial per SC administration of efgartigimod is considered for all patients.

Table 4: Scenario analyses for efgartigimod vs Established Clinical Management with updated PAS

	Scenario description	Incr Costs, £	Incr QALYs	ICER (£/QALY)	ICER % change vs base case
1a	IVIg use based on EAMS data from England, assuming same percentage of patients using IVIg in MG-ADL 5-7, 8-9 and ≥10	[redacted]	[redacted]	56,679	89%
2a	ToT KM data for 33 months, followed by exponential extrapolation (Original Company approach)	[redacted]	[redacted]	11,742	-61%
2b	ToT KM data for 24 months, followed by exponential extrapolation	[redacted]	[redacted]	28,325	-6%
3a	Proportion of patients remaining in MG-ADL <5 after permanent discontinuation from efgartigimod is 1%	[redacted]	[redacted]	154,062	414%
3b	Proportion of patients remaining in MG-ADL <5 after permanent discontinuation from efgartigimod is 5%	[redacted]	[redacted]	99,435	232%
3c	Proportion of patients remaining in MG-ADL <5 after permanent discontinuation from efgartigimod is 10%	[redacted]	[redacted]	58,682	96%
4a	No caregiver disutilities	[redacted]	[redacted]	44,683	49%
4b	Caregiver disutilities considered only for the proportion of patients who needed help from a caregiver in MyRealWorldMG (Jacob et al.)	[redacted]	[redacted]	34,598	15%
6a	Costs of complications associated with chronic use of corticosteroids based on Voorham et al.	[redacted]	[redacted]	44,614	49%

6b	Costs of complications associated with chronic use of corticosteroids based on the average between Bexelius et al and Voorham et al.	[redacted]	[redacted]	37,295	24%
7	Subcutaneous administration of efgartigimod	[redacted]	[redacted]	28,016	-7%

References

1. Immunoglobulin Database. Annual Report 2021/22. January 2023. [Internet]. [cited 2023 Jun 13]. Available from: https://igd.mdsas.com/wp-content/uploads/Igd_DataReport_202122.pdf

2. Robins S. Plasma donation restarts in the UK for the first time in more than 20 years [Internet]. Medical Journalists' Association. 2021 [cited 2023 Jun 13]. Available from: https://mjauk.org/2021/06/16/plasma-donation-restarts-in-the-uk-for-the-first-time-in-more-than-20-years/

3. Ban lifted to allow UK blood plasma to be used for life-saving treatments [Internet]. GOV.UK. [cited 2023 Jun 13]. Available from: https://www.gov.uk/government/news/ban-lifted-to-allow-uk-blood-plasma-to-be-used-for-life-saving-treatments

4. argenx. Efgartigimod (ARGX-113-1705) Clinical Study Report (Interim Analysis 4): A Long-term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Study of ARGX 113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT+). 2022;1–165.

5. argenx. Data on file: ADAPT/ADAPT+ discontinuations supplemental analysis.

6. argenx. Data on file: US RWE supplemental discontinuations analysis.

7. Newland AC, Sánchez-González B, Rejtő L, Egyed M, Romanyuk N, Godar M, et al. Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia. Am J Hematol. 2020 Feb;95(2):178–87.

8. Maho-Vaillant M, Sips M, Golinski ML, Vidarsson G, Goebeler M, Stoevesandt J, et al. FcRn Antagonism Leads to a Decrease of Desmoglein-Specific B Cells: Secondary Analysis of a Phase 2 Study of Efgartigimod in Pemphigus Vulgaris and Pemphigus Foliaceus. Front Immunol. 2022 May 18;13:863095.

9. Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Myasthenia gravis - autoantibody characteristics and their implications for therapy. Nat Rev Neurol. 2016/04/23 ed. 2016 May;12(5):259–68.

10. Ward M, Goldman MD. Epidemiology and Pathophysiology of Multiple Sclerosis. Contin Minneap Minn. 2022 Aug 1;28(4):988–1005.

11. Pérez CA, Cuascut FX, Hutton GJ. Immunopathogenesis, Diagnosis, and Treatment of Multiple Sclerosis: A Clinical Update. Neurol Clin. 2023 Feb;41(1):87–106.

12. Hehir MK, Silvestri NJ. Generalized myasthenia gravis: classification, clinical presentation, natural history, and epidemiology. Neurol Clin. 2018/04/16 ed. 2018 May;36(2):253–60.

13. NHS. Myasthenia gravis [Internet]. nhs.uk. 2020 [cited 2023 Jun 1]. Available from: https://www.nhs.uk/conditions/myasthenia-gravis/

14. NHS. Multiple sclerosis [Internet]. nhs.uk. 2022 [cited 2023 Jun 1]. Available from: https://www.nhs.uk/conditions/multiple-sclerosis/

15. Dehbashi S, Hamouda D, Shanina E. Co-occurrence of multiple sclerosis and myasthenia gravis: A case report and review of immunological theories. Mult Scler Relat Disord. 2019 Sep;34:135–6.

16. Basiri K, Etemadifar M, Maghzi AH, Zarghami N. Frequency of myasthenia gravis in multiple sclerosis: Report of five cases from Isfahan, Iran. Neurol India. 2009;57(5):638–40.

17. Isbister CM, Mackenzie PJ, Anderson D, Wade NK, Oger J. Co-occurrence of multiple sclerosis and myasthenia gravis in British Columbia. Mult Scler Houndmills Basingstoke Engl. 2003 Dec;9(6):550–3.

18. Gharagozli K, Shojaei M, Harandi AA, Akbari N, Ilkhani M. Myasthenia Gravis Development and Crisis Subsequent to Multiple Sclerosis. Case Rep Med. 2011;2011:291731.

19. Barkhane Z, Elmadi J, Satish Kumar L, Sree Pugalenthi L, Ahmad M, Reddy S. Multiple Sclerosis and Autoimmunity: A Veiled Relationship. Cereus. 14(4):e24294.

20. Voorham J, Xu X, Price DB, Golam S, Davis J, Zhi Jie Ling J, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. Allergy. 2018/07/11 ed. 2019 Feb;74(2):273–83.

21. Bexelius C, Wachtmeister K, Skare P, Jönsson L, van Vollenhoven R. Drivers of cost and health-related quality of life in patients with systemic lupus erythematosus (SLE): a Swedish nationwide study based on patient reports. Lupus. 2013/06/14 ed. 2013 Jul;22(8):793–801.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Efgartigimod alfa (VYVGART™) for treating generalised myasthenia gravis [ID 4003]

New evidence submission

19 June 2023

File name	Version	Contains confidential information	Date
ID4003_Vyvgart-gMG_New evidence submission_v1.0_[redacted]	1.0	No	19 June 2023

Contents

List of Figures

List of Tables

Abbreviations

EAMS	Early Access to Medicines Scheme
gMG	Generalised myasthenia gravis
IgG	Immunoglobulin G
IVIg	Intravenous immunoglobulin
ITP	Immune Thrombocytopenic Purpura
MG-QoL	Myasthenia Quality of Life Scale
MHRA	Medicines and Healthcare Regulatory Agency
PIM	Promising Innovative Medicine
PV/PF	Pemphigus Vulgaris/ Pemphigus Foliaceus

Preliminary data from the efgartigimod Early Access to Medicines Scheme (EAMS) dataset

In the technical engagement report, Key Issue 1 relates to the EAG's recommendations that maintenance intravenous immunoglobulin (IVIg) use should be set to 0 in the economic model. The Company does not agree that this represents current clinical practice and presents data below on previous therapies for patients in England who have received efgartigimod.

In recognition of its promising efficacy and acceptable safety profile (observed from clinical trials and prior to marketing authorisation) for a population of patients with high unmet clinical need, efgartigimod was granted promising innovative medicine (PIM) status in November 2021 and received a positive scientific opinion from the Medicines and Healthcare Regulatory Agency (MHRA) under the EAMS in May 2022.[1,2]

Efgartigimod was available to patients in the UK through EAMS from May 2022 through to 14 March 2023, when MHRA marketing authorisation was granted. To facilitate ongoing efgartigimod access for existing and new patients up to the point of routine commissioning, an NHS England EAMS+ free-of-charge scheme was developed, approved and launched at the point of MHRA approval. One of the core aspirations of the EAMS and EAMS+ free-of-charge scheme, above and beyond providing access to patients with high unmet medical need, was to generate real-world clinical evidence to support Health Technology Assessment discussions and address residual uncertainty.

Encouragingly gMG specialist centre consultants have aligned on a common core data set to capture early efgartigimod real-world clinical experience. This is being collated on an intermittent basis [redacted] who currently has the largest cohort of efgartigimod-treated patients in the UK ([redacted] as of 1 June 2023).

These data, reflecting [redacted] efgartigimod-treated patients from [redacted] gMG specialist centres in England, demonstrate that [redacted] had received either prior regular or intermittent IVIg treatment, with only [redacted] receiving 1-off or unknown frequency prior IVIg, and [redacted] not having received any prior IVIg treatment.

We accept that these are unpublished data and are based on only a small number of patients. Nonetheless, they present an important window on actual UK practice when clinicians are able to access efgartigimod for clinically appropriate patients, and we believe therefore, that they ought to be taken into consideration. This is an area where data are otherwise hard to obtain.

Permanent treatment discontinuation transition probabilities

In the technical engagement report, Key Issue 3 relates to the EAG's preferred assumptions around post-discontinuation transition probabilities. The Company does not agree with the EAG's preferred assumption that just 1% of the patients who achieved MG-ADL <5 before discontinuation would remain in the same health state. While these data rely on small sample sizes, directionally they point towards a residual treatment effect for efgartigimod. Evidence from three sources relating to a residual treatment effect after treatment discontinuation are presented below.

A.1 ADAPT and ADAPT+[3]

When considering the ADAPT+ population, [redacted] patients received only one cycle of efgartigimod for the entire duration of the study (3 years), suggesting a long-lasting treatment effect after the first cycle of infusions.[4] Therefore, it seems plausible to consider that a similar proportion of long-responders would apply in the cohort of those who discontinue the treatment due to adverse events or intolerance. Based on this concept, the Company analysed the available MG-ADL data post-permanent discontinuation in ADAPT and ADAPT+.

In the ADAPT trial, of the [redacted] patients who permanently discontinued treatment with efgartigimod, [redacted] had an MG-ADL score <5 at the last exposure time point, and [redacted] remained at an MG-ADL score <5 after [redacted] days (Figure 1).

Figure 1: MG-ADL trajectories following permanent discontinuation for patients discontinuing efgartigimod treatment in ADAPT

Abbreviation: MG-ADL, Myasthenia Gravis Activities of Daily Living Scale

In the ADAPT+ trial, of the [redacted] patients who permanently discontinued treatment with efgartigimod; [redacted] had an MG-ADL score <5 at the last exposure time point, and [redacted] remained at an MG-ADL score <5, with the last MG-ADL measurement recorded between [redacted] days after the last efgartigimod exposure (mean: [redacted] days) (Figure 2).

Figure 2: MG-ADL trajectories following permanent discontinuation for patients discontinuing efgartigimod treatment in ADAPT+

Abbreviation; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale

Table 1 summarises the number of patients who maintained an MG-ADL score <5 after permanent efgartigimod discontinuation based on ADAPT and ADAPT+ trials and the respective mean and range of follow-up.

Table 1: Number of patients maintaining an MG-ADL score below 5 after permanent efgartigimod discontinuation based on ADAPT and ADAPT+ trials

Clinical trial	Number of patients with MG-ADL < 5 after the last infusion	Number of patients with MG-ADL <5 in the last measurement who had MG-ADL <5 after the last infusion	Follow-up (days) mean (range)
ADAPT	[redacted]	[redacted]	[redacted]
ADAPT+	[redacted]	[redacted]	[redacted]

Abbreviation; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale

Overall, [redacted] of patients who had MG-ADL scores <5 at the time of permanent treatment discontinuation maintained the residual efgartigimod effect for [redacted] after the last treatment exposure.

A.2 Real-world evidence from US patients who received efgartigimod

In addition to the data from ADAPT and ADAPT+, an additional analysis has been performed, using data from real-world evidence (RWE) from the US, which confirmed the findings from ADAPT and ADAPT+.[5] In this analysis, [redacted]% of patients who had an MG-ADL score <5 at time of permanent treatment discontinuation, still had MG-ADL<5 at the time of their latest MG-ADL measure, which was on average [redacted] after their last infusion.[5]

A.3 Evidence from efgartigimod in other indications

To further supplement the data in gMG from ADAPT/ADAPT+, signals of ongoing efgartigimod treatment effect following permanent discontinuation have also been observed in both our Immune Thrombocytopenic Purpura (ITP) & Pemphigus Vulgaris/ Pemphigus Foliaceus (PV/PF) efgartigimod clinical development programmes.[6,7]

A.3.1 Immune Thrombocytopenic Purpura[6]

In the Phase II study of efgartigimod in adult patients with primary immune thrombocytopenia (ITP), patients were randomly assigned in a 1:1:1 ratio to receive four weekly doses of either placebo, efgartigimod at a dose of 5 mg/kg body weight, or efgartigimod at a dose of 10 mg/kg body weight, administered as an intravenous infusion. The patients were then followed for up to 21 weeks.

Whilst most patients who responded to efgartigimod had a transient increase in platelet counts, with counts returning to baseline levels in the treatment-free follow-up period, at least 3 of 26 (11.5%) efgartigimod-treated patients (two newly diagnosed; one chronic) with ITP remained in remission throughout the follow-up period.

A.3.2 Pemphigus Vulgaris/ Pemphigus Foliaceus[7]

In the Phase II study of efgartigimod in PV/PF, an open-label, multicenter study aimed to determine the optimal dose and posology, efgartigimod as hypothesized, demonstrated a reduction in total IgG levels. However, unlike total IgG, which returned to baseline levels after discontinuation of efgartigimod treatment (with a 10-week treatment-free follow-up), autoreactive antibody levels remained low in several study participants. This suggests a sustained reduction in autoantibody levels during efgartigimod treatment and indicates potential disease modification in peripheral lymphocytes in some patients even after treatment cessation.

[redacted]

argenx plans to explore this further in Phase III trials, to in part, help us understand if efgartigimod has the potential to modify disease course in certain patients.

References

1. Early access to medicines scheme (EAMS): scientific opinions. GOV.UK. Published May 27, 2022. Accessed January 26, 2023. https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions

2. argenx Announces the UK MHRA has Granted Early Access to Efgartigimod for Generalized Myasthenia Gravis. Argenx. Accessed January 26, 2023. https://www.argenx.com/news/argenx-announces-uk-mhra-has-granted-early-access-efgartigimod-generalized-myasthenia-gravis

3. argenx. *Data on File: ADAPT/ADAPT+ Discontinuations Supplemental Analysis.*

4. argenx. Efgartigimod (ARGX-113-1705) Clinical Study Report (Interim Analysis 4): A Long-term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Study of ARGX 113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT+). Published online 2022:1-165.

5. argenx. *Data on File: US RWE Supplemental Discontinuations Analysis.*

6. Newland AC, Sánchez-González B, Rejtő L, et al. Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia. *Am J Hematol*. 2020;95(2):178-187. doi:10.1002/ajh.25680

7. Maho-Vaillant M, Sips M, Golinski ML, et al. FcRn Antagonism Leads to a Decrease of Desmoglein-Specific B Cells: Secondary Analysis of a Phase 2 Study of Efgartigimod in Pemphigus Vulgaris and Pemphigus Foliaceus. *Front Immunol*. 2022;13:863095. doi:10.3389/fimmu.2022.863095

STUDY REPORT

Title:	Burden of informal caregivers for patients with generalised myasthenia gravis (gMG)
Sponsor	argenx
Geographic scope	United Kingdom
Version	V1.0, 28/06/2023

Table of Contents

List of Tables:

List of Figures:

Abbreviations

gMG	Generalised myasthenia gravis
HRQoL	Health-related quality of life
IQR	Interquartile range
MDUK	Muscular Dystrophy UK
RiDC	Research Institute for Disabled Consumers Charity
SD	Standard deviation

1. INTRODUCTION

Generalised myasthenia gravis (gMG) is a rare neuromuscular autoimmune disease-causing debilitating muscle weakness, disrupting the ability to perform normal daily activities and profoundly impairing HRQoL[1–3]. The muscle weakness experienced by gMG patients severely impacts their day-to-day functioning including work and lifestyle planning limitations, productivity losses, and the need for caregivers[4].

The substantial caregiver impact of gMG arises from the physically and mentally disabling symptoms of the disease. For example, muscle weakness experienced by gMG patients severely impacts their day-to-day functioning, which can lead to difficulties with swallowing, vision, speech, breathing, mobility and extreme fatigue.[4]

Consequently, patients may require help with personal care, eating or mobility, all of which a regular caregiver would be required to support.

1.1. Rationale

NICE methodology permits the inclusion of health-related quality of life (HRQoL) burden on relevant caregivers to assess the cost-effectiveness of technologies[5]. The impact of the disease on patients with gMG has been demonstrated. However, no studies have directly assessed the caregiver burden for people with gMG. There is a need for disease-specific data demonstrating this burden on informal caregivers for gMG patients to support NICE in assessing efgartigimod.

2. OBJECTIVES

2.1. Primary objective

The primary objective of this study is as follows:

- To understand the impact of gMG and its treatment on informal caregivers for patients with gMG

2.2. Secondary objective

No secondary objectives are included.

3. RESEARCH METHODS

3.1. Study Design

This study is a cross-sectional observational study of informal caregivers for patients with a confirmed diagnosis of gMG. The study variables were designed to address the study's primary objective which was to understand the impact of gMG and its treatment on informal caregivers of gMG patients. Specifically, the study aimed to understand the impact of caregiving on caregiver employment, daily living and quality of life.

A cross-sectional survey was the most appropriate study design as this study required data collection to be completed within a defined timeframe. Caregivers were included in the study and data collection was completed between 13th June and 21st June 2023. The overall study duration was between April-June 2023.

3.2. Study setting and study population

This study is a cross-sectional survey completed by informal caregivers of gMG patients in the United Kingdom. Given the timeframe, the study aimed to be inclusive and to recruit as many caregivers as possible. Convenience sampling from the target population (i.e., informal caregivers in the UK) was employed to reach the target population of ~20 caregivers. No other sampling methods were used.

3.2.1. Caregiver eligibility criteria

The following inclusion criteria were included for this study:

- Informal caregivers for patients with a confirmed diagnosis of gMG (myasthenia gravis affecting different muscles around the body and not just the eyes)

No exclusion criteria were included in this study.

3.3. Data Source/Data Collection

Data were collected using a cross-sectional survey. The study was run in collaboration with Muscular Dystrophy UK (MDUK) and the Research Institute for Disabled Consumers Charity (RiDC). A propriety web-based survey was developed and hosted by RiDC.

MDUK was responsible for recruiting caregivers using their membership network, who were invited to enrol on the study by RiDC, via telephone. If the caregiver agreed to enrol in the study and provided consent (see Section 3.4), RiDC conducted a telephone interview to extract the relevant variables and inputted the caregiver answers into the web-based survey.

3.4. Ethical Considerations

Eligible caregivers were requested to provide consent before enrolling in the study. Each caregiver was provided with information on the study's objectives and the intended use and dissemination of their data. Each caregiver was required to consent to the terms of the study before any data provided.

3.5. Variables

Variables were collected from all caregivers at the point of data collection. All variables were extracted to address the primary objective of the study. Variables were extracted about the caregiver demographics and impact of caregiving on employment, activities of daily living

and quality of life (Table 1) as well as the person they care for (patient) demographics and clinical characteristics (

Table ***2***).

For questions on usual activities, pain and discomfort, anxiety, and depression, where the caregiver indicated problems, additional open-ended questions were included to add qualitative insight to these variables.

Table 1: Variables extracted regarding the caregiver population

Variable Name	Description	Variable Type	Variable Definition
Caregiver age	Caregiver age (years)	Categorical	• 18-25 • 26-35 • 46-55 • 56-65 • ≥66 • Prefer not to say
Caregiver sex	Caregiver sex	Categorical	• Female • Male • Non-binary/third gender • Transgender • Intersex • Prefer not to say • Other (please specify)
Caregiver employment	Caregiver employment status	Categorical	• Full time employed • Part time employed • Self employed • Retired • Not employed • Prefer not to say • Other (please specify)
Caregiver impact on hours worked	Hours worked less due to caregiving responsibilities	Categorical	• Yes • No
Caregiver impact on retirement	Retire early due to caregiving responsibilities	Categorical	• Yes • No
Carer impact on daily activities	Impact of caregiving on daily activities	Categorical	• Mobility/ moving around • Personal care (E.g: washing/ dressing) • Ability to undertake your usual activities such as personal shopping/ hobbies • Pain/Discomfort • Anxiety/ depression • Other (Please specify)
Carer impact on usual activities	Impact on caregiving on usual activities	Categorical	• No problems doing usual activities • Some problems doing usual activities • Unable to do usual activities
Carer impact on pain/discomfort	Impact of caregiving on pain/discomfort	Categorical	• Mild • Moderate • Severe
Carer impact on anxiety/depression	Impact of caregiving on anxiety/depression	Categorical	• Mild • Moderate • Severe
Carer impact on essential activities	Impact of caregiving on essential activities	Categorical	• Sleeping • Eating • Working/studying • Social life • Other (Please specify)

Carer impact on overall effect on quality of life	Impact of caregiving on overall quality of life	Continuous	-
Carer impact on overall effect on quality of life	Impact of caregiving on overall quality of life	Categorical (Likert scale 1-5)	• 1 (not at all effected) • 2 • 3 • 4 • 5 (significantly effected)

Table 2: Variables extracted regarding the patient

Variable Name	Description	Variable Type	Variable Definition
Patient age	Patient age (years)	Categorical	• 18-25 • 26-35 • 46-55 • 56-65 • ≥66 • Prefer not to say
Patient sex	Patient sex	Categorical	• Female • Male • Non-binary/third gender • Transgender • Intersex • Prefer not to say • Other (please specify)
Patient time since diagnoses	Time since diagnoses calculated by June-2023-month/year diagnoses (years)	Categorical	• 0-5 • 5-10 • 10+
Patient myasthenic crisis[a]	If the patient has experienced a myasthenic crisis within the last 12 months	Categorical	• Yes • No • I don't know
Patient exacerbation[b]	If the patient has experienced an exacerbation within the last 12 months	Categorical	• Yes • No • I don't know
Patient MG-ADL score	Patient MG-ADL score (1-24)	Continuous	-
Patient treatment satisfaction	How satisfied the patient is with their current treatment	Categorical	• The person with gMG you are caring for finds that their condition is well controlled with their current treatment and that side effects (if any) are manageable • The person with gMG you are caring for has had to try several different types of treatment, but at the moment, their disease is under control, and any side-effects are manageable • The person with gMG you are caring for is still experiencing considerable difficulties in finding a treatment or treatments that works for them

a) an incident during which their breathing becomes impaired often leading to hospitalisation and sometimes the need for ventilation
b) a sudden worsening of symptoms

3.6. Data Analyses

This study was descriptive and no formal were hypotheses tested. All quantitative variables (as described in Table 1 and

Table ***2***) were summarised using descriptive statistics. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as mean, median, standard deviation (SD) and interquartile range (IQR).

Qualitative insights from open-ended questions were analysed using thematic analyses. All responses were reviewed to identify any themes repeated in the data.

4. RESULTS

The final sample that completed the survey was 21 caregivers.

4.1. Caregiver characteristics

4.1.1. Caregiver demographics

Caregiver age and sex are presented in Table 3. Out of the total sample of 21 caregivers, 12 (57.0%) were men and 7 (33.3%) were female. The largest group was young and middle-aged caregivers, with individuals aged 18-25 and 26-35 accounting for 9 (42.9%) and 11 (52.4%) participants, respectively (Table 3).

Table 3: Caregiver demographics

	Demographics, n (%)
Caregiver sex	
Male	12 (57.0)
Female	7 (33.3)
Non-binary / third	2 (9.5%)
Caregiver age (years)	
26-35	11 (52.4%)
18-25	9 (42.9%)
46-55	1 (4.8%)

4.1.2. Caregiver employment

The employment status of caregivers in the study was reported, with 7 (33.3%) participants identifying as being employed on a full-time basis, while 8 (38.1%) were engaged in part-time employment (Table 4). Out of the 21 participants, 3 (14.3%) caregivers reported being self-employed, 2 (9.5%) caregivers reported being unemployed and 1 (4.8%) caregiver was employed but on long-term medical leave. The impact of caregiving responsibilities on employment is also shown in Table 4. Among the 11 participants for whom this information was available (those who were part time or self-employed), 9 (81.8%) indicated that their caregiving responsibilities reduced their working hours. No patients reported that they retired early due to their caregiving responsibilities.

Table 4: Caregiver employment

	Employment, n (%)
Caregiver employment status (n=21)	
Part time employed	8 (38.1%)
Full time employed	7 (33.3%)
Self-employed	3 (14.3%)
Not employed	2 (9.5%)
Other: Long term medical leave	1 (4.8%)
Fewer hours worked due to caregiver responsibilities (n=11)	
Yes	9 (81.8%)
No	2 (18.2%)

4.2. Patient demographics and clinical characteristics

Table 5 presents the age, sex, and clinical characteristics of gMG patients cared for by the caregivers enrolled in this study. Among the 21 patients, the largest age group was 36-45, comprising 9 (42.9%). Patients aged 46-55 and 56-65 accounted for 5 (23.8%) and 4 (19.0%), respectively. More female patients (57.1%) than males (42.9%) were included in the study.

Patient clinical characteristics were reported as patients experiencing a myasthenic crisis and exacerbation within the last year and their MG-ADL scores (Table 5). Within the last year, 18 (85.7%) gMG patients experienced a myasthenic crisis and 13 (61.9%) gMG patients experienced an exacerbation. The MG-ADL scores of gMG patients were also reported. However, 13 (61.9%) caregivers reported an unknown for this score. For the non-missing sample, the mean score was 10.0 (2.5) (Med: 9.5, IQR: 8.75;10.5, Min:Max: 7:15).

Table 5: Patient demographics and clinical characteristics

	Characteristics, n (%)
Patient age (years)	
36-45	9 (42.9)
46-55	5 (23.8)
56-65	4 (19.0)
66+	3 (14.3)
Patient sex	
Female	12 (57.1)
Male	9 (42.9)
Time since diagnoses	
0-5	15 (71.4%)
6-10	3 (14.3%)
10+	1 (4.8%)
Unknown	2 (9.5%)
Myasthenia crisis in the last 12 months	
Yes	18 (85.7%)
No	3 (14.3%)
Exacerbation in the last 12 months	
Yes	13 (61.9%)
No	8 (38.1%)

4.3. Patient treatment satisfaction

Table 6 shows the level of gMG patient treatment satisfaction. Among the 21 gMG patients, 11 (52.4%) caregivers reported that several treatments had been tried, but the disease was under control and side effects were manageable for gMG patients that they are caring for. Additionally, 8 (38.1%) caregivers reported that their gMG patient finds their disease well-controlled with manageable side effects under their current treatment. 2 (9.5%) caregivers expressed treatment dissatisfaction as the person with gMG being cared for is still experiencing difficulty finding an effective treatment.

Table 6: gMG patient satisfaction with current treatments

Patient treatment satisfaction	**n (%)**
The person with gMG you are caring for has had to try several different types of treatment, but at the moment, their disease is under control, and any side-effects are manageable	11 (52.4%)

The person with gMG you are caring for finds that their condition is well controlled with their current treatment and that side effects (if any) are manageable	8 (38.1%)
The person with gMG you are caring for is still experiencing considerable difficulties in finding a treatment or treatments that works for them	2 (9.5%)

4.4. Impact of caregiving

Table 7 presents the impact faced by caregivers on daily living. Daily activities of caregivers were impacted by their caregiving role, with 90.5% reporting an impact on their usual activities, 76.2% reporting an impact on their mobility and 52.4% reporting an impact on their personal care activities.

Usual activities, pain/discomfort and anxiety and depression were further quantified. For usual activities, 13 (61.9%) reported some problems, 5 (23.8%) reported they were unable and 3 (14.3%) reported no problems. Of the 21 caregivers, 5 (23.8%) reported pain/discomfort being impacted by caregiving duties, of which 60.0% and 40.0% experienced moderate and mild pain/discomfort, respectively. Caregiving duties impacted anxiety and depression for 14 (66.7%) respondents, classified as mild (57.1%), moderate (28.6%) and severe (14.3%).

Regarding essential activities, 21 (100.0%) stated that their social life was impacted, 19 (90.5%) that work or studying was affected, 18 (85.7%) reported an impact of caregiving on sleeping and 8 (38.1%) stated an impact on eating.

Table 7: Impact on caregiving daily living

	Daily living activity, n (%)
Daily activities (n=21)	
Usual activities (e.g., personal shopping/hobbies)	19 (90.5%)
Mobility/moving around	16 (76.2%)
Anxiety/Depression	14 (66.7%)
Personal care (e.g., washing/dressing)	11 (52.4%)
Pain/Discomfort	5 (23.8%)
Usual activities (n=21)	
Some problems completing usual activities	13 (61.9%)
Unable to complete usual activities	5 (23.8%)
No problems completing usual activities	3 (14.3%)
Pain/discomfort (n=5)	
Mild	2 (40.0%)
Moderate	3 (60.0%)
Severe	0 (0.0%)
Anxiety/depression (n=14)	
Mild	8 (57.1%)
Moderate	4 (28.6%)
Severe	2 (14.3%)
Essential activities (n=21)	
Social life	21 (100.0%)
Working/Studying	19 (90.5%)
Sleeping	18 (85.7%)
Eating	8 (38.1%)

4.5. Additional qualitative insights

Caregivers reported additional qualitative insights on previous responses to impact on usual activities, pain, discomfort, anxiety and depression. The majority of caregivers (19, 90.5%) reported an impact on their usual activities. In addition, 17 (81.0%) provided further insight into their quantitative response to usual activities.

Caregivers reported that their caregiving responsibilities impacts “most” of their daily activities as they must plan their life around the person they care for. Many caregivers reported a lack of free time and felt they needed to be constantly available. One caregiver commented that they are unpaid and cannot afford professional help therefore had to provide personally provide full-time support. The commitment to their caregiving responsibilities impacted their daily routine as well as that of their families:

“I always have to be around”

“I am always self-conscious that something might go wrong if I am not around”

“I find it harder to take my personal routine in the house because I have to take care of her, take her to the hospital and keep her company”

“I don't get time to spend with my children… It has affected my family life with my children and partner”

Many caregivers also reported on the impact their caregiving responsibilities had on their social life from doing sport, hobbies to spending time with friends:

“I love sport, but I have to limit the time I spend outside as the person I am caring for may need me at any time”

“My hobby was too time consuming, so I am unable to continue doing what I like, I have had to stop”

Caregivers also provided qualitative insight into their quantitative responses on pain/discomfort and anxiety/depression (Table 7). 13 caregivers (61.9%) reported additional insights into their anxiety and depression. Caregivers reported anxiety, insomnia and feeling “mentally disturbed”.

Many caregivers reported that their anxiety and depression were driven by feeling helpless to improve the situation of the person that they care for including worrying about their health and the difficulty of watching them suffer:

“Seeing someone at their worst and not being able to do anything about it”

“..I feel down because this is someone I love so much and having to watch her go through such problems can be disheartening..I wish I could prevent it”

“One of the greatest challenges when..going into a crisis is what can I do to help? You just hold his hand and you wait for the emergency services to arrive”

“I am always worried when my father is down, I just want him to be healthy and it makes me worried”

Many caregivers also reported that their anxiety and depression were driven by the detrimental impact on their own life, feeling like they were required to sacrifice a lot due to their caregiving responsibilities and difficulty taking care of themselves or other members of the family:

“Fell into depression…I feel that my life is wasting away and I think too much and it doesn't get better...I can't make him feel that he is making my life (be put on) pause”

"I see my friends doing a lot of things such as working or starting a family. It is really hard”

“Being a carer is difficult because sometimes we have no choice. You must make huge sacrifices you cannot achieve your dreams”

"Sometimes I feel I'm not doing well enough cos I can barely take care of myself, let alone of my younger sibling”

Fewer caregivers reported pain/discomfort but all 5 caregivers reported additional qualitative insight. Pain/discomfort was largely driven by stress and some caregivers reported additional physical challenges from their caregiving responsibilities such as helping to support, carry or lift the person they care for.

4.6. Impact of quality of life

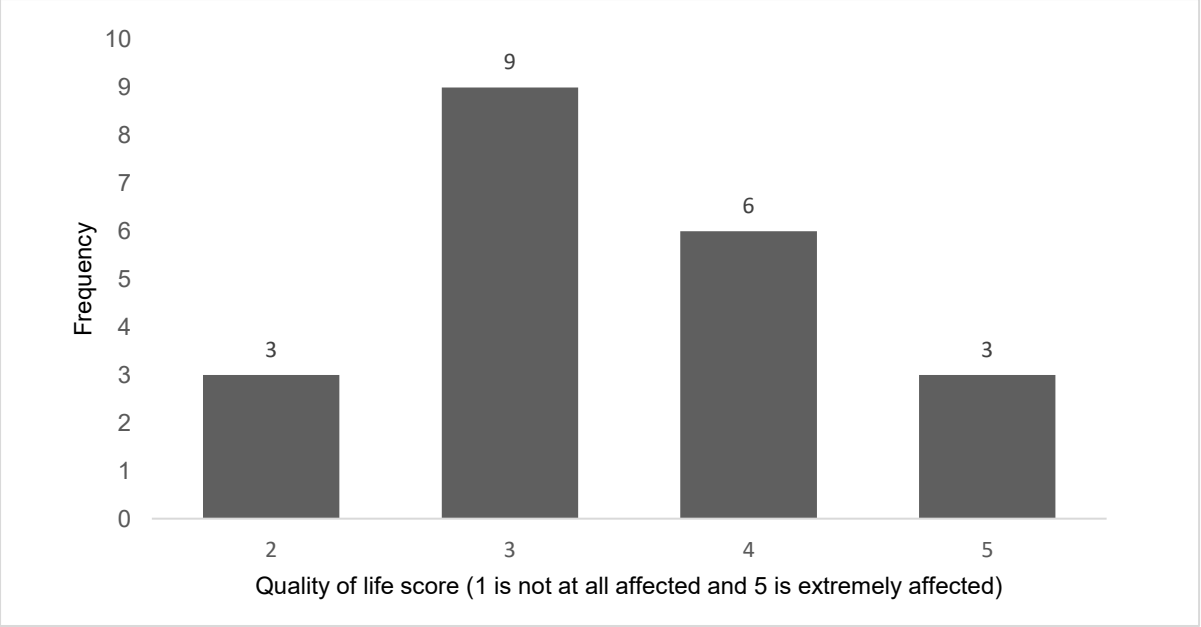
The overall effect on the caregivers' quality of life due to their responsibilities caring for someone with gMG was scored between 1 and 5, where 1 is not at all affected and 5 is extremely affected. Table 8 shows the respondents in the study had a mean quality of life impact score of 3.4 (0.9).

Table 8: Impact on overall quality of life (continuous)

	Mean (SD)	Median (IQR)	Min;Max
Overall quality of life	3.4 (0.9)	3 (3,4)	2;5

Figure 1 shows the quality-of-life score reported as a categorical variable. The majority of caregivers reported a score of 3 (9, 42.9%) or 4 (6, 28.6%). No caregivers reported a score of 1 indicating their caregiving responsibilities did not affect their quality of life. However, 3 caregivers (14.3%) reported a score of 5 indicating their quality of life was extremely affected.

Figure 1: Impact on overall quality of life (categorical)



5. DISCUSSION

To our knowledge, this is the first real-world data on the burden on informal caregivers for patients with gMG, the impact of gMG and its treatment. Given the timeframe for this study, the sample size collected was 21 caregivers. As such, results from this study should be considered descriptive and interpreted with caution.

Overall, the caregiver and patient demographics are in line with the current literature[6]. The patient demographics showed a larger proportion of females (57.1%) than males (42.9%) and the age distribution was in line with current literature. Of note, although most caregivers (90.5%) stated that the person they cared for was receiving treatment that controlled their disease, most patients had experienced either a myasthenia crisis (85.7%) or exacerbation (61.9%) in the last 12 months. This may reflect a disability paradox in this population and further research should be considered. However, when reviewing the burden of caregiving responsibility, the patient population is broadly in line with the general population regarding demographics and disease severity.

Caregiver demographics were reflective of the patient population. More males (57.0%) than females (33.3%) enrolled in the study which is expected as caregivers for gMG are commonly a spouse or partner. However, the caregiver population was generally younger than the patient population implying that the person cared for was a parent or other family member.

The burden of caregiving was evaluated through an impact on employment, daily living and quality of life. The majority of caregivers were employed in some capacity (85.7%) however, the majority of those (81.8%) reported working fewer hours because of their caregiving responsibilities. In addition, 19 (90.5%) reported that working or studying was affected by their caregiving responsibilities. No caregivers reported retiring early however, this likely reflects the age distribution enrolled in this study. Regarding daily living, caregivers reported the impact on their daily activities (mobility, personal care, usual activities, pain and discomfort, anxiety and depression) and essential activities (sleeping, eating, social life). Caregivers reported a high impact on all their daily activities driven by usual activities (90.5%), mobility (76.2%) and anxiety and depression (66.7%). They also reported a high impact on all essential activities.

Caregivers were asked to quantify their responses on usual activities, pain and discomfort, anxiety and depression. It was evident that caregiving responsibilities impact caregivers' ability to complete their usual activities. 18 (85.7%) caregivers reported some problems or inability to do their usual activities. This was supported by the qualitative insights where caregivers highlighted a lack of time to complete their routine and impact on their social activities. All 21 caregivers (100%) reported an impact on their social life caused by caregiving responsibilities.

It was also evident that anxiety and depression were high. 14 (66.7%) reported anxiety and depression which ranged from mild (57.1%), moderate (28.6%) to severe (14.3%). Anxiety and depression were driven by feelings of helplessness to help the person they care for and frustration at their perceived lack of opportunities due to their caregiving responsibilities.

Finally, caregivers reported the overall effect on quality of life due to carer responsibilities. The quality-of-life score was reported on a Likert scale of 1-5 with 1 being not at all affected and 5 being extremely affected. The mean score was 3.4 (0.9) reflecting a high impact on quality of life for caregivers of gMG patient and 3 caregivers (14.3%) reported the highest score of 5. Importantly, no caregivers reported a score of 1 demonstrating that all caregivers

considered their caregiving responsibilities to have an impact on their quality of life. However, this result should be interpreted cautiously as the 1-5 Likert scale is not validated, and the consistency of responses cannot be confirmed.

5.1. Limitations

There are limitations related to the study design. Cross-sectional studies are difficult to interpret as they do not estimate a cause-and-effect relationship. The survey format used to collect data also has limitations, as caregivers may be susceptible to recall bias. In addition, the sample size is small, and the results are not generalisable. However, given that the study objective was to provide disease-specific data from caregivers of gMG patients to demonstrate the presence of caregiver burden in this population, these limitations are not considered to have impacted addressing the objective of this study.

The survey was developed in collaboration with MDUK in order to provide information on caregiver burden including quality of life within the given time frame. The variables extracted were planned to mirror those collected in validated tools such as the EQ-5D (EuroQoL) which was not possible to administer in the given the time, resource and sample size for this study. However, the authors recognise that further research using validated tools is required.

6. CONCLUSION

Patients with gMG have debilitating muscle weakness and require caregivers for help with eating, mobility, and other activities of daily living. This study provides the first disease-specific data on the burden on informal caregivers for patients with gMG. This study demonstrates the burden of caregiving responsibilities (driven by impact on usual activities, anxiety, and depression) as well as reduced quality of life with caregivers scoring 3.4/5 for impact on their quality of life. Given the small sample size, it is difficult to state generalisability to a wider caregiver population. However, it is clear that caregiver responsibilities constitute a large burden for informal caregivers of patients with gMG.

7. REFERENCES

1. Berrih-Aknin S, Claeys KG, Law N, et al. Patient-reported impact of myasthenia gravis in the real world: protocol for a digital observational study (MyRealWorld MG). *BMJ Open*. 2021;11(7):e048198. doi:10.1136/bmjopen-2020-048198

2. Cortés-Vicente E, Álvarez-Velasco R, Segovia S, et al. Clinical and therapeutic features of myasthenia gravis in adults based on age at onset. *Neurology*. 2020;94(11):e1171-e1180. doi:10.1212/WNL.0000000000008903

3. De Meel RHP, Lipka AF, Van Zwet EW, Niks EH, Verschuuren JJGM. Prognostic factors for exacerbations and emergency treatments in myasthenia gravis. *Journal of Neuroimmunology*. 2015;282:123-125. doi:10.1016/j.jneuroim.2015.03.018

4. argenx. Efgartigimod (ARGX-113-1704) Clinical Study Report: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT). Published online 2020.

5. NICE. *NICE Health Technology Evaluations: The Manual*.; 2022. https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741

6. Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia Gravis: Epidemiology, Pathophysiology and Clinical Manifestations. *JCM*. 2021;10(11):2235. doi:10.3390/jcm10112235

16th June, 2023

For the attention of the NICE Technical Team

I understand that there is an open question regarding the practical utilisation and availability of maintenance IVIg therapy for patients with generalised myasthenia gravis (gMG) in England. I and other experts also recognise that this issue has a high level of relevance to the NICE decision-making process for new treatments in this indication where therapeutic advancement will be very welcome.

IVIg as a treatment has been subject to a number of supply interruptions and difficulties over recent years but this has been a constant feature as opposed to a new or emerging issue. As a result, NHS England have provided clear commissioning guidance for the use of IVIg across numerous different conditions, including gMG (https://www.england.nhs.uk/wp-content/uploads/2021/12/cpag-policy-for-therapeutic-immunoglobulin-2021-update.pdf). Multiple brands are used to secure supply.

Despite these issues, maintenance IVIg remains an important aspect of clinical management for gMG patients in need of viable treatment options when first and-second line medications have failed.

I collated and analysed data from my practice and also collected anonymized data from [redacted] additional gMG specialist centers in England ([redacted] efgartigimod-treated patient cohort) who have participated in the efgartigimod Early Access to Medicines Scheme (EAMS) and subsequent EAMS+. The goal of this analysis was to explore the balance of acute vs. maintenance usage of IVIg prior to efgartigimod initiation, and to demonstrate the real-world usage of maintenance IVIg in a space where formal reports are limited. These data demonstrate that [redacted]% ([redacted]) of efgartigimod treated patients in England have previously been treated with regular or intermittent (i.e. maintenance) IVIg, prior to efgartigimod initiation. It is important to note that prior treatment with maintenance IVIg was not a pre-requisite for efgartigimod treatment in EAMS/EAMS+.

It is the collective opinion of the clinical experts who provided data for this analysis, that this is a realistic illustration of maintenance IVIg utilisation in England, in the population of patients for whom efgartigimod is likely to be considered when used in routinely commissioned practice.

Yours sincerely,
Dr Jennifer Spillane

Consultant Neurologist, Guy's and St Thomas' NHS Foundation Trust, University College London Hospitals NHS Foundation Trust, London

gMG specialist centres in England that provided data for this analysis:
University College London Hospitals NHS Foundation Trust
King's College Hospital NHS Foundation Trust
Nottingham University Hospitals NHS Trust
The Walton Centre NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
University Hospitals Birmingham NHS Foundation Trust
Newcastle Hospitals NHS Foundation Trust

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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

In part 1 we are asking you about living with generalised myasthenia gravis or caring for a patient with generalised myasthenia gravis. 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 (section 1.1).

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.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

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

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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.

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.

Patient expert statement

The deadline for your response is **5pm** on **30 June 2023.** 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	Frances Copeland
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/Muscular Dystrophy UK
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**	gMG has affected every aspect of my daily life for 40 years. My ability to work, study, care for the needs of my family has been severely impacted. My symptoms include weakness of legs (difficulty walking, standing, rising from chair etc), arms (difficulty with personal hygiene, housework, employment, etc), facial muscles (trouble with expressions), mouth (slurred speech, difficulty chewing and swallowing, episodes of choking), eyes (constant double vision, drooping eyelids), neck (drooping head), lungs (shortness of breath). I have had crisis periods in ICU on a ventilator. My husband acts as my carer. He does all the housework, cooking, shopping, cleaning etc. He helps me bathe and dress. When outdoors he will either push me in wheelchair or hold my arm depending on level on leg weakness and distance to travel. My adult children also help with these tasks.
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. I rely on six daily doses of Pyridostigmine, and have personal experience of a great number of treatments. Very few of these have led to sustained or noticeable improvements, and the side-effects often had too great a negative effect on my overall health. The most useful treatment was a trial of Eculizumab, which gave a huge improvement but which is not NHS funded. Pyridostigmine (Mestinon) has been most useful in my own treatment but only to minimal extent.
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	Steroid treatment made my gMGM worse and had a detrimental effect on my mental health. Immunoglobulin (IVIg) infusion had no positive effect. Plasma exchange was useful during gMG crisis but positive results are very short-lived (one week) Rituximab did not help my symptoms in any way. Azathioprine led to serious chest infections and pneumonia.
9a. If there are advantages of efgartigimod over current treatments on the NHS please describe these. For example, the effect on your quality of life, your	**a.I have been treated with Efgartigimod since February 2023, and the improvement has been positive and life altering. I am now able to take daily walks, cook for the family, help with housework, and importantly for my dignity, dress and bathe myself. My quality of life has improved immensely, I**

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 efgartigimod 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**	**enjoy family activities that I previously could not join, and my self-confidence has increased. Not only has Efgartigimod been beneficial to my physical well-being, but also my mental well-being, and to the welfare of my family.** **b.Simply being able to safely undertake small activities, from dressing to walking with my family, has made a huge difference to my life. For so long, I have watched from the side-lines, and Efgartigimod has allowed me a chance to participate again.** **c.For me, Efgartigimod is far more effective than Pyridostigmine or steriods, gives a longer lasting boost than plasma exchange, and does not carry the fear of infections that I suffered with other immunosuppressant treatment.**
10. If there are disadvantages of efgartigimod over current treatments on the NHS please describe these. For example, are there any risks with efgartigimod? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have experienced mild side-effects including headache after infusions, and urine infections. These have been quickly treated. The visits to the hospital are easy to cope with, and take only two or three hours**.**
11. Are there any groups of patients who might benefit more from efgartigimod 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	
12. Are there any potential equality issues that should be taken into account when considering generalised myasthenia gravis and efgartigimod? 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.	
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

Key Issue 1: ***We consider patient perspectives may particularly help to address this issue:*** **Exclusion of maintenance intravenous immunoglobulin (IVIg) – Is maintenance IVIg currently available?**	Maintenance intravenous immunoglobulin (IVIg) had no positive effects on my gMG. I have had more than one course of treatment with IVIg at different points in my life, and none of them produced any symptom improvement.
Key Issue 2:	

Patient expert statement

Extrapolation of time on treatment (ToT) curve	
Key Issue 3: **Permanent treatment discontinuation transition** **probabilities**	
Key Issue 4: ***We consider patient perspectives may particularly help to address this issue:*** **Caregiver disutilities – Do people with generalised myasthenia gravis typically need caregivers whose health-related quality of life would be adversely affected?**	My husband acts as my carer, he is in his late sixties and since my improvement with efgartigimod, the amount of physical assistance he has to provide has lessened. He has more rest and leisure time, which has benefits for physical and mental health. I have always had falls due to the weakness in my legs, and these falls have stopped with efgartigimod. My husband no longer has to be constantly vigilant outdoors, and he wishes to point out how this has improved his own mental health. The stress and anxiety of constant care giving has eased for my husband since the success of my treatment.
Key Issue 5: **Disutilities associated with corticosteroid use**	Corticosteroid treatment had such an adverse effect on my mental health (mood swings, depression) that it was discontinued. I have no wish to ever be treated with steroids again.
Key Issue 6: **Costs of complications**	

Patient expert statement

associated with corticosteroid use	
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:

- Myasthenia Gravis has a long-term severely limiting effect on my life.
- Efgartigimod has improved my quality of life to a noticeable extent.
- Efgartigimod has produced superior results to my current and past treatments.
- Side effects are minimal.

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.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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

In part 1 we are asking you about living with generalised myasthenia gravis or caring for a patient with generalised myasthenia gravis. 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 (section 1.1).

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.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

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

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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.

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.

Patient expert statement

NICE National Institute for Health and Care Excellence

The deadline for your response is **5pm** on **30 June 2023.** 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	Penelope Henrion
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**	Diagnosis 2016, thymoma removed 2016 – no improvements in symptoms which included breathlessness, inability to eat (lost 20 lbs in weight) due to difficulty in swallowing, inability to speak normally, weakness in arms and legs, difficult to walk and not able to carry things or pick up a kettle. Then long-term high dose steroids leading to many infections, multiple hospital admissions and IVIG and plasma exchange. Then azathioprine which caused pre-cancerous lesions, removed by wide excision. Now treated with methotrexate but not symptom free and still need IVIG. This condition impacts on my life due to reasons above, and my partner and carer's life as I need constant help. I cannot do activities I used to enjoy e.g., gardening. Have had many emergency admissions to hospital. Anxiety and depression led to non-epileptic seizures now controlled by pregabalin.
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?**	**No treatment has removed all symptoms or very much improved my quality of life, especially fatigue, droopy eyes, difficulty walking, carrying out normal activities I used to enjoy, e.g. gardening. I still sometimes have difficulty swallowing and breathing.** **My partner and carer shares my views**
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	Steroids have many side effects including infections leading to hospital admissions I once had shingles which went systemic and was in hospital for 5 weeks. Azathioprine gave me pre-cancerous lesions that had to be removed under general anaesthetic
9a. If there are advantages of efgartigimod 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?	**I have never taken efgartigimod so I do not know its advantages**

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does efgartigimod 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**	
10. If there are disadvantages of efgartigimod over current treatments on the NHS please describe these. For example, are there any risks with efgartigimod? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from efgartigimod 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	
12. Are there any potential equality issues that should be taken into account when considering generalised myasthenia gravis and efgartigimod? 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	It would be difficult for patients in rural areas to access this treatment as there may not be a large hospital nearby with a neurology department or clinicians familiar with myasthenia. It would cause problems for people affected by poverty if the patient had to go to hospital for multiple treatments – e.g. cost of childcare, availability and cost of transport

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.	
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

Key Issue 1: ***We consider patient perspectives may particularly help to address this issue:*** **Exclusion of maintenance intravenous immunoglobulin (IVIg) – Is maintenance IVIg currently available?**	Maintenance IVIG not readily available
Key Issue 2:	

Patient expert statement

Extrapolation of time on treatment (ToT) curve	
Key Issue 3: **Permanent treatment discontinuation transition** **probabilities**	
Key Issue 4: ***We consider patient perspectives may particularly help to address this issue:*** **Caregiver disutilities – Do people with generalised myasthenia gravis typically need caregivers whose health-related quality of life would be adversely affected?**	My partner and carer provides transport, physical and personal care. Her stress levels and general quality of life are affected and she gets very tired, having to do all household duties and shopping etc as well as look after me.
Key Issue 5: **Disutilities associated with corticosteroid use**	
Key Issue 6: **Costs of complications**	

Patient expert statement

associated with corticosteroid use	
Are there any important issues that have been missed in EAR?	See equalities section above, in relation to rural patients and those living in poverty.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- MG has meant I have had many emergency admissions to hospital
- I was adversely affected by the use of steroids leading to multiple hospital admissions
- All drugs I take have side effects that affect my physical and mental health
- Little attention has been given to rural patients and those living in poverty regarding access to treatment
- My quality of life and that of my carer has been greatly disadvantaged.

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.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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 (section 1.1). 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 **19 June 2023.** 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.

Clinical expert statement

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	Dr Fiona Norwood
2. Name of organisation	King's College Hospital
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?	To restore muscle strength to normal using the minimal effective dose/s of well-tolerated medication/s.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. 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)	Qualitatively, an improvement for the patient so that they find symptoms acceptably controlled and can continue their normal life. Quantitatively, an improvement in the disease assessment scales, usually MG-ADL by >3 points and ideally also on the QMG scale.
10. In your view, is there an unmet need for patients and healthcare professionals in generalised myasthenia gravis?	Definitely. The disease-modifying drugs available for us have changed little over decades. Many are accompanied by short- and/or long-tern side-effects. Rituximab has not fulfilled the hopes that we had for its use in refractory patients. We are not able to access Eculizumab. To have new drugs available that have novel mechanisms of action and are effective, safe and well-tolerated would be very welcome.
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 across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The ABN guidelines (Sussman, 2015) are often used in the UK but predominantly by general neurologists. There are treatment guidelines published from other countries and these are revised intermittently. The American Academy of Neurology guidelines (most recent: 2021) are also available. The pathway of care for newly diagnosed patients is fairly standard and implemented mainly by general neurology colleagues in district hospitals. Patients who are atypical are often discussed with those of us in specialist centres. Opinion among those in specialist centres may vary and multidisciplinary meetings can be helpful to clarify a way forward for patients whose disease is difficult to control. Patients with more refractory forms of myasthenia tend to be managed mainly in or in conjunction with specialist centres. A new agent such as Efgartigimod would be used in specialist centres first and is likely to lead to referral of other patients from the district hospitals or for a variety of special circumstances. Examples might include patients with complex co-morbidities.

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)	As above, I would expect Efgartigimod to be used exclusively in specialist centres initially, ideally after MDT discussion. It is likely to be instructive to review early experience and refine patient selection criteria as needed. The patients in whom the drug may be used first are likely to be those, often termed refractory, who have significant residual symptoms despite current optimal therapies. Many of this group are likely to be on a combination of disease-modifying agents as well as receiving regular intravenous or subcutaneous immunoglobulin (IVIg / scIg) or therapeutic plasma exchange ((PLEx). In time and with increased familiarity with the new drug, I would expect it to be considered for use in selected other groups of patients. These might include “explosive-onset” severely affected patients in intensive care. Again an MDT process within the hospital setting to consider each case would be useful. Facilities needed will be infusion space in hospital, staff trained in administration of the drug and additional clinical supervision, particularly in the early phase of treatment and when patients transition to homecare.
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?	I would hope that the technology will improve symptom control and hence quality of life by reducing the burden of other medications that may shorten life through treatment-related complications.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients who may be unable to give an accurate assessment of their symptoms via remote means, perhaps due to communication issues.
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)	I would not expect significant changes in ease of use, although additional infusion space and nursing staff can be difficult to obtain. For those on regular treatments such as IVIg or PLEX, the infusion time for Efgartigimod is much shorter than their existing treatments. Some additional tests will be required at baseline and at intervals, and there may be practicalities associated that need to be resolved locally.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I am not aware of any such rules but perhaps they will emerge following expert use and early experience.
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	As above, the infusion is quite short and so patients receiving this in hospital or at home should find this more convenient.
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?	Yes: this is innovative with a novel mode of action. I think it too early to say how this may be reflected in real-world experience and so early evaluation will be important.

• 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?	There are some patients who have not attained reasonable or stable symptom control despite the use of our current full range of treatments. In those patients it will be of particular interest to see if they gain new or additional benefit.
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?	So far my patients have not reported significant side-effects.
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?	UK myasthenia patients are likely to be similar. Patients in the trial appear to be of a wide range in severity with some (probably) milder patients included. The most important outcomes are of improvement in the disease assessment scores. However there may be additional benefits that are not captured. Although some may be anecdotal those are also valid. Again, real-world experience will be instructive here.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	To follow: I am involved in a small group gathering real-world data on the UK experience of early Efgartigimod use. I anticipate that additional data will be available by the time of the appraisal meeting.
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	I expect that pregnant patients will not be among those in whom we will try the medication in the early days, but further information should come to light in time. I cannot see that any other group will be disadvantaged.

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.	

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

Key Issue 1: **Exclusion of maintenance intravenous immunoglobulin (IVIg)**	A significant proportion of my (and some others in specialist centres) refractory myasthenia patients are on maintenance / regular IVIg / sclg or plasma exchange (PLEx) in addition to their other treatment. This is an important issue in view of: • direct costs of IVIg / sclg itself • ongoing limited supply of IVIg in UK • resources required to administer IVIg in hospital (or to administer PLEx) • risk to patients of receiving a human blood-derived product • possible treatment-associated complications such as thrombosis • patient time spent receiving treatment. To be able to replace IVIg / sclg / PLEx with Efgartigimod cycles will, I anticipate, make a significant direct and indirect cost saving and improve quality of life for patients.

	Across the UK, it is likely that those patients on regular / maintenance therapies will be based mainly in specialist centres. I expect further information to be available following the real-world early experience UK study which is currently underway. Please note that the data on regular IVIg use may not be complete if the National Immunoglobulin Database is used as the sole data source. This is partly due to the way the data are entered into the database by different operators and in which categories of use the patients are deemed to lie. For example, many myasthenia patients may be listed as being for repeated “short-term” use whereas they are actually on continuous or maintenance IVIg. These data are difficult to capture. The more recent commissioning process requires approval for long-term use via peer review in the sub-regional IVIg panel. However existing patients will not be captured by this process unless their cases are submitted for discussion. This will therefore lead to an underestimate of maintenance use. Another group of patients is those on immunoglobulin replacement therapy for secondary antibody deficiency. In my patient cohort, for example, there are myasthenia patients who have previously received Rituximab treatments and who became hypogammaglobulinaemic. They now receive regular IVIg via a different commissioned indication, i.e. of secondary antibody deficiency, and so may not be captured on a database search for a myasthenia indication. If Efgartigimod treatment is successful then one might anticipate a reduction in short-term IVIg use for crisis indications, in keeping with better disease control. At present that is speculative but may emerge in time.
Key Issue 2: **Extrapolation of time on treatment (ToT) curve**	
Key Issue 3: **Permanent treatment discontinuation**	

transition probabilities	
Key Issue 4: **Caregiver disutilities**	I understand that small studies are to be presented. I have not seen those results as yet.
Key Issue 5: **Disutilities associated with corticosteroid use**	Short- and long-term potential complications from corticosteroid use are well-known. More modern management tends to try to keep the steroid dose lower but there is a significant number of patients who remain on at least some steroid for many years, either alone or in conjunction with other drugs. Disutilities from treatment I would expect to be similar to use in comparable conditions, most likely autoimmune conditions that relapse and remit.
Key Issue 6: **Costs of complications associated with corticosteroid use**	
Are there any important issues that have been missed in the EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Efgartigimod may offer patients, currently refractory to treatment or with inadequately-controlled disease, a clinically-significant improvement in symptom control and associated quality of life.
For those on regular IVIg or PLEx, home care treatment should greatly reduce the burden of treatment on the patient and likely costs to the healthcare system.
Efgartigimod has a novel mode of action which is useful as an additional treatment option.
The place of Efgartigimod in real-world UK use is under review. Additional data should be available by the time of the technology appraisal meeting.
Click or tap here to enter text.

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

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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 (section 1.1). 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 **19 June 2023.** 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	Channa Hewamadduma
2. Name of organisation	Sheffield Teaching Hospitals Foundation Trust
3. Job title or position	
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)	☐
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?	Obtain remission of disease and minimise burden from treatment

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. 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)	It depends from patient to patient what is actual improvement to them In trials improvement in MGADL of more than 2 points, CMGS more than 3 points may be considered significant.
10. In your view, is there an unmet need for patients and healthcare professionals in generalised myasthenia gravis?	Yes
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 across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	ABN guidelines, but this is only a frame work developed to guide clinicians manage MG using existing treatments such as Pyridostigmine, Steroids, ISTs such as Azathioprine and surgical intervention likeThymectomy. Rituximab is positioned for those who have tried 2 ISTs. New evidence suggest earlier use of Rituximab. ABN guidelines and NHSE Ritux centres for MG provides a frame work for delivery of novel therapies via centres with more than average experience in MG. New drugs will give additional options to treat MG and open up the therapeutic options to manage MG.
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)	When positioning of a new drug in the treatment pathway there are several important considerations: 1 Onset of efficacy 2 Mechanism of action 3 Side effect profile and tolerability 4 Drug interactions 5 Patient specific factors 6 Cost of the drug

	Proposed technology has rapid onset of action. Mechanism somewhat similar to PLEX and fairly tolerated. Therefore it could be considered at various levels of the treatment pathway, in-addition to refractory MG, drug could also be used earlier in the pathway to minimise the steroid burden some patients requiring higher doses of steroids. Home care nursing and extra clinical nurse support for the treatment centres
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 yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	MG patients who need rapid control of symptoms, treatment refractory MG, those on regular IVIG and PLEX
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)	May need more frequent review initially in the hospital setting to monitor treatment effects and monitor immunoglobulin levels.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes – defining non responder and responder state is important.

	Non responder – someone whose MGADL doesn't improve by >2 points after the second cycle (responder is someone whose MGADL improves by >2 points by the end of first or second cycle) Sustained response- next drug dosing cycle can be delayed
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	There are lot more QOL issues that can be improved than those captured from regular instruments Patient community and carers will help you capture these aspects
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's a step change Provides a treatment that works rapidly and can be had at home
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?	Fairly well tolerated from trials
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes it reflects UK population

• 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?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	ADAPT+ data
22. How do data on real-world experience compare with the trial data?	Too early to comment
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	All MG patients have a right to access fast acting, safe, well tolerated drugs provided they meet the criteria set out by NICE/NHSE. Selection of such criteria will be tricky as it can make some feel left out therefore we need to be carefully think it through.

• 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.	

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

Key Issue 1: **Exclusion of maintenance intravenous immunoglobulin (IVIg)**	Chronic recurrent IVIG users or PLEX users can be stopped when proposed drug starts. Rapidly cycling brittle MG patients on adhoc IVIG could also be migrated to proposed treatment
Key Issue 2: **Extrapolation of time on treatment (ToT) curve**	
Key Issue 3: **Permanent treatment discontinuation transition probabilities**	

Key Issue 4: Caregiver disutilities	
Key Issue 5: Disutilities associated with corticosteroid use	No direct data for MG but other diseases like lupus could be used to answer
Key Issue 6: Costs of complications associated with corticosteroid use	Morbidity from steroid use is huge- HT, weight gain, skin discoloration, facial dysmorphism, bone health issues, diabetes, fluid retention, cataracts, muscle weakness etc
Are there any important issues that have been missed in the EAR?	Not acutely aware

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

MG patients lack fast acting well tolerated therapies
Available therapies have significant adverse effect profiles, take a long time to take effect and are unlicensed
Proposed treatment gives an effective, safe, evidence based treatment modality to manage MG patients
Treatment responder, non responder, stopping criteria need defining
Depending on cost implications, we need to consider earlier positioning of the fast acting drugs to maximise the benefit

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

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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 **19 June 2023**. 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.

Technical engagement response form

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 and 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.	Myaware has received no such funding in the last 12 months. • MDUK will receive £3,132.00 from Argenx UK Ltd to support work conducted in May 2023 into the impact on carers of myasthenia gravis • MDUK received £6,600.00 from Roche Products Ltd in January 2023 for sponsorship of the UCL Neuromuscular Translational Research Conference • MDUK received £720.00 from Roche Products Ltd in March 2023 in relation to participation in the SMA Adult Activation Advisory Board • MDUK received £9,600.00 from Pfizer Ltd in March 2023 for sponsorship of the UCL Neuromuscular Translational Research Conference • MDUK has received a pledge of grant funding of £50,000 from Roche Products Ltd. This is funding for the work of the UK SMA Newborn Screening Alliance and is not being retained by MDUK
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	Myaware and MDUK have no past links, direct or indirect, to the tobacco industry.

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
Key Issue 1: Exclusion of maintenance intravenous immunoglobulin (IVIg)	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Key Issue 2: Extrapolation of time on treatment (ToT) curve	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Key Issue 3: Permanent treatment discontinuation transition probabilities	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Key Issue 4: Caregiver disutilities	**Yes**/No	In our previous submission for this appraisal, we put forward strong testimony showing the benefit caregivers provide to patients with gMG and of the impact that being a caregiver can have. The substantial caregiver burden of gMG arises from both physical, emotional and financial impact caused by symptoms experienced by gMG patients. Firstly, the physical impact of gMG such as difficulties with swallowing, vision, speech,

		breathing, and mobility, as well as extreme fatigue mean that patients often require help with eating or mobility, both of which a regular caregiver is required to support. Secondly, our previous submissions to the appraisal found that 50% of patients with gMG believe that their symptoms have negatively impacted their family's mental health. Carers of MG may experience anxiety and depression due to their caregiving responsibilities or worry about the patient's health. Finally, the financial impact of gMG contributes to the caregiver burden. In previous submission to the appraisal we found that 30% of gMG patients stated their condition has negatively impacted their family financially. Carers for gMG patients often become responsible for upholding the family finances which is significant given that they may also have to reduce or stop working due to their responsibilities. We were therefore disappointed by the following statements provided in the EAR: "*Clinical advice to the EAG is that the majority of gMG patients would be independent and not require a caregiver*." And: "*The EAG's view is that the company submission has not provided sufficient evidence to show that gMG has a substantial effect on carers*." In addition to the evidence that we have already provided on this, Myaware conducted a survey of 156 members.

		In our survey, we asked members of myaware to describe their experience of receiving care – specifically support or assistance from family, partners, or friends as a result of living with MG. Of those receiving this care, 82% receive carer support from family all week. A time investment of this scale does not align with the statement that gMG does not have a substantial effect on carers. In addition, requiring care all week suggests these respondents are not able to be independent. When asked to respond to the statement "*The support I receive from family, a partner, or friends positively impacts me*" 80% of respondents strongly agreed, with a further 17% agreeing. This in itself emphasises the importance of these carers to gMG patients. In response to the statement "*Supporting me has an impact on my family members, partner, or friends who do so*" 72% strongly agreed with this, with a further 22% agreeing. This suggests that, contrary to the EAG's view and the company submission, that gMG has a substantial effect on carers. Finally we wanted to provide some quotes from our survey respondents which in our opinion underlines the dependency on carers and the effect gMG has on them. "My *husband has been my carer since diagnosis. He gave up work to care for me full-time. It is both physically and mentally demanding. When our two children were young, he also had a greater share of childcare because of my MG. Now they are grown, they both contribute to my care, helping with chores and shopping. My MG has an effect on the whole family, and we make extra efforts to ensure we stay positive and loving to each other*."

		"Caring for me is a big job, its pretty much a full time job as my symptoms never go away. We never know when muscle weakness will strike next, so we are always on high alert. My partner has completely changed his life to give me love, care and support. It's a very debilitating condition not only for the patient but also for those around us. Its not just a case of a bit of looking after, its intense and every part of our lives is governed by the high demands of MG." In addition, one of our respondents was a carer of their husband with gMG and had the following to say: "*I have had to give up a well-paid full-time job in order to care for my husband. His is very unsteady and cannot walk more than a few paces. Without me help he would find it almost impossible to get out of bed. The house is also full of mobility aids so feels cluttered and we can no longer sleep in the same bedroom due to him needing a hospital bed and walking frame which would not fit into our room even if we changed the kingsize bed for a single. I find it depressing that we can no longer do the things we used to enjoy like fell walking every weekend and scuba diving I find life really depressing now but do not mention this as I know he feels bad enough being reliant on me without worrying about me too*." In addition to this new survey of gMG patients by Myaware, MDUK supported research conducted by the Research Institute for Disabled Consumers (RIDC) that recruited 21 carers of people with a diagnosis of gMG. In line with NICE's definition of a carer, participants confirmed that they supported a family member, partner or friend with needs that resulted from living with gMG. The research was conducted between 13 June 2023 and 21 June 2023 through one-to-one in-depth telephone interviews. Participants were asked to what extent their responsibilities around caring for someone with generalised myasthenia gravis effects their quality of life on a scale of 1-5, where 1 is not at all affected and

		5 is extremely significantly affected. The average score given was 3.4 and no one gave a score of 1 (three people gave a score of 2; nine people gave a score of 3; six people gave a score of 4; three people gave a score of 5). Participants were asked in which aspect of daily living (if any) they experienced any impact due to caring for someone with generalised myasthenia gravis. Participants could select more than one option. None said that it had no impact. • 19 people (90%) said it impacted their ability to undertake their usual activities such as personal shopping/ hobbies • 16 people (76%) said it impacted their mobility/ ability to move around • 14 people (67%) said it caused anxiety/depression • 11 people (52%) said it impacted their personal care e.g. washing/dressing • 5 people (24%) said it caused them pain/discomfort Asked about the impact that caring for someone with generalised myasthenia gravis has on specific activities (participants could select more than one option); • 21 people (100%) said their social life • 19 people (90%) said working/studying • 18 people (86%) said sleeping • 8 people (38%) said eating Comments relating to the impact on social life included; *"You can't do anything social or working. I like music and the cinema and you cannot go to music or jazz clubs. You can't socialise."* *"My social life is affected, and I cannot hang out as much as I want to. I can't be free and be outdoors as much as I would like to."* *"Social life and dating are impossible. No sports or any other things like you could do before. You try to do them, but you get a call and then you have to go home."*

		"It becomes very difficult as I have no time for leisure anymore. My personal life is tough as my caring takes a whole lot of time and I do not have much sleep." *"Getting to leisure and recreational activities. I love sport but I have to limit the time I spend outside as the person I am caring for may need me at any time. [It alters] the way I would live otherwise."* *"I was able to crochet more before care giving. My hobby was too time consuming so I am unable to continue doing what I like. I have had to stop."* In terms of the impact of caring for someone with generalised myasthenia gravis on employment, only two participants (10%) in the research were not employed; eight (38%) were employed part-time; seven (33%) were employed full-time; three (14%) were self-employed; and one (5%) was employed but on long-term medical leave. Nine participants (43%) said they worked less hours as a result of their responsibilities as a care giver. *"My part-time job is online as you cannot be taken away physically from the person you are taking care of. Some days he cannot move his body."* *"I can't commute because my dad is more important."* *"Mostly at work I get called home. It is really stressful. I have no peace of mind. I can get called at any time."* In terms of the impact of caring for someone with generalised myasthenia gravis on studying, comments from participants included; *"I would love to further my education but I can only do a little online study. Taking care of your relation takes up your time and is paramount."*

		"Academics are online but there is no social element for you to do some interaction. You can get the qualifications online but it is not the same experience." Five participants (24%) in the research stated that being a carer for someone with generalised myasthenia gravis caused them pain or discomfort, with comments including; *"The stress sometimes and always being active it gets very stressful and heavy on my lower back."* *"Lifting her with my legs. Helping her stand and communicating with her for a long time is tiring. Standing for a long time to communicate and support her."* *"In terms of pain I am constantly having to be up all of the time and being on my feet and moving around has caused mild pain and feeling lightheaded due to a lack of sleep."* 14 participants (67%) said that they experienced anxiety and/or depression as a result of caring for someone with generalised myasthenia gravis. 8 of these 14 (57%) said this was to a mild extent; 4 of these 14 (29%) said that it was to a moderate extent; and 2 of these 14 (14%) said that this was to a severe extent. *"At times I feel down because this is someone I love so much and having to watch her go through such problems can be disheartening and I feel down and bad and I wish I could prevent that but it is beyond me. At times I feel it is my fault."* *"Generally being a carer is difficult because sometimes we have no choice. You have to make huge sacrifices. You cannot achieve your dreams. You cannot maintain relationships or friendships and cannot travel around."*

		I fell into depression. I had a lot in life I liked to do. Being stuck makes me think a whole lot. I am not getting paid, and I feel that my life is wasting away, and I think too much, and it doesn't get better. Sometimes it is okay and then there is another crisis. I do not want to lose him, but I am scared, and I am stuck. I can't overreact and I have to be gentle and can't show my own side and my own feelings. I can't make him feel that he is making my life pause. No one is there to talk to, and you feel like sometimes social media makes things harder. I see other people doing a whole lot of stuff [such as] working or starting a family. It is really hard." *"Sometimes I look forward to when my care giving role comes to an end and I can get on with my life. Doing the same thig over and over again sometimes I think about the end of life and is this what life is about. It gives me anxiety."* *"You have no control of the situation. You just worry because if you had your way you would have your loved one fully well and you could return to your normal life."* *"My life turned all of a sudden and I can't get a grip on it at the moment."* With this new evidence put forth, we hope that this key issue will be reconsidered.
Key Issue 5: Disutilities associated with corticosteroid use	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Key Issue 6: Costs of complications associated with corticosteroid use	Yes/**No**	Please provide your response to this key issue, including any new evidence, data or analyses

CONFIDENTIAL UNTIL PUBLISHED

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

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Evidence Review Group's summary and critique of the company's response to technical engagement

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Fay Chinnery, Research Fellow, Health Economics Keith Cooper, Senior Research Fellow, Health Economics Joanna Picot, Senior Research Fellow, Evidence Synthesis,
Correspondence to	Dr. J. Picot Southampton Health Technology Assessments Centre (SHTAC) Wessex Institute Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	24/7/2023

Contents

List of tables

[redacted]

[redacted]

LIST OF ABBREVIATIONS

EAG	External Assessment Group
EAMS	Early Access to Medicines Scheme
ECM	Established clinical management
gMG	Generalised myasthenia gravis
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IVIg	Intravenous immunoglobulin
MDUK	Muscular Dystrophy UK
MG-ADL	Myasthenia Gravis Activities of Daily Living Scale
MHRA	Medicines and Healthcare Regulatory Agency
MS	Multiple sclerosis
PAS	Patient access scheme
PDDS	Patient Determined Disease Steps
PSA	Probabilistic sensitivity analysis
QALYs	Quality-adjusted life years
RiDC	Research Institute for Disabled Consumers
SLE	Systemic lupus erythematosus
ToT	Time on treatment
US	United States

1. Introduction

This document is the External Assessment Group's (EAG) summary and critique of the response by the company, argenx, to the key issues for technical engagement (TE) proposed in the EAG report for this appraisal (submitted to NICE on 26/04/2023). The key issues for technical engagement are summarised in Table 1. The EAG received the company's response on 20/06/23.

The company's TE response included the following:

- The completed TE response form
- A word document containing new evidence on:
    - The efgartigimod Early Access to Medicines Scheme (EAMS) dataset
    - Permanent treatment discontinuation transition probabilities
- A confidential letter about IVIg usage in England
- An updated economic model

In this report we present the following:

- Our critique of the company's response to each of the six issues for technical engagement (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis (Section 3) and update of the EAG's base case results.

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 maintenance intravenous immunoglobulin (IVIg)	Yes
2	Extrapolation of time on treatment (ToT) curve	No
3	Permanent treatment discontinuation transition probabilities	Yes
4	Caregiver disutilities	Yes/No
5	Disutilities associated with corticosteroid use	No
6	Costs of complications associated with corticosteroid use	No
Additional issue 1[a]	Price for the efgartigimod subcutaneous formulation	Yes

2. Critique of the company's response to key issues for technical engagement

2.1 Issue 1 – Exclusion of maintenance intravenous immunoglobulin (IVIg)

Summary of the issue

The company provided data on maintenance IVIg utilisation in England from the MHRA efgartigimod Early Access to Medicines Scheme (EAMS) and subsequent EAMS+ programs. [redacted] The EAMS/EAMS+ data from England showed that, overall, [redacted]% of patients had received either prior regular or intermittent (i.e. maintenance IVIg treatment). The company states that "*it is the collective opinion of the clinical experts who provided data for this analysis, that this is a realistic illustration of maintenance IVIg utilisation in England, in the population of patients for whom efgartigimod is likely to be considered when used in routinely commissioned practice.*"

On the basis of the EAMS data, the company assumed that 100% of patients with MG-ADL ≥ 10 and [redacted]% of patients with MG-ADL 8-9 are treated with maintenance IVIg. The percentage of [redacted]% was calculated using the baseline distribution of the patients over the health states so that the overall baseline population in the model reflects the proportion of EAMS/EAMS+ patients in England that are treated with maintenance IVIg ([redacted])

Critique of the company's response

The company provide NHSE commissioning guidance for the use of IVIg across numerous conditions, including gMG (https://www.england.nhs.uk/wp-content/uploads/2021/12/cpag-policy-for-therapeutic-immunoglobulin-2021-update.pdf). The commissioning guidance for myasthenia gravis states that IVIg can be used if a patient has an acute exacerbation, weakness requiring hospital admission or prior to surgery and / or thymectomy. We note that it does not state that IVIg can be used for maintenance treatment.

The company has provided data from a survey of [redacted] on the use of IVIg therapy as a maintenance treatment. This appears to indicate that IVIg is used for maintenance therapy in England for a significant proportion of patients with gMG. The EAG is unclear how this is possible, given that it is not commissioned in this population group by NHS England. Do patients have to go through a formal process in order to be allowed this treatment? We are also unclear how representative these data are of the rest of England, for example what proportion of centres in England have contributed to this survey?

Given these uncertainties, the EAG maintains their position that IVIg should not be included for maintenance therapy. We have included scenario analyses with fewer patients receiving maintenance therapy than in the company's base case. We also suggest that NICE take a consistent position on the use of maintenance treatment with IVIg across technology appraisals for myasthenia gravis.

2.2 Issue 2 – Extrapolation of time on treatment (ToT) curve

Summary of the issue

The company accepts the EAG's standpoint to use the extrapolated exponential curve from the start of the model for the modelling of time on treatment.

Critique of the company's response

No further EAG comments.

2.3 Issue 3 – Permanent treatment discontinuation transition probabilities

Summary of the issue

The company accepts that the method used to calculate the transition probabilities after permanent treatment discontinuation in the company submission is inappropriate and therefore accepts the methodology adopted by the EAG. This methodology required the assumption of a specific proportion of patients to remain in the MG-ADL <5 health state, which the EAG assumed to be 1%.

Based on a post hoc analysis of data from ADAPT and ADAPT+, there appears to be residual benefit from treatment with efgartigimod for a significant proportion of discontinued patients [redacted].
The company also presents real-world data from US patients who received efgartigimod in a Patient Support Programme where [redacted] of patients who had an MG-ADL score <5 at the time of permanent treatment discontinuation still had an MG-ADL score <5 on average more than four months after their last infusion. Therefore, the revised company base case assumes that 15% of these patients remain in the MG-ADL <5 health state six months after discontinuation of therapy.

Critique of the company's response

The EAG considers the company's new assumption is reasonable, based on the evidence presented, and we have changed our base case accordingly.

2.4 Issue 4 – Caregiver disutilities

Summary of the issue

The company considers that caregivers' health-related quality of life (HRQoL) is significantly impacted and therefore has not changed its base case assumption. The company observed that the literature on caregiver disutilities in gMG is lacking and so conducted a comparative analysis to explore the appropriateness of using the multiple sclerosis (MS) caregiver burden as a proxy for gMG (detailed in Table 1 in the company TE response form).

Working with the Research Institute for Disabled Consumers Charity (RiDC) and Muscular Dystrophy UK (MDUK), the company developed a cross-sectional observational study of informal caregivers for patients with a confirmed diagnosis of gMG, to examine the impact of the disease on caregivers. Twenty-one caregivers were surveyed:

- [redacted] reported an impact on their usual activities
- [redacted] reported an impact on their mobility
- [redacted] reported experiencing anxiety/depression
- [redacted] reported an impact on their personal care activities
- [redacted] reported experiencing pain/discomfort

Although most caregivers [redacted] stated that the person they cared for was receiving treatment that controlled their disease, most patients had experienced either a myasthenia crisis [redacted] or exacerbation [redacted] in the last 12 months. The majority of caregivers were employed in some capacity [redacted] however, the majority of caregivers who were employed [redacted] reported working fewer hours because of their caregiving responsibilities. In addition, [redacted] reported that working or studying was affected by their caregiving responsibilities. It was also evident that anxiety and depression were high: [redacted] reported anxiety and depression which ranged from mild [redacted], moderate [redacted] to severe [redacted].

The company comments that this study provides the first disease-specific data on the burden on informal caregivers for patients with gMG, and concludes that the results demonstrate that "*caregiver responsibilities constitute a large burden for informal caregivers of patients with gMG*."

Critique of the company's response

The EAG maintains its position that caregiver's utility should not be included in the base case analysis. We acknowledge that there are some similarities between MS and gMG,

however there may be some aspects of each disease that affect quality of life adversely, which are not comparable, such as mobility.

The EAG notes the Patient Determined Disease Steps (PDDS) score used to elicit disutilities for MS patients focusses on a person's walking ability, whereas the MG-ADL score does not include a walking component and only asks about a person's ability to rise from a chair. The remaining questions in the MG-ADL scale concern the functions of talking, chewing, swallowing, breathing, the ability to brush teeth/comb hair, double vision and eyelid droop. The EAG does not consider that the PDDS score is comparable with the MG-ADL scale and so it is not an appropriate proxy.

The DSU report on caregiver HRQoL in NICE appraisals[1] states that there is no generic approach to estimating caregiver HRQoL across disease areas, and highlights that it is unclear to what extent caregiver HRQoL estimates are transferable between diseases. The EAG notes that including caregiver HRQoL always increases incremental QALYs and therefore decreases the ICER. Consequently, using the same decision-making criteria between appraisals will favour interventions where caregiver HRQoL is included. Therefore, the EAG suggests NICE take a consistent approach with regard to caregiver disutilities across the technical appraisals for myasthenia gravis.

The results of the company's survey on caregiver burden in gMG was made available to the EAG on 29th June 2023. The authors describe the limitations of the study including:

- The study design:
  - Cross-sectional studies do not estimate a cause-and-effect relationship and so are challenging to interpret
  - Survey format: caregivers may be susceptible to recall bias
- Small sample size: the results are not generalisable

The data collected were *"planned to mirror those collected in validated tools such as the EQ-5D (EuroQoL)*". The company explains that it was not possible to administer the EQ-5D given the restricted time, resource and sample size of the study, and acknowledges that further work using validated tools is needed.

We note that this study has a small sample size, collecting data from 21 caregivers. Full details of the patients' MG-ADL scores are not reported (missing from Study Report Table 5). In the text the company says "[redacted]." With only [redacted] caregivers providing details about patient MG-ADL scores, it is not clear how appropriate it would be to include caregiver disutilities for all MG-ADL states.

The EAG observes that the company's survey found that a high proportion of patients experienced a myasthenia crisis in the past 12 months ([redacted]), or experienced an exacerbation in the last 12 months ([redacted]) (Table 5 in the Study Report).

Using Hospital Episode Statistics data recorded during 1997–2016, a recent retrospective longitudinal cohort study of adult patients in England (n=1149) with treatment-refractory or non-refractory gMG reported that 18.4% of all patients experienced myasthenic crises and 24.6% of all patients experienced exacerbations.[2] The study notes that most of these events occurred within 2–3 years of diagnosis. Harris et al. demonstrate that the proportions of patients experiencing myasthenia crises and exacerbations are highest in the first year after first diagnosis with gMG, and then decrease progressively in both the refractory and non-refractory gMG cohorts.[2] The EAG notes the proportion of patients experiencing a crisis or exacerbation within the first year from the date of first gMG diagnosis is much lower than the proportions reported in the company's survey (Table 2). We therefore consider that the patients in the company's survey may not be representative of the overall population of people in England with gMG and appear to have more severe disease, and the potential impact on caregivers may be greater in the survey group of patients.

Table 2 Proportions of patients with gMG who experienced gMG-related events in the first year following the date of first gMG diagnosis

Patients	Crises (%)[a]	Exacerbations (%)[a]
Refractory disease	6.0	17.0
Non-refractory disease	4.5	9.0

Abbreviations: gMG, generalised myasthenia gravis
[a] Percentages are approximate readings from Figure 1 in Harris et al. (2022)[2]

Lastly, the company's survey is descriptive in nature and so does not provide data to determine caregiver disutilities in gMG that could be used in the economic model. We consider the results from this study should be interpreted with caution.

2.5 Issue 5 – Disutilities associated with corticosteroid use

Summary of the issue

The company acknowledges the EAG's view that the utilities from the ADAPT trial already captured the effect of corticosteroid use, and therefore the revised company base case does not consider the utility decrement for patients treated with corticosteroids.

Critique of the company's response

No further EAG comments.

2.6 Issue 6 – Costs of complications associated with corticosteroid use

Summary of the issue

The company believes systemic lupus erythematosus (SLE) is a better proxy disease for gMG than asthma (as used in Voorham et al.[3]). Additionally, the socioeconomic status of the UK and Sweden are not significantly different, and therefore healthcare costs can be reasonably assumed to be comparable between the countries. Therefore, the company's observation is that the estimate of costs in Bexelius et al.[4] provides a better proxy for the costs associated with the chronic use of corticosteroids in gMG patients. It has not updated its base case following this issue raised by the EAG.

Critique of the company's response

As stated in the EAG report, we consider the study by Voorham et al.[3] to be a better source as there are considerably more patients in each arm in this study and it appears to be more representative of the costs associated with corticosteroid use in the UK. We therefore maintain our position that the study by Voorham et al.[3] is more appropriate.

2.7 Additional Issue – Price for the efgartigimod subcutaneous formulation

The PAS discount for efgartigimod has been increased by the company from [redacted] to [redacted].

3. Updated cost-effectiveness results – EAG summary and critique

3.1 Company's revised base case cost-effectiveness results

The results of the company's revisions to their original base case, including the new PAS discount price, are shown in Table 3.These revisions decrease the base case ICER from £28,702 to £17,327 per QALY.

Table 3 Cumulative results for the company's changes to their original base case

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company original base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£28,702
	ECM	[redacted]	[redacted]	-	-	
IVIg use based on EAMS England data, weighted by MG-ADL states	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£11,911
	ECM	[redacted]	[redacted]	-	-	
Exponential function to model efgartigimod ToT	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£31,349
	ECM	[redacted]	[redacted]	-	-	
Disutilities associated with chronic corticosteroid use removed	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£39,467
	ECM	[redacted]	[redacted]	-	-	
15% of patients in MG-ADL <5 after permanent treatment discontinuation	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£92,378
	ECM	[redacted]	[redacted]	-	-	
PAS discount increased to [redacted]	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£17,327
	ECM	[redacted]	[redacted]	-	-	
Company revised base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£17,327
	ECM	[redacted]	[redacted]	-	-	

EAMS, early access to medicines scheme; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; PAS, patient access scheme; QALYs, quality-adjusted life years; ToT, time on treatment

The company presents the results of their probabilistic sensitivity analysis (PSA) in Table 2 of their response to technical engagement form.

3.2 EAG's revised preferred assumptions

Following the company's response to technical engagement, there remain some differences between the company's and EAG's base cases. As noted above, in response to technical engagement, the EAG has changed their assumption on the permanent treatment discontinuation transition probabilities (issue 3). The EAG's revised base case assumptions and resulting ICERs are shown in Table 4. The EAG's revised base case ICER of £338,434 per QALY remains considerably higher than the company's revised base case ICER of £17,327 per QALY.

Table 4 Cumulative results for the EAG's preferred model assumptions

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company revised base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£17,327
	ECM	[redacted]	[redacted]	-	-	
IVIg costs not included	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£212,408
	ECM	[redacted]	[redacted]	-	-	
Caregiver disutilities not included	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£316,616
	ECM	[redacted]	[redacted]	-	-	
Using cost data from Voorham et al. for complications costs from corticosteroid use	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£338,434
	ECM	[redacted]	[redacted]	-	-	
EAG's revised base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£338,434
	ECM	[redacted]	[redacted]	-	-	

ECM, established clinical management; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; QALYs, quality-adjusted life years

We ran the PSA with our revised base case assumptions and the results are shown in Table 5.

Table 5 EAG revised PSA results

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG revised base case	[redacted]	[redacted]	£338,434
EAG PSA results (1,000 simulations)	[redacted]	[redacted]	£345,643

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

3.4 Scenario analyses conducted on the EAG's revised preferred assumptions

We conducted scenario analyses for parameters where uncertainty remains (Table 6). The model is sensitive to the costs used for IVIg treatment (scenarios 1-4). Using IVIg costs based on the EAMS England data and weighted by MG-ADL states (scenario 1) had the most notable effect on the ICER, decreasing it to £47,647 per QALY. Including caregiver disutilities (scenario 5) also had a large effect on the ICER, reducing it to £227,045 per QALY.

Table 6 Scenario analysis results for the EAG's preferred model assumptions

Scenario		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
EAG's revised base case		Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£338,434
		ECM	[redacted]	[redacted]	-	-	
1	IVIg use based on EAMS England data, weighted by MG-ADL states	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£47,647
		ECM	[redacted]	[redacted]	-	-	
2	Company original base case: IVIg only used in MG-ADL 5-7, MG-ADL 8-9 and MG-ADL≥10 in 12.5%, 50% and 100%; PLEX not used	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£79,625
		ECM	[redacted]	[redacted]	-	-	
3	50% reduction of IVIg use from company's original base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£209,030
		ECM	[redacted]	[redacted]	-	-	
4	75% reduction of IVIg use from company's original base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£273,732
		ECM	[redacted]	[redacted]	-	-	
5	Caregiver disutilities included	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£227,045
		ECM	[redacted]	[redacted]	-	-	
6	Caregiver disutilities considered only for the proportion of patients who needed help from a caregiver in MyRealWorldMG (Jacob et al.)	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£262,054
		ECM	[redacted]	[redacted]	-	-	
7	Using cost data from Bexelius et al. for complications costs from corticosteroid use	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£316,616
		ECM	[redacted]	[redacted]	-	-	
8	Using the average of cost data from Bexelius et al. and Voorham et al. for complications costs from corticosteroid use	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£327,525
		ECM	[redacted]	[redacted]	-	-	
9	Subcutaneous administration of efgartigimod	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£335,565
		ECM	[redacted]	[redacted]	-	-	

EAMS, early access to medicines scheme; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; QALYs, quality-adjusted life years

References

1. Pennington B, Wong R. *Modelling carer health-related quality of life in NICE technology appraisals and highly specialised technologies.* https://www.sheffield.ac.uk/media/33950/download?attachment, accessed 27th June 2023.
2. Harris L, Graham S, MacLachlan S, et al. A retrospective longitudinal cohort study of the clinical burden in myasthenia gravis. *BMC Neurol* 2022;22(1):172.
3. Voorham J, Xu X, Price DB, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy* 2019;74(2):273-83.
4. Bexelius C, Wachtmeister K, Skare P, et al. Drivers of cost and health-related quality of life in patients with systemic lupus erythematosus (SLE): a Swedish nationwide study based on patient reports. *Lupus* 2013;22(8):793-801.

1. How is immunoglobulin currently commissioned for generalised myasthenia gravis patients? Is it currently available for clinicians to use? If yes, how widely used is this treatment?

   Ig in MG is commissioned in line with the NHSE 'Commissioning Criteria Policy for the use of therapeutic Immunoglobulin (Ig) in England (2021)', available at: NHS England » Commissioning Criteria Policy for the use of therapeutic Immunoglobulin (Ig) in England (2021) . The guidance recommends use for short-term use in acute exacerbations (crisis), weakness requiring hospital admission or prior to surgery/thymectomy. The guidance also refers to – '*In rare circumstances where a patient has failed all standard treatments (including steroids and immunosuppression) and where authorised by a specialist in MG from a centre with a specialist neuromuscular service, maintenance therapy may be considered'*.

   Maintenance use is limited – [redacted]. This is a small but important group for whom there are generally no other options. They may be patients who don't respond to other immunosuppressant agents or those who have intolerable side effects. IVIg is reduced/withdrawn if not necessary but reinstated after review if it is clear that it is required

   It should be noted that IVIG use in the patients now receiving efgartigimod via EAMS is higher – because these were the patients who more urgently required treatment. [redacted] Therefore although the % of MG patients requiring regular IVIG as a whole is relatively small- this rate is likely to be higher in the group in whom efgartigimod is considered a treatment option

2. What is NHSE's and the clinical position about administrating efgartigimod at home (please note that the company provided a scenario where from Year 2, 100% of patients receive administration at home at no cost (supported by argenx)?)

   The Dose is 10mg/kg as a 1 hour IV infusion, once weekly for four weeks then according to clinical evaluation. Information from the clinical trial suggests that most patents will receive four annual cycles.
   As part of the EAMS and EAMs + scheme NHSE have treated a small number of patients at home. **We would expect that patients can receive cycle 2 onwards via homecare**.

   After the 1st cycle, patients are reviewed at week 6 (2 weeks after the end of treatment) to do full outcome scores (MG ADL MG QOL MG Composite) followed by weekly ADL scores - once the ADL has increased > 2 points /is greater than 5, the patient can receive home care treatment. ADL scores are continued weekly to identify need for future cycles of treatment.

   This has worked well as it allows use of patient reported outcomes using validated clinically meaningful scores. Patients have anecdotally said it gives them ownership of their condition.

Patients will continue to come to clinic to be seen on average 3-4 times a year and at least twice a year full outcome measures will be taken. This is standard clinical care so we would not expect an increase in activity costs.

3. Are there other commissioning issues that you want to raise?

   For patients on regular treatment with efgartigimod a treatment holiday at appropriate intervals (e.g. yearly) would be planned to help determine ongoing need. Treatment would be withdrawn if no longer clinically needed.