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Efgartigimod for treating generalised myasthenia gravis [ID4003]

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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.

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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

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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.

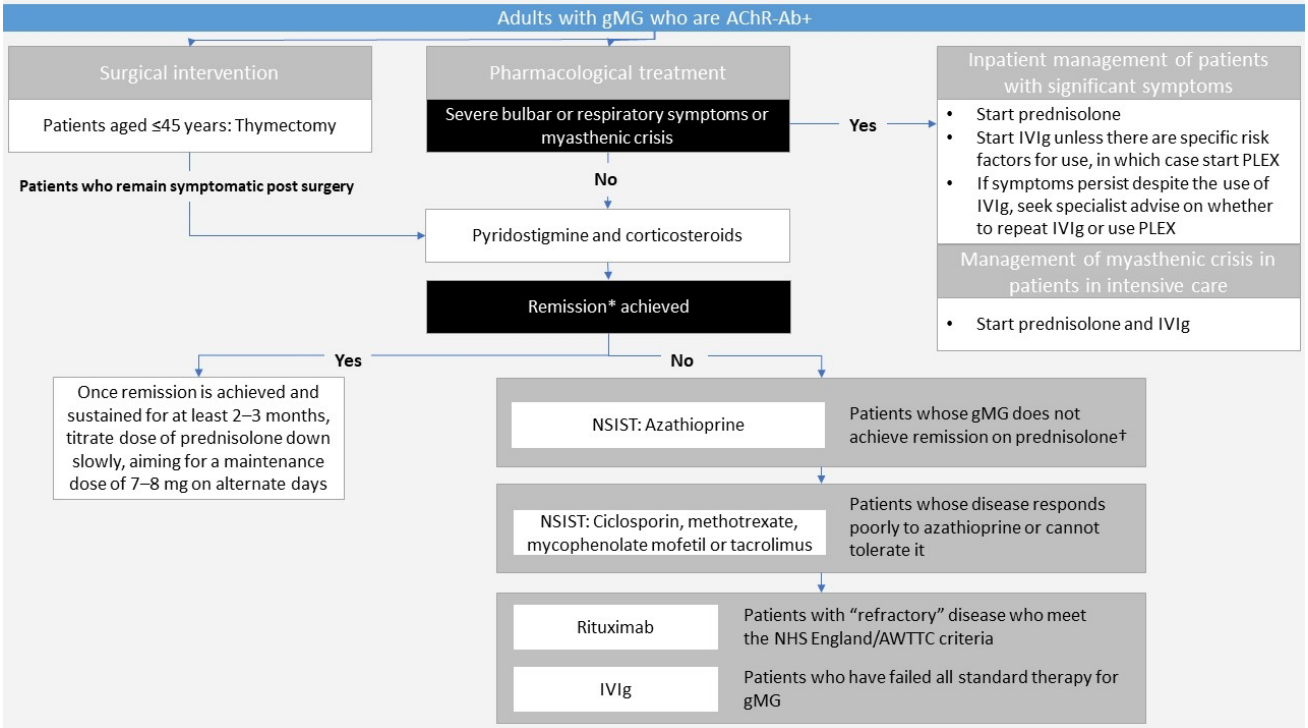

Figure 1 UK treatment pathway for gMG based on ABN guidelines and national commissioning policies

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.

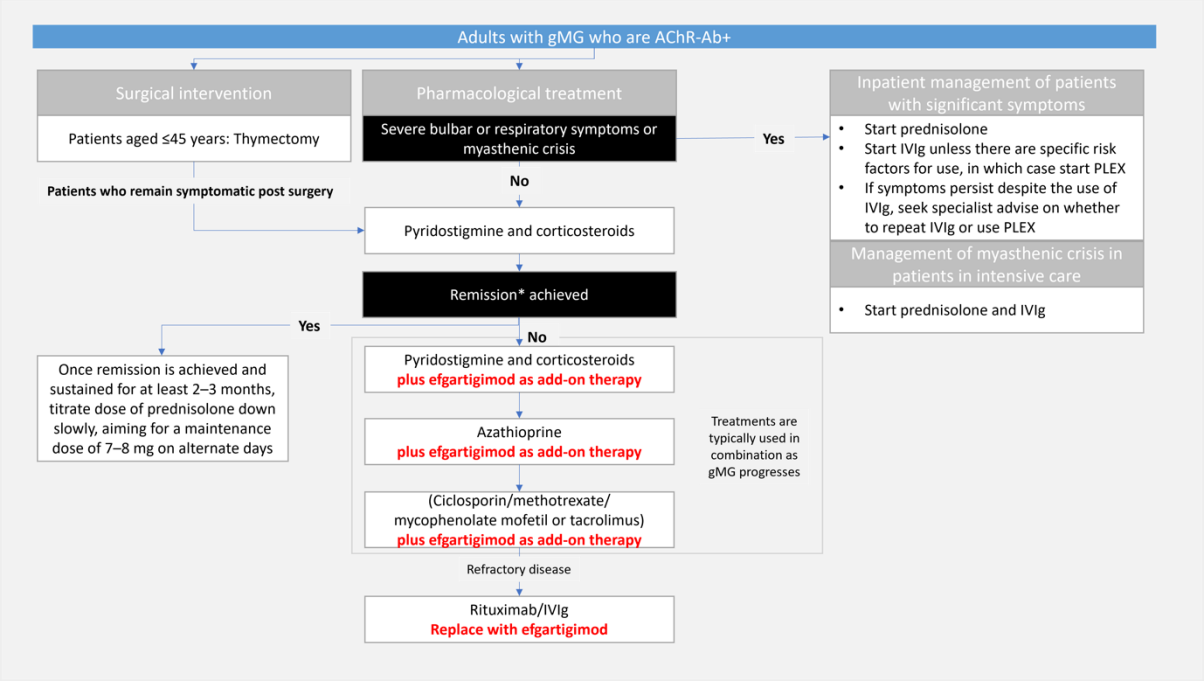

Figure 2 Proposed place of efgartigimod in the current treatment pathway

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.

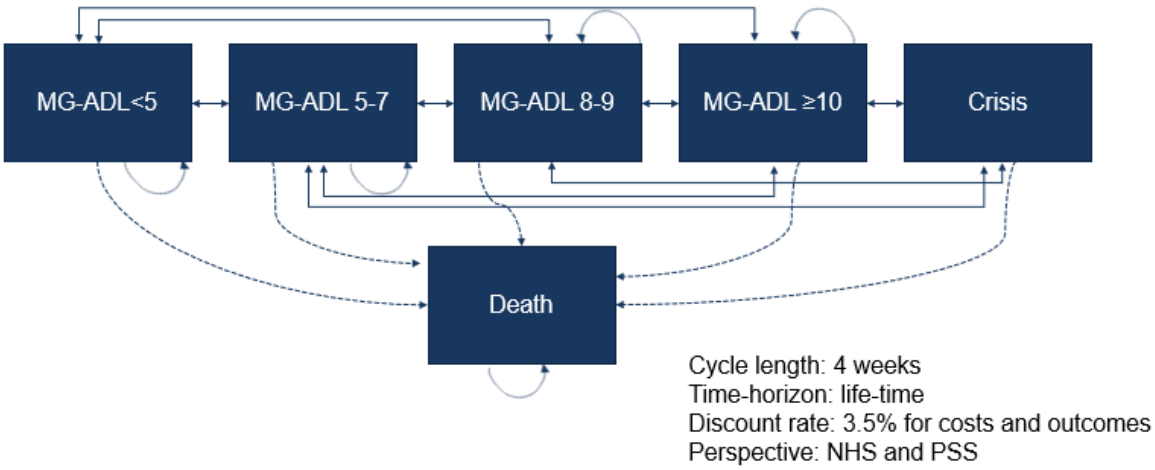

Figure 3 Model structure

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

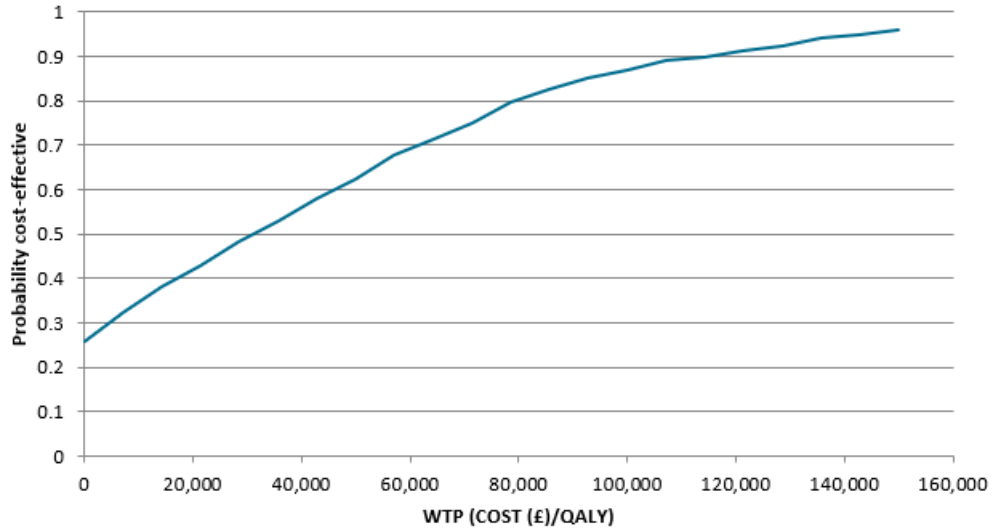

Figure 5 Cost-effectiveness acceptability curve

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.

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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.