NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Contents:

The following documents are made available to stakeholders:

Appraisal Committee meeting 3 – 9 May 2024

1. **Draft Guidance Document 2 (DG2)** as issued to consultees and commentators

2. **Comments on the Draft Guidance from** Argenx:
   a. Response form
   b. Additional evidence
   c. Response appendices

3. **Consultee and commentator comments on the Draft Guidance** from:
   a. Myaware & MDUK joint response

4. **Comments on the Draft Guidance Document from experts:**
   a. Fiona Norwood, Consultant Neurologist – clinical expert, nominated by myaware
   b. Channa Hewamadduma, Consultant Neuromuscular Neurologist and Honorary Senior Lecturer – clinical expert, nominated by Argenx:
      i. Main response
      ii. Annotations on draft guidance document
      iii. Efgartigimod EAMS UK RWE Preprint Report

5. **Comments on the Draft Guidance received through the NICE website**

6. **External Assessment Group critique of company response to DG2**

Appraisal Committee meeting 4 – 5 December 2024

7. **Company additional information provided post-appraisal committee meeting 3:**
   a. Summary of new evidence
   b. Technical appendix

8. **External Assessment Group critique of company post-appraisal committee meeting 3 additional information**

9. **Company letter to NICE and updated base case results**

10. **External Assessment Group critique of updated company base case and cost-effectiveness scenario results**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Efgartigimod for treating generalised myasthenia gravis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using efgartigimod in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: December 2023

Note that this document is not NICE's final guidance on efgartigimod. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using efgartigimod in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 31 January 2024
- Third evaluation committee meeting: 9 May 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Efgartigimod is not recommended, within its marketing authorisation, as an add-on to standard treatment for generalised myasthenia gravis in adults who test positive for anti-acetylcholine receptor antibodies.

1.2 This recommendation is not intended to affect treatment with efgartigimod that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Standard treatment for generalised myasthenia gravis in adults who test positive for anti-acetylcholine receptor antibodies includes surgery, acetylcholinesterase inhibitors or immunosuppressants. Efgartigimod would be used as an add-on to standard treatment.

Clinical trial evidence suggests that efgartigimod plus standard treatment improves symptoms and people's ability to carry out their normal activities compared with standard treatment alone. But it is uncertain if the people in the trial reflect the people who would have efgartigimod in the NHS because the company have proposed a target population with more severe disease.

There are also uncertainties in the economic model that make the likely cost-effectiveness estimates for efgartigimod uncertain. The most likely cost-effectiveness estimates are substantially above what NICE considers an acceptable use of NHS resources. So, efgartigimod is not recommended.

2 Information about efgartigimod

Marketing authorisation indication

2.1 Efgartigimod (Vyvgart, Argenx) is indicated as 'an add-on to standard therapy for the treatment of adult patients with generalised Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for efgartigimod.

Price

2.3 The list price of efgartigimod is £6,569.73 per 400-mg solution for infusion vial and £15,307.47 per 1,000-mg solution for injection vial (excluding VAT, company submission).

2.4 The company has a commercial arrangement, which would have applied if efgartigimod had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Argenx, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Myasthenia gravis is an autoimmune condition that can affect multiple muscle groups, and causes muscle weakness and fatigue. At first, it usually only affects the eye muscles. But, in around 80% of people, it will affect other muscle groups and become generalised myasthenia gravis (gMG). Most people with gMG have anti-acetylcholine receptor (AChR) antibodies. The patient experts explained that symptoms of gMG can vary and that their impact can also change from day to day. They explained the

condition can have substantial physical, emotional and financial impacts on the person with gMG, as well as their family. There is currently no cure for gMG. The patient experts noted that treatments for gMG are associated with side effects that need managing and that there is a high unmet need for effective treatments. They explained that many people with gMG take corticosteroids, but finding a dose that manages symptoms while minimising the risk of side effects is challenging. They also said that strict treatment schedules can impact daily life and that managing these and side effects of multiple treatments together is difficult. The patient experts explained that people with gMG and their carers spend their life fearing a myasthenic crisis. Myasthenic crisis is the most common cause of gMG-related deaths and occurs when the muscles that control breathing stop working. The committee concluded that gMG is a debilitating condition with a high treatment burden.

Clinical management

Treatment options

3.2 gMG is a chronic condition and most people need lifelong treatment. The clinical experts explained that people would usually have treatments outlined in the Association of British Neurologists (ABN) guidelines. But they added that, at the time of this evaluation, the ABN guidelines are being updated. The ABN (2015) guidelines recommend that people are first offered pyridostigmine at the lowest effective dose and that surgery to remove the thymus gland can be considered for people under 45 years. If symptoms continue, people should be offered prednisolone. The clinical experts explained that corticosteroids like prednisolone are associated with notable side effects and that they aim to use minimal doses to minimise side effects. The ABN guidelines recommend that people are offered a non-steroidal immunosuppressant, such as azathioprine, if remission is not achieved on corticosteroids alone. If their condition does not respond to immunosuppressants or they experience notable side effects on increasing corticosteroid doses, expert advice should be sought on the use of plasma exchange or intravenous immunoglobulin (IVIg). The

NHS England commissioning criteria policy for the use of therapeutic immunoglobulin recommends IVIg should be used:

- when urgent inpatient treatment is needed and plasma exchange is not available
- in rare circumstances as a maintenance treatment when all standard treatments have failed and the person is having treatment in a specialist neuromuscular service.

NHS England considers rituximab, an anti-B-cell monoclonal antibody treatment, to be an equally effective treatment to IVIg. It has stated that rituximab should be considered for several populations. The patient experts explained that existing treatments are not only associated with notable side effects but can be slow to take effect. The committee concluded that an effective and fast-acting treatment option would be welcomed by people with gMG and clinicians.

Treatment population

3.3 Efgartigimod has a marketing authorisation as an add-on to standard treatment for gMG. The company positioned efgartigimod as a treatment for gMG in people with uncontrolled symptoms despite established clinical management. The clinical experts considered that efgartigimod could be positioned at several points in the clinical pathway. They added that, initially, it would be used in specialist centres for gMG in people with substantial symptoms despite optimal standard treatment. But, they also explained that, in time, the treatment could be used in additional populations, including the much larger population whose symptoms remain sub-optimally controlled despite standard treatment. The clinical experts explained that this is because gMG becomes more severe over time and so they aim to use the most effective treatments as early as possible. They stated that efgartigimod could also potentially reduce the corticosteroid dose needed. The committee noted that the marketing authorisation indication for efgartigimod positions it at any point after

standard treatment has started. The committee also noted that the company used efficacy data from the ADAPT trial in its model (see section 3.7). The committee considered that the inclusion criteria for ADAPT may not reflect the population that could have efgartigimod in NHS clinical practice if it was recommended within its marketing authorisation. The committee highlighted that the clinical and cost effectiveness of efgartigimod would change for different populations. It concluded that further input is needed from clinical experts to help define a population in which efgartigimod is both clinically and cost effective. It considered that the characteristics of this population should be clearly defined to enable efgartigimod's use in the NHS.

Target population

3.4 As part of its response to draft guidance consultation, the company held a Delphi panel involving 6 experts from neuromuscular specialist centres to identify a target population description. The company explained that the description it proposed closely aligned with the Early Access to Medicines Scheme (EAMS) eligibility criteria (see section 3.8). It proposed that the target population should be people:

- with active, refractory disease, with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 5 or more (over 50% of MG-ADL score from non-ocular symptoms) and
- who cannot tolerate or are ineligible for standard treatment, or in whom standard treatment has failed. (Standard treatment was defined as a maximal dose of steroids, and at least 2 additional treatments, such as non-steroidal immunosuppressants and rituximab, for an adequate period of time, at an adequate dose.)

The company stated that this population has few alternative treatment options and high unmet need, and could be identified in specialist centres. The EAG noted that the company's target population description referred to a group of people ineligible for standard treatment. It considered that this group falls outside the licensed indication for efgartigimod, which

states its use as an add-on to standard treatment. The company said that 'ineligible' did not refer to all standard treatments, and said it is possible that one of the standard treatments may not be suitable. The EAG considered that the company's proposed description could be clearer. It proposed an alternative description for the target population which states that people are ineligible for 'at least one' of the standard treatments. The committee considered that the company and EAG target population descriptions described notably different populations, with the EAG's proposed wording potentially including a population with less-severe disease. The committee understood the difficulties of identifying a target population description for a condition with no single universally accepted treatment pathway. The committee concluded that the company's target population description broadly described the most suitable population to have add-on treatment with efgartigimod, and acknowledged the high unmet need in this population, but some uncertainty remained.

Maintenance IVIg

3.5 The company considered that maintenance IVIg is part of established clinical management in the NHS and that it is used by a notable proportion of the people who would be offered efgartigimod. The EAG explained that it had received clinical advice that IVIg is not regularly used as a maintenance treatment because of a shortage, and because an NHS England commissioning policy substantially restricts maintenance use (see section 3.2). The EAG excluded maintenance IVIg from its base case. At technical engagement the company updated the proportion of people that have maintenance IVIg in its base case based on data collected as part of the EAMS for efgartigimod (see section 3.8; this data is confidential so cannot reported here). At technical engagement, a commissioning expert provided an estimate of the proportion of people with gMG that have maintenance IVIg (this data is confidential so cannot be reported here), which was substantially lower than the proportion used in the company's base case. The commissioning expert said that the higher proportion of people having maintenance IVIg in the EAMS data

may be because people who had efgartigimod through the EAMS were people who urgently needed treatment. At the first evaluation committee meeting the clinical experts provided estimates of the proportion of people with gMG that would likely have maintenance IVIg, for overall use and by model health state. These were substantially lower than the proportion assumed in the company's base case. The clinical experts said that the proportion of people having maintenance IVIg varies between treatment centres, noting higher use in specialist centres, and highlighted that IVIg is more frequently used for severe disease. They also explained that maintenance IVIg use can be continuous or intermittent. The committee noted that the company's model included the cost of maintenance IVIg but assumed no clinical benefits. The committee considered that this was implausible. It noted that this biases the cost-effectiveness results in favour of efgartigimod because the company model assumed substantially more IVIg use in the established clinical management arm. The committee considered that the difference in IVIg use estimates was likely because different populations were being considered. It recalled it was uncertain which population would have efgartigimod if it was recommended in line with the marketing authorisation (see section 3.3).

Maintenance IVIg in target population

3.6 In response to draft guidance consultation, the company used a Delphi panel to directly estimate the proportion of people eligible for maintenance IVIg in its new target population (see section 3.4). The company updated its base case and assumed maintenance IVIg use of 69.17%, distributed between the MG-ADL 5 to 7, 8 to 9, and 10 or above health states based on clinical expert opinion and weighted by the baseline cohort distribution in the model. The EAG considered the evidence from the Delphi panel was appropriate for the proposed target population, but it noted that the model remained sensitive to maintenance IVIg use assumptions. In response to draft guidance consultation, NICE received a comment from a clinical expert stating there is regional variation but maintenance IVIg is a relatively uncommon treatment. The committee noted that the panellists

recruited to the company's Delphi panel were all from specialist centres. It noted the panellists were asked to estimate the proportion of people who would be eligible for IVIg, but that this was different to asking about the proportion of people who would actually have maintenance IVIg. It further noted that the panellists were asked to assume there were no issues around the supply of IVIg and were not asked about IVIg use by MG-ADL health state. The clinical experts explained that not everyone who was eligible for maintenance IVIg would have it. A patient expert noted that although they might be considered eligible for maintenance IVIg they have not had it. Another patient expert noted that they would not be able to access maintenance IVIg at their current treatment centre. The committee further noted that the company's approach to modelling IVIg use did not account for a proportion of people whose disease did not respond to IVIg. Another important limitation in the company's modelling of IVIg was that it did not account for people who would stop IVIg over the lifetime of the model (which is over 50 years in length). The committee considered that IVIg may be stopped because of adverse events, patient choice or a loss of efficacy. Also, few people, if any, would remain on IVIg for such long periods of time as implied by the modelling. The committee also noted that the company's model assumed the maximum dosing frequency for IVIg, which may also overestimate IVIg use. The clinical experts noted that IVIg would usually be a last-line treatment and some people may therefore continue it for some time, but they could not advise on how long IVIg might be used. The committee noted that in the company's base case, undiscounted IVIg acquisition and administration costs accounted for well over £1 million in the established clinical management arm. The committee also noted that there was uncertainty around using MG-ADL scores to estimate IVIg use. This was because other clinical details, alongside MG-ADL score, would likely be used in the NHS when deciding whether to offer IVIg. Overall, the committee concluded that the evidence from the Delphi panel and the company's approach to modelling IVIg use substantially overestimated the use of maintenance IVIg. It noted that the IVIg estimates and modelling used by the company also impacted other

issues, such as placebo effect (see section 3.12) and treatment effect after discontinuation (see section 3.11). This causes them to have greater impact on cost-effectiveness results. It considered that the model should be updated to model IVIg use in a more appropriate and plausible manner (see section 3.23). It also concluded that because of how IVIg use was estimated and modelled, it could not have confidence in any estimate of IVIg use provided by the company's model.

Clinical effectiveness

ADAPT and ADAPT+

3.7 The clinical evidence for efgartigimod came from the ADAPT trial and ADAPT extension (ADAPT+) study. ADAPT was a phase 3, multicentre, double-blind, placebo-controlled trial. It recruited adults with an MG-ADL total score of 5 points or more with over 50% of the total score attributed to non-ocular symptoms and who were on a stable dose of established clinical treatment. Of the 167 people recruited, 129 (77%) tested positive for AChR antibodies. After the first treatment cycle, 68% of the AChR antibody-positive population who had efgartigimod had a reduction of at least 2 points on the MG-ADL scale (clinically meaningful improvement) compared with 30% of people who had placebo. ADAPT+ is an ongoing, open-label, single-arm, multicentre, 3-year extension of the ADAPT trial. Of the 151 people who rolled over from ADAPT to ADAPT+, 111 (74%) tested positive for AChR antibodies. Data from the January 2022 data cut showed that, on average, a clinically meaningful improvement was achieved in cycles 1 through 14. The committee concluded that efgartigimod as an add-on to established clinical management is more effective at improving MG-ADL score than established clinical management alone.

EAMS and EAMS+

3.8 The EAMS aims to provide people who have a high unmet clinical need with earlier access to promising new unlicensed medicines and medicines used outside of their license. The Medicines and Healthcare Products

Regulatory Agency considered that there was unmet need in the AChR antibody-positive population when gMG does not respond to currently available treatments or when these treatments are not suitable. The committee considered that this population had more severe disease than that included in the company's model, with a need for urgent treatment. Efgartigimod was available through the EAMS from May 2022 until its marketing authorisation was granted in March 2023, and since then it has been available through the EAMS+ programme. The company said that the EAMS+ programme will be open until NICE publishes final guidance on efgartigimod. The company explained that it intends to collect additional data through the EAMS to support health technology assessment. At the first meeting, the committee noted that the EAMS data was only used to inform the proportion of people who have maintenance IVIg in the company's base case.

Data sources and generalisability

3.9 In response to draft guidance consultation, the company updated the target population description (see section 3.4). The company said that evidence from ADAPT showed that the efficacy observed in the AChR antibody-positive population is generalisable to the updated target population. So, it did not make any changes to the modelling of clinical effectiveness. The EAG stated that there were low levels of certainty around the evidence supporting the generalisability of the clinical-effectiveness estimates. The EAG also considered that age and gender distribution of people enrolled in EAMS should be used in the model. It noted that the company's proposed target population aligned closely with the EAMS cohort. That cohort was larger than the UK cohort in the MyRealWorld MG study used by the company to inform the baseline age and gender distribution in its revised base case. The company stated that the baseline characteristics of the UK cohort in MyRealWorld MG were similar to those of the EAMS cohort. Therefore, it did not update its base case. The committee noted that no alternative approaches to the modelling of clinical effectiveness were presented to overcome the

uncertainty. The committee concluded that using clinical-effectiveness results from a population broader than the updated target population was a source of uncertainty. The committee considered that baseline characteristics used in the model should align with other inputs, such as quality of life (see section 3.13) and clinical-effectiveness estimates. It therefore concluded that age and gender distribution captured in ADAPT should be used in the model.

Economic model

Company's modelling approach

3.10 The company used a state transition model to estimate the cost effectiveness of efgartigimod plus established clinical management compared with established clinical management alone. It included 4 health states based on the MG-ADL total score (MG-ADL below 5, MG-ADL 5 to 7, MG-ADL 8 to 9, and MG-ADL 10 or more) to capture disease severity, as well as crisis and death health states. The clinical experts explained that the MG-ADL health states used in the model should broadly capture differences in costs and quality of life. But, they further explained that there may be rare circumstances when they do not. They suggested, for example, that someone with the most severe score for a single activity while the other activities are unaffected would have a score of 3. They would therefore be included in the least severe health state. But, a person who scores 1 for all 8 activities would be included in the second-worst health state. The clinical experts also noted that MG-ADL score would not be used on its own to decide whether IVIg should be offered. gMG exacerbations needing hospitalisation were included in the model as an acute event that could occur in any of the MG-ADL health states and that was associated with an additional cost and a utility decrement. The EAG considered that the company's model structure and key assumptions were reasonable. The committee recalled that in the company's model people did not have a subsequent cycle of treatment with efgartigimod if they remained in the MG-ADL below 5 health state. The clinical experts explained that in clinical practice they would not offer

efgartigimod to people with an MG-ADL score below 5 and would stop treatment if a person's MG-ADL score falls below 5. The committee concluded that the company's model structure was generally appropriate for decision making. But, there was some uncertainty with how closely MG-ADL scores inform disease severity, and significant limitations to some aspects of the modelling (see sections 3.6, 3.9, 3.11 and 3.12).

Treatment effect after stopping efgartigimod permanently

3.11 The EAG highlighted that in the company's original base case, the transition probabilities for people who had permanently discontinued efgartigimod resulted in a notable proportion of people remaining in the MG-ADL below 5 health state after 6 months. The EAG also highlighted that the company had stated in its clarification response that it was not aware of any evidence of a residual treatment effect for efgartigimod. So the EAG provided updated transition probabilities assuming that 1% of people remain in the MG-ADL below 5 health state after stopping efgartigimod permanently. At technical engagement, the company provided an additional analysis of ADAPT and ADAPT+ data, real-world evidence from the US and evidence on efgartigimod in other indications that it believed supported a residual treatment effect for efgartigimod after treatment had stopped permanently. It updated its base case to assume that 15% of people remain in the MG-ADL below 5 health state after stopping treatment with efgartigimod. The EAG considered that the company's assumption was reasonable and updated its base case to match the company's. The committee noted that this assumption had a substantial effect on the cost-effectiveness results and accounted for around 50% of incremental quality-adjusted life year (QALY) gains for efgartigimod in the EAG's base case. At the first meeting, it concluded that a residual treatment effect after treatment stops was plausible but uncertain. The committee stated it would have preferred more evidence about the possible residual treatment effect, which should include clinical expert input. At the second meeting the company maintained its base-case position, assuming that 15% of people remain in the MG-ADL below

5 health state after permanently stopping treatment with efgartigimod. It provided a statement from one clinical expert who, after reviewing the additional evidence provided at technical engagement, believed a 15% residual effect is plausible. One of the clinical experts at the meeting stated that they could not comment on the plausibility of such an effect. The EAG noted that the population in ADAPT and ADAPT+ was broader than the company's proposed target population (see section 3.4). It explained that it was uncertain if the company's proposed target population and the ADAPT populations would have a similar proportion of people with a residual treatment effect after stopping efgartigimod. In response to draft guidance consultation, NICE received a comment from a clinical expert that stated that they were unaware of evidence that some people can stop efgartigimod without a relapse. They further stated that most people seem to need 7- to 8-week cycles and become rapidly symptomatic once treatment is stopped or postponed. The committee considered that the company's approach to modelling a residual treatment effect after treatment stops continued to be plausible but highly uncertain. The committee noted that the available evidence was limited with short follow up. It further noted that it had not been presented with the reasons for discontinuation in those who maintained an MG-ADL score of below 5 after permanently stopping efgartigimod . The committee recalled that varying the percentage (from 15% to 1%) of people that remain in the MG-ADL below 5 health state after permanently stopping efgartigimod had a substantial effect on the cost-effectiveness results. The committee also noted that treatment effect after permanent discontinuation may be linked to the placebo effect (see section 3.12). But, the committee noted the EAG's comments that the company's model could not adjust the treatment effect after permanent discontinuation assumptions, while also retaining the placebo effect in the established clinical management arm. The committee considered that it would like to see further input on this issue (see section 3.23). It concluded that it would consider the company's assumption alongside other scenarios, but noted the uncertainty assocatied with these assumptions.

Placebo effect

3.12 In the company's model, the transition probabilities for the first 4 model cycles in the established clinical management arm were derived from observations over the first 16 weeks in the placebo arm of ADAPT. After the fifth model cycle, people in the established clinical management arm were assumed to return to baseline health state distribution and remain in the same health state unless a crisis or death occurred. The company stated that this assumption was conservative because it meant that the condition would not get worse. After the first meeting, the NICE technical team asked the company to explain:

- why the observed effect in the established clinical management arm would not persist over the long term and
- if it believed the observed effect was due to any of the following mechanisms:
  - regression to the mean (a tendency for extreme values to move closer to the mean when measures are repeated over time)
  - a trial effect (benefit from being in the trial that would apply to both arms, and not in routine practice)
  - a 'true placebo' effect (benefit from the expectation that treatment may lead to improvement, which would apply to both arms, and may apply in practice).

The company noted that the average duration of established clinical management from disease diagnosis was 9.3 years in the AChR antibody-positive population in ADAPT. It also noted that the ADAPT inclusion criteria required people to have an MG-ADL score of at least 5, despite treatment with established clinical management. The company stated that this suggested that established clinical management would be unlikely to reduce disease activity. The company explained that no long-term data from the placebo arm of ADAPT is available. The company believed that regression to the mean, a trial effect and a placebo effect all likely played a role in the observed response. But, it stated that these mechanisms are

specific to a trial setting. The company recalled that in ADAPT, 30% of the established clinical management arm had an MG-ADL response. It suggested that a response of this size could likely only be attributed to a placebo effect. The company stated that in its model the efgartigimod cohort are assumed to worsen during the off-treatment period after each treatment cycle and after permanent treatment discontinuation. The EAG considered the company's approach to modelling the established clinical management arm was reasonable. The committee noted that randomised controlled trials, such as ADAPT, provide evidence for relative treatment effects. It considered that by assuming that the observed effect in the established clinical management arm does not persist, the company's model no longer reflected the relative treatment effect observed in ADAPT and instead artificially inflated the treatment effect. This problem was compounded when assuming a treatment effect for efgartigimod persists after permanently stopping treatment (see section 3.11). The committee noted the size of the response observed in the placebo arm. But, it believed that it was unlikely that a true placebo effect would have such a response and instead it was most likely a statistical consequence of regression to the mean. The committee agreed that in the model the efgartigimod cohort should be assumed to worsen during the off-treatment period. But it did not consider that this justified removing the observed treatment effect from the established clinical management arm. The committee therefore concluded that the benefit observed in the placebo arm of ADAPT should be maintained over the time-horizon of the model.

Utility values

Source of utility values

3.13 Health-related quality of life data was collected in ADAPT using the EQ-5D-5L and was mapped to the EQ-5D-3L. At the first meeting, the company's model used utility values 0.105 higher in the efgartigimod arm than in the established clinical management arm. The company stated that MG-ADL does not fully capture the effect of efgartigimod, so the benefit of efgartigimod would be underestimated if it were only captured in

the model using the transition probabilities. The EAG considered that the method the company used to derive utility values and that using higher utility values in the efgartigimod arm were reasonable. It explained that clinical advice it had received suggested some of the difference in utility values between the 2 arms may be because of differences in corticosteroid use. The committee noted the magnitude of the difference in utility values between the 2 arms and that it was greater than the utility benefit associated with transitioning to the next less-severe MG-ADL health state. The committee further noted that the company's model used higher utility values in the efgartigimod arm for the MG-ADL below 5 health state, in which the model assumed people would not have efgartigimod, which did not appear valid. The committee noted it had not seen evidence to support the higher utility values used in the efgartigimod arm for example, due to differences in corticosteroid use between arms. It considered that corticosteroid use in specific MG-ADL health states might not differ substantially between the 2 arms, and noted that in the model it was assumed people in the MG-ADL below 5 health state would not use corticosteroids. It highlighted that in the more severe MG-ADL health states, corticosteroid use would be optimised regardless of whether efgartigimod was used or not. The committee concluded that the same utility values should be used for the 2 arms. In response to draft guidance consultation, the company revised its base case to use the same utility values from the MyRealWorld MG study for the 2 arms. It considered that data from MyRealWorld MG (a prospective, observational, longitudinal study that aimed to capture the impact of MG from the perspective of people with the condition) was more accurate than data collected in ADAPT. The company proposed that because data from ADAPT was collected in a clinical trial setting, where people were monitored closely, this may have resulted in overvaluation of health state utility. It considered that using pooled data from ADAPT would include some of the effect of efgartigimod. It highlighted that data from MyRealWorld MG is representative of people having established clinical management, including immunoglobulins and rituximab. The EAG noted that the

populations included in both ADAPT and MyRealWorld MG are different to the new proposed target population (see section 3.4). It further stated that it considered the MyRealWorld MG study to be at high risk of bias. The EAG considered that there remained significant uncertainty around the source of health state utility values, but that utilities from the EAMS or the subgroup in ADAPT that meets the new target population description would be more appropriate. The committee noted that the NICE health technology evaluations manual states that EQ-5D data can be sourced from the literature when it is not available in the relevant clinical trials. It recalled that EQ-5D data was available from ADAPT. The committee considered that utility values used in the model should align with other inputs, such as the baseline characteristics (see section 3.9) and clinical-effectiveness estimates. On balance, the committee concluded that pooled utility values from ADAPT should be used in decision making.

Carer quality of life

3.14 The company said that the symptoms people with gMG experience and their need for support has a substantial impact on carers. Carers' health-related quality of life was not measured in ADAPT. Instead, in its original base case, the company used a published study that reported carer disutility at different severity stages of multiple sclerosis, measured using the Patient-Determined Disease Steps (PDDS) scale, to map to the MG-ADL and crisis health states. The company said that multiple sclerosis data was chosen because multiple sclerosis and gMG are both chronic, autoimmune conditions with similar symptoms that mainly affect young women. The EAG acknowledged that there are some similarities between multiple sclerosis and gMG. But, it noted that the conditions each have different characteristics that could have an impact on carer health-related quality of life, such as the impact on a person's mobility, which limit the generalisability of the 2 conditions. At technical engagement, the company provided the results of a survey it conducted exploring the impact of gMG on carers. It said that the survey showed that caregiver responsibilities constitute a large burden on carers. The EAG noted that

the survey results should be interpreted with caution. It explained that the survey was descriptive and did not provide values that could be used directly in the model. The EAG further explained that the population who completed the survey may not be generalisable to the overall population of people with gMG in England. The EAG's base case did not include carer disutilities because it considered that the company had not provided robust evidence for their inclusion. The EAG also received clinical expert advice that most people with gMG are independent and would not need lots of caregiver time. The patient experts explained how gMG has a notable impact on carers and how carers often spend a substantial amount of time providing care. The patient experts noted that carers will sometimes need to help prevent choking and that this can have a substantial impact on their mental health and prevent carers going out and leading independent lives. The committee recognised that, depending on the severity of the condition, gMG can have a substantial impact on carers' lives. But it further noted that MG-ADL examines a range of symptoms, while the PDDS focuses on a person's ability to walk, so the committee considered that mapping between MG-ADL and PDDS was not appropriate. The committee noted that carer disutilities contributed substantially to the overall QALY gain associated with efgartigimod in the company's model. The committee considered that the carer disutilities used appeared large and that it had not seen evidence to suggest that a person with gMG and their carer would experience a similar level of disutility. The committee concluded that depending on the severity of the condition, gMG could have a substantial impact on carers' lives, which it would take into account qualitatively. But that the disutilities used in the company's model were not appropriate for decision making without further evidence.

Updated carer disutilities

3.15 In response to draft guidance consultation, the company updated its base case to include disutilities obtained from 2 unpublished studies. The company noted that in these studies the utility values of the carers

generally declined with the severity of the condition but that no linear relationship was found. The EAG explained that the lack of linear relationship could result from the small sample size. It further explained that these studies did not include a matched-control group so it could not determine if the utility decrements were only from caregiving. The EAG noted that the 2 studies were observational and potentially subject to selection bias because people taking part were self-selecting. In response to draft guidance consultation, NICE received a comment from the ABN stating that comparison of carer support is not appropriate in an MG population. The committee considered that because the disutilities presented at the second meeting were collected from carers of people with gMG they were potentially more appropriate and relevant than the disutilities presented at the first meeting. The committee recognised that the availability of carer disutilities data sources are often limited. But, it noted the limitations identified by the EAG and that some of the values lacked face validity. The committee concluded that it would continue to take into account the impact on carers' lives qualitatively in its preferred assumptions for decision making.

Costs

Corticosteroid complications

3.16 The company said that the published literature shows that higher doses of corticosteroids are associated with higher costs from treating complications. In its original submission, the company identified 3 studies that estimated the costs for corticosteroid-related chronic complications with low- and high-dose corticosteroid use. The company's base case used corticosteroid complication costs from a study in people with systemic lupus erythematosus (SLE) done in Sweden (Bexelius et al. 2013). The company explained that it selected this study because SLE and gMG are both autoimmune conditions. It said that it could also be assumed that costs were comparable between the UK and Sweden because the 2 countries have similar socioeconomic conditions. The EAG used corticosteroid complication costs from the second study identified by

the company, which was in people with asthma in the UK (Voorham et al. 2019). The EAGbelieved that this study was more representative of costs in the UK. The clinical experts explained that the costs from the Voorham et al. study are unlikely to be generalisable to gMG because asthma does not share similar characteristics. The committee noted that the third study identified by the company (Janson et al. 2018) shared similarities with the other 2 studies because it was done in Sweden and included people with asthma. The clinical experts further explained that in all 3 studies, the doses of corticosteroids and the threshold used in the company's model to define high-dose corticosteroids were notably lower than what they would expect for people with gMG. The clinical experts noted that higher doses of corticosteroids could result in different complications and therefore costs. The committee considered that the Voorham et al. study excluded key weight-related adverse events such as sleep apnoea. The committee noted that the company had not provided evidence that resource use and costs from Sweden are generalisable to the NHS. It further noted that costs from the Bexelius et al. study were notably higher than the costs from the other studies. The committee was unsure whether SLE is directly generalisable to gMG. It felt that the costs from Bexelius et al. lacked face validity and may be confounded, because the study did not account for condition severity or exclude condition-related costs. The committee concluded that none of the studies identified by the company were suitable for decision making. It also concluded that corticosteroid complication costs should be generalisable to NHS clinical practice, applicable to gMG and valued using prices relevant to the NHS.

Updated corticosteroid complication costs

3.17 In response to draft guidance consultation, the company updated its base case to use corticosteroid complication costs derived from NHS reference costs and the frequency of corticosteroid-related adverse events from a US study in people with MG (Lee et al. 2018). The company's updated base case applied the same costs for both low- and high-dose corticosteroid use. The EAG considered that the company's estimates of

complication costs were not fit for purpose and lacked face and methodological validity. It explained that it had concerns related to the use of adverse event frequencies reported by Lee et al. and the approach taken by the company to assign costs. The EAG provided a scenario in which corticosteroid complication costs were applied only for people in Lee et al. who found their side effects intolerable. In response to draft guidance consultation, NICE received a comment from a clinical expert who suggested that most people with refractory disease will have stopped taking steroids because they were not effective. The committee recognised that the corticosteroid complication costs used in the company's revised base case used data from a study in people with MG. But, it felt that the costs lacked face validity. The committee considered that some of the costs used were not appropriate and that some of the complications considered would be treated as part of ongoing routine care. The committee recalled the clinical expert comment received during draft guidance consultation. It considered that it was likely that some of the people captured in the company's proposed target population description would have stopped having corticosteroids. The committee concluded that the EAG's scenario, in which costs were only applied for people in Lee et al. who found their side effects intolerable, was appropriate for decision making.

Subcutaneous formulation of efgartigimod

3.18 In response to draft guidance consultation, the company stated that both subcutaneous and intravenous formulations of efgartigimod will soon be licensed. The company provided a scenario analysis that assumed 80% of people had the subcutaneous formulation while 20% had the intravenous formulation. Acquisition and administration costs were adjusted accordingly but it was assumed all other costs and outcomes were unchanged. The company stated that the subcutaneous formulation would enable faster administration, reducing burden on people with gMG, carers and healthcare providers. The clinical experts explained that it is difficult to estimate the exact proportion of people who would have the

subcutaneous formulation, but that 80% was a reasonable assumption because of the potential additional benefits. The committee concluded that a scenario in which 80% of people have the subcutaneous formulation was appropriate for decision making. But, the committee recognised that it would not be able to recommend efgartigimod based on these assumptions until the subcutaneous formulation is included in the marketing authorisation.

Cost-effectiveness estimates

3.19 Because of confidential commercial arrangements for efgartigimod and some of the established clinical management treatments, the exact cost-effectiveness results are confidential and cannot be reported here. Only the company's base-case incremental cost-effectiveness ratio (ICER) was within the range normally considered to be a cost-effective use of NHS resources. The EAG's base-case ICER was substantially above this range.

3.20 The committee considered that the ICERs presented by the company and EAG were uncertain. But it considered that, given the impact of its preferred assumptions, it was highly likely that its preferred ICER would be substantially above the range usually considered a cost-effective use of NHS resources.

The committee's preferred assumptions

3.21 The committee's preferred assumptions included:

- using population characteristics from ADAPT (see section 3.9)
- considering a range (1% to 15%) of people remaining in the MG-ADL below 5 health state 6 months after permanently stopping efgartigimod (see section 3.11)
- maintaining the benefit observed in the placebo arm of ADAPT over the time-horizon of the model (see section 3.12)

- using the same pooled utility values from ADAPT for both the efgartigimod and established clinical management arms (see section 3.13)
- considering carer disutilities qualitatively (see section 3.15)
- including corticosteroid complication costs only for people in the Lee et al. study who found their side effects intolerable (see section 3.17)
- 80% of people having the subcutaneous formulation and 20% having the intravenous formulation (see section 3.18).

The committee considered that the company's target population (see section 3.4) broadly described the most suitable population to have add-on treatment with efgartigimod but there was still some uncertainty. The ADAPT and ADAPT+ studies recruited a broader population than the one covered by the company's target population description. So, using data from these studies to inform modelling assumptions was also associated with uncertainty (see section 3.9). The committee noted that the cost-effectiveness estimates were highly sensitive to changes in maintenance IVIg use. It considered that the evidence from the Delphi panel and the company's approach to modelling IVIg use substantially overestimated the use of maintenance IVIg. It could therefore have no confidence in these estimates.

Acceptable ICER

3.22 NICE's health technology evaluations manual notes that, above a most plausible ICER of £20,000 per QALY gained, decisions about the acceptability of the technology as an effective use of NHS resources will consider the degree of uncertainty around the ICER and any benefits of the technology that were not captured in the QALY calculations. The committee will be more cautious about recommending a technology if it is less certain about the evidence presented. The committee noted the high unmet need in the company's target population (see section 3.4). The committee also noted that gMG could have a substantial impact on carers' lives (see section 3.15). The committee agreed that the maximum

acceptable ICER would be at the upper end of the £20,000 to £30,000 per QALY gained range that NICE considers a cost-effective use of NHS resources. But, this would require the areas of outstanding uncertainty to be resolved (see section 3.21).

Additional analysis

3.23 The committee outlined the analysis that it would like to see the company provide. In particular, it stated that IVIg use should be modelled to address the wide range of committee concerns (see sections 3.5 and 3.6). These concerns included:

- the IVIg use assumed for MG-ADL health states was likely overestimated because the question in the company's Delphi panel asked about eligibility rather than uptake and assumed no supply issues
- there was no discontinuation modelled for IVIg but it may be stopped, for example, because of adverse events, lack of clinically meaningful response or patient choice
- no QALY benefit was assumed for IVIg use, which biased cost-effectiveness results in favour of the efgartigimod arm
- maximum dose frequency was assumed.

The committee would also like to see further analysis and input on:

- Treatment effect after permanent discontinuation (see section 3.11), including specific input on:
    - the plausibility of a residual treatment effect once efgartigimod has been stopped permanently and how this is biologically possible
    - how long a residual treatment effect may persist if an effect is plausible

- how the effect may be linked to the placebo effect (see section 3.12)

- The generalisability of data used in the model to estimate the cost-effectiveness of efgartigimod in the company's target population (see sections 3.4, 3.7 to 3.9), including:
  - Further input on how baseline characteristics, treatment effectiveness, utility values, and other model inputs compare to what would be expected in a population with a more severe disease (as proposed by the company).

Other factors

Equality

3.24 The committee noted the patient experts' comments that a person's socioeconomic status and how close they live to a gMG specialist centre may impact their ability to access efgartigimod. The committee also noted the clinical experts' comment that pregnant people may not be able to have efgartigimod until additional information is available. But, the committee noted that access to specialist centres is an implementation issue that cannot be addressed by a NICE technology appraisal recommendation. The committee considered that if efgartigimod was recommended, the decision to use efgartigimod during pregnancy should be made by a patient and their clinician if the clinical benefit outweighs the risks. No other potential equalities issues were identified.

Innovation

3.25 The company and clinical experts considered efgartigimod to be innovative, stating that it had a novel mechanism of action that specifically targets the underlying cause of gMG. The clinical experts also noted that efgartigimod can be given at home, and works rapidly. The committee considered that all additional benefits of efgartigimod had already been taken into account.

Conclusion

3.26 The committee considered that the cost-effectiveness estimates presented by the company and EAG were highly uncertain, and that given the uncertainty, it would like to see additional analysis. But the committee considered that, given its preferred assumptions, and based on the analysis it had seen, the cost-effectiveness estimates were highly likely to be above the range that NICE considers a cost-effective use of NHS resources. The committee concluded that efgartigimod could not be recommended for treating gMG in adults who test positive for AChR antibodies.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Megan John

Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Ross Wilkinson

Technical lead

Alan Moore

Technical adviser

Celia Mayers

Project manager(s)

ISBN: [to be added at publication]

NICE National Institute for Health and Care Excellence

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

The Appraisal Committee is interested in receiving comments on the following:

- has all of the relevant evidence been taken into account?
- are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- are the provisional recommendations sound and a suitable basis for guidance to the NHS?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;
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Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Comment number *(and theme)*	**Comments**
1. Definition of the target patient population and where efgartigimod is expected to be used in clinical practice (Relevant section from DG) 3.4 The committee understood the difficulties of identifying a target population description for a condition with no single universally accepted treatment pathway. The committee concluded that the company's target population description broadly described the most suitable population to have add-on treatment with efgartigimod, and acknowledged the high unmet need in this population, but some uncertainty remained.	The Company confirms that the target population is: Patients with active, refractory disease, with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥5 (>50% of MG-ADL score due to non-ocular symptoms), who have failed, not tolerated or are ineligible for standard therapy. *Standard therapy includes a maximal dose of steroids and at least 2 non-steroidal immunosuppressive therapies (NSISTs) for an adequate period of time at an adequate dose.*

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Efgartigimod for treating generalised myasthenia gravis [ID4003]

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	This population is consistent with the criteria outlined in the Blueteq form, which has been a requirement for all patients entering the EAMS/EAMS+ programme. Therefore, the EAMS/EAMS+ population is representative of the target population. Efgartigimod will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements to provide specialised neurology services. The EAMS/EAMS+ programme is currently offered within MG specialist centres, and efgartigimod, once commissioned, will follow the same model of service provision. All patients will continue to be registered through Blueteq, to ensure alignment with the target patient population, as described above. See further details in the New Evidence Submission document (Area 1).
2. Estimating the level of usage of maintenance IVIg in the target patient population (Relevant section from DG) 3.6 Overall, the Committee concluded that the evidence from the Delphi panel and the Company's approach to modelling IVIg use substantially overestimated the use of maintenance IVIg. It considered that the model should be updated to model IVIg use in a more appropriate and plausible manner.	Existing evidence on the level of maintenance IVIg usage in gMG is limited and of poor quality, with the National Database for IVIg recognised as insufficient for this purpose. Therefore, a Delphi panel of a geographically representative sample of six expert clinicians was conducted to address this evidence gap. Despite this evidence being submitted ahead of ACM2, the Company notes that it was dismissed by the Committee as it considers that the analysis provided may lead to a substantial overestimate of the use of IVIg. However, the Committee did not indicate what figure or range of figures for maintenance IVIg use it considers plausible. The Committee has indicated that modelling should consider commissioning restrictions and supply issues concerning the off-label usage of IVIg, which is subject to various local hospital/trust purchasing and which differs across the UK. While we appreciate that NICE can consider off-label comparator technology use, the supply issues and commissioning restrictions of a third party's product used off-label are not relevant considerations to the appraisal of efgartigimod within its licensed indication.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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	Seeking the most relevant, independent data to inform this decision problem, the Company has revised its approach using real-world evidence from the EAMS/EAMS+ programme, estimating the level of maintenance IVIg use in the target patient population. This evidence is based on an independent report that has been compiled and co-authored by 20 gMG expert clinicians from 13 MG specialist centres, which describes the real-world experience of using efgartigimod in a cohort of gMG patients (n=48) in the UK, and documents prior maintenance IVIg usage within these patients. See further details in the New Evidence Submission document (Area 2).
3. Appropriately modelling the efficacy of maintenance IVIg (Relevant section from DG) 3.5 The committee noted that the company's model included the cost of maintenance IVIg but assumed no clinical benefits. The committee considered that this was implausible. It noted that this biases the cost-effectiveness results in favour of efgartigimod because the company model assumed substantially more IVIg use in the established clinical management arm.	During ACM2, the Company explained that the short-term clinical effect of IVIg was implicitly accounted for in the model by the assumption that patients in the established clinical management (ECM) arm do not experience disease progression. Instead, patients remain in the same health state for the model time horizon. The Company considers this a reasonable assumption when considering what is demonstrated in the available literature. However, to progress with the evaluation and support the Committee in reaching a positive decision, the Company has revised its base case to explicitly include IVIg efficacy. This is based on evidence identified via the systematic literature review of the efficacy of treatments in scope, which was included in the Company's original evidence submission. The evidence was analysed and synthesised using a Network Meta Analysis (NMA). See further details in the New Evidence Submission document (Area 4).
4. Appropriately modelling maintenance IVIg dosing and discontinuation (Relevant section from DG) 3.6 The Committee further noted that the Company's approach to modelling IVIg use did not account for a proportion of people whose disease did not respond to IVIg. Another important limitation in the Company's modelling of IVIg was that it did not account for people who would stop IVIg over the lifetime of the model (which is over 50 years in length). The Committee considered that IVIg may be stopped because of	The Committee stated that the Company's model assumed the maximum dosing frequency for IVIg, which is factually inaccurate. The model considers an IVIg dose of 1g/kg per administration cycle, in line with the relevant NHS Commissioning Policy. The model also considers IVIg administration every 4 weeks, in accordance with MG guidelines from the Association of British

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Draft guidance comments form

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adverse events, patient choice or a loss of efficacy. Also, few people, if any, would remain on IVIg for such long periods of time as implied by the modelling. The Committee also noted that the Company's model assumed the maximum dosing frequency for IVIg, which may also overestimate IVIg use.	Neurologists, which states that IVIg duration of response (efficacy) is approximately 3-4 weeks. Therefore, the use of IVIg every 3 weeks is also plausible and could be considered a maximum dose under UK guidelines. This is further evidenced by clinical trials, identified via the systematic literature review, of the efficacy of IVIg as a maintenance treatment, which was included as part of the Company's initial submission. In these studies, the efficacy of IVIg was investigated by administering 1g/kg of IVIg to patients every 3 weeks. The Company sought to explore and validate assumptions through facilitated interviews with six gMG clinical experts to strengthen the evidence related to maintenance IVIg administration in line with UK clinical practice. Results confirm that the median dose and frequency for maintenance IVIg is 1g/kg every 4 weeks. Additionally, discontinuation data of maintenance IVIg was confirmed from the available literature and validated by the clinical experts. See further details in the New Evidence Submission document (Area 3) and Appendix C, which outlines the methodology and key outcomes from the facilitated interviews and explains how the resulting estimates have been incorporated into the cost-effectiveness model.
5. Generalisability of data sources used in the model (Relevant section from DG) 3.9 The Committee concluded that using clinical-effectiveness results from a population broader than the updated target population was a source of uncertainty	The Company acknowledges the Committee's observations that clinical data from the ADAPT trial are informing the cost-effectiveness results and that the full ADAPT population is not directly representative of the intended target population. The Company maintains that evidence from ADAPT in the AChR-Ab+ population and from the EAMS/EAMS+ programme is generalisable to the target population. Generalisability can be demonstrated by comparing ADAPT data with data from the ADAPT AChR-Ab+ refractory subgroup as well as the EAMS/EAMS+ population, both of which can be considered as a good proxy of the target population.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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	There is alignment of baseline characteristics across these patient populations, and efgartigimod has been shown to have similar clinical efficacy, irrespective of the subgroup considered or prior lines of therapy received by patients. Furthermore, QoL utilities obtained in the post-hoc analysis from the ADAPT refractory subgroup are aligned with utilities used in the model. These factors underline that the outcomes of the economic model are generalisable to the intended target population. As per the Committee's preferred modelling inputs, baseline characteristics in the revised model are derived from the ADAPT population, in line with other inputs. The generalisability of data sources used in the model has also been demonstrated in detail in the New Evidence Submission document (Area 1) and Appendix A.
6. Placebo effect (Relevant section from DG) 3.12 The Committee noted that randomised controlled trials, such as ADAPT, provide evidence for relative treatment effects. It considered that by assuming that the observed effect in the established clinical management arm does not persist, the Company's model no longer reflected the relative treatment effect observed in ADAPT and instead artificially inflated the treatment effect. This problem was compounded when assuming a treatment effect for efgartigimod persists after permanently stopping treatment. The Committee noted the size of the response observed in the placebo arm. But it believed that it was unlikely that a true placebo effect would have such a response and instead it was most likely a statistical consequence of regression to the mean. The Committee agreed that in the model the efgartigimod cohort should be assumed to worsen during the off-treatment period. But it did not consider that this justified removing the observed treatment effect from the established clinical management arm. The Committee therefore concluded that the benefit observed in the placebo arm of ADAPT should be maintained over the time-horizon of the model.	To address the challenges raised by the Committee, in the revised base case analysis, the model maintains the benefit observed in the placebo arm of ADAPT. This is applied equally to both treatment arms. As highlighted by the EAG, this would conflict with any assumption specifically regarding any residual effect post discontinuation of efgartigimod. For this reason, the latter was removed from the base case analysis. More specifically, patients in the efgartigimod arms are assumed to receive conventional therapy post-discontinuation. They are, therefore, assumed to remain distributed between model health states in the same manner as the ECM cohort. This approach allows consistency in the simulation assumptions between modelled treatment arms. The Company also developed scenario analyses where different assumptions on the placebo effect are considered. In these scenario analyses, the effect of a potential residual treatment effect following cessation of treatment with efgartigimod is also considered.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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	See further details in the New Evidence Submission document (Area 5) and Appendix E, which contains the updated base-case analysis and supplementary sensitivity analyses.
7. Treatment effect after stopping efgartigimod permanently, and link to the placebo effect (Relevant section from DG) 3.11 At the second meeting the company maintained its base-case position, assuming that 15% of people remain in the MG-ADL below 5 health state after permanently stopping treatment with efgartigimod. It provided a statement from one clinical expert who, after reviewing the additional evidence provided at technical engagement, believed a 15% residual effect is plausible. One of the clinical experts at the meeting stated that they could not comment on the plausibility of such an effect. The Committee considered that the Company's approach to modelling a residual treatment effect after treatment stops continued to be plausible but highly uncertain. The Committee noted that the available evidence was limited with short follow up. It further noted that it had not been presented with the reasons for discontinuation in those who maintained an MG-ADL score of below 5 after permanently stopping efgartigimod. The Committee recalled that varying the percentage (from 15% to 1%) of people that remain in the MG-ADL below 5 health state after permanently stopping efgartigimod had a substantial effect on the cost-effectiveness results. The Committee also noted that treatment effect after permanent discontinuation may be linked to the placebo effect. But the Committee noted the EAG's comments that the Company's model could not adjust the treatment effect after permanent discontinuation assumptions, while also retaining the placebo effect in the established clinical management arm. The Committee considered that it would like to see further input on this issue. It concluded that it would consider the Company's assumption alongside other scenarios.	During technical engagement, the Company provided an analysis of data from the Phase 3 ADAPT/ADAPT+ clinical trials, real-world evidence of efgartigimod use and evidence which examined a persistent effect for efgartigimod in another indication, which suggested the presence of a disease-modifying effect. The assumption of a 15% residual treatment effect was seen as reasonable by the EAG. At ACM1, the Committee concluded that a residual treatment effect after treatment, which stops at a level of 15% of patients, was plausible but uncertain and asked for further clinical input. The additional clinical validation provided by the Company for ACM2 was from a prominent clinical expert, one of the two clinical experts on the panel for the Committee Meeting. Although the inclusion of this effect in the model was based on clinical data and validated by a leading clinical expert, as per the Committee's initial request, it was rejected by the Committee. The guidance states that the Company's base case at ACM2 assumed that 15% of people remain in the MG-ADL below 5 health state after permanently stopping treatment with efgartigimod. This statement is misleading, as this figure of 15% does not refer to the entire cohort of patients that receive efgartigimod. Rather, 15% of patients who are in the MG-ADL below 5 health state at the point of treatment discontinuation with efgartigimod remain in this health state. However, the assumption of a maintained placebo effect in the ECM arm is incompatible with the residual treatment effect for some patients who discontinue treatment with efgartigimod.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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	Therefore, the residual treatment effect assumption was removed entirely from the base case to align with the placebo effect assumption (as detailed above). See further details in the New Evidence Submission document (Area 5) and Appendix E, which contains the updated base-case analysis and supplementary sensitivity analyses.
8. Source of utility values (Relevant section from DG) 3.13 The Committee noted that the NICE health technology evaluations manual states that EQ-5D data can be sourced from the literature when it is not available in the relevant clinical trials. It recalled that EQ-5D data was available from ADAPT. The Committee considered that utility values used in the model should align with other inputs, such as the baseline characteristics and clinical-effectiveness estimates. On balance, the Committee concluded that pooled utility values from ADAPT should be used in decision making.	In response to the Committee's request to use pooled utility values from ADAPT, the Company has used utility values estimated from ADAPT data using a mixed model without treatment covariate for the efgartigimod and ECM arms. See further details in the New Evidence Submission document (Area 1).
9. Caregiver disutilities (Relevant section from DG) 3.15 The company noted that in these studies the utility values of the carers generally declined with the severity of the condition but that no linear relationship was found. The EAG explained that the lack of linear relationship could result from the small sample size. It further explained that these studies did not include a matched-control group so it could not determine if the utility decrements were only from caregiving. The EAG noted that the 2 studies were observational and potentially subject to selection bias because people taking part were self-selecting. In response to draft guidance consultation, NICE received a comment from the ABN stating that comparison of carer support is not appropriate in an MG population. The Committee considered that because the disutilities presented at the second meeting were collected from carers of people with gMG they were potentially more appropriate and relevant than the disutilities presented at the first meeting. The Committee recognised that the availability of carer disutilities data sources are often limited. But it noted the limitations identified by the EAG and that some of the values lacked face validity. The Committee concluded that it would continue to take into account the impact on carers' lives qualitatively in its preferred assumptions for decision making.	During the appraisal, evidence on the burden of gMG on caregivers was presented in multiple instances, including testimony from clinical experts and patients, as well as a bespoke survey commissioned by the Patient Advocacy Groups (MDUK and MyAware) explaining how gMG has a notable impact on carers and how carers often spend a substantial amount of time providing care. Based on this evidence, the Committee recognised that, depending on the severity of the condition, gMG can have a substantial impact on carers' lives. The company maintains that the evidence presented at ACM2, based on a Quality-of-life study on 39 gMG patients and caregivers, should be relevant for decision-making despite the limitations described by the EAG and the Committee. Though the Company disagrees with the Committee's stated approach, it is willing to make concessions to facilitate Committee decision-making. Therefore, caregiver disutilities have been removed from the revised base case analysis and are explored only in sensitivity analysis.

NICE National Institute for Health and Care Excellence

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 February 2024. Please submit via NICE Docs.

10. Costs of corticosteroid complications in the model (Relevant section from DG) 3.17 The Committee concluded that the EAG's scenario, in which costs were only applied for people in Lee et al. who found their side effects intolerable, was appropriate for decision making.	In alignment with the Committee's preferred approach, the cost of corticosteroid complications was calculated based on the frequency of only intolerable adverse events reported in the study by Lee et al. The Company notes that there is significant burden associated with the use of corticosteroids, that is recognised by clinical experts and gMG patients. But this burden is not fully captured in the economic assessment of established clinical management, due to the decision taken by the Committee to only incorporate costs for the most severe corticosteroid related adverse events.
11. Subcutaneous formulation of efgartigimod (Relevant section from DG) 3.18 The committee concluded that a scenario in which 80% of people have the subcutaneous formulation was appropriate for decision making. But, the committee recognised that it would not be able to recommend efgartigimod based on these assumptions until the subcutaneous formulation is included in the marketing authorisation.	The Company is pleased to confirm MHRA approval, on 6 February 2024, of the subcutaneous formulation of efgartigimod. As such, the Company's base case analysis includes a mix of 80% of people receiving the subcutaneous formulation and 20% receiving the intravenous formulation, aligned with the Committee's preferred assumption.

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Single technology appraisal

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

New evidence submission

7 March 2024

File name	Version	Contains confidential information	Date
Efgartigimod summary of new evidence [redacted] Post DG2 Final_updated	1.0	Yes	7 March 2024

1 Provision of new information for consideration: ID4003 Efgartigimod for treating generalised myasthenia gravis (gMG)

Following the second Appraisal Committee Meeting (ACM2) regarding efgartigimod for treating gMG on 16th November 2023, Draft Guidance was published (NICE, 2023)[1]. In the Draft Guidance, the Committee described gMG as a debilitating condition with a high treatment burden and considered that existing treatments are not only associated with notable side effects but can also be slow to take effect. The Committee concluded that an effective and fast-acting treatment option would be welcomed by both clinicians and patients with gMG.

The clinical benefit of efgartigimod is well-established and accepted by the Committee. The Draft Guidance states that efgartigimod plus standard treatment improves symptoms and people's ability to carry out their normal activities compared with standard treatment alone. There is also strong advocacy from gMG clinical experts and patient organisations, who recognise the importance of an additional treatment option for patients and, specifically, the benefit provided by efgartigimod. The Company has also provided substantial supportive real-world evidence demonstrating the benefits of efgartigimod for UK patients with gMG, which has been further strengthened in this submission to address the outstanding areas of uncertainty that the Committee has highlighted in its Draft Guidance.

The Company remains committed to ensuring patients with gMG in England and Wales can benefit from this new and efficacious treatment for their debilitating condition. To that end, the Company is willing to make substantial concessions and minimise clinical uncertainty by accepting the Committee's preferred assumptions, even where the Company disagreed with the Committee's position.

When the Committee's preferred assumptions are clear, the Company has aligned the economic model to these assumptions. Where the Committee has not provided clear guidance or preferred assumptions, the Company has worked from the Committee’s position and provided new evidence or additional analyses, as appropriate, alongside corresponding scenario analyses.

Finally, the Company has addressed any remaining commercial uncertainty by offering a significantly improved confidential Patient Access Scheme (PAS) to ensure that the National Health Service (NHS) receives value for money and patients receive access to innovation in a disease area with high unmet need. The confidential discount offered brings the incremental cost/QALY (ICER) for efgartigimod vs. established clinical management well within the acceptable range for medicines considered to be a cost effective use of NHS resources.

2 Summary of additional evidence

The Company believes that many of the areas of uncertainty raised at the second ACM can be approached pragmatically. In some cases, this requires submission of further supporting evidence, which the Company has provided below. Where appropriate, the Company has also conducted additional literature searching, or interviews with expert gMG HCPs, to ensure that the most relevant information is considered for Committee decision making.

Table 1 outlines the considerations highlighted by the Committee and a summary of the Company's proposed approach to address the remaining uncertainty.

Revised economic analyses, which consider the new evidence presented, are provided in Table 2.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Table 1 Key Committee considerations in the Draft Guidance and the Company's approach to reduce uncertainty

	Key Committee considerations	Company position	Company approach	Evidence source
Committee's preferred assumptions	Use population characteristics from ADAPT[2]	**Accept**	Population characteristics from ADAPT[2] used	N/A
	Consider a range (1% to 15%) of people remaining in the MG-ADL below 5 health state, 6 months after permanently stopping efgartigimod	**Accept**	The residual treatment effect was removed in the base case to align with the placebo effect assumption *(Sensitivity analysis was conducted assuming that 7.5% [middle of 1–15% range] of the cohort who were in MG-ADL ≤ 5 at the time of discontinuation, remain in this state after permanently stopping treatment)*	N/A
	Maintain the benefit observed in the placebo arm of ADAPT[2] over the time-horizon of the model	**Accept**	The economic model maintains the benefit observed in the placebo arm of ADAPT[2] in the base case analysis	N/A
	Use the same pooled utility values from ADAPT[2] for both the efgartigimod and established clinical management arms	**Accept**	The utility values estimated from ADAPT[2] data using a mixed model without treatment covariate are applied to both efgartigimod and ECM arms	N/A
	Consider carer disutilities qualitatively	**Accept**	Carer disutilities are removed from the base case analysis	N/A
	Including corticosteroid complication costs only for people in the Lee et al.[3] study who found their side effects intolerable	**Accept**	The cost of corticosteroid complications were calculated based on frequency of only intolerable adverse events reported in the study by Lee et al. 2018[3]	N/A
	80% of people having the subcutaneous formulation and 20% intravenous formulation	**Accept**	Base case analysis includes 80% SC and 20% IV, aligned with Committee's preferred assumption.	N/A

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Areas of uncertainty relating to IVIg	IVIg use was likely overestimated because the question in the Company's Delphi panel asked about eligibility rather than uptake and assumed no supply issues	**Accept with new evidence**	A new approach is used to estimate the level of maintenance IVIg use in standard care	EAMS/EAMS+ Independent report[4]
	No discontinuation modelled for IVIg, though it may be stopped because of adverse events, lack of clinical response or patient choice	**Accept with new evidence**	Discontinuation is modelled for IVIg	Available literature and validated with expert gMG HCPs
	No QALY benefit was assumed for IVIg use, which biased cost-effectiveness results in favour of the efgartigimod arm	**Accept with new evidence**	The effectiveness of IVIg has been determined and included in the model	Indirect treatment comparison
	Maximum dose frequency was assumed	**Accept with new evidence**	A new approach is used to estimate assumptions on IVIg dose and frequency of administration	Validated with expert gMG HCPs
Committee requests for additional analyses	Plausibility of a residual treatment effect after permanent discontinuation of efgartigimod	**Accept with new evidence**	The residual treatment effect was removed from the base case analysis to align with the placebo effect assumption	N/A. Removed from base case analysis
	Generalisability of data used in the model to estimate the cost-effectiveness of efgartigimod in the target population	**Accept with new evidence**	The generalisability of data sources used in the model has been further explored and justified	ADAPT post-hoc analysis, EAMS/EAMS+ independent report[4]

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Summary of revised economic base case

The revised cost-effectiveness model base case incorporates the following changes:

- **Baseline characteristics and utility values:** Baseline characteristics in the model were set equal to population characteristics from ADAPT[2] and the same utility values estimated from ADAPT data were used for both the efgartigimod and established clinical management (ECM) arms.

- **Placebo and residual treatment effect:** Benefit observed in the placebo arm of ADAPT[2] is applied in the model and the potential efgartigimod residual treatment effect was removed.

- **Parameters related to intravenous immunoglobulin (IVIg):** Efficacy for maintenance IVIg and discontinuation due to a lack of response were included based on the available literature. The percentage of patients receiving maintenance IVIg treatment was updated based on real-world evidence from the Early Access to Medicines Scheme (EAMS)[4]. Assumed dosage was informed by existing guidelines and affirmed by input from expert gMG HCPs.

- **Caregiver disutilities:** Disutility values associated with caregivers were removed from the model.

- **Cost of corticosteroid related complications:** These were based on the frequency of only intolerable adverse events in MG patients reported in the study by Lee et al. 2018.[3]

- **Mix of efgartigimod formulations:** Subcutaneous formulation was assumed to be administered to 80% of the cohort, and the remaining 20% would receive the intravenous formulation.

The results of the revised cost-effectiveness model base case analysis are presented in Table 2. These results are based on the efgartigimod list price with a [redacted] patient access scheme (PAS) discount. The difference in QALY between the two arms has been reduced by the updated assumptions requested by the Committee, which have generated an ECM profile unlikely to be reflective of UK clinical practice. Even taking this into account, the confidential PAS offered brings the incremental cost/QALY well within the range generally considered to represent a cost effective use of NHS resources.

Table 2. Revised model base case analysis with PAS

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,110
ECM	[redacted]	[redacted]	[redacted]				

Areas for which new evidence / additional information has been provided

The areas in which the Committee has requested additional information or highlighted uncertainty have been summarised below under five separate headings:

1. **Generalisability of data sources to the target patient population**
2. **Maintenance IVIg in the target population: appropriate assumptions regarding level of usage**
3. **Maintenance IVIg in the target population: defining the standard protocol of care**
4. **Maintenance IVIg in the target population: estimating effectiveness**
5. **Handling of placebo effect and extrapolation of post-treatment discontinuation**

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Area 1: Generalisability of data sources to the target population

Summary

Clinical evidence for efgartigimod efficacy came from the ADAPT phase 3, multi-centre, double-blind, placebo-controlled trial[2] and its open-label extension study, ADAPT+[5]. At ACM2, the Committee expressed concerns about the generalisability of the cost-effectiveness analysis to the target population, and, more specifically, that using clinical-effectiveness results from a population broader than the target population was a source of uncertainty.

The Company maintains that evidence from ADAPT in the AChR-Ab+ population and from EAMS/EAMS+ is generalisable to the target population, based on the following:

- **Alignment of baseline characteristics across relevant patient populations** Generalisability can be demonstrated by comparing the total ADAPT baseline characteristics with data from two populations that can be considered an appropriate proxy of the target population. These are the EAMS/EAMS+ population[4] and the post-hoc refractory AChR-Ab+ subgroup from ADAPT.[6] Furthermore, there is a close similarity between the baseline characteristics and clinical efficacy between ADAPT, the ADAPT AChR-Ab+ refractory subgroup, and patients enrolled in the UK EAMS/EAMS+ programme.

- **Similar efgartigimod efficacy irrespective of subgroup** A post hoc analysis comparing non-refractory and refractory ADAPT AChR-Ab+ subgroups showed no significant difference in the clinical effectiveness of efgartigimod across both groups. For example, 68% (17/25) of non-refractory AChR-Ab+ patients from ADAPT experienced a significant clinical response after one cycle of efgartigimod treatment, compared with 67.5% (27/40) of refractory AChR-Ab+ patients.[6]

Overall, there is a close similarity between the baseline characteristics and clinical efficacy between ADAPT, the AChR-Ab+ ADAPT refractory subgroup, and the EAMS/EAMS+ patients[4]. Furthermore, the QoL utilities obtained in the post-hoc analysis from the ADAPT refractory subgroup are also aligned with utilities used in the model[7]. This further underlines that the outcomes of the economic model are generalisable to the intended target population.

Detailed explanations are provided in Appendix A.

Target patient population and alignment with the EAMS/EAMS+ population

The target population is defined as:

Patients with active, refractory disease, with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥5 (>50% of MG-ADL score due to non-ocular symptoms), who have failed, not tolerated or are ineligible for standard therapy*.

**Standard therapy includes maximal dose of steroids and at least 2 non-steroidal immunosuppressive therapies (NSISTs), for an adequate period of time, at an adequate dose.*

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

The target patient population is consistent with the inclusion criteria described on the Blueteq form, currently in use within NHS England for the EAMS/EAMS+ programme and implemented successfully in the UK (Table 3).

Table 3 Comparison of target population definition and EAMS/EAMS+ inclusion criteria

Population	NICE target patient population	Blueteq (EAMS/EAMS+)
Diagnosis	Adults at least 18 years old with a definite diagnosis of AChR-Ab+ gMG	Adults at least 18 years old with a definite diagnosis of AChR-Ab+ gMG
MG-ADL	MG-ADL score ≥5 (50% of MG-ADL score due to non-ocular symptoms)	MG-ADL score ≥5
Prior therapy	Have failed, not tolerated or are ineligible for standard therapy	Have failed, not tolerated or are not suitable for standard therapy for gMG
Definition of standard therapy	Maximal dose of steroids and at least 2 NSISTs, for an adequate time period, at an adequate dose	Adequate dose of steroids and at least 2 NSISTs, in sufficient dose and for sufficient duration

Alignment of baseline characteristics across relevant patient populations

- The ADAPT trial had a broader gMG population than the intended target population, when considering AChR-Ab status (77% of ADAPT were AChR-Ab+)[2], and baseline treatment regimens

- Despite these differences, the baseline characteristics (demographics) are consistent across both ADAPT and the target patient population. Furthermore, the intended target population closely aligns to the baseline population characteristics of a refractory AChR-Ab+ ADAPT subgroup (n=81 patients; 40 received efgartigimod and 41 received established clinical management)[6]

- The refractory ADAPT subgroup is also closely aligned to the EAMS/EAMS+ cohort, with respect to baseline characteristics and previous treatment failures (Table 4)

- Scenarios analyses have been conducted using baseline characteristics from the refractory ADAPT subgroup and EAMS/EAMS+ report

Table 4 Comparison of population characteristics from ADAPT and EAMS/EAMS+

Population	ADAPT, AChR-Ab+ all patients, (n=129)[8]	ADAPT, AChR-Ab+ efgartigimod patients (n=65)[2]	ADAPT, refractory AChR-Ab+ efgartigimod patients (n=40)[6]	EAMS/EAMS+ efgartigimod patients (N=48)[4]
Average age, years (SD)	46.9 (15.4)	44.7 (15.0)	43.2 (13.89)	49.2
% female	66.7	71	75	75
Baseline MG-ADL, mean (SD)	8.8 (2.3)	9.0 (2.5)	9.2 (1.95)	11.2 (3.2)
Time since diagnosis, mean years, SD	Mean duration 9.3 years (SD 8.2)	Mean duration 9.7 years (SD 8.3)	Mean duration 9.59 years (SD 7.62)	NR
Time since diagnosis, n (%) <1 year 1–5 years	NR	NR	NR	 1 (2.1) 11 (22.9)

5–10 years >10 years				4 (8.3) 32 (66.7)
Previous thymectomy, n (%)	75 (58.1%)	45 (69%)	NR	35 (72.9%)
Baseline treatments, n (%)				
Steroid and NSIST	65 (50)	34 (52)	NR	27 (56)
Any steroid	97 (75)	46 (71)	NR	10 (21)†
Any NSIST	77 (60)	40 (62)	39 (98)	5 (10)‡
No steroid or NSIST	19 (15)	13 (20)	39 (98)	3 (6)

† prednisolone only; ‡ NSIST only

Similar efgartigimod efficacy irrespective of subgroup

- A post-hoc analysis of ADAPT compared MG-ADL efficacy of both non-refractory and refractory AChR-Ab+ subgroups, stratified by baseline treatment regimens. 68% (17/25) of non-refractory AChR-Ab+ patients from ADAPT experienced a significant clinical response after one cycle of efgartigimod treatment, compared with 67.5% (27/40) of refractory AChR-Ab+ patients. This demonstrated consistent clinically significant improvements regardless of prior baseline treatment status.[6]

- Furthermore, the response rates seen in both ADAPT[2] and the refractory ADAPT AChR-Ab+ subgroups[2] are consistent with those seen in the EAMS/EAMS+ report.[4]

- The utility estimates per health state applied in the economic model also show consistency regardless of which population is examined, with the total ADAPT population and the refractory subgroup having similar HRQoL values by MG-ADL health state[7]. For example, amongst patients with an MG-ADL score of 5, HRQoL was [redacted] in the total ADAPT population and [redacted] in the refractory ADAPT subgroup[7]. When considering patients with an MG-ADL score ≥10, HRQoL was [redacted] in the total ADAPT population and [redacted] in the refractory ADAPT subgroup[7].

- The analysis therefore supports the generalisability of the total AChR-Ab+ ADAPT population to inform the economic model and illustrates that efgartigimod is an effective treatment for gMG.

- Given the proven generalisability of the subgroup to the entire ADAPT population, the Company has used the full population from ADAPT for the cost effectiveness analysis. The use of subgroup data in the context of a cost utility analysis would have reduced the sample size substantially, and in a transition probability driven model, this would have introduced instability and uncertainty to the analysis.

Area 2: Maintenance IVIg in the target population: appropriate assumptions regarding level of usage

Summary

Expert gMG HCPs and efgartigimod real-world evidence confirm that maintenance IVIg should be included in the economic model as part of established clinical management (ECM) for the target patient population. However, the Committee has highlighted some residual uncertainty as to the level of maintenance IVIg use and stated that the estimates of maintenance IVIg usage provided thus far do not reflect UK clinical practice.

The Company explored multiple methods to address this uncertainty, including gaining opinions from key UK clinical experts involved in treating gMG and conducting a Delphi panel to gain a UK consensus on maintenance IVIg use.[9] To supplement this existing evidence and further address this uncertainty, the Company is submitting new EAMS/EAMS+ evidence (n = 48 patients treated with efgartigimod between June 2022 and July 2023) based on real-world consumption of IVIg in the target patient population[4]. This independent report has been compiled and co-authored by 20 gMG clinicians from 13 MG specialist centres. It represents the most extensive survey of prior maintenance IVIg use for patients who have received efgartigimod. The analysis demonstrates that 70.8% (n = 34) of patients had previously received IVIg, and 43.8% of efgartigimod patients (n = 21) required maintenance IVIg at the time of efgartigimod initiation[4]. Therefore, the revised base case implements 43.8% maintenance IVIg usage within the target population, a reasonable assumption based on UK real-world evidence / clinical practice.

To supplement the base case analysis, sensitivity analyses were conducted using plausible lower- and upper-bound estimates of maintenance IVIg use in the target population:

- The upper bound figure for the sensitivity analysis is 69%, elicited from UK clinicians in the Delphi panel,[9] as provided during ACM2.

- The lower bound estimate is [redacted], derived from the NHSE IVIg use figure provided by the commissioning expert at ACM1.[10] This is [redacted] of the total gMG population, which equates to [redacted] of the refractory target population for efgartigimod.

Real-world evidence of maintenance IVIg

To address the uncertainty relating to maintenance IVIg use, the revised approach utilises real-world evidence from an independent report of EAMS/EAMS+ data[4] to estimate the proportion of IVIg usage in the target patient population. This target patient population aligns closely with that described on the Blueteq form (see Table 3 for further details), which is currently in use within the EAMS/EAMS+ programme and has been implemented successfully in the UK. This independent report includes data from 48 patients in EAMS/EAMS+ who had efgartigimod between June 2022 and July 2023.[4]

The report states that 70.8% (n = 34) of patients had previously received IVIg as acute and/or maintenance therapy, and 43.8% (n = 21) were still requiring it on a regular basis (i.e. maintenance) at the time of efgartigimod initiation.[4] Therefore, the updated base case has implemented 43.8% maintenance IVIg usage within the target population. Moreover, the report states that 14.6% (n = 7) of patients were using plasma exchange regularly at treatment initiation.[4] While regular plasma exchange is not included in the base case analysis due to the scarce data available on its clinical effectiveness, a scenario analysis was added that included this treatment.

Summary of additional evidence

As summarised above, sensitivity analyses were conducted using lower- and upper-bound estimates of maintenance IVIg use in the target population. The upper bound figure for the sensitivity analysis is 69%, elicited from UK clinicians in the Delphi panel,[9] as provided during ACM2. Although this data was challenged by the Committee as a potential overestimate regarding maintenance IVIg usage in the target population, it was collected from a geographically representative sample of expert gMG clinicians and, therefore, forms a clinically plausible upper boundary for modelling / scenario analyses.

The lower bound estimate has been derived from the NHSE IVIg use figure provided by an NHS commissioning expert before ACM1 (in the Committee papers, Section 11)[10], which, was stated to be derived from the national IVIg database. The commissioning expert mentioned that the usage of maintenance IVIg is around [redacted] of eligible gMG patients, but also acknowledged expert gMG HCPs' belief that maintenance treatment is much higher [redacted]

It has subsequently been confirmed by an NHSE commissioning expert that all of the information and analysis provided for ACM1 were derived from clinical experts who consulted for the appraisal, rather than from the National IVIg database as was incorrectly stated in the Draft Guidance. Notably, this confirmation further reinforces the importance of real-world evidence within this target patient population. In summary, we can conclude that the NHS commissioning expert reported a range of IVIg from [redacted] of the total adult gMG patient population. Due to the inherent uncertainty and the likely underestimation of this range, it would be reasonable to use the midpoint of this range ([redacted]) as the source for the lower bound of the sensitivity analysis.

As the refractory patient population would be the only users of maintenance IVIg and represent approximately [redacted] of the total adult gMG patient population (as reported by a panel of clinical experts in the Delphi panel submitted for the ACM2)[9], the IVIg usage in this group would be calculated as equating to approximately [redacted] of the target population for efgartigimod. This value was considered as the lower bound for the sensitivity analysis.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Area 3: Maintenance IVIg in the target population: defining the standard protocol of care

Summary
In its Draft Guidance, the Committee challenged that IVIg should be modelled more appropriately, specifically considering dose, frequency of administration and treatment discontinuation.

The Company has accepted the Committee's request and has revised its base case accordingly.

Model inputs on IVIg dosing and frequency of administration are based on the NHSE IVIg Commissioning Framework[11] and UK ABN gMG guidelines.[12] IVIg discontinuation is based on evidence identified via a targeted literature review (TLR) of studies on IVIg as maintenance treatment. Furthermore, the Company facilitated interviews with a geographically representative sample of six expert gMG HCPs to validate the revised base case assumptions, namely:

- Dosing and frequency: The model includes IVIg at a dose of 1g/kg every 4 weeks; this aligns with published documentation, and opinion from expert gMG HCPs.

- Discontinuation: The updated model base case includes discontinuations due to non-response and discontinuations due to unplanned reasons, based on available literature data. During facilitated interviews, the clinicians supported conclusions from the literature, that the primary reason for IVIg discontinuation is due to a lack of response in the initial treatment phase. The non-responder IVIg discontinuation rate of 19.5%, obtained from the literature, was also confirmed by the expert gMG HCPs.

These assumptions provide further confirmation of how maintenance IVIg is used in UK clinical practice.

The Company revised base case, supported by the additional evidence on maintenance IVIg dosing, frequency and discontinuations (and along with the alternative scenarios explored) minimise the uncertainty around the inclusion of IVIg in the model.

Maintenance IVIg dose and frequency
While it is evident that maintenance IVIg is used within the target patient population, as confirmed by the MDSAS database, EAMS/EAMS+ report[4] and expert gMG HCP opinion, neither the UK ABN guidelines[12] nor the NHS England (NHSE) IVIg commissioning guidelines[11] provide clear recommendations for maintenance IVIg dosage or usage. However, the NHSE IVIg commissioning guideline[11] recommends 1g/kg dosing for acute treatment, and the UK ABN guidelines[12] suggest that the duration of efficacy of IVIg is 3–4 weeks. An assumption that patients receiving maintenance IVIg receive 1g/kg every 4 weeks was therefore considered appropriate for the base case.

The Company sought validation of these assumptions by conducting facilitated interviews incorporating a structured survey with six expert gMG HCPs involved in prescribing, administering or approving maintenance IVIg treatment across the UK. The base case assumption was confirmed by clinical expert opinion. The survey was geographically representative and a detailed description of the expert gMG HCP validation exercise and its results is reported in Appendix C.

Other scenario analyses, including one analysis considering the frequency of administration as reported in IVIg efficacy studies, were included to explore uncertainty (see Appendix F for details).

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Initial discontinuation

A TLR was conducted to retrieve observational studies of maintenance IVIg in addition to the randomised controlled trials (RCTs) identified in the systematic literature review (SLR) included in the Company's original submission.

There were limited published data available. Two studies reported information on initial discontinuations or discontinuations due to lack of response:

- Hellmann et al. 2014[13] reported that 15 out of 52 IVIg patients discontinued treatment due to lack of response, measured after one loading dose and two maintenance doses of IVIg administered at 3.5 week intervals.
- Bril et al. 2023[14] reported information on initial discontinuation vs long-term discontinuation, with 1 out of 30 IVIg patients discontinuing the study before Week 9. Considering that the dosing regime in the RCT by Bril et al.[14] was a loading dose followed by maintenance doses every 3 weeks, a similar definition of initial discontinuation as reported by Hellmann et al. 2014[13] can be assumed.

A percentage of non-responders of 19.5% (=15 + 1 / 52 + 30) was estimated by pooling data from Hellmann and Bril studies[13,14]. To further strengthen this assumption, interviews were conducted with expert gMG HCPs through facilitated interviews (see Appendix C for further details). The experts proposed that [redacted] was a feasible range for patients discontinuing treatment in the initial treatment once effectiveness had been established, and that few patients would be expected to discontinue over the long term. The experts reported that the majority of discontinuations are due to a lack of response in the initial treatment phase and that [redacted] cycles of IVIg in maintenance treatment would be given before measuring response.

In alignment with the simulation in the efgartigimod arm, the non-responder cohort is separated from the responder cohort at the beginning of the simulation. However, the cost of three administrations of IVIg treatment is still applied. The non-responder cohort is excluded from treatment with IVIg and is subsequently assumed to receive conventional therapy treatments. Therefore, the costs, effects, and health-related quality of life (HRQoL) of conventional therapy are applied to this proportion of the cohort from the point of discontinuation across the entire time horizon.

The base case has therefore been updated to include an initial discontinuation rate of 19.5% for IVIg. In addition, a scenario analysis was included based on the average estimate obtained from the expert gMG HCP interviews. The results of this scenario are reported in Appendix F.

Long-term discontinuation

To inform the per-cycle probability of discontinuing IVIg treatment due to unplanned reasons over the time horizon of the analysis, available evidence from the literature on maintenance IVIg discontinuation was pooled together to reconstruct a time to discontinuation curve (Appendix B).

A parametric fitting of the reconstructed time to discontinuation curve was performed using the standard distributions, and the exponential parametric function was selected (see further details in Appendix B). From a expert gMG HCP point of view, a constant rate of unplanned discontinuations seems appropriate as after the initial discontinuations (due to lack of response), the remaining discontinuations would occur at a constant rate (of adverse events or other reasons). The probability of discontinuations per cycle, estimated from the exponential function, is applied at every cycle of the analysis to the cohort on treatment with IVIg. The proportion of the cohort discontinuing is thereafter assumed to receive conventional therapy treatments.

Thereafter, the costs, effects, and HRQoL of conventional therapy are applied.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Area 4: Maintenance IVIg in the target population: estimating effectiveness

Summary

The Committee noted that the Company's model included the cost of maintenance IVIg but assumed no clinical benefits. The Committee considered that this was implausible.

The Company's position was that the long-term stability assumed for the ECM arm included some additional efficacy of maintenance IVIg treatment necessary to keep control of more severe patients. However, to provide a pragmatic path to patient access and address the concerns raised by the Committee, the Company has amended the model to explicitly include efficacy for IVIg treatment.

The Company has revised its base case to include IVIg efficacy based on evidence identified via a network meta-analysis (NMA) of the efficacy of maintenance IVIg.

The revised base case addresses the Committee's request that both the costs and clinical benefits of maintenance IVIg are included in the economic model.

Introduction/background

The NMA was conducted based on ADAPT[2] and the only two relevant RCTs of maintenance IVIg (Wolfe et al., 2002[15] and NCT02473952, 2019[16]) identified via an SLR and indirect treatment comparison (ITC) feasibility assessment.

The results of the NMA showed that efgartigimod achieved a reduction in the MG-ADL from baseline that is [redacted] points greater than the reduction achieved with IVIg, and the difference was significant. The results of the NMA were then used to recalibrate the health-states transitions observed in the placebo arm of ADAPT[2], to define the additional benefit of IVIg in the model.

To reduce the uncertainty around the magnitude of clinical benefit for efgartigimod vs IVIg, two scenario analyses were conducted based on the estimates of comparative efficacy obtained from targeted population-adjusted ITCs vs the two IVIg studies separately[15,16]. To allow the inclusion of efficacy and discontinuations for IVIg in the revised model, the ECM arm was modelled via two separate engines for conventional therapy and IVIg cohort. The total QALYs and costs in the ECM arm were then calculated as the sum of the QALYs and costs resulting in the conventional therapy and IVIg engines, weighted by the respective assigned percentages.

Identification of relevant evidence for maintenance IVIg efficacy in gMG

No direct head-to-head trial evidence exists comparing the efficacy of efgartigimod and maintenance IVIg in patients with gMG. A comprehensive SLR was conducted, and a feasibility assessment for an ITC between efgartigimod and maintenance IVIg was conducted for the MG-ADL change from baseline, the efficacy outcome relevant to the cost-effectiveness model. Full details are presented in Appendix D.

An overview of the included studies is presented in Table 5. Further study details, a table of excluded studies and PRISMA diagram are presented in Appendix D. Only two relevant RCTs were identified, and these included studies were comparable in reported eligibility criteria, suggesting that they enrolled similar trial populations. Where reported, available baseline characteristics appeared similar between studies. Data on change in MG-ADL from baseline were available from the ADAPT[2] and Wolfe et al., 2002[15] studies; however, study NCT02473952[16] only reported change from baseline in Quantitative Myasthenia Gravis (QMG). For this study, change from baseline MG-ADL could be imputed from QMG. The imputation followed accepted multivariate meta-analysis methods published by NICE [17].

After imputing data for NCT02473952[16], a connected network of evidence is available for the MG-ADL change from baseline, and an NMA was considered feasible. By considering pooled estimates from the two eligible IVIg trials, the sample size to inform efficacy estimates of IVIg is greater in the NMA than if target comparisons with each single study were to be conducted. An NMA was therefore considered the preferred approach given that the studies were comparable in terms of eligibility criteria, trial design, population characteristics and outcomes. Targeted matching adjusted indirect comparisons (MAIC) vs each of the two IVIg trials separately were run as sensitivity analysis. The MAICs included placebo as the anchor.

Table 5 Overview of included studies

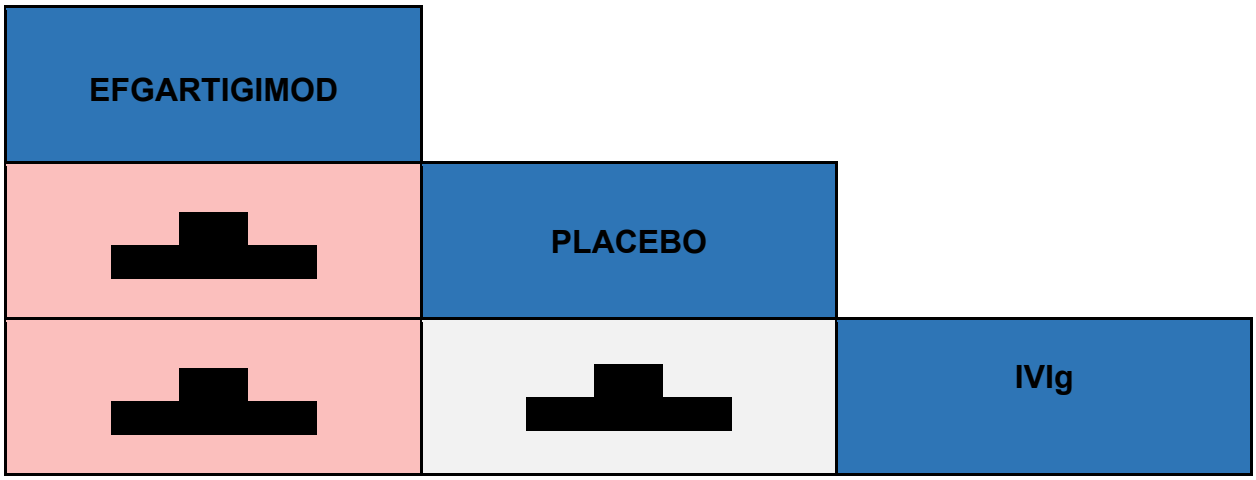
Included studies	Details
ADAPT[2]	• Phase III clinical trial of efgartigimod (NCT03669588[18]) • 26 week global, multi-centre, randomised, double-blind, placebo-controlled • N=129 (the AChR-Ab+ cohort)
NCT02473952[16]	• 24 week Phase II, global, multicentre, randomised, double-blinded study of IVIg in adults with AChR-Ab+ gMG • Initial loading dose of 2g/kg of IVIg administered at baseline followed by maintenance doses of 1g/kg every third week • N=62
Wolfe 2002[15]	• USA-based randomised, double-blinded study of IVIg in adults with AChR-Ab+ gMG. The planned study duration was 42 days. • Initial loading dose of 2g/kg of IVIg administered at baseline followed by maintenance dose of 1g/kg at day 22 • N=15

Network meta-analysis (base case analysis)

The NMA was performed using a Bayesian framework in R and JAGS, based on the code outlined in the NICE Evidence Synthesis DSU Technical Support Document Series (Dias et al., 2013a[19]; Dias et al., 2013b[20]; Dias et al., 2013c[21]). Placebo was the reference treatment for the NMA, as it was the only common anchor treatment across all studies in the network. Given the lack of multi-study connections in the evidence network, a random effects NMA was deemed unfeasible and a fixed effects NMA was performed for all outcomes. Vague prior distributions that assume no pre-existing information according to NICE DSU TSD 3 (Dias et al., 2012[22]) were assigned for the treatment effects and trial baselines. Further details are provided in Appendix D.

Efgartigimod ranked first for change from baseline in MG-ADL in the fixed effects NMA model (Figure 1). Efgartigimod had a better change from baseline in MG-ADL compared to both IVIg and placebo, as demonstrated by non-overlap in 95% credible intervals with zero. Interventions in Figure 1 are ordered from left to right in order of decreasing surface under the cumulative ranking curve (SUCRA) value.

Figure 1 Fixed effects league table of mean differences for change from baseline in MG-ADL



Comparison from left to right. Numbers are mean change in MG-ADL score from baseline with 95% credible intervals in brackets. For each pairwise comparison, the row treatment serves as the reference group. Shading indicates comparisons where 95% credible intervals do not include 1.

MAICs of efgartigimod vs individual IVIg studies (sensitivity analysis)

An overview of the methods used for the targeted MAICs for ADAPT[2] vs. Wolfe et al. 2002[15] and ADAPT[2] vs. NCT02473952[16], key results and analysis limitations, are provided in Appendix D**.** Briefly:

- The anchored MAIC vs Wolfe et al. 2002[15] shows that patients treated with efgartigimod achieved a reduction in the MG-ADL from baseline that is [redacted] points greater than the reduction achieved with IVIg (SE = [redacted], 95%CI=[redacted], p-value <0.05).
- The anchored MAIC vs NCT02473952[16] showed an MG-ADL change from baseline, which was [redacted] greater for efgartigimod than IVIg (SE = [redacted] 95%CI=[redacted], p-value <0.05).

Use of the ITC estimates to model IVIg treatment effectiveness in the cost-effectiveness model

The estimates of IVIg comparative efficacy in terms of MG-ADL change from baseline, obtained from the ITC, were used to recalibrate the health-state transitions observed in the placebo arm of ADAPT[2] during each 4-week cycle starting from the baseline to Week 16. An additional probability of improvement for IVIg vs placebo was estimated based on the mean time of transitioning to the next best health state for IVIg. This was based on the distance in average MG-ADL points between health-states and the estimated difference in MG-ADL change from baseline between IVIg and placebo of [redacted], calculated from the NMA outcomes (i.e. the MG-ADL difference for efgartigimod vs IVIg of [redacted] from the NMA was subtracted to [redacted] MG-ADL difference for efgartigimod vs placebo, to obtain the estimate of IVIg vs placebo).

The additional IVIg cycle probability of transitioning to the next best health state compared with placebo was then estimated as the inverse of the mean number of cycles required to transition. This probability was used to increase the proportion of the cohort that transitioned to the next best health states, as observed in the placebo arm of ADAPT[2], during each 4-week cycle from baseline to Week 16. Beyond cycle four, the model assumes the effect is maintained as long as the cohort remains on treatment. Full details are included in Appendix D.

Area 5: Handling of placebo effect and extrapolation of post-treatment discontinuation

Summary

The Committee concluded that the benefit observed in the placebo arm of ADAPT should be maintained over the time horizon of the model. The Committee also considered that the Company's approach to modelling a residual treatment effect after treatment stops was plausible but subject to uncertainty and that this assumption had a large effect on the results of the analysis.

The Committee noted that the treatment effect after permanent discontinuation may be linked to the placebo effect, and that, as described in the Draft Guidance the assumptions on placebo effect and on residual treatment effect are interconnected.

To address the challenges raised by the Committee, in the revised base case analysis, the model maintains the benefit observed in the placebo arm of ADAPT. Furthermore, the residual treatment effect assumption was removed entirely from the base case model to align with the placebo effect assumption.

Introduction/background

The Committee noted that randomised controlled trials, such as ADAPT[2], provide evidence for relative treatment effects. It considered that by assuming that the observed effect in the ECM arm does not persist, the Company's model no longer reflected the relative treatment effect observed in ADAPT and instead artificially inflated the treatment effect. The Committee, therefore concluded that the benefit observed in the placebo arm of ADAPT should be maintained over the time horizon of the model.

The Committee also considered that the Company's approach to modelling a residual treatment effect after treatment stops continued to be plausible but highly uncertain and that this assumption had a big effect on the results of the analysis. The Committee noted that the treatment effect after permanent discontinuation may be linked to the placebo effect. However, the Committee noted the EAG's comments that the Company's model could not adjust the treatment effect after permanent discontinuation assumptions while retaining the placebo effect in the ECM arm.

To address the Committee's concerns, in the revised model, the benefit observed in the placebo arm of ADAPT is maintained over the time horizon of the analysis. This is applied equally in all treatment arms of the model. As highlighted by the EAG, this would be conflicting with any assumption on residual effect post discontinuation of efgartigimod, and for this reason, the latter was removed from the base case analysis:

- Transition probabilities observed in the placebo arm of ADAPT up to cycle 4 are applied to the conventional therapy cohort in the ECM arm, and thereafter the distribution remains as last observed, rather than returning to baseline as in the initial Company submission.

Table 6 Placebo distribution at the end of cycle four

Health-states	Proportion of the cohort
MG-ADL <5	[redacted]
MG-ADL 5–7	[redacted]
MG-ADL 8–9	[redacted]
MG-ADL ≥10	[redacted]

- The IVIg cohort in the ECM arm is applied with the recalibrated placebo transitions (details in Appendix E) and thereafter assumed to remain distributed as last observed, thus maintaining

both the placebo and additional IVIg benefit over the time horizon of the analysis, for as long as the cohort remains on treatment. Post discontinuation, the cohort is assumed to receive conventional therapy and, therefore, is assumed to remain distributed between the health states as in the conventional therapy cohort.

- The cohort in the efgartigimod arm is applied with the on- and off-treatment probabilities as observed in ADAPT[2] and ADAPT+[5] for as long as it does not permanently discontinue treatment. Post discontinuation, the cohort is assumed to receive conventional therapy and, therefore, is assumed to remain distributed between the health states as in the conventional therapy cohort (Table 6), in line with post-IVIg discontinuation.

This approach allows consistency in the simulation assumptions between modelled treatment arms.

Placebo effect and residual treatment effect sensitivity analyses

The Company developed a first scenario analysis where the placebo effect is not maintained with conventional therapy in the ECM arm. In this scenario a residual effect is applied post efgartigimod and IVIg discontinuation for a duration of 6 months. This is done by assuming that 7.5% (mid-point of the range 1% to 15%) of the cohort located in MG-ADL<5 health-state at the time of discontinuation, would remain in the MG-ADL<5 health-state, for a duration of 6 months. Thereafter, the residual effect is not further applied.

The Company also developed a second scenario to solve the issue of inflated relative efficacy without adding a permanent placebo effect to the ECM arm. This solution attempts to remove the placebo effect from efgartigimod efficacy data. In this scenario, the conventional therapy cohort in the ECM arm returns to baseline beyond the four cycles of observed transitions in the placebo arm of the ADAPT. Removing the placebo effect from the benefit of the intervention arm is complex. Nevertheless, an attempt was made to remove the placebo effect from the efgartigimod transitions: the MG-ADL change from baseline in the placebo arm of ADAPT and the distance to better health states were used to estimate the improvement due to the placebo. This was removed from the probability of improving to better health states in the efgartigimod transitions. Therefore, the resulting transition matrix can be considered representative of what could be observed after removing the placebo effect from the total effect observed in the efgartigimod arm. These transition probabilities were applied from Cycle 5 of the analysis (in line with the timepoint at which the placebo effect is removed in the conventional therapy cohort). Also, in this scenario, a residual treatment effect of 7.5% post efgartigimod and IVIg discontinuation is considered, and the duration was limited to 6 months.

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4 Appendices

Appendix A Generalisability of data sources to the target population
Appendix B Long-term discontinuation from maintenance IVIg treatment
Appendix C A report based on expert gMG HCP facilitated interviews and implementation in the model
Appendix D Targeted literature review and indirect treatment comparison
Appendix E Handling of placebo effect and extrapolation of post treatment discontinuation
Appendix F Economic analyses
Appendix G Confidential information checklist

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Abbreviations

ABN	Association of British Neurologists
AChEi	Acetylcholinesterase inhibitor
ACM	Appraisal Committee Meeting
AChR-Ab+	Acetylcholine receptor antibody positive
CI	Confidence interval
DSU	Decision Support Unit
EAMS	Early access to medicines scheme
ECM	Established clinical management
gMG	Generalised myasthenia gravis
HCP	Healthcare professional
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
IV	Intravenous
IVIg	Intravenous immunoglobin
KOL	Key opinion leader
LYG	Life-years gained
MAIC	Matching adjusted indirect comparisons
MDSAS	Medical Data Solutions and Services
MG-ADL	Myasthenia Gravis Activities of Daily Living
MG	Myasthenia gravis
N/A	Not applicable
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSIST	Nonsteroidal immunosuppression treatment
PAS	Patient access scheme
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SUCRA	Surface under the cumulative ranking curve
TLR	Targeted literature review
TSD	Technical support documents

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

New evidence submission

7 March 2024

File name	Version	Contains confidential information	Date
ID4003_Appendices_DG2[ACIC]		Yes	7 March 2024

Abbreviations

ABN	Association of British Neurologists
AChEi	acetylcholinesterase inhibitor
AChR-Ab+	acetylcholine receptor antibody positive
CEM	cost-effectiveness model
CI	confidence interval
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EAMS	Early Access to Medicines Scheme
ECM	established clinical management
EFG	efgartigimod
ESS	effective sample size
gMG	generalised myasthenia gravis
HCP	healthcare professional
ICER	incremental cost-effectiveness ratio
IgG	immunoglobulin g
IGIV-C	immune globulin (human), 10% caprylate/chromatography purified
IPD	individual patient data
IVIg	intravenous immunoglobin
ITC	indirect treatment comparison
LS	least squares
LYG	life-years gained
MAIC	matching-adjusted indirect comparison
MCSE	Monte Carlo standard error
MG-ADL	Myasthenia Gravis Activities of Daily Living
MG	myasthenia gravis
MGFA	Myasthenia Gravis Foundation of America
MIMS	Medical Information Management System
MMRM	mixed model for repeated measurements
N/A	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NSAID	non-steroidal anti-inflammatory drug
NSIST	nonsteroidal immunosuppression treatment
MAIC	matching adjusted indirect comparisons
PAS	patient access scheme
PLEX	plasma exchange
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
QMG	quantitative myasthenia gravis
QXW	every x weeks
RDI	relative dose intensity

SAS	statistical analysis software
SC	subcutaneous
SD	standard deviation
SE	standard error
SLR	systematic literature review
TLR	targeted literature review
TSD	technical support documents

Contents

List of tables

List of figures

Appendix A Generalisability of data sources to the target population

A.1 Definition of the target population

The proposed target patient population for efgartigimod treatment on the NHS is: Those patients with active, refractory disease, with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥5 (>50% of MG-ADL score due to non-ocular symptoms), who have failed, not tolerated or are ineligible for standard therapy*.

*Standard therapy includes maximal dose of steroids, and at least 2 additional therapies, such as non-steroidal immunosuppressive therapies (NSISTs), for an adequate period of time, at an adequate dose.

In the Draft Guidance following ACM2, the Committee concluded that the target population description broadly described the most suitable population to have add-on treatment with efgartigimod.

The target patient population is consistent with that described on the Blueteq form, currently in use as the inclusion criteria for the Early Access to Medicines Scheme (EAMS/EAMS+) programme and implemented successfully in the UK (Table 1). This confirms that such patients are easily identifiable in UK gMG specialist centres. Furthermore, clinical expert validation was obtained, ahead of ACM2, to ensure that this population was appropriately optimised toward those who may benefit most from efgartigimod in clinical practice.

Table 1 Comparison of target population definition and EAMS/EAMS+ inclusion criteria

Population	NICE target patient population	Blueteq (EAMS[1]/EAMS+)
Diagnosis	Adults at least 18 years old with a definite diagnosis of AChR-Ab+ gMG	Adults at least 18 years old with a definite diagnosis of AChR-Ab+ gMG
MG-ADL	MG-ADL score ≥5 (50% of MG-ADL score due to non-ocular symptoms)	MG-ADL score ≥5
Prior therapy	Have failed, not tolerated or are ineligible for standard therapy	Have failed, not tolerated or are not suitable for standard therapy for gMG
Definition of standard therapy	Maximal dose of steroids and at least 2 NSISTs, for an adequate time period, at an adequate dose	Adequate dose of steroids and at least 2 NSISTs, in sufficient dose and for sufficient duration

A.2 Generalisability of the cost-effectiveness analysis

Clinical evidence for efgartigimod efficacy came from the ADAPT[1] phase 3, multi-centre, double-blind, placebo-controlled trial and its extension study ADAPT+[2]. The study recruited adults with an MG-ADL score ≥ 5 (with > 50% of the total score attributed to non-ocular symptoms) and who were on a stable dose of established clinical treatment. Of the 167 people recruited, 129 (77%) were AChR-Ab+. Effectiveness data for the model (i.e. transition matrices) as well as baseline characteristics and QoL utility data are directly sourced from the AChR-Ab+ population of the ADAPT and ADAPT+ studies[1,2].

In the second Draft Guidance[3], the Committee considered that baseline characteristics used in the model should align with other inputs, such as quality of life and clinical-effectiveness estimates. However, the Committee expressed concerns about the generalisability of the cost-effectiveness analysis to the target population, and, more specifically, that using clinical-effectiveness results from a population broader than the target population was a source of uncertainty.

The Company maintains that evidence from ADAPT[1] in the AChR-Ab+ population is generalisable to the target population. Generalisability can be demonstrated by comparing ADAPT[1] data with data from the EAMS/EAMS+ population[4], as this is closely aligned with the target population. An independent report has been compiled and co-authored by 20 gMG clinicians, from 13 MG specialist centres, including data from 48 EAMS/EAMS+ patients treated with efgartigimod between June 2022 and July 2023.[4] In this report, the information on baseline characteristics and on key efficacy parameters in EAMS/EAMS+ patients can be found.[4]

One additional population that can be considered a good proxy of the target population is the refractory sub-population within ADAPT[1]. The definition of MG refractory patients is not always uniform in the literature, but overall, it refers always to patients that have failed to make an adequate improvement following several lines of treatment, including NSISTs. Therefore, a refractory population overlaps with the target population for efgartigimod. A post-hoc analysis was generated by the Company to identify this subgroup of patients in the ADAPT trial who were anti-AChR-Ab+ and refractory to conventional therapy[5]. The baseline characteristics and key efficacy data of this refractory subgroup of ADAPT are reported below to confirm the concept that evidence from ADAPT in the AChR-Ab+ population is generalisable to the target population. Additionally, QoL utility data in the refractory subgroup show a close alignment to QoL derived from ADAPT AChR-Ab+ population, further strengthening the concept of generalisability.

A.3 Baseline characteristics

As per the Committee's request, baseline characteristics used in the economic model should also align with other inputs, such as quality of life and clinical effectiveness-estimates, so age and gender distribution in ADAPT[1] should be used in the model.

The population baseline characteristics, and distribution of baseline disease severity were compared between the ADAPT AChR-Ab+ population (77% of the ADAPT total population),[1] EAMS/EAMS+ population, and the refractory AChR-Ab+ subgroup of ADAPT.

Table 2, below, clearly demonstrates that the population baseline characteristics remain relatively similar whether considering:

1. total ADAPT AChR-Ab+ population (includes placebo ECM patients)[4]
2. ADAPT AChR-Ab+ efgartigimod treated sub-population[1]
3. efgartigimod treated AChR-Ab+ refractory subgroup[5]
4. efgartigimod EAMS/EAMS+ patients[4]

Table 2 Comparison of population characteristics

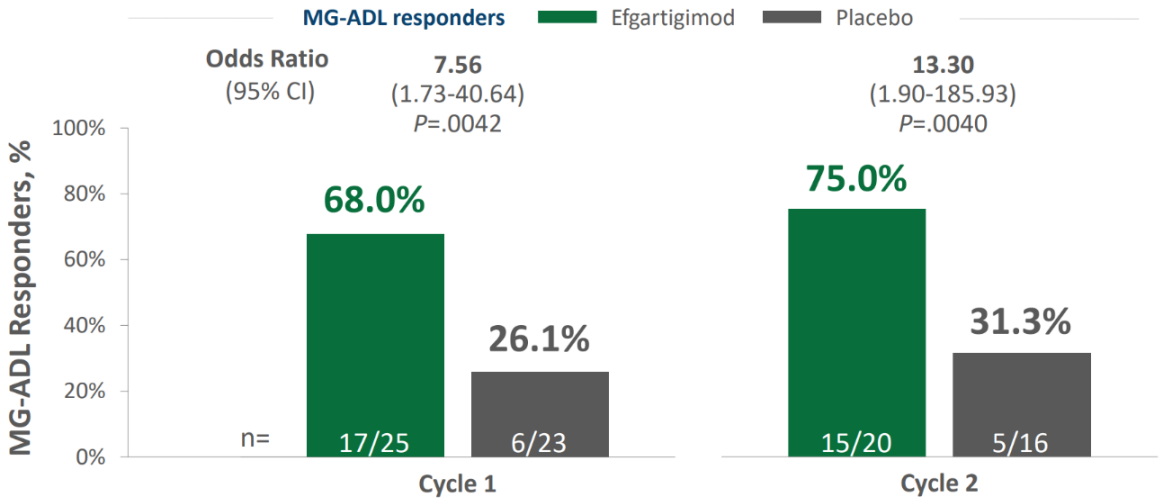
Population	ADAPT, AChR-Ab+ all patients, (N=129)[6]	ADAPT, AChR-Ab+ efgartigimod patients (N=65)[1]	ADAPT, refractory AChR-Ab+ efgartigimod patients (N=40)[5]	EAMS/EAMS + efgartigimod patients (N=48)[4]
Average age, years (SD)	46.9 (15.4)	44.7 (15.0)	43.2 (13.89)	49.2
% female	66.7%	71%	75%	75%
Baseline MG-ADL, mean (SD)	8.8 (2.3)	9.0 (2.5)	9.2 (1.95)	11.2 (3.2)
Time since diagnosis, mean years, SD	Mean duration 9.3 years (SD 8.2)	Mean duration 9.7 years (SD 8.3)	Mean duration 9.59 years (SD 7.62)	NR
Time since diagnosis, n (%) <1 year 1–5 years 5–10 years >10 years	NR	NR	NR	 1 (2.1%) 11 (22.9%) 4 (8.3%) 32 (66.7%)
Previous thymectomy, n (%)	75 (58.1%)	45 (69%)	NR	35 (72.9%)
Baseline treatments, n (%)				
Steroid and NSIST Any steroid Any NSIST No steroid or NSIST (AChEi only)	65 (50) 97 (75) 77 (60) 19 (15)	34 (52) 46 (71) 40 (62) 13 (20)	NR NR 39 (98) 39 (98)	27 (56) 10 (21)† 5 (10)‡ 3 (6)

† prednisolone only; ‡ NSIST only

A.4 Efficacy data

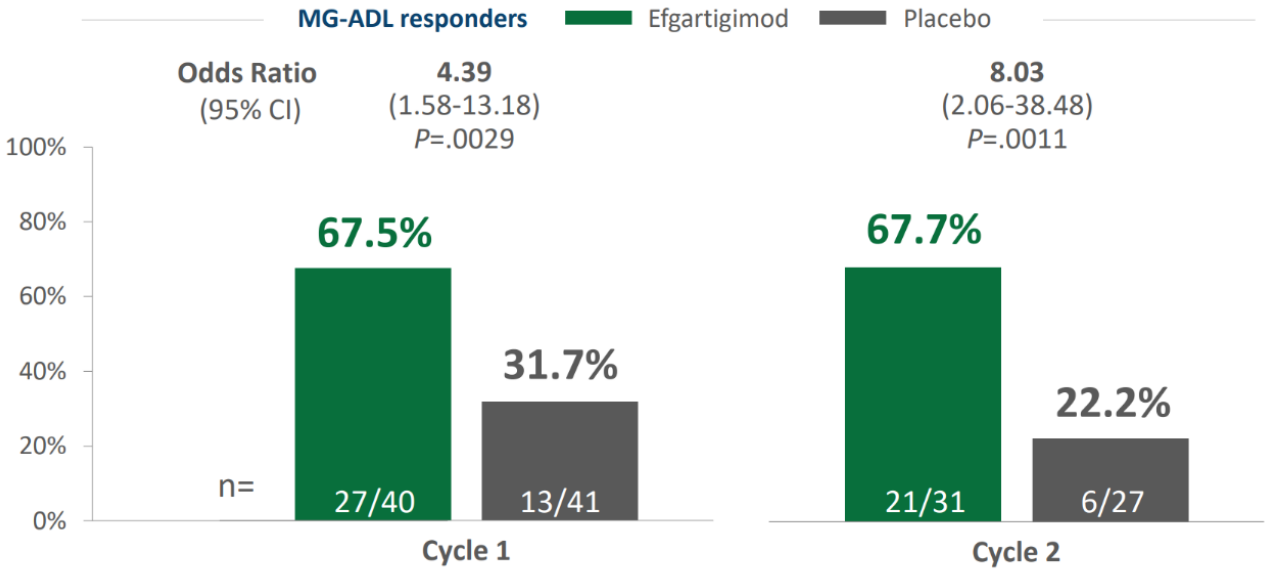
A post-hoc analysis of ADAPT (data on file) compared MG-ADL efficacy of both non-refractory and refractory AChR-Ab+ subgroups based upon baseline treatment regimens.[5] This demonstrated consistent clinically significant improvements regardless of prior baseline treatment status.

Figure 1 Proportion of MG-ADL responders among ADAPT non-refractory AChR-Ab+ patients in cycles 1 and 2



Note: a cycle in ADAPT comprises 4 efgartigimod infusions (1 per week). There is a 4 week break before cycle 2.
Source: Rozsa et al 2023[5]

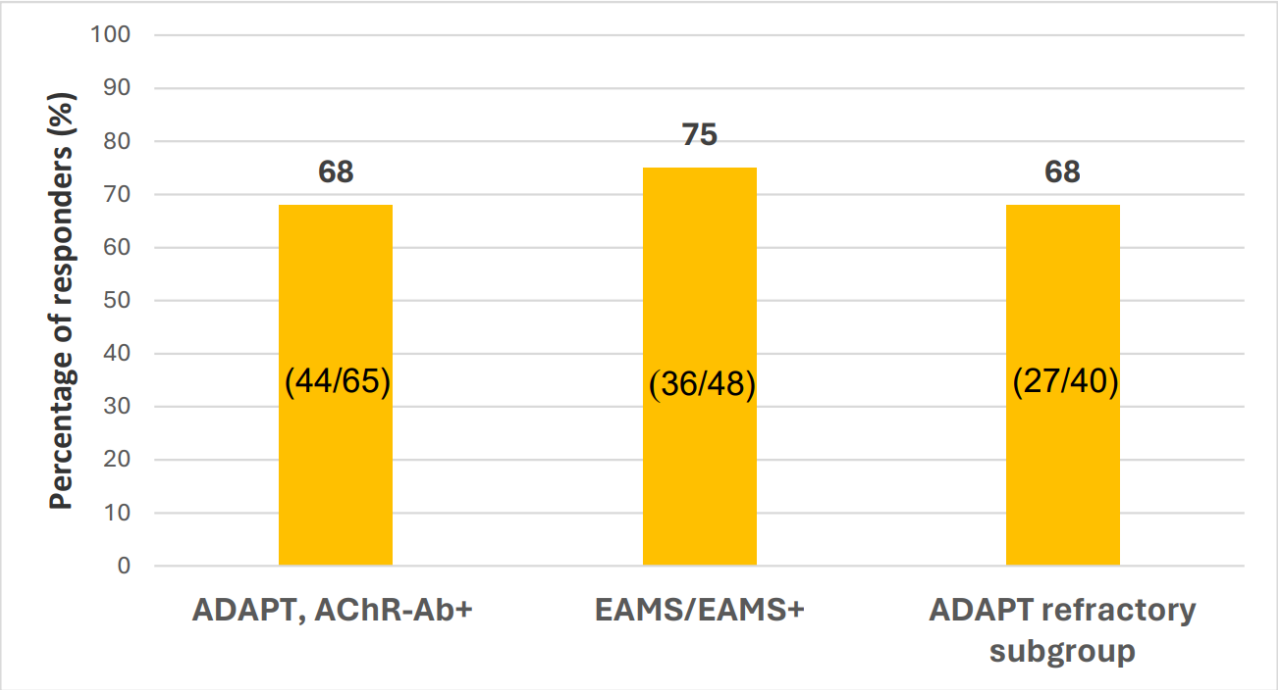
Figure 2 Proportion of MG-ADL responders among ADAPT refractory AChR-Ab+ patients in cycles 1 and 2



Source: Rozsa et al 2023[5]

Figure 3 displays the percentage of MG-ADL responders at cycle 1. It is evident that there are clinically significant and similar responses between ADAPT AChR-Ab+, a refractory ADAPT AChR-Ab+ subgroup and the EAMS/EAMS+ population.

Figure 3 MG-ADL responders after cycle 1 of efgartigimod



Source: Howard et al 2021[1]; Dionisio et al 2024[4]; Rozsa et al 2023[5]

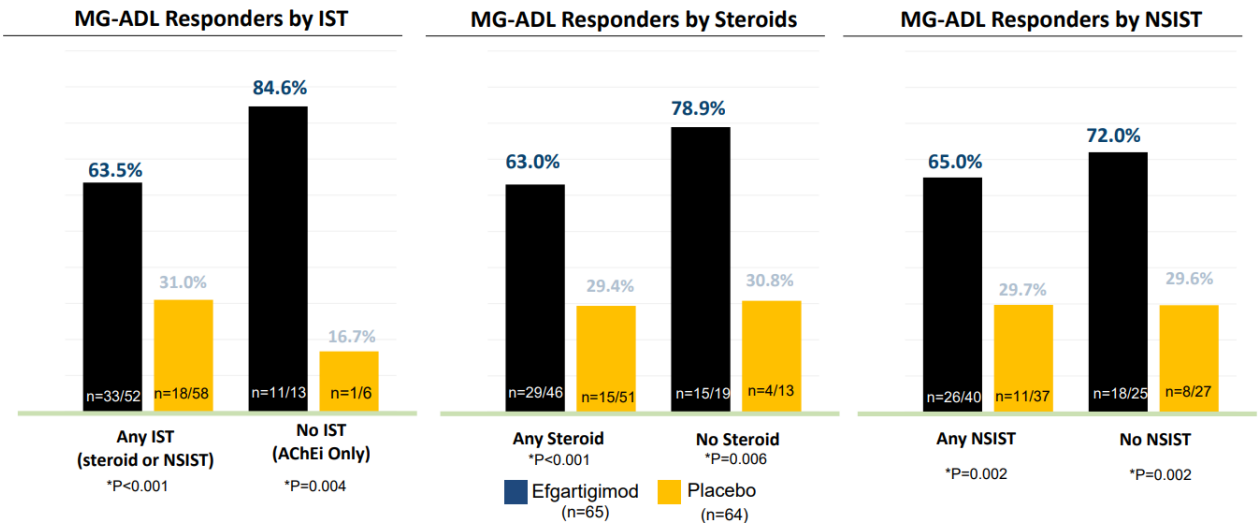
Mean change in MG-ADL score from baseline can also be compared simultaneously between the refractory and non-refractory subgroups within ADAPT[1]. The similarity in response rates observed for each of the groups in the table below further demonstrates how the effectiveness of efgartigimod remains consistent across patient groups (Table 3).

Table 3 Mean change in MG-ADL score from baseline at Week 4, in refractory and non-refractory ADAPT AChR-Ab+ patients[7]

Population	ADAPT, AChR-Ab+ (N = 129)	
	Efgartigimod	Placebo
Refractory AChR-Ab+ subgroup (N=81)		
Mean change in MG-ADL from baseline at week 4 [95% CI]	[Commercial in confidence information removed]	
Difference in change from baseline vs placebo [95% CI]		
Non-refractory AChR-Ab+ subgroup (N=48)		
Mean change in MG-ADL from baseline at week 4 [95% CI]		
Difference in change from baseline vs placebo [95% CI]		
P-value for difference in change from baseline between subgroups		

Figure 4 shows data from ADAPT trial that supports the clinical effectiveness of efgartigimod regardless of prior exposure to NSISTs. The figure includes all AChR-Ab+ patients from the ADAPT trial (n=129).[7] In this population, 67.7% (44/65) of patients in the efgartigimod arm experienced a response, compared with 29.7% (19/64) of patients in the placebo control ECM group.

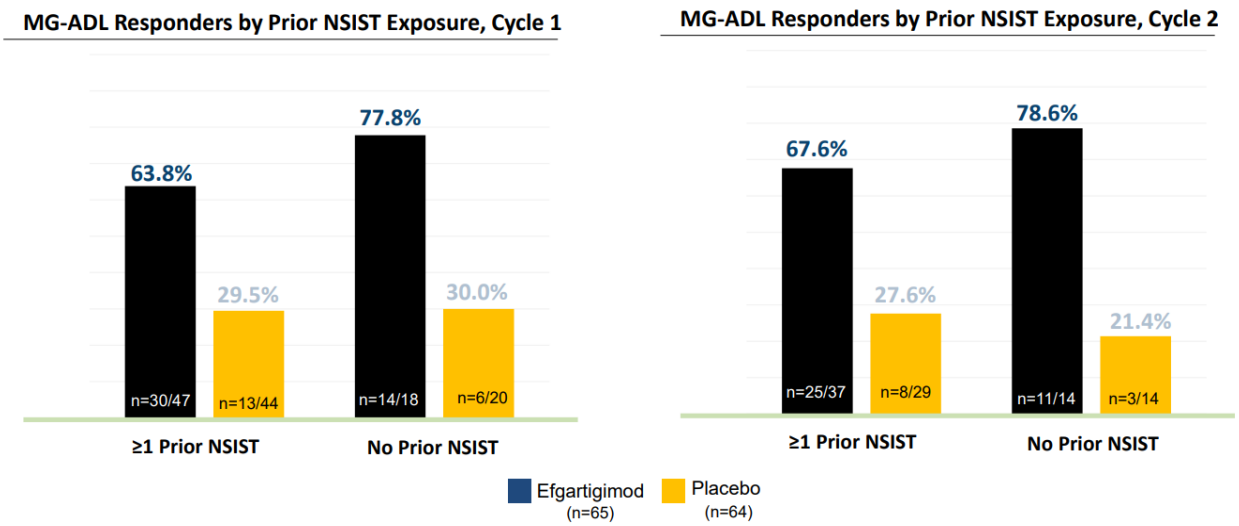
Figure 4 MG-ADL response in AChR-Ab+ patients in ADAPT, stratified by prior NSIST exposure and treatment cycle



Source: argenx data on file, 2024[7]

Similarly, Figure 5 displays MG-ADL response amongst the ADAPT cohort by prior use of immunosuppressive therapy, steroids and NSISTs.[7] The results show that efgartigimod is effective for the treatment of gMG, regardless of concomitant MG therapy.

Figure 5 MG-ADL response in AChR-Ab+ patients in ADAPT, stratified by prior treatment with immunosuppressive therapy, steroids or NSISTs



Source: argenx data on file, 2024[7]

A.5 QoL utility data

To further underline the generalisability of ADAPT data to the target population, Table 4 health-related quality of life utilities by MG-ADL states obtained from the ADAPT AChR-Ab+ population[1] (as used in the model) and the same utilities obtained in the ADAPT AChR-Ab+ refractory subgroup. Health-related quality of life was almost identical across each group.

Table 4 Comparison of health-related quality of life in two groups of patients in the ADAPT trial[7]

Population	ADAPT, AChR-Ab+ patients (N=129)	ADAPT, AChR-Ab+ refractory subgroup (N=81)
MG-ADL 5	[redacted]	[redacted]
MG-ADL 5–7	[redacted]	[redacted]
MG-ADL 8–9	[redacted]	[redacted]
MG-ADL ≥10	[redacted]	[redacted]

Appendix B Long-term discontinuation from maintenance IVIg treatment

To address the Committee's concerns, the revised model includes initial discontinuations of IVIg treatment due to the lack of response and long-term discontinuations due to unplanned reasons. This approach is aligned with how discontinuations are considered in the efgartigimod arm of the model. A targeted literature review (TLR) was conducted to retrieve observational studies of maintenance IVIg in addition to the randomised controlled trials (RCTs) identified in the systematic literature review (SLR) included in the Company's original submission.

Long-term discontinuations

The available evidence from the literature on maintenance IVIg discontinuation was pooled together to reconstruct a time to discontinuation curve (Table 5).

Table 5 Reconstructed time to discontinuation survival function

Study	Days, N	Discontinuation events, N	Patients on treatment, N	Time to discontinuation function (S)
Pooled	[redacted]		[redacted]	[redacted]
Wolfe et al. 2002[8]	[redacted]	[redacted]	[redacted]	[redacted]
NCT02473952[9]	[redacted]	[redacted]	[redacted]	[redacted]
Bril et al. 2023[10,9]	[redacted]	[redacted]	[redacted]	[redacted]
Wilf-Yarkoni 2021[11]	[redacted]	[redacted]	[redacted]	[redacted]
Wilf-Yarkoni 2021[11]	[redacted]	[redacted]	[redacted]	[redacted]
Wilf-Yarkoni 2021[11]	[redacted]	[redacted]	[redacted]	[redacted]

N: number; S: survival function
*Pooled sample from all studies: Wolfe et al. 2002 (N=6), Wilf-Yarkoni 2021 (N=109), NCT02473952 (N=30) and Bril et al. 2023 (N=30). **Reported time of discontinuation. *** Time of discontinuation was not reported, so total follow-up time was considered.

A parametric fitting of the reconstructed time to discontinuation curve was performed using the standard distributions: Exponential, Weibull, Log-Normal, Log-Logistic, Gompertz, and Gamma. The sum of the least square approach was used to assess the fit of the parametric functions (Table 6). However, the values are very similar except for the Gompertz (poorer fit), which can be expected given the few data points available.

Therefore, the exponential parametric function was selected in line with the curve which defines the probability of discontinuation due to unplanned reasons in the efgartigimod arm. From a clinical point of view, a constant rate of unplanned discontinuations seems appropriate since after the initial discontinuations due to lack of response, the remaining discontinuations would occur due to a constant rate of adverse events or other reasons, e.g. patient preference. The probability per cycle estimated from the Exponential function is applied at every cycle of the analysis to the cohort on treatment with IVIg. The proportion of the cohort discontinuing is thereafter assumed to receive conventional therapy treatments. The costs, effects, and quality of life of conventional therapy are therefore applied.

Table 6. Parameters and sum of least square values of each parametric function for IVIg unplanned discontinuations

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Gamma
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scale	NA	NA	[redacted]	[redacted]	[redacted]	[redacted]
Shape	NA	[redacted]	NA	NA	NA	[redacted]
Sum of least square	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix C A report based on expert gMG HCP facilitated interviews and implementation in the model

C.1 Executive summary

- In response to the Draft Guidance, the Company sought to explore and validate assumptions regarding IVIg dose, frequency and discontinuation rates due to a lack of response in UK clinical practice. These factors comprise key elements of the cost-effectiveness model.
- Six facilitated interviews with expert gMG healthcare professionals (HCPs) explored these topics. The experts were asked to answer in relation to the target patient population for efgartigimod.
- There was broad agreement among the clinical experts regarding the dosing and frequency for IVIg, with most patients falling into the 1g/kg every 4 weeks.
- The next most common dosing regimens were 1g/kg every 6 weeks and 1g/kg every 3 weeks.
- The dosing regimens in UK clinical practice broadly align with the Association of British Neurologists (ABN) guidelines[12] and NHS IVIg Commissioning Criteria Policy document.[13]
- All clinical experts agreed that most discontinuations occur in the period after treatment initiation and that the number of maintenance cycles after which response was measured is [redacted] cycles.
- The range of long-term discontinuations due to non-response was [redacted]
- The mid-point/average long-term discontinuation rate aligns with the 19.5% reported in an analysis of the literature.

C.2 Introduction

In response to the Draft Guidance, the Company sought to explore and validate assumptions regarding IVIg dose, frequency, and discontinuation rates due to a lack of response in UK clinical practice. These factors comprise key elements of the cost-effectiveness model. Expert elicitation in the form of facilitated interviews with expert gMG HCPs were conducted to supplement the rationale for the assumptions in the updated base case of the economic model and for insight into potential scenarios.

C.3 Objectives and methodology

NICE is currently considering the clinical and cost-effectiveness of efgartigimod for the treatment of gMG (efgartigimod for treating generalised myasthenia gravis [ID4003], NICE) and have noted that there is remaining uncertainty relating to the population in which efgartigimod will be used. There are also uncertainties associated with elements of current treatment, particularly around the use of IVIg in UK clinical practice and its inclusion in the model.

The expert gMG HCPs were asked to respond with the following target patient population in mind:

Those patients with active, refractory disease, with an Myasthenia Gravis-Activities of Daily Living (MG-ADL) score ≥5 (>50% of MG-ADL score due to non-ocular symptoms), who have failed, not tolerated or are ineligible for standard therapy*.

*Standard therapy includes maximal dose of steroids, and at least 2 non-steroidal immunosuppressive therapies (NSISTs), for an adequate period of time, in an adequate dose.

The survey comprised of key questions aimed to inform the assumptions in the cost-effectiveness analysis, with the following objectives:

- To understand the maintenance IVIg dosing regimens used in routine clinical practice
- To elicit expert gMG HCPs' views on the discontinuation rates from maintenance IVIg due to a lack of response

Six facilitated surveys were conducted to address these objectives. The Company was responsible for identification of appropriate experts for this study. Due to the rarity of the disease, experts were approached from the universe of neuromuscular specialist centres. Selection of the expert gMG HCPs was based on their knowledge, experience in prescribing, and key decision making relating to IVIg in patients with gMG in UK clinical practice. Recruitment of the expert gMG HCPs also considered regional spread across England, to ensure sufficient representation across geographic regions. Six expert gMG HCPs were approached and all six agreed to participate in the facilitated interviews.

C.4 Discussion guide

A discussion guide (see Section C.7) was developed focused on gathering expert gMG HCPsinsights on two specific questions (see below), which provided the questions in advance as well as supporting literature.

1. Based on your knowledge and experience, can you please define which percentage of patients on maintenance IVIg treatment receive treatment at the following dosing and frequency schedules? Please feel free to include any schedule not listed below in "OTHER"

2. Evidence from the literature assumes that the majority of discontinuations are expected/experienced at the initial treatment phase of maintenance IVIg, rather than over the longer term. Is this pattern confirmed in your clinical experience?

YES/NO

Any comment: _____

3. Based on your experience, what is the percentage of patients not responding to maintenance IVIg treatment? How many cycles of maintenance IVIg should be administered before assessing treatment response?

Percentage of IVIg non-responders: _____%

Number of maintenance IVIg cycles after which response is measured: _____

The report details the responses given by the gMG clinical experts regarding these questions.

C.5 Results

C.5.1 IVIg dosing regimen

Table 7 presents an overview of the percentage of patients for each dosing regimen of maintenance IVIg. There was broad agreement among the expert gMG HCPs regarding the dosing and frequency for IVIg, with the most commonly reported being the 1g/kg every 4 weeks regimen. The next most commonly reported dosing regimens were or 1g/kg every 6 weeks and 1g/kg every 3 weeks. The 2g/kg every 4 weeks, 1g/kg every 8 weeks and 2g/kg every 10 weeks dosing schedules were provided by two expert gMG HCPs in the 'other' category, who reported [redacted] of their patients receiving those regimens.

Table 7 Percentage of patients per dosing regimen per HCP

HCP	IVIg dosing and frequency (distribution of regimen, % among treated patients)									
	1g/kg Q3W	1g/kg Q4W	1g/kg Q5W	1g/kg Q6W	2g/kg Q6W	2g/kg Q8W	2g/kg Q12W	2g/kg Q4W†	1g/kg Q8W†	2g/kg Q10W†
HCP 1		[redacted]						[redacted]	[redacted]	[redacted]
HCP 2	[redacted]					[redacted]	[redacted]			
HCP 3	[redacted]	[redacted]	[redacted]	[redacted]					[redacted]	
HCP 4	[redacted]		[redacted]							
HCP 5				[redacted]						
HCP 6		[redacted]	[redacted]	[redacted]	[redacted]					

† provided by the HCPs in response to the 'other' option

C.5.2 Discontinuation rates

The expert gMG HCPs agreed that most discontinuations would occur during the initial period, which was defined as any discontinuation after one loading dose and two maintenance doses of IVIg. Discontinuation due to unplanned reasons or a lack of response in this initial period, was reported to be between [redacted] among treated patients. Most expert gMG HCPs agreed that non-response could be assess after [redacted] maintenance cycles, except for two expert gMG HCPs who would consider lack of response after [redacted] maintenance cycles (Table 8).

Table 8 Discontinuation rates due to non-response to IVIg

Expert gMG HCP	% non-responders during initial treatment period with maintenance IVIg	Number of maintenance cycles after which patients would be reviewed, before being defined as a non-responder
HCP 1	[redacted]	[redacted]
HCP 2	[redacted]	[redacted]
HCP 3	[redacted]	[redacted]
HCP 4	[redacted]	[redacted]
HCP 5	[redacted]	[redacted]
HCP 6	[redacted]	[redacted]

C.5.3 Data analysis and implementation in the model

C.5.3.1 IVIg dosing regimen

A frequency distribution of patients between IVIg dosing regimens was obtained based on the percentage of dosing regimens reported by each clinician and by the number of patients reported by the same clinician. As it can be observed in the histogram in Figure 6, IVIg 1g/kg administered every 4 weeks was largely more frequent than any of the other IVIg dosing regimens (Figure 6 and Table 7). A total of 50.3% of patients receives IVIg 1g/kg administered every 4 week (44.1%) and every 3 weeks (6.2%). Overall, the 1g/kg per administration was more frequent than 2g/kg dose, with a total of 85.5% and 14.5% patients respectively (Figure 6). When looking at the distribution of patients between IVIg intervals of administration for 1g/kg (Figure 7, A) vs 2g/kg (Figure 7, B) doses, the most common are every 4 weeks and every 8 weeks, respectively.

Figure 6 Distribution of patients between maintenance IVIg dosing and frequency regimens

Figure 7 Distribution of patients between different frequency schedules for IVIg dosing of 1g/kg (A) and IVIg dosing of 2g/kg

Table 9 presents an overview of the estimated acquisition and administration costs per 4-weeks cycle in the cost-effectiveness model for each reported IVIg dosing regimen and the average across all patients. The price of IVIg was obtained from the latest published price in MIMS (last accessed in February 2024)[14], considering all available formulations.

The IVIg administration cost included the hospital administration and an inpatient short-stay, to account for the hospitalisation for observation of side-effects, as suggested by clinical experts.

Table 9 Average IVIg administrations per cycle in the cost-effectiveness model and respective costs (£), by reported IVIg dosing regimen and overall

IVIg dosing regimen	Percentage of patients*	Average IVIg admin per model cycle#	Acquisition cost (£) per model cycle#	Administration cost (£) per model cycle#	Total cost (£) per model cycle#
Total	[redacted]				
1g/kg Q3W					
1g/kg Q4W					
1g/kg Q5W					
1g/kg Q6W					
1g/kg Q8W					
2g/kg Q4W					
2g/kg Q6W					
2g/kg Q8W					
2g/kg Q10W					
2g/kg Q12W					

The average total IVIg cost per model cycle for all patients was [redacted] which is only [redacted] lower than the total cost of IVIg 1g/kg every 4 weeks ([redacted]) included in the model base case. Moreover, a total IVIg cost per model cycle of [redacted] or higher was reported for the majority of patients (approximately [redacted]), thus confirming the representativeness of the IVIg dosing schedule considered in the model base case (Figure 8).

Figure 8 Distribution of patients by the average IVIg cost per 4-weeks model cycle

C.5.3.2 Discontinuation rate

A weighted average IVIg discontinuation due to lack of response of [redacted] was calculated based on the percentages of non-response obtained by the 6 expert gMG HCPs and as weights the number of patients reported (Table 8).

C.6 Conclusions

There was broad agreement amongst the clinical experts regarding the dosing and frequency for IVIg, with most patients falling into the 1g/kg every 4 weeks regimen. The next most common dosing regimens were 1g/kg every 3 weeks and 1g/kg every 6 weeks. All clinical experts agreed that most discontinuations occur in the period after treatment initiation and that the number of maintenance cycles after which response was measured is [redacted] cycles. The weighted average of long-term discontinuations due to non-response was [redacted], which is overall aligned with the rate of 19.5% determined by an analysis conducted using the available relevant literature.[10,15]

C.7 Additional information / discussion guide

The following information was included in a slide deck and sent as a pre-read to the HCPs, along with the questions described above in the methods section. In addition, the slides were presented during the facilitated survey/interview.

Purpose of the economic analyses

- The following questions are in relation to the cost-effectiveness model (CEM) developed to assess efgartigimod for the treatment of adult patients with AChR-Ab+ gMG, active and refractory disease, compared with IVIg and established clinical management without efgartigimod
- The CEM model includes assumptions around the use of maintenance IVIg, specifically, typical treatment regimens (dosing and frequency) and rates of discontinuation for IVIg in refractory gMG patients
- argenx is conducting interview with clinicians, such as yourself, in order to validate these assumptions in UK clinical practice

Target patient population for efgartigimod

Licensed indication

As an add-on to standard therapy, adult patients (≥18 years) with generalised Myasthenia Gravis (gMG) positive for acetylcholine receptor (AChR) antibodies AND

Target patient population

Those with active, refractory disease, with an MG-ADL score ≥5 (>50% of MG-ADL score due to non-ocular symptoms), who have failed, not tolerated or are ineligible for standard therapy*.

*Standard therapy includes maximal dose of steroids, and at least 2 non-steroidal immunosuppressive therapies (NSISTs), for an adequate period of time, in an adequate dose.

IVIg treatment regimen

Proposed dose for maintenance IVIg is 1g/kg administered every 4 weeks, in line with available guidelines.

- Planned approach: Treatment regimen for maintenance IVIg not defined in UK guidelines so 1g/kg every 4 weeks adapted from ABN guidelines and NHS commissioning policies is proposed

From treatment guidelines and commissioning guidance:	
Dose:	**Frequency:**
The model considers an IVIg dose of 1g/kg per cycle of administration, in line with the NHS Commissioning Criteria Policy (page 19, use for MG)[13]: *"Patients admitted to hospital should receive 1g/kg in the first instance, only receiving a further 1g/kg if there is further deterioration or no response"*	The model considers IVIg administration every 4 weeks, in line with MG guidelines from the Association of British Neurologists[12] which reports a duration of efficacy of IVIg is 3–4 weeks: *"the duration of efficacy of intravenous immunoglobulin is 3–4 weeks, after which a stable patient may deteriorate if the patient is not established on an effective corticosteroid dose"*

Question related to IVIg dosing and frequency

Please consider gMG refractory patients on maintenance IVIg (aligned with the target patient

population). Based on your knowledge and experience, please define which percentage of patients on maintenance IVIg treatment receive treatment at the following dosing and frequency schedules? Please feel free to include any schedule not listed below in “OTHER

1g/kg every 3 weeks: _____%

1g/kg every 4 weeks: _____%

1g/kg every 5 weeks: _____%

1g/kg every 6 weeks: _____%

2g/kg every 6 weeks: _____%

2g/kg every 8 weeks: _____%

2g/kg every 12 weeks: _____%

OTHER, please specify: _____

IVIg discontinuation

Maintenance IVIg can be discontinued due to 1) lack of treatment effect and 2) unplanned reasons.

- Planned approach: Estimates on discontinuation due to lack of treatment effect and unplanned reasons sourced and then pooled from literature.

Discontinuation due to lack of response or “Initial Discontinuation”: defined as any discontinuation after 1 loading dose and 2 maintenance doses of IVIg

Discontinuation due to unplanned reasons or “long-term discontinuation”: defined as any discontinuation after 2 maintenance doses of IVIg

Summary of the literature

- In a review of studies referring to maintenance IVIg, only Hellmann et al. 2014[15] and Bril et al. 2023[10] reported information on initial discontinuation
- We can assume the same definition of initial discontinuation for both studies
    - Hellmann et al. 2014[15] reported 15 out of 52 IVIg patients discontinuing treatment due to lack of response, measured after 1 loading dose and two maintenance doses of IVIg administered at 3.5 weeks interval.
    - Bril et al. 2023[10] reported 1 out of 30 IVIg patients discontinuing the study before Week 9 (the dose regimen was 1 loading dose followed by maintenance doses every 3 weeks)

Pooling data on initial discontinuations from Hellmann et al. 2014[15] and Bril et al. 2023,[10] we proposed an initial probability of IVIg discontinuations due to lack of response of 19.5% (=15 + 1 / 52 + 30).

Question related to IVIg discontinuation

Please consider gMG refractory patients on maintenance IVIg (aligned with the target patient population)

Evidence from the literature assumes that the majority of discontinuations are expected/experienced at the initial treatment phase of maintenance IVIg, rather than over the longer term. Is this pattern confirmed in your clinical experience?

YES/NO

Any comment: _____

Based on your knowledge and experience, what is the percentage of patients not responding to maintenance IVIg treatment? How many cycles of maintenance IVIg should be administered before assessing treatment response?

Percentage of IVIg non-responders: _____%

Number of maintenance IVIg cycles after which response is measured: _____

Appendix D Targeted literature review and indirect treatment comparison

D.1 Review of the evidence on IVIg efficacy as maintenance treatment in gMG

No direct head-to-head trial evidence exists comparing the efficacy of efgartigimod and maintenance IVIg in gMG patients. A comprehensive SLR was conducted in biomedical electronic literature databases recommended by NICE to retrieve evidence on the efficacy of current therapies in gMG, among which is IVIg. The SLR was conducted in two phases. An initial SLR was conducted in April 2022 to identify clinical evidence relating to efgartigimod and comparators in gMG, and was updated in January 2023. The SLR (initial and update) for clinical evidence identified 13 publications of 9 studies of IVIg in gMG across the databases searched (see Table 10 and Table 11).

D.1.1 Indirect treatment comparison feasibility assessment

A feasibility assessment for indirect treatment comparisons (ITC) between efgartigimod and maintenance IVIg was conducted for the MG-ADL change from baseline which is the efficacy outcome relevant to the cost-effectiveness model. When MG-ADL was not reported, QMG was considered instead since both MG-ADL and QMG are clinically important metrics for measuring gMG severity, and MG-ADL can be imputed from QMG. The eligibility criteria employed for determining study inclusion in the feasibility assessment are detailed in Table 10**.**

Table 10 Feasibility assessment study selection criteria

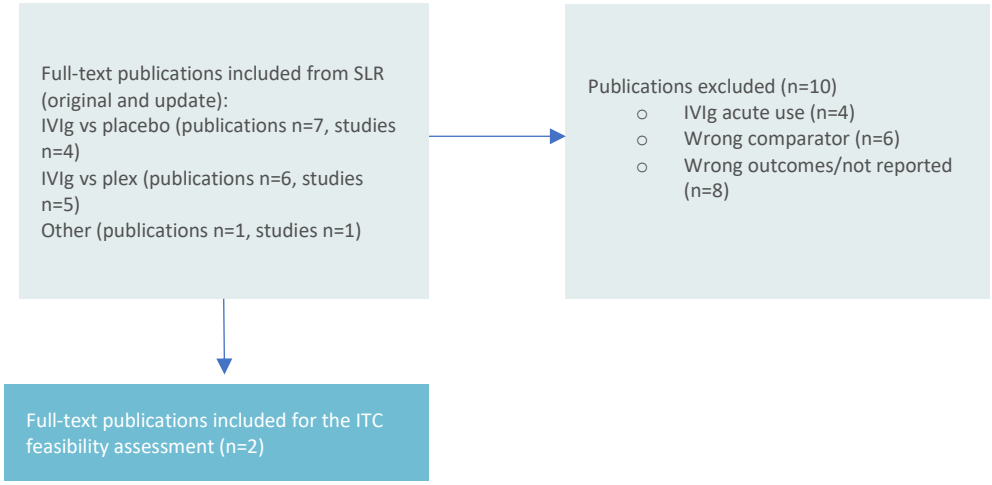
Inclusion criteria	Exclusion criteria
Population	
Adults (aged 18 years and over) who have been diagnosed with AChR-Ab+ generalised myasthenia gravis	Patients under 18 years of age Patients with congenital myasthenia gravis, Lambert-Eaton myasthenic syndrome, or purely ocular MG Non-human/pre-clinical studies
Interventions	
Interventions relevant to the cost-effectiveness analysis: Efgartigimod Maintenance (chronic) IVIg or SCIg	Studies only include other (not listed) active therapies for treating MG IVIg or SCIg used as acute treatments (no repeated administrations)
Comparators	
Placebo	Head-to-head or single-arm trials
Outcomes	
Studies reporting on at least one of the following: MG-ADL change from baseline QMG change from baseline	Studies not reporting any of the listed outcomes (e.g., safety only, steroid-sparing effect only)
Study design & document type	

Inclusion criteria	Exclusion criteria
Randomised controlled trials	Non-randomised studies Editorials, notes, or commentaries Case reports or case series Study protocols Studies not assessing the effects of exposure on the outcomes (e.g., diagnostic studies, assessment of the status quo)

D.1.2 Eligible studies for the ITC feasibility assessment

Very few studies reported the efficacy of maintenance IVIg vs placebo for gMG. Most of the IVIg studies identified considered IVIg as an acute treatment or compared IVIg with plasma exchange (PLEX). Only two studies, Wolfe et al 2002[8] and NCT02473952[9] assessed maintenance IVIg compared with placebo for the treatment of gMG. Both Wolfe et al 2002[8] and NCT02473952[9] included patients with gMG and AChR-Ab+. Wolfe et al 2002[8] study was the only one to report MG-ADL outcomes, whereas the NCT02473952[9] study only reported the change from baseline in QMG. The details for the flow of studies excluded and eligible for the ITC feasibility assessment based on pre-defined selection criteria (Table 10) are presented in the PRISMA in Figure 9. A list of the records excluded from the ITC feasibility assessment is presented in Section D.1.3.

Figure 9 PRISMA flow-chart for IVIg studies eligible for the ITC feasibility assessment



A description of key characteristics of the studies included in the ITC feasibility assessment is provided below.

D.1.2.1 ADAPT: the Phase III Clinical Trial of Efgartigimod (NCT03669588[16])

The efficacy of efgartigimod for the treatment of gMG in adults was established in the 26-week global, multi-centre, randomised, double-blind, placebo-controlled ADAPT trial (Howard et al., 2021)[1]. The ADAPT trial enrolled patients who met the following criteria at screening:

- MGFA clinical classification class II to IV
- Patients with either positive or negative serologic tests for antibodies to acetylcholinesterase receptor (AChR-Ab+). Patients who tested AChR-Ab negative (AChR-Ab-) included patients who were positive for other antibodies (LRP4+ or MuSK+) as well as broadly seronegative patients
- MG-Activities of Daily Living (MG-ADL) total score of ≥ 5
- On a stable dose of gMG therapy prior to screening, that included AChEis, corticosteroids, or NSISTs, either in combination or alone

- IgG levels of ≥ 6 g/L

A total of 167 patients were enrolled across 15 countries and randomised to receive either efgartigimod 10 mg/kg (1,200 mg for those weighing 120 kg or more) (n=84) or placebo (n=83). Initiation of efgartigimod cycles in ADAPT were individualised based on clinical evaluation, which included: total MG-ADL ≥5 points, <2-point reduction of MG-ADL compared to the start of the cycle, and ≥5 (ADAPT) weeks since the last infusion of the previous cycle.
The primary efficacy endpoint was the percentage of MG-ADL responders during the first treatment cycle between treatment groups in the AChR-Ab+ population. The MG-ADL clinically meaningful responders were defined as patients with a ≥2-point reduction in the total MG-ADL score compared to the treatment cycle baseline for at least 4 consecutive weeks during the first treatment cycle (by Week 8), with the first reduction occurring no later than 1 week after the last infusion of the cycle.

D.1.2.2 NCT02473952, 2019: the Phase II Clinical Trial of IVIg

This trial was a Phase II, global, multicentre, randomised, double-blinded study of IVIg in adults with AChR-Ab+ gMG (NCT02473952)[9].

The planned study duration was 24 weeks. In total, 62 patients were enrolled across 10 countries, all of whom tested AChR-Ab+. Patients were randomised 1:1 to receive placebo or an initial loading dose of 2 g/kg of IVIg administered at baseline followed by maintenance doses of 1 g/kg every third week to Week 21. 30 patients were randomised to IVIg treatment, and 32 patients were randomised to placebo. The primary endpoint of NCT02473952[9] was improvement in QMG score from baseline to 24 weeks. Additional secondary endpoints included safety, percentage of patients who improved on total and composite QMG scores, and MG-ADL from baseline to 24 weeks.

D.1.2.3 Wolfe 2002: the Clinical Trial of IVIg

Wolfe et al., 2002 was a USA-based randomised, double-blinded study of IVIg in adults with AChR-Ab+ gMG[8]. The planned study duration was 42 days with a planned open label extension of 6 weeks. In total, 15 patients were enrolled, all of whom tested AChR-Ab+. Patients were randomised 1:1 to receive placebo or 1 gm/kg/day of 5% IVIg on days 1, 2 and 22. 6 patients were randomised to IVIg treatment, and 9 patients were randomised to placebo.

The primary endpoint of the study was change in QMG from baseline to day 42. Additional secondary endpoints included percent decrement at baseline on 2–3 Hz repetitive nerve stimulation and MG-ADL. The small sample size is a potential source of bias that limit the reliability of the study results.

D.1.3 Excluded studies

Table 11 presents the studies excluded from the targeted literature review and the reasons for exclusion.

Table 11 Studies excluded from the targeted literature review

Author, year	Title	Journal; Volume, page number	Reason for exclusion
Gamez J, et al. 2019	Intravenous immunoglobulin to prevent myasthenic crisis after thymectomy and other procedures can be omitted in patients with well-controlled myasthenia gravis	Ther Adv Neurol Disord, 12	Acute IVIg/treatment of exacerbations Wrong outcomes
ClinicalTrials.gov 2015	Efficacy and Safety of IGIV-C in Corticosteroid Dependent Patients With Generalized Myasthenia Gravis (NCT02473965)	https://clinicaltrials.gov/show/NCT02473965. Accessed June 27, 2022.	Wrong outcomes

Author, year	Title	Journal; Volume, page number	Reason for exclusion
EU Clinical Trials Register 2015*	A Study Investigating Immune Globulin (Human), 10% Caprylate/Chromatography Purified (IGIV-C) for the Treatment of Patients With Myasthenia Gravis Dependent on Corticosteroids. 2015	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-005099-17. Accessed June 27, 2022	Wrong outcomes
Gadjos P, et al. 1997	Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group	Ann Neurol, 41(6); 789-796	Acute IVIg/treatment of exacerbations Wrong outcomes Not compared vs placebo
Ronager et al 2001	Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis	Artif Organs. ;25(12):967-973.	Wrong outcomes Not compared vs placebo
Liu et al 2010	Comparing the autoantibody levels and clinical efficacy of double filtration plasmapheresis, immunoadsorption, and intravenous immunoglobulin for the treatment of late-onset myasthenia gravis	Ther Apher Dial. ;14(2):153-160	Not compared vs placebo
Barth et al 201	Comparison of IVIg and PLEX in patients with myasthenia gravis	Neurology. ;76(23):2017-2023.	Acute IVIg/treatment of exacerbations Not compared vs placebo
Barnett et al 2013	Changes in quality of life scores with intravenous immunoglobulin or plasmapheresis in patients with myasthenia gravis	J Neurol Neurosurg Psychiatry. ;84(1):94-97	Wrong outcomes Not compared vs placebo
Alipour-Faz et al 2017	A comparison between IVIG and plasma exchange as preparations before thymectomy in myasthenia gravis patients	Acta Neurol Belg. ;117(1):245-249	Acute IVIg/treatment of exacerbations Wrong outcomes Not compared vs placebo
Bril V, et al. 2022**	A Randomized, Double-Blind, Placebo-Controlled Trial of the Corticosteroid-Sparing Effects of Immunoglobulin in Myasthenia Gravis	Neurology, 45:10; 1212/WNL.0000000000201501.43:36270895.	Relevant outcomes not reported

*Refer to study NCT02473965 **Publications from NCT02473965 trial[17].

D.1.4 ITC approaches

Naïve comparisons are based on a comparison of interventions directly, without accounting for the comparator arm (which is either not present or is discarded). This approach is subject to bias and is not recommended due to the comparison of absolute effects instead of a comparison of relative treatment effects.

Bucher indirect comparisons are considered an improvement to a naïve comparison, whereby the common comparator arm is accounted for (hence denoted an adjusted indirect comparison). This approach is simplistic by design, which is one method to estimate comparative efficacy between two interventions, however, this approach does not account for any observed cross-trial differences, limiting the robustness of a comparison.

In the event that multiple comparators and/or studies per comparator are present in the evidence base, network meta-analysis (NMA) may be considered a robust approach to synthesis and an extension to a Bucher indirect comparison. NMA may be considered feasible where a connected network of evidence is available, and it is considered that there is sufficient homogeneity across the studies under consideration for inclusion in an ITC analysis. An NMA utilises trial-level aggregate-level data (i.e. summary clinical trial estimates) to estimate comparative efficacy. The Bayesian synthesis approach relies on using Markov Chain Monte Carlo (MCMC) methods. It combines prior distributions with the data to construct a posterior distribution as a basis for summary results. One advantage to using an NMA approach for evidence synthesis is its ability to estimate pairwise treatment effects between all interventions included in the network. The NICE DSU published Technical Support Documents (TSD) to provide guidance and recommendations regarding best practices when conducting an NMA. The validity of findings from NMA relies heavily upon whether the evidence base being analysed meets the exchangeability assumption (Salanti, 2012).[18] Exchangeability suggests that all interventions under study could have been included as comparators in a clinical trial and that all are genuinely competing interventions. In practice, the appropriateness of the exchangeability assumption is empirically assessed by the collection of patient and study characteristics for all studies included in an analysis.

Whilst a connected network is available, an alternative method of synthesis based on population adjustment could be considered. The population-adjusted ITC method may be considered an alternative to using aggregate-level trial data when individual patient data (IPD) is available for one of the studies compared. Matching adjusted indirect comparison (MAIC) is based on re-weighting IPD from the index trial (i.e. ADAPT) to overcome observed between-study differences. The MAIC approach allows to adjust for cross-trial differences, including the study design, inclusion/exclusion criteria, baseline characteristics, outcome definitions, and statistical methods, which can be sources of heterogeneity and can bias treatment-effects obtained from an ITC analysis[19]. This form of ITC is designed to work with a single comparator study.

A limitation when few covariates are reported is that there is a risk of residual confounding to be present even after matching. Moreover, this approach cannot overcome differences in outcome definitions or study design, and results based on matched populations may lack robustness where there is a lack of overlap of study populations. In 2016, the NICE DSU published guidance (TSD 18)[20] about best practices when conducting a population-adjusted ITC analysis where IPD are available only for the index trial.

Bucher, NMA and MAIC approaches are considered an improvement to naïve comparisons (which compare interventions of interest without any adjustment for the control arm).

The studies eligible based on pre-defined criteria were compared in detail regarding study characteristics: trial design, patient population and definition of outcomes of interest. Following the recommendations of ITC methodology published by the NICE DSU, a decision on the ITC method was made based on the degree and potential impact of cross-trial heterogeneity and availability of relevant covariates amongst trials, which would be indirectly compared.

D.1.5 Study characteristics

D.1.5.1 Concomitant treatments

Treatment definitions were generally similar between studies. All studies allowed for concomitant corticosteroid treatments (i.e., steroids or NSISTs), but details on the breakdown of actual concomitant medications used were unavailable. Regardless, we have assumed that these treatments did not interact with the therapies under consideration and that any effect was additive. As such, the placebo arm was considered comparable between the studies.

D.1.5.2 Eligibility criteria

Inclusion and exclusion criteria were generally similar across studies. All trials other than ADAPT included only AChR-Ab+ patients. Patients with a recent thymectomy were generally excluded, although the exclusion period ranged from 3 to 12 months before across studies. All trials excluded patients recently receiving either IVIg, SCIg, or PLEX treatment and patients with very mild disease (e.g., MGFA class I). All studies excluded patients under the age of 18. Most studies excluded patients with a history of malignancy or treatment with rituximab in the past 6 to 12 months.

D.1.5.3 Patient baseline characteristics

Baseline characteristics reported among the included studies are summarised in Table 12. The two IVIg trials (Wolfe et al., 2002[8] and NCT02473952[9]) did not report baseline data consistently. Particularly, the study NCT02473952[9] does not provide any information on baseline disease severity. Among those that do report data, baseline characteristics appear reasonably similar between trial populations. Notably, MG-ADL at baseline, QMG at baseline, MGFA at baseline, age, race, and sex were generally comparable among those studies with available data.
Wolfe et al., 2002[8] enrolled younger patients with some lower baseline MG-ADL and baseline QMG scores.

Table 12 **Baseline characteristics among included AChR-Ab+ patients**

Characteristic	**ADAPT[1]**	**NCT02473952[9]**	**Wolfe et al., 2002[8]**
	(N=129)	**(N=62)**	**(N=15)**
Any history of thymectomy - %	58.1	NR	NR
Sex, female - %	66.7	53.2	NR
Race - %			
White	85.3	95.2	NR
Asian	8.5	1.6	NR
Black or African American	3.1	1.6	NR
Other or not reported	3.2	1.6	NR
Age (years) – mean (SD)	46.9 (15.4)	51.2 (15.6)	41.9 (NR)
MG duration (years) – mean (SD)	9.3 (8.3)	NR	NR
Baseline MG-ADL – mean (SD)	8.8 (2.3)	NR	5.7 (3.8)
Baseline QMG – mean (SD)	15.6 (4.8)	NR	9.9 (3.7)
Baseline MGFA - n (%)			
II	41.1	NR	NR
III	55.8	NR	NR
IV	3.9	NR	NR
Use of steroid or NSIST at baseline - n (%)	86.0	NR	NR

D.1.5.4 Outcomes

There was considerable variation in primary and secondary endpoints across the included studies. Responders for MG-ADL and QMG were only reported in ADAPT, while the continuous outcomes change from baseline MG-ADL and QMG were the best reported, appearing in two and three studies, respectively. Although the change from baseline in MG-ADL was not a primary or secondary endpoints for ADAPT, it was selected as a source of comparative efficacy data for this ITC, which aims to provide estimates for the cost-effectiveness analysis. The time of assessment of the outcomes ranged from 4 to 24 weeks in the studies included.

The ADAPT study was unique in that it measured patient response during the first cycle, after four weeks of treatment, and then during subsequent cycles wherein only patients requiring additional treatment for symptom management, as determined by clinicians, were given additional doses. Analyses conducted at the primary timepoint for all trials could be biased against ADAPT, as they could exclude the best responders to efgartigimod. In contrast, ITCs conducted at four weeks only could be biased against any treatments that demonstrated improved responses over time. The ITCs were conducted on the primary time points for all included studies.

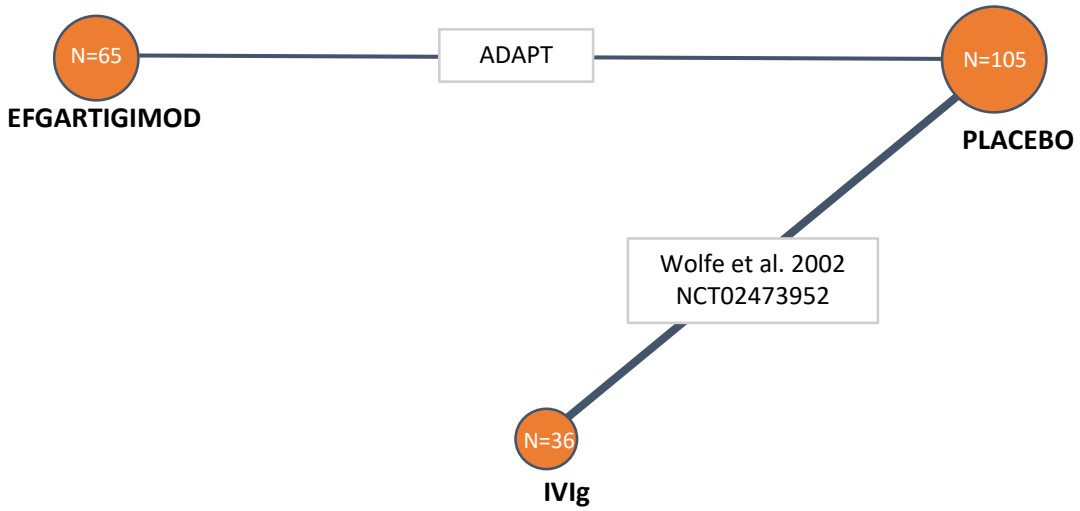
D.1.6 Conclusions from the ITC feasibility assessment

In summary, two studies of IVIg as a maintenance treatment were eligible for the ITC feasibility assessment: Wolfe et al., 2002[8] and NCT02473952.[9] ADAPT was included to inform the efficacy of efgartigimod.

The included studies were comparable in reported eligibility criteria, suggesting that similar trial populations were targeted for enrolment. Where reported, available baseline characteristics appeared similar between studies. Wolfe et al., 2002[8] study included younger patients with some less disease activity as measured by baseline MG-ADL and QMG. Change from baseline MG-ADL was available from all studies except NCT02473952[9], which reported QMG only. For this study, change from baseline MG-ADL could be imputed from QMG. The imputation followed accepted multivariate meta-analysis methods published by NICE Bujkiewicz et al., 2019.[21]

After imputing data for NCT02473952[9], a connected network of evidence is available for the MG-ADL change from baseline, and therefore, an NMA was considered feasible (Figure 10). The primary assessment time points were considered for all studies, accounting for differences in continuous or individualised dosing.

Figure 10 Network diagram for the MG-ADL change from baseline



Targeted comparisons between ADAPT and the single IVIg studies were considered a feasible alternative to the NMA:

- An anchored MAIC was considered feasible between ADAPT[1] and Wolfe et al., 2002[8]. Nevertheless, the study recruited a very small sample size, potentially leading to biased results.
- An anchored MAIC was considered feasible between ADAPT[1] and NCT02473952.[9] Despite the sample size of this study being larger than Wolfe et al. 2002,[8] the very few covariates reported in NCT0247395[9] (i.e. age, sex, race) do not allow adjustment for potential unreported characteristics. Thus, a MAIC vs NCT02473952[9] may not be

considered preferrable over other ITC methods, such as NMA. The MG-ADL change from baseline for the IVIg trial NCT02473952[9] was imputed from QMG data to increase the sample size to inform the efficacy of IVIg in the NMA.

A connected network of evidence exists between efgartigimod via the ADAPT[1] study and IVIg as maintenance treatment, via Wolfe et al., 2002[8] and NCT02473952.[9] An NMA could therefore be conducted. By considering pooled estimates from the two eligible IVIg trials, the sample size to inform efficacy estimates of IVIg is greater in the NMA than if target comparisons with each single study were to be conducted. Moreover, a MAIC NCT02473952[9] would not add large adjustments in characteristics given that only age, sex and race were reported. An NMA was therefore considered the preferred approach, supported by overall good comparability between the studies in terms of eligibility criteria, trial design, population characteristics and outcome definition.

Following the results of this feasibility assessment, an NMA was performed as primary analysis to estimate comparative efficacy between efgartigimod and IVIg in terms of MG-ADL change from baseline at the primary time point. As sensitivity analysis, two separate placebo-anchored MAICs were performed between ADAPT[1] vs Wolfe et al.,2002[8] and vs NCT02473952[9].

D.1.7 NMA (primary analysis)

D.1.7.1 Analytic framework and statistical methods

The NMA was performed using a Bayesian framework[22–24]. The chosen reference treatment was placebo given its presence as the anchor treatment across all studies assessed in the network. Given the lack of multi-study connections in the evidence network, a random effects NMA was deemed infeasible and fixed effects NMA was performed for all outcomes.

An NMA for continuous, arm-based outcomes was used to compare MG-ADL. Data inputs were the MG-ADL mean change from baseline and standard errors. A summary of outcomes reported across studies that were used in the analyses is presented in Table 13. The NMA was performed using SAS V9.4 (The SAS Institute, Cary NC), in alignment with the code outlined in the NICE Evidence Synthesis DSU Technical Support Document Series.[22–24]

Table 13 Summary of raw outcome data used in NMA

Study ID	Treatment	N	MG-ADL change from Baseline			QMG change from Baseline		
			Mean	SE	Primary timepoint (weeks)	Mean	SE	Primary timepoint (weeks)
ADAPT[1]	Efgartigimod	65	-4.10	0.40	4	-5.77	0.66	4
	Placebo	64	-1.27	0.31	4	-0.54	0.37	4
NCT02473952[9]	IVIg	30	[redacted]	[redacted]	[redacted]	-4.60	0.93	24
	Placebo	32	[redacted]	[redacted]	[redacted]	-2.70	1.10	24
Wolfe 2002[8]***	IVIg	6	-0.30	0.82	6	0.00	1.55	6
	Placebo	9	-2.60	0.80	6	-1.60	0.90	6

The MG-ADL results for c were imputed based on the study's QMG results at the same timepoint according to the methodology described by Bujkiewicz[21]

D.1.7.2 Model effects, iterations, and convergence

The model was conducted using a unique set of starting values based on burn-in and sampling durations of 20,000 iterations or more. Convergence was monitored quantitatively using the latest implementation of the Gelman-Rubin diagnostic (Rhat) based on four chains (Vehtari et al.,

2019)[25]. This new implementation captures non-convergence from stationary but non-overlapping chains, over-lapping non-stationary chains, chains with heavy tails, and chains with different variances. Samples were considered to have converged if Rhat was equal to or less than 1.05. After convergence, concern turned to whether there were sufficient independent samples for stable estimates. The newest version of effective sample size (ESS) and Monte Carlo standard error (MCSE) estimation were used to ensure sufficient post-convergence samples were taken to support inference (Vehtari et al., 2019)[25]. If the rank-normalised effective sample size was greater than 400 (i.e., 100 per chain), samples were taken to ensure that MCSE was small enough to allow for stable estimates to at least one decimal place (Vehtari et al., 2019)[25]. All assessments of ESS and MCSE were made for each reported parameter (Spiegelhalter et al., 2002; Dias et al., 2013a)[22,26].

D.1.7.3 Model priors

By default, vague prior distributions that assume no pre-existing information according to NICE DSU TSD 3 (Dias et al., 2011)[27] were assigned for the treatment effects and trial baselines (Table 14).

Table 14 Vague prior distributions used in NMA for the MG-ADL change from baseline

Parameter	Prior distribution
Baselines, unadjusted models (mu)	dnorm (0,100)
Basic parameters (d)	dnorm (0,100)

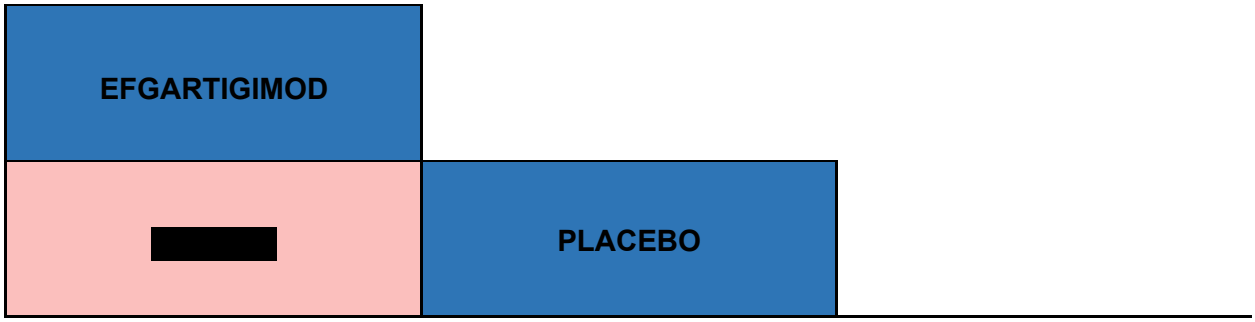
D.1.7.4 Assessment of consistency

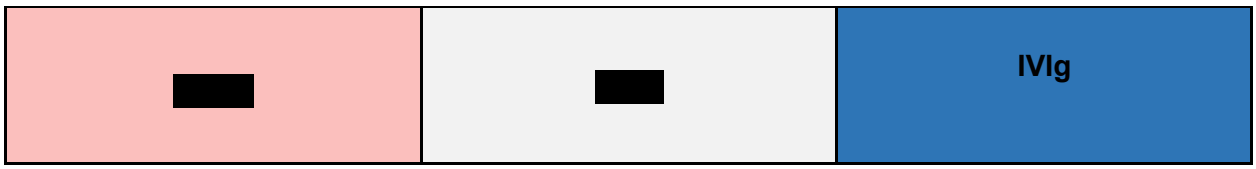
The exchangeability and transitivity assumptions of NMA indicate that the analysed network is consistent, meaning there is no evidence of disagreement between the combined direct and indirect evidence. Inconsistency can be thought of as the statistical realisation of the violation of the transitivity assumption. While the use of an unrelated mean effects model (i.e., an inconsistency model) was planned (to test for inconsistency), there were no independent closed loops in the evidence network, and therefore, no analyses evaluating the consistency of direct and indirect evidence were performed (Dias et al., 2013c)[24].

D.1.7.5 NMA results

Efgartigimod ranked first for change from baseline in MG-ADL in the fixed effects NMA model (Figure 11). Efgartigimod had a better change from baseline in MG-ADL compared to placebo and IVIg, as demonstrated by non-overlap in 95% credible intervals with zero. Interventions in Figure 11 are ordered from left to right in order of decreasing surface under the cumulative ranking curve value.

Figure 11 Fixed effects league table of mean differences for change from baseline in MG-ADL





Comparison from left to right. Numbers are mean change from baseline in MG-ADL with 95% credible intervals in brackets.
For each pairwise comparison, the row treatment serves as the reference group. Shading indicates comparisons where 95% credible intervals do not include 1.

D.1.8 Sensitivity analysis – Anchored MAICs

An overview of the method used for the anchored MAICs between ADAPT[1] vs Wolfe et al. 2002[8] and vs NCT02473952[9] is provided below.

D.1.8.1 Method

Following Signorovitch et al.,[28] the MAIC re-weighted the IPD, so that the population characteristics of ADAPT converged towards those described by the comparator studies[8,9]. The weighted relative effect of efgartigimod vs placebo and the observed relative effect of IVIg vs placebo were then compared to estimate the relative effect of efgartigimod vs IVIg. The *shared effect modifier assumption* was considered (Phillippo et al. 2018)[19]:

- the effect modifiers of all treatments are the same;
- the change in treatment effect caused by each effect modifier is the same for all treatments.

This limited the treatment effect modifiers that could be included in the two MAICs are reported in Table 15. Both Wolfe et al.[8] and NCT02473952[9] reported little information on the baseline characteristics of the included patients. This limited the treatment effect modifiers that could be included in the two MAICs are reported in Table 15.

Table 15 List of covariates used in MAICs between efgartigimod and IVIg

MAIC	Covariates used for adjustment
ADAPT vs Wolfe et al.	Age at baseline; Use of corticosteroid and/or non-steroidal immunosuppressant; MG-ADL score at baseline.
ADAPT vs NCT02473952	Age at baseline; Gender; Race.

Calculation of the weights

The efgartigimod effect was adjusted by applying a specific weight to each patient. The weights were calculated by minimising the following function:

$$\sum_i \exp\left(\boldsymbol{\alpha}^{\boldsymbol{T}} X_i^{EM}\right)$$

where:

- X_i^{EM} was a matrix that contained the values of the selected covariates (effect modifiers) in ADAPT, centered around the mean of the correspondent covariate reported in the comparator studies;
- $\boldsymbol{\alpha}^{\boldsymbol{T}}$ was a vector containing the parameters to be optimised.

The minimisation provides the correct estimate of $\boldsymbol{\alpha^T}$ when the following conditional constraint is true:

$$\bar{X}_i^{EM} = 0$$

This was assured by centring the values of the selected covariates in ADAPT around the mean of the correspondent covariate reported by Wolfe et al.[8] and NCT02473952[9].

The weight associated with each patient *i* (w_i) was then calculated by taking:

$$w_i = \exp\left(X_i^{EM}\boldsymbol{\alpha^T}\right)$$

Estimation of the relative effect

The adjusted relative effect of efgartigimod vs placebo ($\hat{Y}_{EP}$) was calculated using the LS mean obtained by a mixed model for repeated measurements (MMRM), that used the MAIC weights as frequency weights. The model included treatment, visit, and treatment-by-visit interaction terms as fixed effects, with MG-ADL baseline value and stratification factors as covariates. Within-subject correlation has been modelled by assuming an unstructured covariance matrix for the error terms. Stratification factors included ethnicity (Japanese vs non-Japanese) and use of corticosteroids at baseline. The MMRM was chosen to align with ADAPT, which used the same model for the inferential statistics. The adjusted relative effect of efgartigimod vs placebo was estimated by taking the treatment effect predicted by the MMRM at Week 4, which represents the primary timepoint in ADAPT.

The relative effect of efgartigimod vs IVIg ($\hat{Y}_{EIg}$) was estimated based on the difference between $\hat{Y}_{EP}$ and the relative effect of IVIg vs placebo (Y_{IgP}) reported in the comparator studies:

$$\hat{Y}_{EIg} = \hat{Y}_{EP} - Y_{IgP}$$

The NCT02473952[9] trial reports changes in the QMG score but not in the MG-ADL score. However, the latter was estimated using the method described by Bujkiewicz et al. [21] based on the reported changes in the QMG score.

Effective sample size and relative weight distribution

The effective sample size (ESS), which shows the effective number of patients on which the MAIC is based after re-weighting, was calculated for each MAIC to assess whether markedly reduced inferences depend heavily on just a small number of individuals (Phillippo et al. 2018)[19]. In addition, relative weights were estimated using the following formula to assess how much heavier the weight of a single patient is compared to the others:

$$\widetilde{w}_i = \frac{w_i}{\sum_{i=1}^{N} w_i} * total\ number\ of\ patients$$

D.1.8.2 MAICs results

A convergence of the baseline characteristics of the two populations compared in each MAIC was obtained for the included variables, as shown in Table 16 and Table 17.

Table 16 Aggregate value of the baseline characteristics before and after adjustment in MAIC vs Wolfe et al. 2002

Covariates included for adjustment	Mean value		
	ADAPT - unadjusted	ADAPT - adjusted	Wolfe et al
Age at baseline, years	46.9	[redacted]	41.1
Use of corticosteroid and/or NSAID at baseline, %	84.5%	[redacted]	53.3%
MG-ADL score at baseline	8.80	[redacted]	5.72

Table 17 Aggregate value of the baseline characteristics before and after adjustment in MAIC vs NCT02473952

Effect Modifier	Mean value		
	ADAPT - unadjusted	ADAPT - adjusted	NCT02473952
Age at baseline, years	46.9	[redacted]	51.2
Female patients, %	67.2%	[redacted]	53.2%
Race, Asian, %	8.6%	[redacted]	1.6%
Race, Black, %	3.1%	[redacted]	1.6%
Race, White, %	2.3%	[redacted]	0.0%
Race, Other, %	85.2%	[redacted]	95.2%

Effective sample size and relative weight distribution

The ESS amounts to [redacted] and [redacted] of the included sample size in the MAIC vs NCT02473952 and in the MAIC vs Wolfe et al., respectively. There are no outliers that skew the results of the MAIC vs NCT02473952 due to very high weights, and the weight distribution is symmetric (Figure 12). In contrast, few patients are driving the results of the MAIC vs Wolfe et al (Figure 13). This is in line with the observed positively skewed weight distribution, with some extreme outliers on the right side.

Figure 12 - Relative weight distribution, MAIC vs NCT02473952

Figure 13 - Relative weight distribution, MAIC vs Wolfe et al.

Relative effect between efgartigimod and IVIg from the MAIC vs Wolfe et al.

The results of the MAIC suggest that patients treated with efgartigimod achieved a reduction in the MG-ADL from baseline that is [redacted] points greater than the reduction achieved with IVIg (SE = [redacted] 95%CI=[redacted], p-value <0.05) (Table 18). The confidence interval does not cross 0, indicating that the obtained result is statistically significant. However, the results should be interpreted with caution, given the small ESS and the skewed weight distribution. Moreover, the small sample size of the Wolfe et al. study and the few reported covariates contribute to the potential risk of bias in results.

Table 18 Results of the anchored MAIC vs Wolfe et al.

	MG-ADL change from baseline			
	Mean	**SE**	**Lower 95%CI**	**Upper 95%CI**
Efgartigimod vs placebo	[redacted]	[redacted]	[redacted]	[redacted]
IVIg vs placebo	[redacted]	[redacted]	[redacted]	[redacted]
Efgartigimod vs IVIg	[redacted]	[redacted]	[redacted]	[redacted]

Relative effect between efgartigimod and IVIg from the MAIC vs NCT02473952

The results of the MAIC suggest that patients treated with efgartigimod achieved a reduction in the MG-ADL from baseline that is [redacted] points greater than the reduction achieved with IVIg (SE = [redacted], 95%CI=[redacted], p-value <0.05) (Table 19). The confidence interval does not cross 0, indicating that the obtained result is statistically significant. However, the results should be interpreted with caution given that the NCT02473952 study only reported age, gender and race among covariates of interest, thus there is a risk of large residual confounding to be present after matching.

Table 19 Results of the anchored MAIC vs NCT02473952

	MG-ADL change from baseline			
	Mean	**SE**	**Lower 95%CI**	**Upper 95%CI**
Efgartigimod vs placebo	[redacted]	[redacted]	[redacted]	[redacted]

IVIg vs placebo	[redacted]	[redacted]	[redacted]	[redacted]
Efgartigimod vs IVIg	[redacted]	[redacted]	[redacted]	[redacted]

D.1.9 Discussion on the ITC

The objective of this ITC was to estimate the comparative efficacy between efgartigimod and IVIg for the treatment of patients with gMG and AChR-Ab+. Studies on IVIg were retrieved via an SLR and considered eligible for the ITC feasibility assessment if they included repeated administrations of IVIg, were RCTs with placebo as the control arm, and included the change in MG-ADL or QMG from baseline. Only two IVIg trials met these criteria and were therefore considered further for the ITC feasibility assessment. An overview of the results of the primary ITC analysis and sensitivity analysis is presented in Table 20.

Table 20. Summary of comparative efficacy ITCs results for efgartigimod vs IVIg

	Efgartigimod vs IVIg: MG-ADL change from baseline		
	Mean	**Lower 95CI**	**Upper 95CI**
NMA vs Wolfe et al[8] and NCT02473952[9] (primary analysis)	[redacted]	[redacted]	[redacted]
MAIC vs Wolfe et al[8]	[redacted]	[redacted]	[redacted]
MAIC vs NCT02473952[9]MAIC vs NCT02473952[9]	[redacted]	[redacted]	[redacted]

Based on the ITC feasibility assessment conducted, an NMA was conducted as primary analyses to estimate comparative efficacy between efgartigimod and IVIg in terms of MG-ADL change from baseline at the primary time point. By considering pooled estimates from the two eligible IVIg trials, the sample size to inform efficacy estimates of IVIg was increased, thus allowing more a robust estimate of comparative efficacy than if each study was considered separately. The NMA approach was built on rigorous methods developed by NICE and aligned with best practice for NMA. The results of the NMA showed a larger reduction in MG-ADL from baseline with efgartigimod than with IVIg and with placebo, which was statistically significant, The results of the NMA were confirmed in two additional targeted comparisons vs Wolfe et al., 2002[8] vs NCT02473952[9] using a MAIC approach. The results of the NMA and the two MAICs represent a robust evidence base to inform the comparative efficacy of efgartigimod vs IVIg for use in the cost-effectiveness model of efgartigimod, especially in light of the limited data available on the effect of IVIg as maintenance treatment in gMG.

D.1.9.1 Use of the ITC estimates to model the IVIg treatment effectiveness in the cost-effectiveness model

The estimates of IVIg comparative efficacy in terms of MG-ADL change from baseline obtained from the ITC were used to recalibrate the health-states transitions observed in the placebo arm of ADAPT during each 4-week cycle starting from the baseline up to Week 16.

An additional probability of improvement for IVIg vs placebo was estimated based on mean time of transitioning to the next best health state for IVIg. This was based on the distance in average MG-ADL points from the starting state to the next best state (Table 21) and the estimated difference in MG-ADL change from baseline between IVIg and placebo of [redacted], [redacted], calculated from the NMA outcomes (the MG-ADL difference for efgartigimod vs IVIg of [redacted] from the NMA was subtracted to [redacted] MG-ADL difference for efgartigimod vs placebo, to obtain the estimate of IVIg vs placebo).

The number of cycles required to transition to the next best health-state was estimated with the following formula (Table 22):

$$\frac{Distance\ to\ next\ best\ health-state}{IVIg\ MG-ADL\ change\ from\ baseline\ vs\ placebo}$$

Table 21 MG-ADL points distance to next best health-state

Health-states	MG-ADL by health-state			MG-ADL points to next health state
	Lower bound	Upper bound	Average point	
MG-ADL ≥10	[redacted]	[redacted]	[redacted]	[redacted]
MG-ADL 8–9	[redacted]	[redacted]	[redacted]	[redacted]
MG-ADL 5–7	[redacted]	[redacted]	[redacted]	[redacted]
MG-ADL<5	[redacted]	[redacted]	[redacted]	[redacted]

Table 22 Additional IVIg cycle probability of transitioning to next best state vs placebo, based on NMA outcomes

	Estimated number of cycles to transition*	Additional IVIg probability per cycle vs placebo
MG-ADL ≥10 to MG-ADL8–9	[redacted]	[redacted]
MG-ADL8–9 to MG-ADL5–7	[redacted]	[redacted]
MG-AD5–7 to MG-ADL<5	[redacted]	[redacted]

*Considering a difference in MG-ADL change from baseline between IVIg and placebo of [redacted], calculated from the NMA outcomes.

The additional IVIg cycle probability of transitioning to the next best health-state compared with placebo was then estimated as the inverse of the mean number of cycles required to transition. This probability was used to increase the proportion of the cohort that transition to the next best health-states as observed in the placebo arm of ADAPT, during each 4-week cycle starting from baseline up to Week 16. Table 23 to Table 26 show the resulting transition matrices used to define the probabilities from MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 in the IVIg cohort in the first four cycles of the analysis. Beyond cycle four, the model assumes the effect is maintained for as long as the cohort remains on treatment.

Table 23 Transition matrix used for the IVIg cohort arm during the first model cycle

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

Table 24 Transition matrix used for the IVIg cohort during the second model cycle

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

Table 25 Transition matrix used for the IVIg cohort during the third model cycle

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

Table 26 Transition matrix used for the IVIg cohort during the fourth model cycle

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

Appendix E Handling of placebo effect and extrapolation of post treatment discontinuation

To address the Committee's concerns, in the revised model, the benefit observed in the placebo arm of ADAPT is maintained over the time horizon of the analysis. This is applied equally in all treatment arms of the model. As highlighted by the EAG, this would be conflicting with any assumption on residual effect post discontinuation of efgartigimod, and for this reason, the latter was removed from the base case analysis:

- The transition probabilities observed in the placebo arm of ADAPT up to Cycle 4 are applied to the conventional therapy cohort in the ECM arm, and thereafter the distribution remains as last observed (Table 27) rather than returning to baseline as in the initial Company submission.

Table 27 Placebo distribution at the end of cycle four

Health-states	Proportion of the cohort
MG-ADL <5	[redacted]
MG-ADL 5–7	[redacted]
MG-ADL 8–9	[redacted]
MG-ADL ≥10	[redacted]

- The IVIg cohort in the ECM arm is applied the recalibrated placebo transitions (Table 23 to Table 26) and thereafter assumed to remain distributed as last observed, thus maintaining both the placebo and additional IVIg benefit over the time-horizon of the analysis for as long as the cohort remains on treatment. Post-discontinuation, the cohort is assumed to receive conventional therapy and, therefore, is assumed to remain distributed between the health states as in the conventional therapy cohort (Table 27).
- The cohort in the efgartigimod arm is applied the on- and off-treatment probabilities as observed in ADAPT and ADAPT+, as detailed in the Company's submission dossier, for as long as it does not permanently discontinue treatment. Post-discontinuation, the cohort is assumed to receive conventional therapy and, therefore, is assumed to remain distributed between the health states as in the conventional therapy cohort (Table 27), in line with post-IVIg discontinuation.

This approach allows consistency in the simulation assumptions between modelled treatment arms. Nevertheless, the maintenance of placebo benefit forever may not be plausibly representative of disease progression in the real-world especially because of the loss of the placebo effect once the patient is outside of the trial setting.

Placebo effect and residual treatment effect scenario analyses

The Company included two additional scenarios in the revised model, where 1) the placebo benefit is not maintained in conventional therapy cohort over the time-horizon of the analysis and 2) the placebo effect is removed also from all modelled arms.

- Scenario 1: the placebo effect was not maintained with conventional therapy in the ECM arm beyond Cycle 4 (observed transitions in ADAPT). In this scenario a residual effect is applied post efgartigimod and IVIg discontinuation for a duration of 6 months. This is done by assuming that 7.5% (mid-point of the range 1% to 15%) of the cohort located in MG-ADL<5 health-state at the time of discontinuation, would remain in the MG-ADL<5 health-state, for a duration of 6 months. Thereafter, the residual effect is not further applied.

- Scenario 2: this scenario attempts to solve the issue of inflated relative efficacy without adding a permanent placebo effect to the ECM arm. In this scenario, the placebo effect is not maintained in the conventional therapy cohort beyond Cycle 4 and the placebo effect is removed from the efficacy of efgartigimod (Table 28). Removing the placebo effect from the benefit of the intervention arm is complex. Nevertheless, an attempt was made to remove the placebo effect from the efgartigimod transitions: the MG-ADL change from baseline in the placebo arm of ADAPT and the distance to better health states were used to estimate the improvement due to the placebo. This was removed from the probability of improving to better health states in the efgartigimod transitions. The resulting transition matrix can, therefore, be considered representative of what could be observed after removing the placebo effect from the total effect observed in the efgartigimod arm and was applied from Cycle 5 of the analysis (in line with the time at which the placebo effect is removed in the conventional therapy cohort).

Table 28 Transition matrix for efgartigimod on-treatment after removing the placebo effect (applied from Cycle 5 of the analysis)

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

Also, in this scenario a residual effect is applied post efgartigimod and IVIg discontinuation for a duration of 6 months. This is done by assuming that 7.5% (mid-point of the range 1% to 15%) of the cohort located in MG-ADL<5 health-state at the time of discontinuation, would remain in the MG-ADL<5 health-state, for a duration of 6 months. Thereafter, the residual effect is not further applied.

Appendix F Economic analyses

F.1 Overview

The revised cost-effectiveness model base case includes the following changes:

i. The baseline cohort characteristics were set equal to the population characteristics in the ADAPT trial.

ii. The SC formulation of efgartigimod was assumed to be administered to 80% of the cohort in the efgartigimod arm and the remaining 20% are assumed to receive the IV formulation. The revised model also includes the following assumptions concerning home administration:
   - Efgartigimod SC: the cohort receives the first 5 infusions (i.e. all infusions of the first cycle and the first infusion of the second cycle) in the hospital (based on SmPC of efgartigimod SC). Thereafter, 80% of the cohort on efgartigimod SC receives the treatment at home and 20% in the hospital. This assumption was based on the opinion of clinical experts.
   - Efgartigimod IV: 50% of the cohort on efgartigimod IV receives the treatment at home and 50% in the hospital, based on real-world usage data of efgartigimod in EAMS and the opinion of clinical experts.

iii. The disutility values associated with caregivers were removed.

iv. The same health-states utilities were applied to all treatment arms and were based on the mixed model for repeated measure (MMRM) regression on ADAPT data, without considering treatment covariate (Table 29).

Table 29 Health-state utilities based on MMRM on ADAPT data, no treatment covariate

Health-state	Utility (applied to all treatment arms)
MG-ADL<5	[redacted]
MG-ADL 5-7	[redacted]
MG-ADL 8-9	[redacted]
MG-ADL≥10	[redacted]

v. The cost of systemic corticosteroid related complications was calculated based on the frequency of only intolerable corticosteroid related adverse events in MG patients reported in the study by Lee et al. 2018[29] and the associated costs sourced from the latest published NHS Reference Cost. The resulting annual cost of systemic corticosteroid related intolerable complications was £456.73 per cycle.

vi. The percentage of maintenance IVIg treatment among the ECM arm was set equal to 43.8%, based on the percentage patients in the EAMS cohort who had received maintenance IVIg prior to being offered efgartigimod through the EAMS programme. An additional scenario was considered where 69.17% maintenance IVIg use is considered based on the Delphi Panel conducted with local clinicians.

vii. To allow the inclusion of efficacy and discontinuations for maintenance IVIg in the revised model, the ECM arm was modelled via two separate engines for conventional therapy and IVIg cohort. The LYs, QALYs and costs in the ECM arm were then calculated as the sum of these results in the conventional therapy and IVIg engines, weighted by the respective assigned percentages (see bullet point **i.**).

viii. The price of IVIg was updated based on latest available price published in MIMS (last accessed in February 2024)[14]. A description of the calculation of IVIg cost is reported in

Table 30. IVIg was dosed at 1 g/kg, yielding an average of 4 vials per administration for the 20 mg/100 mL formulation considering an average body weight of 78.88Kg (different combinations of vial sizes were explored: 3 vials of the 20mg/100mL and 8 vials of 2.5 mg/25 mL or 7 vials of the 10mg/100mL and 4 vials of 2.5 mg/25 mL, however the resulting total cost would be the same). IVIg is administered once every 4 weeks, therefore one administration per model cycle is considered.

Table 30 IVIg drug cost per cycle in base-case analysis

Drug	Admin per cycle	Drug cost per vial, £	Drug cost per admin, £	Drug cost per cycle, £
IVIg - Privigen (20mg /100mL)	1.00	1,580.00	6,320.00	6,320.00

The revised model includes the possibility to test the following alternative assumptions on maintenance IVIg dosing, the results are presented as scenarios analyses:

a. IVIg dosed at 1g/kg administered every 3 weeks, in line with the dosing schedule of the studies by Wolfe et al., 2002[8] and the NCT02473952[9] study used to inform the comparative efficacy estimates for IVIg in the revised model. In this scenario, the resulting overall costs per cycle for the IVIg cohort are £8,427 and £2,291, for acquisition and administration respectively.
b. IVIg is cost is calculated considering the distribution of patients between alternative IVIg dosing regimens obtained in a survey with six gMG expert gMG HCPs in England (Table 31). In this scenario, the resulting overall costs per cycle for the IVIg cohort are [redacted] and [redacted], for acquisition and administration respectively. Full details of the survey and responses are reported in Appendix C.

Table 31 Distribution of cohort between alternative IVIg dosing regimens suggested by six HCPs in England

IVIg dosing regimen (dose and frequency of administration)	Percentage of IVIg cohort
IVIg, 1g/kg every 3 weeks	[redacted]
IVIg, 1g/kg every 4 weeks	[redacted]
IVIg, 1g/kg every 5 weeks	[redacted]
IVIg, 1g/kg every 6 weeks	[redacted]
IVIg, 1g/kg every 8 weeks	[redacted]
IVIg, 2g/kg every 4 weeks	[redacted]
IVIg, 2g/kg every 6 weeks	[redacted]
IVIg, 2g/kg every 8 weeks	[redacted]
IVIg, 2g/kg every 10 weeks	[redacted]
IVIg, 2g/kg every 12 weeks	[redacted]

ix. The revised model includes discontinuations of IVIg treatment due to a lack of response and long-term discontinuations due to unplanned reasons. This approach is aligned with how discontinuations are considered in the efgartigimod arm of the model. Discontinuations

data reported in the literature were used to inform the simulation of discontinuations in the IVIg cohort of the model. Based on limited available studies on maintenance IVIg, the revised model includes an initial probability of discontinuation due to lack of response of 19.5%. The non-responder cohort is separated from the responder cohort at the beginning of the simulation. However, the cost of one loading dose and two maintenance doses of IVIg treatment is still applied. From the second cycle of the model, a probability of unplanned discontinuations was modelled by fitting an Exponential function to reconstructed time-to-discontinuation data based on available studies on maintenance IVIg. More detail on the estimation of both the percentage of discontinuation due to lack of response and the cycle probability of unplanned discontinuation is provided in Appendix B. The cohort discontinuing IVIg treatment is assumed to receive conventional therapy treatments. Therefore, the costs and effects of conventional therapy are applied to this proportion of the cohort from the point of discontinuation across the entire time horizon.

x. An additional benefit for maintenance IVIg compared with placebo was considered in the revised model for the cohort on IVIg maintenance treatment. The estimate of comparative efficacy for IVIg was obtained from an indirect treatment comparison (ITC) via NMA based on two trials for efgartigimod, the ADAPT and the phase II study, and two trials for maintenance IVIg, Wolfe et al. 2002[8] and NCT02473952[9]. The detail of the review of the literature, ITC feasibility assessment and ITC results are provided in Appendix D. The estimates of IVIg comparative efficacy in terms of MG-ADL change from baseline obtained from the ITC were then used to recalibrate the health-states transitions observed in the placebo arm of ADAPT during each 4-week cycle starting from baseline to Week 16. Beyond cycle four, the model assumes the effect is maintained for as long as the cohort remains on treatment. Full details on the estimation of the transition probabilities in the IVIg cohort are included in Appendix D. The revised model also includes the possibility to estimate the IVIg transition probabilities based on comparative efficacy estimates obtained from targeted ITCs for ADAPT vs Wolfe et al. 2002[8] and vs NCT02473952[9], using matching-adjusted indirect comparison (MAIC) approach. The results are reported as scenario analyses in this document.

xi. In the revised model, the benefit observed in the placebo arm of ADAPT is maintained over the time horizon of the analysis. This benefit is applied equally to all treatment arms of the model. This approach allows consistency in the simulation assumptions between modelled treatment arms. The detail of this approach is provided in the main response document (see Area 5) and in Appendix F. The Company also included two additional scenarios:
    - The placebo effect was not maintained with conventional therapy in the ECM arm beyond Cycle 4 (observed transitions in ADAPT). In this scenario the cohort post discontinuation of efgartigimod and IVIg treatments, maintain a residual effect with 7.5% of the cohort in MG-ADL <5 at the time of discontinuation remaining in that health-state. The duration of the residual effect was limited to 6 months.
    - The placebo effect was removed from each arm in the model. Also in this scenario, the cohort post discontinuation of efgartigimod and IVIg treatments, maintain a residual effect with 7.5% of the cohort in MG-ADL <5 at the time of discontinuation remaining in that health-state. The duration of the residual effect was limited to 6 months.

The results of the revised cost-effectiveness model base case analysis are presented in Table 32. The results are based on efgartigimod list price with a [redacted] PAS.

Table 32 Revised model basecase analysis with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,110
Established clinical management	[redacted]	[redacted]	[redacted]				

F.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to assess the robustness of the model to parameter uncertainty. In the PSA, 1,000 simulations were performed in which model parameters were varied simultaneously by sampling at random from hypothetical distributions. The distributions used for each variable in the PSA are reported in the model. The results of the PSA are presented in Figure 14 and Figure 15.

Figure 14: Incremental cost and QALY cloud in the cost-effectiveness plane with PAS

Figure 15: Cost-effectiveness acceptability curve with PAS

F.3 Deterministic sensitivity analysis

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way sensitivity analyses was performed. The results of the deterministic sensitivity analysis are presented in Figure 16, Table 33 and Table 34.

Figure 16: Results of the one-way sensitivity analysis with PAS

Table 33: Percentage change in base case results with PAS following lower and upper variation in the 10 most influential parameters

Parameter	Lower value	Upper value
Maintenance IVIg use in ECM	1475%	N/A
Discount rate costs	N/A	662%
Average weight, kg	20%	N/A
Efgartigimod RDI	N/A	377%
IVIg non-responders	N/A	352%
Administration costs - Hospital administration, IVIG	322%	N/A
Efgartigimod non-responders	284%	N/A
Initial age (years)	-66%	118%
Weight ≥80kg, % cohort	-35%	76%
Extra mortality associated with corticosteroid use - Corticosteroid high-dose	-48%	43%

Table 34: Detailed results of the one-way sensitivity analysis with PAS

Parameter	ICER (£/QALY)	
	Lower	Upper
Maintenance IVIg use in ECM	222,277	Dominant
Discount rate costs	Dominant	107,584

Average weight, kg	16,943	Dominant
Efgartigimod RDI	Dominant	67,257
IVIg non-responders	Dominant	63,755
Administration costs - Hospital administration, IVIG	59,485	Dominant
Efgartigimod non-responders	54,122	Dominant
Initial age (years)	4,768	30,744
Weight ≥80kg, % cohort	9,110	24,790
Extra mortality associated with corticosteroid use - Corticosteroid high-dose	7,303	20,154

F.4 Scenario analysis

Results of the scenario analyses are shown in Table 35. The assumptions included in response to the Committee's requests have led to an ECM profile that is not reflective of UK clinical practice. Because of this the Company has updated the cost-effectiveness model to address a number of concerns from the Committee, and this included several assumptions that greatly increased the efficacy of the ECM arm, as for instance the addition of maintenance of placebo effect in the conventional therapy cohort and of explicit efficacy terms for IVIg. These assumptions are very conservative and resulted into a small QALY increment for efgartigimod compared with ECM. Since this small delta QALYs stays at the denominator in the ICER calculation, any change in modelling assumptions is greatly amplified in terms of impact on the ICER. Nevertheless, the results of most explored scenarios suggest that efgartigimod remains cost-effective compared with Established Clinical Management for the treatment of gMG in England, at the £30,000/QALY willingness to pay threshold and considering a [redacted] PAS for efgartigimod.

Scenario 9 was included in response to NICE request to explore a lowest bound for the use of maintenance IVIg in ECM. Nevertheless, the Company believes this scenario is not representative of current clinical practice, given the large uncertainty on the data informing this estimate. In fact, an NHSE commissioning expert confirmed to the Company that these data were obtained from clinical experts consulted for the appraisal, rather than from the National IVIg database. The percentage of IVIg use obtained from prior treatment in EAMS patients is expected to be more robust evidence of real-world IVIg use in gMG patients with active disease despite conventional therapy. The Company is also aware that there is a commercial discount in place for IVIg, so Scenario 15 has been added, which includes an assumed value for the commercial discount.

Table 35 Scenario analyses for efgartigimod vs established clinical management with PAS

	Scenario description	**Efgartigimod vs established clinical management**		
		Incr Cost, £	**Incr QALYs**	**ICER £/QALY**
0	Revised base case	[redacted]	[redacted]	14,110
1	Population characteristics based on refractory subgroup in ADAPT (AChR+)	[redacted]	[redacted]	1,709
2	Population characteristics based on EAMS patients	[redacted]	[redacted]	22,421
3	The effect observed in the placebo arm of ADAPT is not maintained beyond Cycle 4 in conventional therapy cohort. Post IVIg and efgartigimod discontinuation a residual effect of 7.5% in MG-ADL<5 is considered for a duration of 6 months.	[redacted]	[redacted]	14,501

4	The placebo effect is removed from all arms beyond cycle 4. Post IVIg and efgartigimod discontinuation a residual effect of 7.5% in MG-ADL<5 is considered for a duration of 6 months.	[redacted]	[redacted]	74,347
5	The effect in IVIg cohort was based on the MAIC vs NCT02473952[14]	[redacted]	[redacted]	24,339
6	The effect in IVIg cohort was based on the MAIC vs Wolfe et al. 2002[8]	[redacted]	[redacted]	12,926
7	PLEX use in ECM arm: 14.6% based on EAMS	[redacted]	[redacted]	Dominant
8	Maintenance IVIg use in ECM arm: 69.17% based on Delphi Panel	[redacted]	[redacted]	Dominant
9	Maintenance IVIg use in ECM arm[redacted]based on NHS limited data (approximation)	[redacted]	[redacted]	345,319
10	Maintenance IVIg dosing regimen: 1g/kg administered every 3 weeks	[redacted]	[redacted]	Dominant
11	Maintenance IVIg dosing regimen: based on distribution of cohort between dose and frequency alternatives from interview with 6 gMG HCPs	[redacted]	[redacted]	95,499
12	Proportion of IVIg cohort discontinuing due to lack of response: [redacted]_weighted average from interview with 6 gMG HCPs	[redacted]	[redacted]	Dominant
13	Maintenance IVIg dosing regimen and proportion of IVIg cohort discontinuing due to lack of response from interview with 6 gMG HCPs	[redacted]	[redacted]	35,242
14	Caregiver disutilities are included based on gMG Caregiver Burden Study	[redacted]	[redacted]	7,909
15	IVIg commercial discount of 14%	[redacted]	[redacted]	133,345

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Efgartigimod for treating generalised myasthenia gravis [ID4003]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Myaware and Muscular Dystrophy UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Muscular Dystrophy UK are due to receive from the company (Argenx) £2,610 (plus VAT) fee for support provided in May 2023 for the gathering of carer insight into the carer disutility caused by generalised myasthenia gravis. Not ongoing. Muscular Dystrophy UK have received the following funding from comparator treatment company Roche. • £720.00 from Roche on 17 April 2023 for participation in its SMA Adult Activation Advisory Board. Not ongoing. • £1,710.83 in June 2023 towards pass, accommodation and travel costs associated with MDUK attendance of the European Paediatric Neurology Society congress. Not ongoing. • MDUK received grant funding of £25,000 on 24 August 2023 and £25,000 on 31 October 2023. This is funding for the work of the UK SMA Newborn Screening Alliance and is not being retained by MDUK. Not ongoing. • £900.00 fee for participation by Director of Care, Campaigns and Support in the Roche Neuromuscular Summit: Advocacy Panel on 5 September 2023. Not ongoing. Not ongoing. • £417.50 reimbursement for Conservative Party Conference Not-for-Profit ticket fee to participate in a Health and Care Forum fringe event on 2 October 2023. Not ongoing. • £190.00 covering of accommodation costs associated with participation in Health and Care Forum fringe event at Conservative Party Conference on 2 October 2023. Not ongoing. • £2,750.00 on 1 November 2023 for sponsorship of SMA patient information virtual seminar. Not ongoing. • £600.00 fee for participation by Director of Care, Campaigns and Support alongside SMA UK in co-creation exercise on health inequity on 2 November 2023. Not ongoing. • MDUK will receive a donation for a member of staff to attend the Muscular Dystrophy Association Conference 2023, covering the cost of registration, accommodation and travel. Amount to be confirmed. Not ongoing. Myaware has received funding from comparator UCB totalling £334.78 to cover the cost of accommodation associated with attendance of the MG: Connects meeting in Manchester. Not ongoing.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Neither myaware nor MDUK have such links, direct or indirect.

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Efgartigimod for treating generalised myasthenia gravis [ID4003]

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Name of commentator person completing form:	[redacted], myaware) [redacted] Muscular Dystrophy UK)

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that this recommendation does not reflect the clear need for access to new treatments for myasthenia gravis. We welcome recognition in the draft guidance that "Clinical trial evidence suggests that efgartigimod plus standard treatment improves symptoms and people's ability to carry out their normal activities compared with standard treatment alone". There is great concern that, despite several therapeutics coming through the appraisal process, none may receive a positive guidance from NICE. This outcome would be deeply distressing for a community that already feel isolated and experience limited treatment options. Myasthenia means muscle weakness. But this definition does not capture the constrictive nature of the disease. The weakness described can occur without warning. It can affect the eyes, limbs, and/or bulbar muscles. Patients with myasthenia learn to live with this uncertainty and manage as best as possible with the treatment options available. But this means they often need to live their lives at the mercy of the clock and are heavily dependent on medication that isn't specific to their disease. Steroids are a commonly used medication with a heavy burden, which we have outlined in previous submissions, illustrated by the two quotes below from the community. For myasthenia patients, this could mean anything from weight gain to insomnia. While they can offer some level of control over myasthenia, this is not the case for everyone, and it can take lengthy and careful tweaking to find the right dose. *"The prednisolone caused severe osteoporosis with 4 wedged vertebrae, prediabetes, Cushing's syndrome etc etc but I couldn't get below 30mg."* *"They [steroids] have totally ruined (my life). I have gone from walking up mountains to being wheelchair bound in no time at all… I now have steroid induced myopathy, pancreas and gall bladder problems caused by steroids. Cataracts appeared almost overnight as a result of steroids and I have had two operations. Steroids have also caused type 2 diabetes which is controlled by insulin injections."* In contrast, the newer more targeted therapeutics that are currently undergoing appraisal by NICE offer quick relief and have been described as feeling 'cleaner' by patients. The clinical benefits of these medicines are well reported and have become available in other

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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	countries. We fear the myasthenic community in England may fall behind and the unmet needs of these patients will continue to go unresolved. What looked like a positive picture for the community six months ago in terms of potential treatment availability has swiftly become one of concern and uncertainty, with the termination of the appraisal of ravulizumab and this second negative draft guidance for efgartigimod. We are hopeful that the concerns raised by the committee in this draft guidance are ones that can be addressed through ongoing dialogue between NICE and the company, supported by activity that we know is being undertaken by the clinical community. As shared in our consultation submission after publication of the first draft guidance, one patient told us *"I started efgartigimod and the improvement was immediate… The thought of going back to the way my life was before this treatment scares me; I finally felt like I was getting my life back after 3 years of hell*".
2	We are concerned that this recommendation does not fully take account of the evidence and insight that has been provided by the patient community. We have brought forward a wealth of patient and carer testimony during the appraisal process that demonstrates the real-world benefit that efgartigimod has brought for some people. Throughout this appraisal process, the community has also put forth significant testimony regarding the unmet needs of myasthenia patients across the country. We are concerned that the committee does not view the evidence and insight that has come from the patient community as sufficiently robust, and this is a situation that is hard to resolve in light of the resources available to patient groups. In reference to two unpublished studies on carer disutility, section 3.15 of the draft guidance states that "The EAG noted that the 2 studies were observational and potentially subject to selection bias because people taking part were self-selecting". Muscular Dystrophy UK supported the recruitment of carers to take part in this research, which was conducted by a third party (The Research Institute for Disabled Consumers). The insight and evidence that we have gathered throughout this appraisal has come from surveying the community, inviting discussion and experience sharing, and from distributing survey links via the EAMS centres. All of the people we have gathered insight from could be seen as 'self-selecting' because of how we connect with them - we are inviting people to come to us to share their experience.
3	We are concerned that this recommendation may in part be based on a distorted assessment of the use of maintenance IVIg. Paragraph 3.5 of the draft guidance states that "The EAG explained that it had received clinical advice that IVIg is not regularly used as a maintenance treatment because of a shortage and because an NHS England commissioning policy substantially restricts maintenance use". We do not believe that shortage of supply should be a factor in assessing how maintenance IVIg is treated in

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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	any modelling, as we would hope that this is a changing situation that will be addressed in future. Furthermore, paragraph 3.6 of the draft guidance states that "A patient expert noted that although they might be considered eligible for maintenance IVIg they have not had it. Another patient expert noted that they would not be able to access maintenance IVIg at their current treatment centre". We understand these comments to have been in reference to shortages and/or barriers to accessing this treatment; not as a validation that maintenance IVIg should not be considered a regularly used treatment. We are further concerned by the Committee's concerns about the Delphi panel that was assembled by the company to explore maintenance IVIg, expressed in paragraph 3.21. Our understanding of this approach is that it is a technically robust one for evidence gathering. We welcome work that we understand has been undertaken by the company and by clinicians to explore this further and are hopeful that this will address the issue.
4	We note that concerns raised in Appraisal Committee Meeting 2 regarding the treatment of the placebo effect in clinical trials appeared to diverge from the assessment provided by the EAG and we hope that this can be clarified and addressed.
5	We are concerned that the conversation surrounding carer disutility in gMG is becoming overshadowed by the company's use of a study which focused on multiple sclerosis. We are aware that at present there is a lack of peer-reviewed studies which provide clear quantitative data on the effect of gMG on carers. However, both patient groups and experts have provided a significant level of testimony regarding this. When we surveyed our community, we received 246 responses. Over 80% of respondents stated they received carer support all week. The key tasks that carers were reported to assist with were; making meals and eating (this will include assistance to reduce choking risk), mobility, emotional support, and transport. These are every day tasks that a significant proportion of our communities require help with. We are therefore concerned that, as noted in **Section 3.14** of the second draft guidance: *"The EAG's base case did not include carer disutilities because it considered that the company had not provided robust evidence for their inclusion. The EAG also received clinical expert advice that most people with gMG are independent and would not need lots of caregiver time."* We question why evidence provided by the patient groups and testimony from the experts was not considered at this time. And while the clinical advice may state that most people with gMG are independent and would not rely on carers significantly, this appraisal is for a treatment for which the target patient population is those who are refractory and have minor if any control of symptoms. As quoted in **Section 3.4**: "• *with active, refractory disease, with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 5 or more (over 50% of MG-ADL score from non-ocular symptoms) and* • *who cannot tolerate or are ineligible for standard treatment, or in whom standard treatment has failed."*

NICE National Institute for Health and Care Excellence

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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	These are the patients that are most vulnerable and are heavily reliant on carer support. Therefore, we implore the committee consider the QALY gain that carers provide gMG patients, the impact of gMG on carers, and the benefit that a treatment which controls symptoms that have been without solution.
6	We are concerned again that, while there has been uncertainty regarding the target patient population definition and the addendum regarding eligibility for standard treatment, that the company has treated and seeks to continue to treat patients for which standard treatment is not working. While there may not be a clear definition of what the standard treatment pathway looks like in gMG, there remains the fact that a large proportion of the diagnosed undergo a significant journey to find a regime that works for managing symptoms. And for a minority portion of the community, that journey continues. These are patients in desperate need of relief of their symptoms and the side effects of any standard treatment they are able to tolerate. We appreciate, as has been said, that it is difficult to robustly define the standard treatment pathway, but emphasise that this is even more reason to encourage these add-on therapies to become options for those seeking treatment for gMG. The testimony of the Delphi panel, which involved 6 experts from neuromuscular centres, appears clear to the patient groups as a usable set of criteria for treatment with efgartigimod.
7	We note the concern regarding residual effect for patients after stopping efgartigimod treatment permanently and recognise that it may be some time before this can be efficiently explored.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

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- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Insert organisation name]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Fiona Norwood

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Efgartigimod has been shown in real-world data (Early Access to Medicines (EAMS) scheme) to be effective. Please see paper submitted by Dr J Spillane and others, including myself. on behalf of treating clinicians in the EAMS scheme. The target population was patients with active,

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NICE National Institute for Health and Care Excellence

Efgartigimod for treating generalised myasthenia gravis [ID4003]

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	refractory disease with an MG ADL score of 5 or more, or those who were ineligible for standard treatment or in whom this had failed for other reasons.
2	Concerns were raised by the Committee as to the lack of a standard treatment pathway. As I explained during the second Committee meeting, there is no currently-accepted standard treatment pathway in the UK although I suggest that there is often broad agreement among specialists working in the highly-specialised myasthenia centres. Therefore in my view Efgartigimod treatment should only be approved for use in these specialist centres, ideally via an MDT approach. This will ensure rational management and, if needed, challenge.
3	Maintenance IVIg use emerged as common in the patients included in the EAMS scheme. This, as well as subcutaneous immunoglobulin (scIg) and therapeutic plasma exchange, are important for a significant proportion of those patients whom we see in the specialist centres. Previously there was a shortage of IVIg but that has now been largely resolved although it is still a resource to be used carefully. I suggest that the national immunoglobulin database may under-represent the number of patients on maintenance IVIg due to the need to submit a detailed request to the subregional panel should one wish to use this treatment long-term.
4	Rituximab is a useful treatment in some patients but does not work for all. The national guidance in the UK is, I understand, under review.
5	We do need other options to treat myasthenia patients. Those with easy-to-control myasthenia are not the intended target for new medications. There is a significant proportion of myasthenia patients in whom treatment is more complex, either due to the nature of the myasthenia itself or due to individual patient factors or both. To have a range of additional treatment options for refractory patients would be ideal and is long overdue.
6	

Insert extra rows as needed

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Date 27-02-2024

Dear Dr Megan John and the NICE HTA committee for Efgartigimod

Re: NICE reports uncertainty about the disease severity in the trial vs Proposed population:

I here by like to thank NICE for appraising new technologies to this rare group of neuromuscular patients with myasthenia gravis. Whilst I acknowledge the vast amount of work that has gone into this appraisal I would like to highlight some inaccuracies where further consideration is warranted, areas where I support NICE comments and sections where consulting the patient group about their lived experience particularly with the side effects of steroids.

I have annotated the PDF copy of the NICE report with my comments with highlights and also attempted to outline the key areas for your information.

1. **Proposed severity is not different = MGADL > 5**

   Disease characteristic of refractoriness = ADAPT trial population was not refractory MG patients although it did include those patients (Perhaps the company can provide data for this subset in ADAPT and ADAPT+). I have also attached manuscript produced by UK MG centres from EAMS data on Efgartigimod use.

   The clinical trials are designed to assess an impact on a broad range of people with a condition. In the ADAPT study included range of severities and range of prior treatments in MG. However the refractory MG patients are the ones with the most unmet need and this is where the Efgartigimod is proposed to be positioned currently. Trial selected patients with MGADL >5 and this is not different to the proposed MGADL threshold wherein is similar to the ADAPT trial.
   Novel therapies are costly, therefore limiting them to a subset of patients who are continuing to be symptomatic in spite of ISTs and on steroids warrant an option to treat them. Currently there is none. IVIG and PLEX are treatments used for rescuing MG patients in crisis (NHSE commissioning guidelines).

   Furthermore NICE report acknowledges that NHSE restricts IVIG use in MG but yet considers IVIG as a potential option in chronic uncontrolled MG patients. NICE contradicts itself here. I agree with NICE that some centres don't have access to IVIG and PLEX and these treatment options are used very much as rescue treatments unlike the company's suggestion.

2. **Factually incorrect statement need correcting: Rituximab is equally effective treatment to IVIG in MG**

   This is an incorrect statement. IVIG is commissioned by NHSE as a rescue treatment and may be used with approval in a select group. Where as Rituximab is not used as a rescue therapy and the onset of efficacy is much delayed in MG. I have made further comments as annotations to the NICE outcome PDF.

3. **Clarity on the Target population of MG patients' clinical experts recommend Efgartigimod**
   Several MG experts met in Dec 2023 and the overwhelming consensus was to use Efgartigimod in the cohort of MG patients with the biggest unmet need. This group is defined in the EAMS Treatment refractory MG with an MGADL >5.

4. **Factually misrepresented items of information: Group of MG patients ineligible for SOC.**
   This is factually misrepresented; the proposed group of MG patients are not ineligible for SOC but has NOT responded and as a result are suffering with symptomatic MG. The proposed target group of patients would have tried Pyridostigmine and Prednisolone AND Two or more other NSITs in addition to having had a thymectomy.

5. **Committee reported that the clinical experts were finding it difficult to identify a target group: This is not correct.**

   Clinical experts were clear that considering the gravity of the unmet needs in refractory MG patients and potential costs of the drug, an acceptable sub group of MG patients is what is proposed.
   Furthermore we have had discussion on two occasions (Dec 2023 and Feb 2024) in the presence of a large gathering of UK MG specialists. Overwhelming proposition was that target population for Efgartigimod was treatment refractory MG patients.

6. **IVIG use in MG**
   I agree with NICE that additional to NICE comments about using IVIG on a lifelong use model, that this is not the case as many reasons can play to stop IVIG as indicated by NICE and additionally IVIG is not likely to be continued indefinitely as it is subjected to annual review and if patients are stable, the dose will be reduced or subjected to an IVIG dependence test as per NHSE commissioning guidance.

7. **Theory of continued benefit from cessation of Efgartigimod**
   I had reiterated that there was a deduced theoretical possibility that some patients could remain stable after FcRn blockage, based on PLEX data and very limited data from the company (this caveat I raised has not been highlighted in the NICE report). However I was unaware that a substantial economic advantage was built on the back of it. If that was the case I agree with NICE this calculation is best dropped or 15% margins should be revised in an acceptably evidenced based approach.

8. **NICE observes that MG patients are independent of carers support**
   This is an over simplification and borders on insult to the carers of a significant proportion of MG patients (both ocular and gMG).

   It is possible that not all MG patients need a carer. However many patients will need the support of a carer at some stage and a significant proportion of gMG patients in the refractory group would have a carer support them through ADLs, clinic appointments, transport, monitoring disease and sharing the disease anxiety of a potential crisis.

9. **Steroid burden of MG patients**[1]

[1] Dr Channa Hewamadduma, Clinical Expert comments

This is a real burden to the MG patients. The number of patients who we see in clinics [2]who have become dysmorphic, depressed because of permanent changes to their faces and [3]bodies is heart breaking. Most patients end up on moderate doses of Prednisolone and dose down titrations can take months to years. The damage is done by then. I should stress that listening to the MG patient community and seeking their views is the only fair way to obtain a complete understanding of patients lived experience of steroids

10. Are steroids stopped in refractory gMG patients

I note NICE report stressing about an expert comment that many gMG patients refractory to treatments would have stopped steroids. This is not entirely true.

This could be true for a small proportion of patients who are treatment refractory where a significant proportion of gMG patients if symptomatic with MGADL >5 are highly likely to be on steroids and is further evidenced by data from the REGAIN trial where Eculizumab was used in refractory MG patients: Across the total population of the study 78% patients were on steroids at baseline. (Lancet December 2017).

May I mention that gMG patients in the UK will consider the unavailability of effective, fast acting, safe novel therapies a severe anomaly in a developed health care system like that of UK. They will be at a disservice when compared to European countries and America when it comes to accessing novel therapies if the companies responsible and NICE are unable to facilitate a mutually conducive agreement. As clinicians treating gMG patients many of our tools to manage gMG are old and blunt and not really fit for the purpose of gaining rapid control of a debilitating and an unpredictable potentially deadly yet controllable disease (with emerging novel therapies).

Thank you again for the opportunity to contribute to the process

Best wishes

Channa

Dr Channa Hewamadduma
MBBS(Hons), FRCP(Neuro), FRCPE, MSc(Genomics), PhD
Neuromuscular Lead
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NICE National Institute for Health and Care Excellence

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 15 January 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Insert organisation name]

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	[Insert disclosure here]
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
Name of commentator person completing form:	Channa Hewamadduma

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Comment on "Why the committee made these recommendations", highlighted text "But it is uncertain if the people in the trial reflect the people who would have efgartigimod in the NHS because the company have proposed a target population with more severe disease.":**

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	Indications are different
2	**Comment on "Why the committee made these recommendations", highlighted text "There are also uncertainties in the economic model that make the likely cost-effectiveness estimates for efgartigimod uncertain. The most likely cost-effectiveness estimates are substantially above what NICE considers an acceptable use of NHS resources. So, efgartigimod is not recommended.:** Without details difficult to comment for us
3	**Comment on section 3.1 (the condition), "The committee concluded that gMG is a debilitating condition with a high treatment burden.":** What is missing here is the fact that there are no effective, fast acting treatments that are recommended and licensed for MG
4	**Comment on section 3.2 (treatment options), "minimal doses to minimise side effects":** However significant proportion of patients end up on high doses of steroids 20-50mg/day
5	**Comment on section 3.2 (treatment options), "If their condition does not respond to immunosuppressants or they experience notable side effects on increasing corticosteroid doses, expert advice should be sought on the use of plasma exchange or intravenous immunoglobulin (IVIg).":** But IVIG and PLEX are limited to patients in crisis or impending crisis as per commissioning guidelines
6	**Comment on section 3.2 (treatment options), "NHS England considers rituximab, an anti-B-cell monoclonal antibody treatment, to be an equally effective treatment to IVIg.":** This is factually incorrect. Rituximab can take 6-12 months to take effect where it is currently positioned in the guidelines (use in refractory patients who have had the condition for longer period)
7	**Comment on section 3.2 (treatment options), "The committee concluded that an effective and fast-acting treatment option would be welcomed by people with gMG and clinicians.":** This is not a welcome option but it is an obviously serious unmet need
8	**Comment on section 3.3 (treatment population), "Tr":** Where the biggest unmet need it
9	**Comment on section 3.3 (treatment population), "But, they also explained that, in time, the treatment could be used in additional populations, including the much larger population whose symptoms remain sub-optimally controlled despite standard treatment.":** We reported that fast acting, safe novel drugs which ever they are are required in the MG pathway. However the specialist clinicians at specialist centres use the drugs responsibly in accordance with NHSE guidance. Good example of this is the EAMS data (attached publication from the UK cohort)
10	**Comment on section 3.3 (treatment population), "It considered that the characteristics of this population should be clearly defined to enable efgartigimod's use in the NHS.":** Several MG experts met in Dec 2023 and the overwhelming consensus was to use Efgartigimod in the cohort of MG patients with the biggest unmet need. This group is defined in the EAMS Treatment refractory MG with an MGADL>5
11	**Comment on section 3.4 (target population), "The EAG noted that the company's target population description referred to a group of people ineligible for standard treatment.":**

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	This is factually misrepresented. Proposed group of MH patients are not ineligible for SOC but has NOT responded and as a result are suffering with symptomatic MG
12	**Comment on section 3.4 (target population), "The company said that 'ineligible' did not refer to all standard treatments, and said it is possible that one of the standard treatments may not be suitable. The EAG":** The proposed target group of patients would have tried pyridostigmine and prednisolone AND Two or more other NSITs
13	**Comment on section 3.4 (target population), "disease. The committee understood the difficulties of identifying a target population description for a condition with no single universally accepted treatment":** Clinical experts were clear that considering the gravity of the unmet needs in refractory MG patients and potential costs of the drug, an acceptable sub group of MG patients is what is proposed
14	**Comment on section 3.4 (Maintenance IVIg), "England commissioning policy substantially restricts maintenance use":** I agree that IVIG is not frequently used due to NHSE restrictions, availability, tolerance and side etc reasons
15	**Comment on section 3.4 (Maintenance IVIg), "people who urgently needed treatment.":** There are significant pressures on clinicians to justify the use of IVIG use in MG patients who are not in crisis. There are logistical issues. Not every IVIG using patient was converted to Efgartigimod. I don't agree that the treatment urgency was a factor, although disease burden and logistics were the main drivers.
16	**Comment on section 3.6 (Maintenance IVIg in target population), "NICE received a comment from a clinical expert stating there is regional variation but maintenance IVIg is a relatively uncommon treatment.":** I continue to support this statement
17	**Comment on section 3.6 (Maintenance IVIg in target population), "IVIg may be stopped because of adverse events, patient choice or a loss of efficacy":** Additionally, IVIG is not likely to be continue indefinitely as it is subjected to annual review and if patients are stable, the dose will be reduced and subjected to an IVIG dependence test.
18	**Comment on section 3.11 (Treatment effect after stopping efgartigimod prematurely), "after reviewing the additional evidence provided at technical engagement, believed a 15% residual effect is plausible":** I agreed the plausibility is based on the very limited data but this caveat I raised is not recorded. If there was a substantial effect gained from such an assumption based on thin evidences, I agree with NICE that this source of data and argument should be parked/dropped in the economic analysis.
19	**Comment on section 3.14 (Carer quality of life), "The EAG's base case did not include carer disutilities because it considered that the company had not provided robust evidence for their inclusion":**

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	It is possible that not all MG patients don't need a carer. However many patients will need to the support of a carer at some stage and significant proportion of gMG patients in the refractory group would have a carers support them through ADLs, clinic appointments, transport, monitoring and sharing the disease anxiety of a potential crisis.
20	**Comment on section 3.17 (Updated corticosteroid complication costs), "NICE received a comment from a clinical expert who suggested that most people with refractory disease will have stopped taking steroids because they were not effective.":** This could be true for a small proportion of patients who are treatment refractory where a significant proportion of gMG patients if symptomatic with MGADL >5 are highly likely to be on steroids. This is further evidenced by data from the REGAIN trial where Eculizumab was used in refractory MG patients: Across the total population of the study 78% patients were on steroids (Lancet December 2017)

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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TITLE PAGE

TITLE: Efgartigimod efficacy and safety in refractory Myasthenia Gravis - UK's first real-world experience

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Word count: 3491 words
Numbers of figures and tables: 2 figures and 3 tables
This study did not receive any funding.

ABSTRACT

Background: We report our experience of patients with generalised MG (gMG) treated with Efgartigimod, an FcN antagonist, under the Early Access to Medicine Scheme (EAMS) in the UK.

Methods: Data from all UK patients treated with Efgartigimod under the EAMS June 22-July 23 were collected retrospectively. Efgartigimod was administered as per the ADAPT protocol (consisting of a treatment cycle of 4 infusions at weekly intervals with further cycles given according to clinical need).

Results: 48 patients with AChR antibody-positive gMG were treated in 12 centres. Most (75%) were female and most had a disease duration of over 10 years. The average MG-ADL score at baseline was 11.2. Most (72.9%) patients had undergone thymectomy. 77.0% were taking prednisolone at baseline. All patients had utilized non-steroidal immunosuppressant treatments, the average number tried was 2.6 (range 1-6). 51% had received Rituximab. 54.2% of patients required regular IVIg/PLEX.

75% of patients had a mean reduction in the MG-ADL of ≥2 points in the first cycle and this remained stable throughout the study. The mean intracycle reduction in the MG-ADL score in the 1st, 2nd, 3rd and 4th cycles were -4.6, -3.9, -3.4 and -4.2 respectively. Side effects were generally mild though one patient stopped treatment due to severe hypokalemia. No rescue treatments were required. At the end of the study, 96% of patients remained on Efgartigimod.

Conclusion: Efgartigimod is a safe and effective treatment for patients with refractory, treatment-resistant gMG.

INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune disorder of the neuromuscular junction that causes fatigable neuromuscular weakness. 85% of patients have antibodies against the acetylcholine receptor (AChR) and a varying proportion of the remainder have antibodies against muscle-specific kinase (MuSK), an important post-synaptic clustering protein. A smaller proportion of patients have antibodies against low-density lipoprotein receptor-related protein 4 (LRP-4), another post-synaptic protein. Up to 10% of patients do not have detectable antibodies on the conventional assay but about one-third of this cohort will have antibodies detectable on a more specific cell-based assay[1].

The hallmark of MG is fatigable neuromuscular weakness of skeletal muscles. Ocular symptoms – diplopia and ptosis can occur alone, but most patients develop generalized symptoms of fatigable limb weakness, facial weakness, and difficulties with speech, chewing and swallowing. Up to 15% of patients can develop myasthenic crisis; or ventilatory failure due to respiratory muscle weakness[2].

MG is a treatable neuromuscular disease and due to advances in the care of patients with MG including progress in intensive care, there has been a reduction in the mortality of MG from 70% in the 1930s to <10% nowadays[3]. The first line treatment is pyridostigmine which can provide short-term symptomatic relief but has no disease-modifying effect. Surgical removal of the thymus is almost always indicated for patients with a thymoma, but MG symptoms will generally persist post-operatively. In patients without a thymoma, thymectomy has been shown in a randomized controlled trial to be associated with better outcomes in younger onset seropositive generalized MG but the effects are variable and may not be evident for many years[4]. Treatments such as intravenous immunoglobulin (IVIg) and therapeutic plasma exchange (TPE) can improve symptoms rapidly, though the effects are short-lasting, and these treatments are generally reserved for acute severe exacerbations. The mainstay of management of MG therefore rests on nonspecific broad-spectrum immunosuppression with steroids and non-steroid immunosuppressant therapies such as azathioprine, mycophenolate, and methotrexate, with Rituximab occasionally used in refractory patients who demonstrate active disease despite treatment with at least two trials of immunosuppressant agents[5].

Despite advances in treatment, there is a clear unmet need for patients with MG[5]. Steroids though effective are associated with a plethora of well-documented side effects. Immunosuppressive agents are not tolerated in many patients with one review showing that over 30% of patients taking azathioprine have adverse events and up to 11% have to discontinue the drug[6,7]. Moreover, oral immunosuppressants have a slow onset of action meaning that patients are exposed to high-dose steroids for months and sometimes years. Approximately 15% of patients are refractory to standard therapies and are often dependent on costly treatments such as IVIg and TPE[3]. Real-world studies have shown that over 40% of patients with MG have unacceptable disease control[8] and MG is known to have a significant impact on quality of life[9].

There has therefore been a longstanding need for more targeted therapies in MG that are more efficacious and have a faster onset of action with a favorable side-effect profile. Advances in the understanding of the pathogenesis of MG have unveiled several potential treatment targets including B cells, complement, IL-6 and other cytokines[2].

A novel therapeutic target that has emerged in recent years is the neonatal FC receptor (FcRN). This is a ubiquitous MHC Class 1-like molecule that allows the recycling of IgG by protecting it from

lysosomal degradation thus prolonging its half-life. Efgartigimod (ARGX-113) is a human IgG Fab fragment that has been engineered to have a higher affinity for the Fc receptor than native IgG, thus reducing IgG recycling and lowering IgG levels in circulation. The mechanism of lowering IgG levels can be thought of as analogous to therapeutic plasma exchange which is known to improve symptoms in MG rapidly but the availability of TPE is limited and can be associated with significant side effects.

In phase 1 and 2 trials Efgartigimod was found to significantly reduce IgG levels and improve symptoms in generalized MG[10,11]. The efficacy and safety of Efgartigimod were then studied in a phase 3 double-blind randomized placebo clinical trial (the ADAPT trial)[12]. Efgartigimod was given as an intravenous (IV) infusion weekly for four weeks with further cycles repeated as necessary (based on clinical progression) no sooner than 8 weeks after the beginning of the previous cycle. Efgartigimod was found to be safe and well tolerated and a significantly higher number of patients treated with Efgartigimod met the primary outcome: the number of patients who had more than a 2-point reduction in the MG Activities of Daily Living (MG-ADL) score sustained for >4 weeks in the first treatment cycle. The MG-ADL score is a patient-reported outcome measure that allows an estimation of MG symptoms and their impact on daily living activities, ranging from 0 to 24, with greater values related to severe symptoms[13].

Efgartigimod alfa is now approved by the FDA and the EMA. It was licensed by the Medicines and Healthcare Products Regulatory Authority (MHRA) in the United Kingdom (UK) in March 2023 but is not yet commercially available. However, it has been available for adults with generalised AChR antibody under the (MHRA) Early Access to Medicines Scheme (EAMS) in specialist UK MG centres since May 2022. The aim of an EAMS scheme is to provide earlier access to unlicensed treatments for patients with a high unmet clinical need. After licensing, Efgartigimod was made available under the EAMS Plus Scheme (EAMS +) whilst NICE approval was sought.

Under the EAMS scheme, Efgartigimod was indicated for the treatment of adult patients with AChR antibody-positive gMG including those who had failed, did not tolerate or were ineligible for licensed treatment. Patients could not have received Rituximab within 6 months or IVIg within 4 weeks and IgG levels had to be ≥ 6g/L prior to starting Efgartigimod. The consensus achieved before the introduction of the scheme with UK MG clinicians was that it would be reserved for patients with refractory disease who had not responded to ≥ 2 non steroids immunosuppressant agents who were intolerant or ineligible for such therapies and those patients who were dependent on IVIG and TPE. Clinicians also agreed to collect data regarding ADL scores, treatment failures and any adverse events.

According to the EAMS treatment protocol, Efgartigimod was given as per the ADAPT trial as a cyclical treatment as an IV infusion weekly for four weeks (10 mg/kg in one-hour intravenous infusion), with subsequent treatment cycles dependent on the patient's symptoms. A home care service was provided for some patients after their initial cycle in hospital.

Our objective with this study was to provide the first real-world experience regarding the Efgartigimod efficacy, safety and tolerability in the UK population.

METHODS

Study design
This was a retrospective observational multicenter study designed to analyse the efficacy and safety of Efgartigimod in AChR antibody-positive generalised MG patients who met the EAMS criteria for its use.

Participants
All UK MG specialist centres were invited to provide deidentified data regarding patients treated with Efgartigimod between March 2022 and July 2023.

Outcomes
Our primary outcome was to determine the percentage of MG-ADL responders in the first cycle. Similar to what was defined in the ADAPT trial[11], we considered that a patient had responded to the treatment when there was a 2-point reduction in the MG-ADL score sustained for >4 weeks. We also sought to understand the variation of MG-ADL at different time points (day 0, day 22 and day 36) for each cycle, to describe the incidence of adverse events and to determine the need for rescue treatments and the rate of Efgartigimod discontinuation.

Statistical analysis
Statistical analysis was done using SPSS Statistics® version 28. Demographic data was presented descriptively, with mean values, standard deviation (SD), total number (N) and percentage (%). The variation of MG-ADL along the different time points, in each cycle, was analyzed with a mixed linear model for repeated measures, assuming missing at random data. A *p*-value of <0.05 was considered statistically significant.

STROBE cohort checklist was used when writing our report[14].

RESULTS

Our analysis included 48 patients from 13 centres who had completed at least one cycle of Efgartigimod under the EAMS scheme in the UK by 20th July 2023. At the time, this represented 100% of MG patients who had completed at least one cycle of treatment. No patients were excluded from the analysis.

Most patients were female (75.0%, N = 36), with an average age of 49.2 (21.0 – 75.0, SD = 14.2) years old. The majority (66.7%, N = 32) had been diagnosed with MG more than 10 years before starting Efgartigimod. The average MG-ADL score at baseline was 11.2 (5 – 19, SD = 3.2). Most patients (72.9%, N = 35) had undergone thymectomy in the past (mean time since thymectomy = 12.5 years, 1 – 38, SD = 8.3).

All patients had utilized at least one non-steroidal immunosuppressant treatment (NSIST) in the past, and the average number tried prior to Efgartigimod was 2.6 (range 1 - 6). The most frequent NSISTs used included Azathioprine (79.2%, N = 38), Mycophenolate Mofetil (64.6%, N = 31) and Methotrexate (41.7%, N = 20). Six patients had received Cyclosporin, one had taken Tacrolimus and two had received Eculizumab. Just above a half (52.1%, N = 25) had previously received Rituximab.

70.8% (N = 34) had previously received IVIg and 43.8% (N = 21) were still requiring it on a regular basis at the time of Efgartigimod initiation. More than a quarter (27.0%, N = 13) had previously been treated with TPE in the previous year and 14.6% (N = 7) were still using it regularly at treatment initiation.

Just prior to the initiation of Efgartigimod, the majority of patients were taking a combination of NSIST and prednisolone (54.2%, N = 26). Ten patients were taking prednisolone only, and five were taking an NSIST only. Six patients were not on any immunosuppressive treatment at baseline though three of these patients were on regular IVIg. The NSISTs used included Azathioprine (7 patients), Mycophenolate Mofetil (14 patients), Methotrexate (8 patients) and Cyclosporin (2 patients). The average prednisolone dose was 20.5 mg daily (range 2-60 mg).

The reasons for starting Efgartigimod were listed as follows (participants could list more than one reason): refractory MG (77.0%, N = 37), the burden of treatment (35.4%, N = 17), dependent on IVIg/TPE (29.2%, N = 14), side-effects (12.5%, N = 6) and other reasons (4.2%, N = 2; participants specified needing bridging treatment). The detailed demographic and clinical data are available in Tables 1 and 2, respectively.

In our population, 75.0% (36 patients, N = 48) were defined as responders in the first cycle as they achieved a reduction in the MG-ADL score of ≥ 2 points. This percentage decreased slightly in the following cycles but remained stable throughout the study: 65.6% were responders in the second cycle (21 patients, N = 32), 72.0% in the third cycle (18 patients, N = 25) and 64.3% in the last cycle (9 patients, N = 14). Four patients who were not responders on the first cycle responded to the second cycle.

The mean reduction in MG-ADL score at the end of each cycle (day 22) comparing to its beginning (day 0) was, respectively, -4.6 points in the 1st cycle, -3.9 points in the 2nd cycle, -3.4 points in the 3rd cycle, and -4.2 in the 4th cycle (see Table 3). When comparing the MG-ADL score at the end of each cycle versus the beginning of treatment with Efgartigimod (see Table 3), the mean reductions were: -4.5 points for cycle 1, -6.0 points for cycle 2, -6.9 points for cycle 3 and -7.8 points for cycle 4 (considering just the patients that completed each cycle: 48, 32, 23 and 14, see Figure 1).

Using an MG-ADL score of 0 or 1 to define Minimal Manifestation Status, we observed that 10.4% (5 patients, N = 48) of all patients achieved this status by the end of the 1st cycle. By the end of the 2nd cycle, 12.5% (4 patients, N = 32) reached MMS; this was achieved by 14.3% by the end of the 3rd cycle (4 patients, N = 25) and 35.7% by the end of the 4th cycle (5 patients, N = 14).

A two-way repeated measures ANOVA with a Greenhouse-Geisser correction was performed in the subgroup that completed the first three cycles and analysed the longitudinal variation considering day 0 and day 22 (N = 25). The mean MG-ADL score differed statistically significantly between time points ($p < 0.01$). A *post-hoc* analysis with a Bonferroni adjustment confirmed that the MG-ADL score was statistically significantly decreased from pre-treatment to the end of the 1st cycle (mean reduction of 5.54, $p < 0.001$, 95% CI, 3.26 – 7.82), to the end of the 2nd cycle (mean reduction of 6.7, $p < 0.001$, 95% CI, 4.46 – 8.96), to the beginning of the 3rd cycle (mean reduction of 3.1, $p = 0.032$, 95% CI, 0.17 – 6.08) and to the end of the 3rd cycle (mean reduction of 6.9, $p < 0.001$, 95% CI, 4.4 – 9.3). The complete analysis between each cycle is shown in Figure 2 and the full analysis of the MG-ADL score variation in the three cycles can be found in the supplementary material (Table 1).

The timing of Efgartigimod treatment is bespoke with a varying time between the end of one cycle and the start of the next one depending on patient symptoms. The mean time interval between finishing the first cycle and starting the 2nd cycle was 6.4 weeks (3 – 15.7 weeks, SD 2.4). This interval decreased slightly between the second and third cycles [approximately 5.5 (3 - 10.9) weeks, SD 1.6] and between the third and fourth cycles [approximately 4.6 (3.0 -6.7) weeks, SD 0.9]. In a *post-hoc* analysis, the interval was not statistically significantly correlated to MG-ADL at the beginning of each cycle, and it was not found to be related to an increase in MG-ADL score at the beginning of the next cycle. MG-ADL variation within each cycle (calculated from the difference in MG-ADL at day 22 and day 0) was not correlated with interval duration.

More than a quarter (27.0%, N = 13) of the patients reported a side-effect on the 1st cycle, most of them of mild severity. Three patients reported infections (SARS-CoV-2 infection and urinary tract infection). One patient had severe hypokalemia that required hospitalisation. Seven patients reported flu-like symptoms, one patient reported skin bruising and another reported reduced sensation in the lower legs.

No patients in this study required rescue treatment with IVIg or TPE. Two patients dropped out from this study – one of them did not show any improvement with Efgartigimod after one cycle, and the other patient had a severe adverse reaction (hypokalemia), which was considered to be related to Efgartigimod administration. No deaths were reported.

DISCUSSION

This is a retrospective real-world study that captured all Efgartigimod-treated patients in the UK from May 2022 to July 2023. The cohort treated were those with long-term refractory MG – the disease duration in the majority of patients was over 10 years, most patients had been on multiple immunosuppressant agents, more than half of patients had received Rituximab, and 54.2% (N = 26) required regular IVIg and/or TPE.

In this group of patients with severe MG, 75.0% were defined as MG responders, as they showed a sustained ≥ 2-point reduction in MG-ADL over 4 weeks, according to what was defined as clinically significant in the ADAPT trial[11]. In our cohort, the mean reductions in MG ADL score were 4.6, 3.9, 3.4 and 4.2 in the first, second, third and fourth cycles, respectively. Though the numbers are small there seemed to be an accumulation of response with average lower baseline scores at the start of Cycle 4 compared to that at the start of cycle 1.

No patients required rescue treatment with IVIG or TPE and no patients had an unplanned admission because of their MG. Efgartigimod had an IVIg and TPE-sparing effect in patients previously dependent on these treatments.

In our population, Efgartigimod seemed to be relatively safe, with about a quarter of patients reporting mild side effects after the first cycle. One patient had a severe metabolic disturbance with hypokalemia which was considered to be related to Efgartigimod, although the physiological explanation for this us unclear and no case reports or drug company notifications exist on this matter.

We observed an excellent response in a few patients (for instance, a patient who started the trial with an MG-ADL score of 11, and, after the 1st cycle, the score lowered to 0, reaching a score of 4 at the beginning of the 2nd cycle, and afterwards keeping a score of 2), but we also detected some cases

that seemed to have no response at all (for instance, the one patient that dropped out of the study after the 1st cycle because no difference on the MG-ADL score was observed).

There are some limitations to our study. Although it captured all patients treated with Efgartigimod in the UK between May 22 and July 23, the sample size is small and our average duration of follow-up from the first cycle is 130.9 days (47 – 207, SD 43.2). It was a retrospective real-world study with a heterogeneous group of patients. Our study was also not designed to analyse what factors were associated with response to Efgartigimod. There were no definite criteria for inclusion in the study other than AChR-antibody-positive generalized disease that was not adequately controlled on standard therapies and, depending on access to clinical trials, clinical experience, and access to infusion centre facilities, individual sites may have had different thresholds for patient inclusion. Moreover, the timing of Efgartigimod treatment is variable and dependent on the clinicians' and patients' assessment of their disease severity.

The interval between treatments declined after Cycle 1 – likely because the patient and clinician could predict when the symptoms were likely to deteriorate and adjusted the timing of the next cycle to preempt the worsening of symptoms. A significant proportion of patients (at least 35.2%) received home treatments since Cycle 2.

We also do not have long-term follow-up data to show whether Efgartigimod has a steroid-sparing effect or not and this is something that should be studied in future.

Our findings are broadly in keeping with those of the ADAPT study[15], though our patient cohort was slightly different, the average disease duration was longer in our cohort whereas 26% of those in the international trial had not been treated with an oral immunosuppressant agent, all our patients had.

Our findings were also in keeping with data from elsewhere; an Italian centre presented data regarding Efgartigimod efficacy and safety in refractory MG patients[16], having included 19 patients. After two cycles, a mean 5-point reduction in MG-ADL was observed, minimal manifestation status (MMS) was achieved in 16% of the patients with an improved status was found in 63%[16].

In our total cohort, a mean 3.9 points reduction in MG-ADL was observed after two cycles. Minimal manifestation state was achieved in 12.5% by the end of the second cycle, and an improved status (considering a 2-point reduction) was obtained in 65.6% of our patients. It is worth noting, however, that both triple negative MG and MuSK patients were also included in the Italian study, whereas in our study only anti-AChR positive patients were included.

Our cohort was mainly composed of patients with refractory long-term MG. As such, our study did not answer the question of where Efgartigimod should fit in the treatment pathway – there can still be potential for its use in situations other than refractory disease. In the UK Efgartigimod is only licensed for AChR-positive MG patients though the ADAPT trial did include MuSK-positive and seronegative patients. There is a rationale for the use of Efgartigimod in these groups, but they have not been studied in detail to date.

CONCLUSION

Efgartigimod seems to be an efficacious and safe drug for refractory MG patients. However, the profile of the group of patients that are more likely to benefit from Efgartigimod, as well as its exact timing in

refractory Myasthenia gravis, remains to be determined. Also, it is not yet clarified if there is an advantage in maintaining other drugs that act in different pathways of the pathophysiology of MG-related neuromuscular junction dysfunction.

Larger prospective studies are also required to establish efficacy and safety in real-world settings.

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TABLES

Table 1. Demographic and Clinical Data (N = 48)

Gender	
Female	36 (75.0%)
Male	12 (25.0%)
Age (years) (range, SD)	49.2 (21.0 – 75.0, SD 14.2)
Body mass index (range, SD)	32.3 (18.0 – 56.0, SD 9.2)
Time since diagnosis	
< 1 year	1 (2.1%)
1-5 years	11 (22.9%)
5-10 years	4 (8.3%)
More than 10 years	32 (66.7%)
Previous thymectomy	35 (72.9%),
Time since procedure (years) (range, SD)	12.5 (1 – 38, SD 8.3)
Baseline MG-ADL score	11.2 (SD 3.2)
Number of previous NSIST (N patients)	48 (100%)
1	12 patients
2	13 patients
3	11 patients
4	7 patients
5	4 patients
6	1 patient
NSIST utilized prior to Efgartigimod (N patients)	
Azathioprine	38
Mycophenolate Mofetil	31
Methotrexate	20
Cyclosporin	6
Eculizumab	2
Tacrolimus	1
Rituximab	25 (52.1%)
Reason for starting Efgartigimod*	
Refractory MG	37 (77.1%)
Burden of treatment	17 (35.4%)
Dependent on IVIg/TPE	14 (29.2%)
Side-effects	6 (12.5%)
Other Reasons	2 (4.1%)
NA	2 (4.1%)

*Data presented in n (%), mean (SD) and median (IQR). Abbreviations: IQR – interquartile range; MG-ADL: Myasthenia Gravis Activities of Daily Living; NSIST: non-steroid immunosuppression. *More than one reason could be selected.*

Table 2. MG treatment at the time of commencing Efgartigimod and cycles completed (N = 48)

No immunosuppressive/immunomodulatory treatment	3
Prednisolone only	10
Prednisolone and NSIST	27
NSIST only	5
Regular IVIg with additional NSIST/prednisolone	18
Regular IVIg only	3
Regular PLEX	7
Steroid dose	20.5 mg/day (2-60 mg, SD 14.9)

Cycles

Cycles completed at data collection*	

1st Cycle	48 (100%)
2nd Cycle	32 (66.7%)
3rd Cycle	25 (52.1%)
4th Cycle	14 (29.2%)
Reported side-effects	
1st Cycle	13 (27.0%), median severity grade = 1 (1-4)
2nd Cycle	8 (25.0%), median severity grade = 1
3rd Cycle	2 (8.3%), median severity grade = 1
4th Cycle	0

Data presented in n (%), mean (SD) and median (IQR). Abbreviations: IVIg: intravenous immunoglobulin; IQR – interquartile range; MG-ADL: Myasthenia Gravis Activities of Daily Living; NSIST: non-steroid immunosuppression; TPE: plasmapheresis. *Patients started Efgartigimod in different time periods, which means that by the time data was collected, patients could be at different time points/cycles. Only one patient stopped Efgartigimod because of side effects.

Table 3. The mean difference in MG-ADL Scores comparing MG-ADL at baseline with the last day of each cycle

	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference	
				Lower	Upper
Cycle 1, Day 22 vs Baseline (N = 48)	-4.50000	4.11536	.59400	-5.69498	-5.30802
Cycle 2, Day 22 vs Baseline (N = 32)	-5.96875	3.64987	.64521	-7.28467	-4.65283
Cycle 3, Day 22 vs Baseline (N = 25)	-6.87500	3.68679	.75256	-8.43179	-5.31821
Cycle 4, Day 22 vs Baseline (N = 14)	-7.76923	3.53916	.98159	-9.90792	-5.63054

ILLUSTRATIONS

Figure 1. Mean intracycle MG-ADL score [Cycle 1, N = 48 (available data at day 36: 33 patients); Cycle 2, N = 32 (available data at day 36: 22 patients); Cycle 3, N = 25 (available data at day 36: 16 patients); Cycle 4, N = 14 (available data at day 36: 7 patients)]

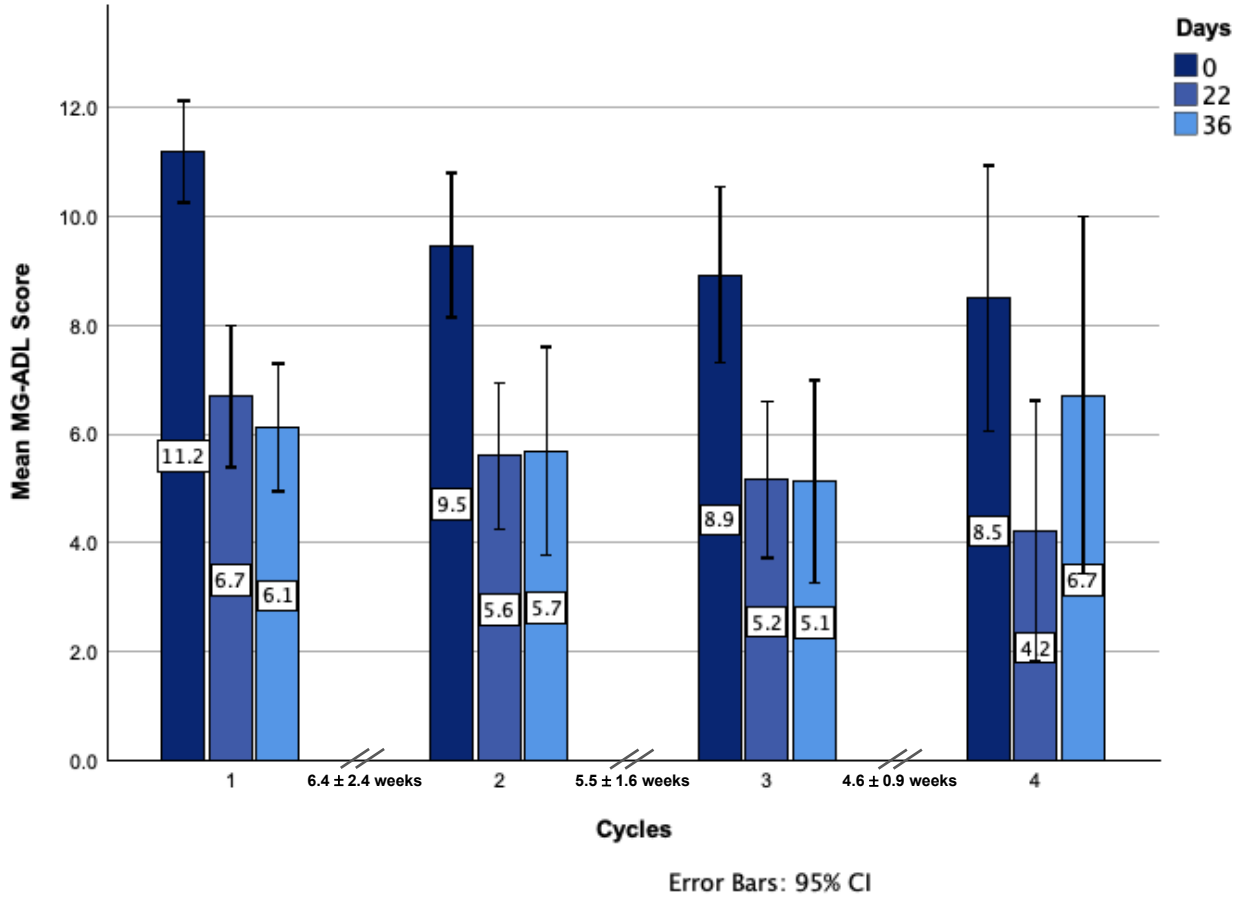
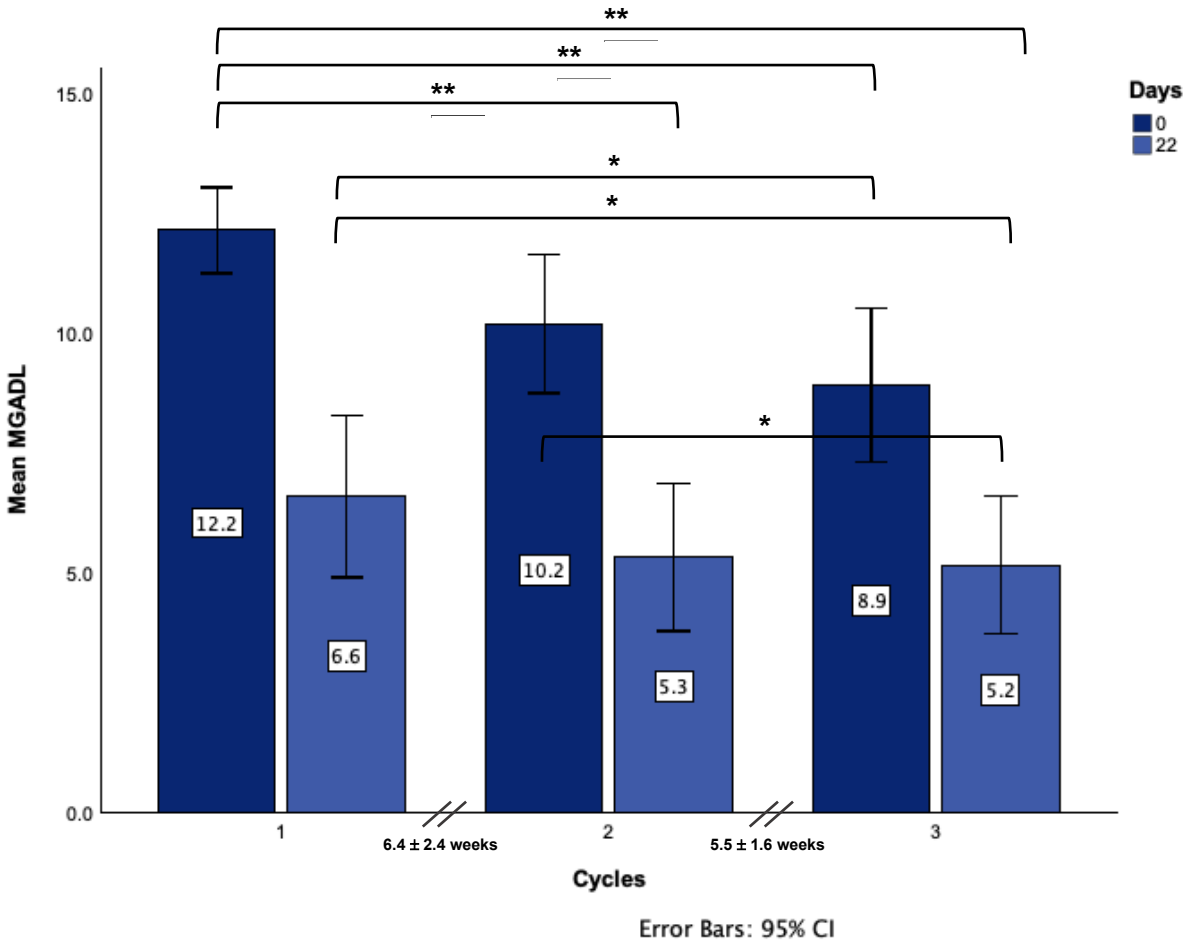


Figure 2. MG-ADL Score variation in the three cycles (N = 25)



Notes: * significance level < 0.05; ** significance level < 0.01

ABBREVIATIONS

IQR: interquartile range
IVIg: intravenous immunoglobulin
gMG: generalised MG
MG: Myasthenia Gravis
MG-ADL: Myasthenia Gravis Activities of Daily Living
NSIST: non-steroid immunosuppression treatment
TPE: plasmapheresis

SUPPLEMENTARY MATERIAL:

Table 1. MG-ADL variation in the three first cycles (N = 25)

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
Cycle 1, Day 0 (C1D0)	C1D22	5.542*	.697	<.001	3.261	7.823
	C2D0	2.125	.806	.221	-.514	4.764
	C2D22	6.708*	.688	<.001	4.457	8.959
	C3D0	3.125*	.904	.032	.167	6.083
	C3D22	6.875*	.753	<.001	4.411	9.339
Cycle 1, Day 22 (C1D22)	C1D0	-5.542*	.697	<.001	-7.823	-3.261
	C2D0	-3.417*	.857	.009	-6.224	-.610
	C2D22	1.167	.693	1.000	-1.103	3.436
	C3D0	-2.417	.895	.191	-5.346	.512
	C3D22	1.333	.846	1.000	-1.437	4.104
Cycle 2, Day 0 (C2D0)	C1D0	-2.125	.806	.221	-4.764	.514
	C1D22	3.417*	.857	.009	.610	6.224
	C2D22	4.583*	.796	<.001	1.977	7.190
	C3D0	1.000	.493	.812	-.613	2.613
	C3D22	4.750*	.854	<.001	1.954	7.546
Cycle 2, Day 22 (C2D22)	C1D0	-6.708*	.688	<.001	-8.959	-4.457
	C1D22	-1.167	.693	1.000	-3.436	1.103
	C2D0	-4.583*	.796	<.001	-7.190	-1.977
	C3D0	-3.583*	.819	.003	-6.263	-.904
	C3D22	.167	.527	1.000	-1.559	1.892
Cycle 3, Day 0 (C3D0)	C1D0	-3.125*	.904	.032	-6.083	-.167
	C1D22	2.417	.895	.191	-.512	5.346
	C2D0	-1.000	.493	.812	-2.613	.613
	C2D22	3.583*	.819	.003	.904	6.263
	C3D22	3.750*	.740	<.001	1.326	6.174
Cycle 3, Day 22 (C3D22)	C1D0	-6.875*	.753	<.001	-9.339	-4.411
	C1D22	-1.333	.846	1.000	-4.104	1.437
	C2D0	-4.750*	.854	<.001	-7.546	-1.954
	C2D22	-.167	.527	1.000	-1.892	1.559
	C3D0	-3.750*	.740	<.001	-6.174	-1.326

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

Single Technology Appraisal

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No - we now have real world data from the EAMS scheme of UK patients and a recent paper from Italy - Frangiamore et al, Eur J Neurol 2023

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. The ADAPT trial provides clear evidence of the efficacy of the drug in patients with myasthenia. The cost of the drug is high, but this has to be set against the very high cost of care for the cohort of patients with frequent severe myasthenia relapses leading to ICU care and prolonged hospital admissions. This has not been taken into account in the provisional guidance.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - I believe this provisional NICE judgement to be highly flawed. My reasns are set outr below.

I am a consultant neurologist at the Wessex Neurological Centre in Southampton. I completed my training in neurology and Ph.D in neuro immunology at the Oxford myasthenia centre. I run a large regional clinic for patients with myasthenia and prescribe complex therapies including rituximab and efgartigimod, the latter as part of the Early Access to Medicines Scheme (EAMS) scheme.

I was extremely disappointed to learn that NICE have not given approval for efgartigimod for the treatment of generalised antibody positive myasthenia.

There is an urgent need for new treatments for myasthenia as most of the current therapies are slow to achieve clinical benefit and often cause significant adverse effects.

Efgartigimod is the first drug in a new class of therapies designed to rapidly eliminate circulating autoantibodies thereby resulting in fast improvement in symptoms.

The inclusion criteria for the ADAPT trial are entirely reasonable in identifying a cohort of seropositive myasthenia patients who would likely benefit from treatment. In my experience of prescribing efgartigimod through EAMS, the drug has been life changing, enabling patients to get back to normal daily activity, including those who have proven resistant to existing therapies.

As with all new complex therapies, it is sensible for prescription to be limited to specialised regional centres with experience in the treatment of myasthenia. We have demonstrated with EAMS across specialist myasthenia centres in England appropriate use of this drug in a cohort of patients who otherwise are poorly served by current drug treatments and and hitherto have lived with considerable symptom burden from myasthenia.

We now have robust patient reported outcome scores in myasthenia such as MG-ADL and MG-QoL coupled with objective measures of myasthenia severity (composite MG score) enabling clinicians to stop treatment where there is no clear benefit.

I would strongly urge you to reconsider your provisional judgement on efgartigimod and support its use for this rare and often debilitating disease which, in our experience, has brought about highly significant improvement in symptoms to allow patients to return to work.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No - it is important to ensure that we do not discriminate patients on grounds of geography. The only alternative to efgartigimod, where rapid treatment response is required, is plasma exchange which is not nationally commissioned and not widely available across the UK.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

Patient voice needs to be taken into account more to show how it has transformed lives and has potential to give hope to many more patients.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am not able to compare directly the cost of my treatments but since I have been on efgartigomod I have not had any emergency admissions to hospital and lengthy hospital stays. I only need to take pyridostigme for 2 weeks out of 8 and my steroids have been halved . I used to have ivig every six weeks but this was becoming less effective so was going to be moved to 5 weekly. If I wasn't on efgartigomod I would probably have to retire early.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I disagree with the recommendations. I have been having efgartigomod since January 2023 and it has improved my quality of life immensely.
My treatment path has been exemplary by the neurologists and NHS- Pyrisdostigme then steroids , methatrexate then mycophenalate. I was still having emergency admissions into hospital , usually staying at least 7 days and having Ivlg. I was then approved for maintenance ivig but there was always uncertainty as to when this would stop and the fear that my symptoms would return.
Maintenance ivig became a big part of my life and for two days every six weeks I would go in as an outpatient I would also suffer horrendous headaches after treatment but felt it was worth it as I could talk, eat and breath again. The effectiveness however started to become shorter between treatments.
We then decided to look at rituximab but due to COViD delayed . This delay meant that when I went for my consultation I found out about efgartigomod. Unlike other drugs this one was designed specifically for my condition.
The results have been amazing and I am far more affective in everything I do. I am still not off steroids or mycophenalate and my symptoms start to come back about 17- 20 days after the last infusion of the cycle but for 35 days I am scoring 0 on the daily living scores.
I have the treatment at home or work so don't have to pay train fares or take time off work. This has resulted in a more productive and positive life in which I can still contribute to society.
I feel tat people with refractory MG should have access to this as it is life changing

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I do feel the comment on lower socio-economic backgrounds is no longer relevant as the treatment can be had at home or work.

Name	[redacted]

Organisation	N/A
Conflict	N/A – clinical expert for this appraisal
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No. Please see my comments in the letter up loaded with the annotated PDF of the Dec 2023 NICE guidance publication

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Some what accurate but there are inaccuracies.

Please see my comments in the letter up loaded with the annotated PDF of the Dec 2023 NICE guidance publication

Are the recommendations sound and a suitable basis for guidance to the NHS?

No.

Please see my comments in the letter up loaded with the annotated PDF of the Dec 2023 NICE guidance publication

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I personally feel that the lived experience of gMG patients, lack of highly effective treatments as a standard of care and unacceptable side effects from treatments need to be given more room for discussion by the NICE team.

Please see my comments in the letter up loaded with the annotated PDF of the Dec 2023 NICE guidance publication

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Please see my comments below regarding wider cost analysis to include hospital admissions and use of plasma exchange.

Are the recommendations sound and a suitable basis for guidance to the NHS?

See comments below. With correct patient selection this treatment should be available - especially to those with disease that is refractory to steroids and IVIG.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Comment on draft guidance consultation

As a patient with difficult to control myaethenia gravis I am disappointed to see that this treatment has not been approved -essentially on cost grounds but also due to concerns over patient selection. My own myaethenia is refractory to both steroids and IVIG treatment. Hence I have to rely on plasma exchange to treat my condition. My Acetylecholine antibodies are very high and I have spent 7 weeks in hospital this year with complications related to my myasthenia including 2 ITU admissions. One of these lasted 14 days receiving respiratory support. I doubt studies have addressed a cost model that looks at reduced admission and wonder if this should be considered as part of the consultation. The consultation highlights that immunotherapy is the mainstay of treatment but even that has its problems. After two doses of rituximab I developed pneumonia due to PCP. This has required antibiotics which require regular blood test monitoring and visits to hospital. I have received 16 plasma exchanges between August and December 2023. For these I have to travel to [redacted] which is a two hour journey each time - plus 2-3 hours of treatment. Again I wonder if the costs of such treatment, staff time and consumables should be considered in the cost analysis.
Finally, I would like to highlight just how debilitating having myaesthenia is. Bulbar symptoms mean you are unable to speak properly or swallow safely. Weakness of the intercostal muscles and diaphragm means breathlessness - particularly at night, with an inability to lie flat and significant sleep deprivation. Double vision means reading and writing is difficult and skeletal muscle weakness essentially means extreme fatigue. I previously worked as a full time physician before my diagnosis. I would cycle 20-40 miles per week. Since the onset of my condition I have been unable to work or exercise. I suspect, had this treatment already been approved I would have been considered for it.

Clearly there is an issue with patient selection but I would urge the committee to define the group where it should be considered. In my opinion those on regular maintenance plasma exchange (refractory to steroids and IVIG) or where immunotherapy leads to problems should be considered for efgartigimod.
Regards
[redacted]

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No: the consultation document makes erroneous comments regarding the relative efficacy of rituximab and IVIg, and does not acknowledge the emerging evidence that rituximab is less effective in AChR than MuSK myasthenia. It also fails to acknowledge the unique mode of action of efgartigimod.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No: the document makes some confusing comments about availability of IVIg, but then fails to take into account that efgartigimod can be administered much more easily. The potential decrease in bed use has not been considered.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Relevant trial data has been considered.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The clinical effectiveness is based on the trial, and interpretation appears reasonable. I am highly skeptical of the cost-effectiveness assessment - the patients who would benefit from the treatment usually require regular intravenous immunoglobulin or plasma exchange, both which incur

significant costs (e.g. infusion unit / blood product costs), require patients to take substantial time off work, and given the specialist-centre delivered nature of these therapies, is likely to result in significant travel expense for the patients.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, I genuinely do not think so, some of the descriptions of clinical care in this document are frankly wrong, it appears that the committee have been advised by people with inadequate experience in managing myasthenia (see comments below).

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Potentially. Efgartigimod can be administered in patients' homes, whereas IVIg / PLEX require hospital attendance. This puts both those in lower socioeconomic groups and those with disabilities at a substantial disadvantage in accessing these alternative treatments. Efgartigimod would allow greater parity of access to effective treatment.

Comment on draft guidance consultation

I am [redacted] at Addenbrookes in Cambridge, and sit as part of a group of national MG experts who have met to discuss this recommendation. We are unanimous in our opinion that this drug should be made available for certain patients with MG.

The decision not to recommend efgartigimod for MG is an extremely disappointing one, and in my opinion ill-judged. This is the first medication developed for MG in decades, and represents a novel class of drugs which provide a whole new mechanism of action, which has been shown irrefutably to be effective. The proportion of MG patients requiring this treatment would be small (i.e. those who are dependent on maintenance IVIg or PLEX to maintain acceptable function), and therefore the overall cost would be low, but the benefit to those patients would be significant. Importantly, this drug (especially given the potential for subcutaneous administration) represents an important route to relieving hospital infusion unit / PLEX unit burden (which is a significant issue nationally), reduce the use of blood products which have inherent supply issues (there have been alternating IVIg and albumin shortages recently which have compromised out patients' safety and care), and to allow for the delivery of care closer to patients' homes (I have patients who routinely have to travel 120 mile roundtrips for PLEX.

I have significant concerns about the descriptions of clinical care described in this document; there are a number of inaccuracies which compromise the face-validity of the guidance. Notably errors such as 1) the age cut off for thymectomy (65, not 45), 2) that IVIg and rituximab are considered equivalent (these therapies are completely different, and their use is in no way comparable - IVIg is fully effective within ~2 weeks, and is used for rescue therapy, whereas rituximab is used to maintain remission and can take up to two years to reach full effect), and 3) that IVIg is not used as maintenance therapy (this is completely fictitious - I cannot express how absolutely frustrating it is to read this misinformation - WHO DID YOU TALK TO?? DO THEY TREAT MYASTHENICS?? Although it is rare that myasthenics cannot be controlled on usual treatment, there are a small proportion who remain IVIg or PLEX dependent [around 2% of our cohort]).

Where this therapy would be most useful would be: in patients dependent on regular IVIg/PLEX, and in patients with refractory gMG who have failed treatment despite two immunosuppressant agents.

A really important point to make about this drug is that it works quickly, and therefore if it is not effective, it can be rapidly stopped (i.e. there is essentially no risk that treatment will be continued without benefit). The relative cost effectiveness of this will therefore certainly be more favourable than drugs where the effect takes month - years to become apparent.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Comment on draft guidance consultation

I understand the committee's role in establishing that NHS resources are used adequately but reading the documents, I got the sense that it focuses on the technicalities of what the company presented, and not the essence - this is a treatment that works and spares us, patients, from the serious side effects that both steroids & immunosuppressants cause.
I have spoken to several neurologists, and all shared the opinion that this treatment will be a game-changer in gMG treatment.
As a patient, I can testify that the quality of our life is severely compromised. Our ability to work, to maintain social interactions & relationships as well as the relationship with our loved ones (partners, siblings & children) who become carers, are all compromised. This leads to a lot of mental health issues, such as anxiety and depression, that only exacerbate our MG symptoms. It's a vicious cycle with no end. At the same time, our loved ones/ cares also suffer due to the extra burden of the illness & the restrictions it imposes on our lives.
We become the illness & the illness becomes us.
There must be research on the additional cost burden due to claiming benefits, the cost burden of co-morbities like diabetes/ cataract/ bone thinning/ liver problems/ mental health problems caused by the standard

treatments. As well as the financial cost for the mental health problems of our carers. All this needs to be taken into account too.
Women patients also develop MG when we are young with increased family & work responsibilities which become incompatible with the illness. It also happens to be a very temperamental illness with no two days being the same, and not two patients having the same experience/ problems/ trajectory which makes putting us into groups problematic. Reading the document, I don't feel that the committee has recognised this particular characteristic of the illness.
Our lives matter, our holistic wellbeing matters. I feel that the committee is happy to leave us with decades-old treatments that just ""manage"" our condition (i.e. as long as we don't use more NHS resources -GPs/ hospital visits/ IVIG-, it's ok).
We have a right to live lives not plagued by illness & if there are treatments that can help us more that the existing ones, we should be able to have access to them.
The NHS, the experts, the affected community (patients & carers), and the manufacturing company, we should all work together to make this happen in a way that both takes into account NHS' finite resources & our need for better treatments.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

It would be interesting to find what percentage of patients with speaking and swallowing difficulties find the drug highly effective.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

On clinical costs yes
At the second meeting the company maintained its base-case position, assuming that 15% of people remain in the MG-ADL below 5 health state after permanently stopping treatment with efgartigimod.
What about the other 85%? There must be a high percentage who totally rely on efgartigimod....clinical effectiveness should be researched further

Comment on section 3.26 (conclusion), text “The committee concluded that efgartigimod could not be recommended for treating gMG in adults who test positive for AChR antibodies”

On what basis did you come to that conclusion? Having been through an agonising experience of being unable to eat or speak, mental anguish and more anxieties than an expectant father I am disturbed by your statement. I realise you cannot make me an exception but there must be other patients who rely on this completely innovative medication. To me this is as

important as the discovery of penicillin! One must appreciate the costs involved and I wonder whether this is a factor. Having gone through hell the last 4 years I wonder what the future holds now. If I could afford it I would by it tomorrow

Comment on section 3.2 (Treatment options)

The guidelines have been followed to the letter regarding my MG. Just as stated the use of pyridostigmine, steroids, can cause numerous side effects...in my case both caused stomach problems and with steroids considerable GERD, infections of the bladder and chest. Immunoglobulin was the next step which was effective but longevity and effectiveness of the medication was short lived. Rituximab along with steroids was also tried but I never felt well having this treatment. Plasma was the next treatment.....very effective but only lasted 2 weeks.

Comment on section 3.7 (ADAPT and ADAPT+), text "The committee concluded that efgartigimod as an add-on to established clinical management is more effective at improving MG-ADL score than established clinical management alone"

Quite correct. Without Efgartigimod (intravenous) my MG-ADL score would be considerably higher than 5. It is a drug that helps me swallow, converse, and promotes dexterity in my tongue. Naturally it is totally effective in my everyday lifestyle including my ability to cope with mental aspects of the condition.

Comment on section 3.11 (Treatment effect after stopping efgartigimod permanently), text "At the second meeting the company maintained its base-case position, assuming that 15% of people remain in the MG-ADL below 5 health state after permanently stopping treatment with efgartigimod. It provided a statement from one clinical expert who, after reviewing the additional evidence provided at technical engagement, believed a 15% residual effect is plausible."

I am not in the 15%....it depends which part of the body is affected by MG. In my case efgartigimod allows me to consume food.....without it I would probably be liquid diet only.....god knows how long I would survive on that!

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No, the benefit seen in the UK population was not considered as was not available at the time of the consultation.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The proposed cost of the drug is high but one admission to ITU with an MG crises results in a prolonged hospital stay at much higher cost. The Muscular Dystrophy UK audit on emergency admissions demonstrated that MG patients were the largest cohort of patients being admitted to hospital, often with the complications of prolonged corticosteroid use (e.g. fractures, infections) which is not captured.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Efficacy and clinical need have been demonstrated for Efgartigimod. In my opinion, NICE have approved other high cost treatments for neuromuscular disorders with much less proven benefit in adults (e.g. in Spinal Muscular Atrophy) and therefore I cannot understand why this treatment has not been approved.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There are only a few specialist MG centres in England meaning some patients travel long distances to receive treatments such as IVIG, plasma exchange and Rituximab. Efgartigimod can be administered at home which helps mitigate geographical discrimination.

Comment on draft guidance consultation

I was really disappointed to find out that NICE has not yet approved efgartigimod for treating generalised antibody positive Myasthenia Gravis (MG), which is a rare and often debilitating disease. People with MG urgently need new treatments because the current ones are slow to work and often have serious side effects. Efgartigimod is a new type of medication that can quickly get rid of harmful antibodies in the body, leading to fast relief from symptoms.

The inclusion criteria from the ADAPT trial, a research study for this drug, are reasonable and help identify patients who could benefit from it. Based on my experience prescribing efgartigimod through a program called Early Access to Medicines Scheme (EAMS), this drug has been life-changing for patients, even those who didn't respond to other treatments.

Since efgartigimod is a complex medication, it makes sense to limit its use to specialised medical centres with expertise in myasthenia treatment, similar to what is recommended for complex treatments in Multiple Sclerosis. Myasthenia specialists in England prescribing efgartigimod using

EAMS have demonstrated that this approach works well, ensuring highest priority for refractory MG patients.

Myasthenia specialists routinely monitor patients, using their reported outcomes and objective measurements of myasthenia severity, to help decide when to stop treatment if it's not working. This would apply to patients treated with efgartigimod.

I strongly encourage you to reconsider your decision on efgartigimod and support its use for this rare and often devastating disease. In my experience, it has significantly improved the lives of MG patients, allowing them to return to work and lead more normal lives.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

I believe that this treatment should be changed to recommended, not as it currently stands.

Comment on draft guidance consultation

I am one of the people that has been receiving Efgartigimod for Myasthenia Gravis and I believe that this treatment should be recommended to all with the condition. It has been a life changing treatment for myself and a far more effective treatment than what I have been previously receiving (which includes Pyrodostigmine) giving me a far greater quality of life. I strongly believe that this is a treatment that should be offered to others as the improvements it has given myself have enabled me to have a second chance of life, having been made quite severely disabled by the condition previously. I feel it could work well for others too.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

There is additional evidence from the EAMS that is to be published by Dr Jennifer Spillane.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The concern with regard to the difference in the clinical cohort included in the ADEPT trial and the intended marketing recommendation is reasonable but should not prevent an agreement being reached with the manufacturer to enable use of the drug within the NHS given the substantial positive response within the intended disease population to the drug seen within the EAMS. This might be along the lines of the previous schemes used in MS where the efficacy in improvement in QoL and saving in IVIG or PLEX costs is underwritten by the manufacturer.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. Please see comments below.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No.

Comment on section 1.1 (recommendations)

I am a neurologist who runs a regional specialist myasthenia clinic in the North-East of England. I disagree with the basis of the decision not to recommend efgartigimods use in the NHS.

As recognised by the committee, gMG is a debilitating condition with a high treatment burden and so an effective and fast-acting treatment option with a novel mechanism of action to current available therapies would be welcomed by people with gMG and clinicians.

My experience in treating 1 patient under the EAMS is that they improved substantially to efgartigimod where they had been refractory to previous treatment including steroids, rituximab, methotrexate and IVIG.

I have spoken to other colleagues who run specialist myasthenia clinics in the UK and they have similar experience of responses in patients refractory to standard therapies. This experience is to be published shortly by Dr Jennifer Spillane.

Furthermore although not specifically targeted at gMG patients with refractory disease, the ADEPT study did include patients who would be considered refractory (see standard definition in the consultation document) and they also did improve with treatment in a similar fashion to the overall trial cohort.

Thus I would contend that there is evidence of treatment efficacy to efgartigimod in a refractory group of gMG patients both in the ADEPT trial and through the EAMS. I have been impressed by its tolerability and efficacy in a difficult group of patients for us to treat and feel this is a valuable opportunity to substantially improve the QoL of these patients with this rare condition. To prevent its use (assuming that an acceptable cost can be negotiated with the company) would be a mistake.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

Yes
But I would like to add this treatment has changed my life.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes
I would like to add having myasthenia you always have fear of a myasthenia crisis having this drug takes the fear because I feel stronger and my breathing and strength is a lot stronger

Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes however I am positive ACrH antibodies

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I feel all patients with this disease should be given the right to be offered the treatment, myasthenia is a horrid disease that can make you housebound and disabled

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

Since this report was written we have uploaded our EAMS data as a pre print to the following site
https://www.medrxiv.org/content/10.1101/2024.01.31.24302082v1.full.pdf

There has also been more real world data published from an Italian group

Frangiamore R, Rinaldi E, Vanoli F, Andreetta F, Ciusani E, Bonanno S, Maggi L, Gallone A, Colasuonno A, Tramacere I, Cheli M, Pinna A, Mantegazza R, Antozzi C. Efgartigimod in generalized myasthenia gravis: A real-life experience at a national reference center. Eur J Neurol. 2024 Jan 2:e16189. doi: 10.1111/ene.16189. Epub ahead of print. PMID: 38164996.

I again highlight the statement that 'NHS England considers rituximab, an anti-B-cell monoclonal antibody treatment, to be an equally effective treatment to IVIG' . I am not aware of any evidence regarding this.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is important to be clear that the patient population who have the most to benefit from Efgartigimod are the refractory MG cohort - this includes those who have ongoing symptomatic disease with an MG ADL >/= 5 (50% non occular) despite treatment with two immunosuppressants OR those dependant on IVIG or PLEX. Although this group are not typical of the MG population as a whole they do exist - and are well described in the EAMS paper (https://www.medrxiv.org/content/10.1101/2024.01.31.24302082v1.full.pdf). These patients account for the majority of patients with unplanned hospital admissions, have a high risk of ICU admission, are more likely to be on high dose steroids and do require regular IVIg /PLEX (over 50% of the cohort in the EAMS paper required regular IVIg/PLEX). These patients often cannot work because of the burden of disease and burden of treatment and all of this must be taken into account when assessing cost effectiveness.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I am commenting as an individual but as mentioned previously a group of approximately 13 English/Welsh MG specialists had a meeting on the 20th Dec regarding this draft guidance. The main points from that meeting were:

1. It was universally acknowledged that there is a clinical need for targeted therapies that have a novel mechanism of action .There have been no specific targeted therapies for patients with MG since

pyridostigmine was first used in the 1930s and efgartigimod represents a major step forward in the management of MG.

2. The criteria for the ADAPT trial should be used when deciding who should be eligible (MGFA II- IV, ADL at least 5 - 50% non ocular, on stable dose of at least one other MG treatment)
(Note inclusion criteria were as follows:
Patients aged at least 18 years with generalised myasthenia gravis, with or without acetylcholine receptor antibodies, were eligible if their disease was categorised as Myasthenia Gravis Foundation of America class II to IV and they had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 5 (with >50% of the MG-ADL score due to non-ocular symptoms). Diagnosis was supported by a history of abnormal neuromuscular transmission tests, a positive edrophonium chloride test, or improvement with acetylcholinesterase inhibitors. Eligibility criteria also required patients to be on a stable dose of at least one treatment for generalised myasthenia gravis (ie, acetylcholinesterase inhibitors, corticosteroids, or NSISTs) before screening and throughout the trial. There was no requirement for specific generalised myasthenia gravis therapies.

3. The target group for Efgartigimod treatment should be refractor MG patients (ie those with MG ADL >5 who have not responded to two or more immunosuppressant agent) .

4. Patients who are dependant on regular IVIg/PLEX should also be considered a target group for Efgartigimod

5. The decision to start Efgartigimod should be made by a consultant neurologist with a special interest in gMG after discussion in an MDT

6. There should be clear criteria to assess whether a patient has responded or not – these should include the MG ADL score (with a change of 2 or more being clinically significant) AND another outcome measure that is applicable to a patient with neuromuscular weakness – options include but are not limited to MG composite, MRC sum score, CIDP or MMN RODS score, QMG score) and these outcome measures should be recorded at the end of the 1st and 2nd cycle

7. There should be a further review after 12 months treatment looking at whether there has been a reduction in steroid dose

8. A patient should have had 2 cycles of Efgartigimod before deciding whether it has been effective or not.

9. The treatment should be stopped if no clear improvement on outcome measures as listed above or if rescue treatment (IVIG or PLEX is required)

10. Once a stable treatment cycle has been established there should be a clear aim to reduce steroid dose and after this there should be a plan to lengthen out the interval between treatment cycles so that patients are being treated in the most efficient way.

11. The group have collected data on the first 48 patients who were treated with Efgartigimod and have submitted it for publication and have posted a preprint on Efgartigimod efficacy and safety in refractory Myasthenia Gravis - UK's first real-world experience | medRxiv

Thee above statements were then sent to 24 of the UK neurologists who are involved in treating gMG to gain consensus.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Concern and special mention should be given to elderly patients who form a large proportion of MG cases and are at risk of complications from standard treatments.

Comment on section 1.2 (recommendations)

As a group of UK MG specialists we have written up our experience of treating patients with gMG under the EAMs and EAMS+ scheme with Efgartigimod

https://www.medrxiv.org/content/10.1101/2024.01.31.24302082v1

Comment on sections 1.2 (recommendations), text "But it is uncertain if the people in the trial reflect the people who would have efgartigimod in the NHS because the company have proposed a target population with more severe disease."

This is an issue with all trials for a variable disease such as gMG. Patients need to be on a stable dose of treatment before entering such a trial and generally cannot remain in the trial if rescue therapy such as IVIg or PLEX is required. Therefore the most brittle, refractory patients are not generally recruited for trials Our EAMS data available on

https://www.medrxiv.org/content/10.1101/2024.01.31.24302082v1

looks at the real world efficacy of Efgartigimod in 48 pts with refractory Mg (average disease duration > 10 yrs, MG ADL score of 11.2 at baseline, high prednisolone use, average of NSISTs tried, 50% had previously tried Rituximab and almost 50% were on regular IVIG /PLEX). This more severe cohort reflects the type of patients are most likely to benefit from FcRN inhibition.

Comment on section 3.1 (The condition), text "he committee concluded that gMG is a debilitating condition with a high treatment burden"

This cannot be understated. Looking at our EAMS data most patients were on prednisolone (mean dose of 22mg) and given that the majority had a disease duration of >10yrs, the cumulative treatment burden of this is huge. Most of these patients will be under the care of a metabolic bone consultant, have a high risk of fractures, have a high risk of diabetes and weight gain is a significant problem

There would be a clear plan when starting Efgartigimod to reduce prednisolone use

Comment on section 3.2 (Treatment options), text ". The ABN (2015) guidelines recommend that people are first offered pyridostigmine at the lowest effective dose and that surgery to remove the thymus gland can be considered for people under 45 year"

Although thymectomy is offered early for patients with gMG, the effect is not appreciated for many yrs. This was shown in the MGTX trial - so although thymectomy is an important treatment for gMG, myasthenic symptoms typically last for years after surgery even in those whom the surgery is thought to be a success. There is very little evidence of the use of thymectomy in those over the age of 65 except in those that have a thymoma. This is important as the elderly account for the largest proportion of patients with newly diagnosed gMG.

Comment on section 3.2 (Treatment options), text "NHS England considers rituximab, an anti-B-cell monoclonal antibody treatment, to be an equally effective treatment to IVIg"

There are no data at all to substantiate this statement and I dispute its accuracy. I would recommend that it is withdrawn from the NHSE commissioning statement on use of IVIg in gMG.

IVIg and Rituximab have different mechanisms of action. IVIg is mainly used as a rescue treatment though in some refractory patients it is used regularly - this is when no other treatment options are possible.
Rituximab is indicated for refractory gMG (as defined by failure of 2 immunosuppressant agents given in adequate dose for sufficient time), explosive onset gMG, or gMG with frequent relapses. Rituximab is very rarely used as a rescue treatment.

Furthermore there is increasing evidence that Rituximab is more effective in early onset gMG compared to longstanding more refractory gMG (see RINOMAX trial - https://pubmed.ncbi.nlm.nih.gov/36121672/) compared to the negative BEAT MG study (https://pubmed.ncbi.nlm.nih.gov/34857535/).

Our EAMS data show that almost 50% of those who received Efgartigimod had received Rituximab but it was not efficacious - hence their inclusion in the EAMS. .

Comment on section 3.2 (Treatment options), text "has stated that rituximab should be considered for several populations"

See above comment. The efficacy of Rituximab in longstanding gMG is very uncertain.

Comment on section 3.3 (Target population)

On the 20th Dec 2023 a meeting was held by MG specialists from around England and Wales - there were approximately 13 consultant neurologists present all of whom are MG experts. The discussion centred around the target group of gMG pateints that would be suitable for Efgartigimod treatment.
It was acknowledged and recognised that Efgartigimod (and other FcRNs) are expensive drugs and the target population should be clearly defined.

The outcome of that discussion was as follows:

1. It was universally acknowledged that there is a clinical need for targeted therapies that have a novel mechanism of action .There have been no specific targeted therapies for patients with MG since pyridostigmine was first used in the 1930s and efgartigimod represents a major step forward in the management of MG.

2. The criteria for the ADAPT trial should be used when deciding who should be eligible (MGFA II- IV, ADL at least 5 - 50% non ocular, on stable dose of at least one other MG treatment)
(Note inclusion criteria were as follows:
Patients aged at least 18 years with generalised myasthenia gravis, with or without acetylcholine receptor antibodies, were eligible if their disease was categorised as Myasthenia Gravis Foundation of America class II to IV and they had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 5 (with >50% of the MG-ADL score due to non-ocular symptoms). Diagnosis was supported by a history of abnormal neuromuscular transmission tests, a positive edrophonium chloride test, or improvement with acetylcholinesterase inhibitors. Eligibility criteria also required patients to be on a stable dose of at least one treatment for generalised myasthenia gravis (ie, acetylcholinesterase inhibitors, corticosteroids, or NSISTs) before screening and throughout the trial. There was no requirement for specific generalised myasthenia gravis therapies.

3. The target group for Efgartigimod treatment should be refractor MG patients (ie those with MG ADL >5 who have not responded to two or more immunosuppressant agent) .

4. Patients who are dependant on regular IVIg/PLEX should also be considered a target group for Efgartigimod

5. The decision to start Efgartigimod should be made by a consultant neurologist with a special interest in gMG after discussion in an MDT

6. There should be clear criteria to assess whether a patient has responded or not – these should include the MG ADL score (with a change of 2 or more being clinically significant) AND another outcome measure that is applicable to a patient with neuromuscular weakness – options include but are not limited to MG composite, MRC sum score, CIDP or MMN RODS score, QMG score) and these outcome measures should be recorded at the end of the 1st and 2nd cycle

7. There should be a further review after 12 months treatment looking at whether there has been a reduction in steroid dose

8. A patient should have had 2 cycles of Efgartigimod before deciding whether it has been effective or not.

9. The treatment should be stopped if no clear improvement on outcome measures as listed above or if rescue treatment (IVIG or PLEX is required)

10. Once a stable treatment cycle has been established there should be a clear aim to reduce steroid dose and after this there should be a plan to lengthen out the interval between treatment cycles so that patients are being treated in the most efficient way.

11. The group have collected data on the first 48 patients who were treated with Efgartigimod and have submitted it for publication and have posted a preprint on https://www.medrxiv.org/content/10.1101/2024.01.31.24302082v1.full.pdf

Efgartigimod efficacy and safety in refractory Myasthenia Gravis - UK's first real-world experience
J Moniz Dionísio, P Ambrose, G Burke, M Farrugia, P Garcia-Reitboeck, C Hewamadduma, M Hill, RS Howard, S Jacob, DM Kullmann, MI Leite, J Miller, A Pinto, J Pritchard, T Riswick, S Sathasivam, N Thambarigjah, S Viegas, F Norwood, J Spillane
medRxiv 2024.01.31.24302082; doi: https://doi.org/10.1101/2024.01.31.24302082

Comment on section 3.5 (Maintenance IVIg)

It is correct that maintenance IVIg is not used frequently for the management of gMG. However in the specific group that would potentially be eligible for drugs such as Efgartigimod it is used - our EAMS data showed that 43.8% required regular IVIg and 14.6% required regular PLEX

prior to Efgartigimod. These patients are the most refractory gMG patients for whom there are limited other treatment options. We would not consider Efgartigimod (or indeed maintenance IVIG/PLEX) in the group of MG patients who can be well controlled on standard treatments.

Moreover due to difficulty in accessing IVIg patients who have refractory disease with a unacceptably high symptom burden may not receive IVIg and are instead exposed to high dose steroids or are at risk of frequent exacerbations. For example I took over a patient from a non specialist centre who had persistent symptoms despite 2 adequate trials of immunosuppressants, was on high dose prednisolone (60mg) and had 4 or 5 emergency admissions a year requiring ITU/HDU stays with IVIg treatment. He was not regarded as being on maintenance IVIg but was sub optimally treated. Patients such as this gentleman do not qualify for maintenance /regular IVIG and are not counted and are at risk of serious morbidity and mortality. This patient is now on Efartigimod under the EAMS scheme, has not required any further IVIg , has reduced his prednisolone by 60% and has had no unplanned hospital admissions in 12 months - this is the first winter that he was not required ITU /HDU in over 5 yrs.

It is also important to acknowledge the variability in access to IVIg in different centres. This has important implications for equity and fair access to treatments

Comment on section 3.5 (Maintenance IVIg), text "The commissioning expert said that the higher proportion of people having maintenance IVIg in the EAMS data may be because people who had efgartigimod through the EAMS were people who urgently needed treatment."

As is outline in the EAMs paper
https://www.medrxiv.org/content/10.1101/2024.01.31.24302082v1
most patients had a disease duration of over 10 yrs, had tried multiple immunsuppressant agents and had ADL scores of 11.2. Efgartigimod was not licensed for crisis so although the patients who received it were at the most severe end of the gMG spectrum it was not given as an urgent treatment. Patients at risk of crisis would still have been treated as per guidelines with IVIG/PLEX. I believe that the EAMS data reflects the typical population of patients with refractory gMG rather than patients requiring urgent treatment.

Comment on section 3.6 (Maintenance IVIg in target population), text ". In response to draft guidance consultation, NICE received a comment from a clinical expert stating there is regional variation but maintenance IVIg is a relatively uncommon treatmen"

As stated above maintenance IVIG is uncommon in the gMG population as a whole but is used not infrequently in the refractory population who may be eligible for Efgartigimod.

The regional variation also reflects inequity of access to specalised treatment.
The MG specialists in England/Wales are proposing regional MDTs to guide treatment decisions regarding newer drugs to improve equity and to reduce regional variations /inequality.

Comment on section 3.6 (Maintenance IVIg in target population), text "he committee further noted that the company's approach to modelling IVIg use did not account for a proportion of people whose disease did not respond to IVIg."

There has been little/no mention of maintenance PLEX. There are access issues with this as well but the EAMS data show that over 25% had received PLEX in the previous year and 14.3% of required maintenance (Regular scheduled plex) in the 12 months prior to starting Efgartigimdo

Comment on section 3.7 (ADAPT and ADAPT+)

The data from the EAMS paper regarding effectiveness is as follows:

The mean reduction in MG-ADL score at the end of each cycle (day 22) comparing to its beginning
(day 0) was, respectively, -4.6 points in the 1
st cycle, -3.9 points in the 2nd cycle, -3.4 points in the 3rd
cycle, and -4.2 in the 4th cycle (see Figure 1). When comparing the MG-ADL score at the end of each cycle versus the beginning of treatment with Efgartigimod (see Table 3), the mean reductions were: -
4.5 points for cycle 1, -6.0 points for cycle 2, -6.9 points for cycle 3 and -7.8 points for cycle 4
(considering just the patients that completed each cycle: 48, 32, 23 and 14).

Using an MG-ADL score of 0 or 1 to define Minimal Manifestation Status, we observed that 10.4% (5
patients, N = 48) of all patients achieved this status by the end of the 1st cycle. By the end of the 2ndcycle, 12.5% (4 patients, N = 32) reached MMS; this was achieved by 14.3% by the end of the 3rdcycle (4 patients, N = 25) and 35.7% by the end of the 4th cycle (5 patients, N = 14).

It is important also to highlight that the MG specialists propose the use of two objective validated outcome measures to ascertain response to Efgartigimod. The drug would not be continued if there is no clear benefit. It is also proposed that outcome measures would be used to increase the interval between infusions to ensure that the drug is being used in the most efficient way.

Comment on section 3.9 (Data sources and generalisability)

Data from the first 48 patients treated under the EAMS scheme are presented here
https://www.medrxiv.org/content/10.1101/2024.01.31.24302082v1.full.pdf

Our analysis included 48 patients from 13 centres who had completed at least one cycle of
Efgartigimod under the EAMS scheme in the UK by 20th July 2023. At the time, this represented 100%
of MG patients who had completed at least one cycle of treatment. No patients were excluded from
the analysis.
Most patients were female (75.0%, N = 36), with an average age of 49.2 (21.0 – 75.0, SD = 14.2)
years old. The majority (66.7%, N = 32) had been diagnosed with MG more than 10 years before
starting Efgartigimod. The average MG-ADL score at baseline was 11.2 (5 – 19, SD = 3.2). Most
patients (72.9%, N = 35) had undergone thymectomy in the past (mean time since thymectomy = 12.5
years, 1 – 38, SD = 8.3).
All patients had utilized at least one non-steroidal immunosuppressant treatment (NSIST) in the past,
and the average number tried prior to Efgartigimod was 2.6 (range 1 - 6). The most frequent NSISTs
used included Azathioprine (79.2%, N = 38), Mycophenolate Mofetil (64.6%, N = 31) and Methotrexate
(41.7%, N = 20). Six patients had received Cyclosporin, one had taken Tacrolimus and two had
received Eculizumab. Just above a half (52.1%, N = 25) had previously received Rituximab.0.8% (N = 34) had previously received IVIg and 43.8% (N = 21) were still requiring it on a regular
basis at the time of Efgartigimod initiation. More than a quarter (27.0%, N = 13) had previously been
treated with TPE in the previous year and 14.6% (N = 7) were still using it regularly at treatment
initiation.
Just prior to the initiation of Efgartigimod, the majority of patients were taking a combination of NSIST
and prednisolone (54.2%, N = 26). Ten patients were taking prednisolone only, and five were taking
an NSIST only. Six patients were not on any immunosuppressive treatment at baseline though three
of these patients were on regular IVIg. The NSISTs used included Azathioprine (7 patients),
Mycophenolate Mofetil (14 patients), Methotrexate (8 patients) and Cyclosporin (2 patients). The
average prednisolone dose was 20.5 mg daily (range 2-60 mg).

Comment on section 3.12 (Placebo effect), text “if it believed the observed effect was due to any of the following mechanisms:

regression to the mean (a tendency for extreme values to move closer to the mean when measures are repeated over time) a trial effect (benefit from being in the trial that would apply to both arms, and not in routine practice)a 'true placebo' effect (benefit from the expectation that treatment may lead to improvement, which would apply to both arms, and may apply in practice).”

I cannot comment on the trial but our clinical experience in the EAMS scheme was of a very treatment heavy cohort - they had an average of 2.4 NSISTs in tje past, over half were on either regular IVIG/PLEX, the majority were on steroids and 50% had tried Rituximab in the past. Therefore although it was not a randomised controlled trial I think it is not plausible that the reduction in ADL scores seen in the EAMS cohort were due to placebo effect or a regression to the mean.

Comment on section 3.13 (Source of utility values)

Once again commenting on the EAMS data - 50%required regular IVIg or PLEX - treatments that have to be delivered in the hospital setting. Efgartigimod can be given at home, the infusion is shorter and it is hoped that a sub cut version will be available in the future. Two of my patients have the infusion at work - hence economic input should be thought of in terms of productivity, hospital days, absence from work etc

Comment on section 3.16 (Corticosteroid complications)

From personal experience corticosteroid related complications are a huge unseen cost ranging from treatment of diabetes, management of obesity, treatment of osteoporosis, use of bone scans, referrals to metabolic bone clinic, treatment of infections etc.

Comment on section 3.17 (Updated corticosteroid complication costs), text “e. In response to draft guidance consultation, NICE received a comment from a clinical expert who suggested that most people with refractory disease will have stopped taking steroids because they were not effective”

It is true that some patients with refractory gMG will stop taking steroids because they are not effective - however a significant proportion do derive benefit from steroids and keep taking them with resultant side effects. 75% of the EAMS patients were still taking prednisolone with an average dose of 22mg
https://www.medrxiv.org/content/10.1101/2024.01.31.24302082v1.full.pdf

Comment on section 3.24 (Equality)

The MG special interest group has already planned to expand our use of regional MDTs to address access and equality issues.
I would also highlight that Efartigimod seems to be well tolerated in the elderly population who account for the biggest proportion of new gMG

diagnoses. The elderly are particularly susceptible to steroid induced side effects and may be more at risk from the thromboembolic complications of IVIg/PLEX - hence may benefit from alternative approaches such as FcRN antagonism

Comment on section 3.25 (Innovation), text "he company and clinical experts considered efgartigimod to be innovative, stating that it had a novel mechanism of action that specifically targets the underlying cause of gMG. The clinical experts also noted that efgartigimod can be given at home, and works rapidly. The committee considered that all additional benefits of efgartigimod had already been taken into account."

This is the 1st new drug specific for the action of antibodies in gMG since the introduction of pyridostigmine in the 1930s.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Are the recommendations sound and a suitable basis for guidance to the NHS?

Additional weight should be given to the advantages of having an additional treatment available for patients with new-onset or refractory disease. ABN guidelines are a starting point for treatment, but are not suitable in all cases. I was diagnosed with gMG in 2021 and experienced rapidly worsending symptoms requiring several lengthy hospital stays, feeding via NG tube, and a number of different treatments in order to stabilise my condition. As not all treatments work for all patients, the availability of additional treatments may mitigate the length of hospitalisation required for patients with severe disease.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

As gMG disproportionately affects certain groups (classically younger women and older men), the treatment needs of these groups should be taken into account when formulating final recommendations. The burden on carers, who are normally disproportionately female, should also be borne in mind.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries reflect the challenges of determining the cost effectiveness of treatments where there is limited data available and considerable variability in practice around the country. Where the main comparator is oral steroids, many of the costs are hidden as they relate to treatment complications.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is difficult to make a comment on this given the uncertainty around the agreed cost of the treatment. However, there is significant unmet need in the treatment of myasthenia gravis and if it is not possible to use efgartigimod, people with refractory MG will be significantly disadvantaged.

Comment on section 3.2 (Treatment options), text "The clinical experts explained that corticosteroids like prednisolone are associated with notable side effects and that they aim to use minimal doses to minimise side effects."

I would agree that there is considerable morbidity associated with steroids. Often people need to take high doses to get the disease under control. Some people with MG do not find steroids effective.

Comment on section 3.2 (Treatment options), text "NHS England considers rituximab, an anti-B-cell monoclonal antibody treatment, to be an equally effective treatment to IVIg."

I don't think that there is any evidence that this is the case and the indication for IVIG and rituximab are very different. The former is generally used as a rescue treatment when someone is in crisis while the latter is currently used as a 4th line treatment though there is some evidence it can be of benefit used early in the disease. It is not a rescue treatment.

Comment on section 3.3 (Treatment population), text "hey added that, initially, it would be used in specialist centres for gMG in people with substantial symptoms despite optimal standard treatment."

There is a consensus amongst MG specialists that initially efgartigimod should be used in refractory patients who remain symptomatic, despite optimisation of immunosuppressants. However in the long term it could be very useful in the management of patients earlier in the disease course without the need for steroids.

Comment on section 3.4 (Target population), text "with active, refractory disease, with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 5 or more (over 50% of MG-ADL score from non-

ocular symptoms) andwho cannot tolerate or are ineligible for standard treatment, or in whom standard treatment has failed. (Standard treatment was defined as a maximal dose of steroids, and at least 2 additional treatments, such as non-steroidal immunosuppressants and rituximab, for an adequate period of time, at an adequate dose.)"

I agree that this is an appropriate patient population for this treatment

Comment on section 3.5 (Maintenance IVIg), text "he EAG explained that it had received clinical advice that IVIg is not regularly used as a maintenance treatment because of a shortage"

There is significant variability in the use of routine IVIG as a treatment for MG around the country so this should not be used as an indication for suitability for efgartigimod treatment. The previous criteria: MG ADL>=5 and failed two immunosuppressants would be more widely applicable.

Comment on section 3.7 (ADAPT and ADAPT+), text "The committee concluded that efgartigimod as an add-on to established clinical management is more effective at improving MG-ADL score than established clinical management alone."

Clinical experience confirms that the benefits of efgartigimod can be potentially life changing in some patients. It works quickly and is very well tolerated, providing people with immediate benefit with a low side effect profile. Moreover the SC formulation will make it easier for people to have treatment while continuing with their other daily activities.

Comment on section 3.10 (Company's modelling approach), text "would stop treatment if a person's MG-ADL score falls below 5"

I am surprised by this comment as presumably if the person's MG ADL score falls below 5, this means that the treatment is working and should be continued. however the interval between treatment cycles could be extended.

Comment on section 3.14 (Carer quality of life), text "The company said that multiple sclerosis data was chosen because multiple sclerosis and gMG are both chronic, autoimmune conditions with similar symptoms that mainly affect young women."

I think these are very different conditions, in terms of time course, affected population and response to immunosuppression.

Comment on section 3.16 (Corticosteroid complications), text "It also concluded that corticosteroid complication costs should be generalisable to NHS clinical practice, applicable to gMG and valued using prices relevant to the NHS."

Notwithstanding all of these arguments, steroids undoubtedly cause considerable morbidity in patients, particularly in doses above 15-20 mgs a day. Patients hate taking steroids because of the side effects and their low drug costs definitely hide their true cost in terms of treatment complications and monitoring.

Comment on section 3.18 (Subcutaneous formulation of efgartigimod), text "The company stated that the subcutaneous formulation would enable faster administration, reducing burden on people with gMG, carers and healthcare providers. T"

There is a huge potential advantage to the SC version in that people can self administer without having to wait for a nurse etc and the dosing schedule could "iron out" fluctuations in symptoms. I am surprised that the cost is the same as the company will not be paying for home care nurses to deliver the treatment once a patient is trained to self administer.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes, as much evidence existent as possible.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes, they are, taking into account the current evidence (from clinical trails and real world use, including in UK)

Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes, they are and I believe they are a suitable and reliable basis for guidance.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Clinical trials usually target a particular populations seen in the expert centres with ability to organise clinical trails. However, the access to the medication via the EAMS in UK has provided great opportunity for a wide range of patients of different races, social status, education, access to NHS and geographic areas within the UK. The outcome of this study, uploaded or summarised by my colleagues, and soon to submit for publication, is very

relevant and shows a more realistic outcome of the safety and use of efgartigimod in patients with active disease requiring escalation of treatment because:
1. refractory disease though with transient response to acute therapies (IVIG or plasma exchange), reassuring that NMJ remains protected and functional though requiring extra treatments without which their MG would be significantly affected (crisis).
2. severe complications or signs of intolerance to steroid and or other standard immunosuppression, including rituximab.

Of note: it is vital and urgent that NHSE facilitates the updating of the rituximab use in MG, so the efartigimod as well as other new very expansive medications, take a deserved place following steroid, immunosuppression and rituximab. Rituximab is much more efficacious in MG with AChR abs if given early; so, any delays in this and other more accessible treatments will delay improvements, will risk disease burn-out and reduce efficacy of new agents such as efgartigimod when eventually given.
I would like to summarise some illustrative cases of severe forms of generalised MG with AChR abs, in some of our patients who spent years extremely disabled despite of all treatments given in a sequence or combination of steroids, immunosuppression, rituximab, thymectomy and regular PLEX or IVIG, in addition to hospital admissions and inability to do school or work. The costs associated with NHS treatments and associated admissions for treatments, MG crises and for complications, reached approximately £250,000 per year per patient. Their improvement with new target medications leads to weaning off of underlying therapies, including regular rescue therapies, reduction in admissions and complications, and a (not estimated cost of) return to normal life, including school, work and family life.
I will be happy to provide real examples of this type of patients.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am one of the patients who was previously told that IVIg treatment was in short supply. I had to wait years, change hospitals and become severely ill before being able to access it. Once that happened, while grateful, I was astonished to see that rescue therapies (IVIg and PLEX) were regularly given to some and not to others, depending on guidelines. While I am grateful that they are there in cases of emergencies, a lot of work is involved in providing these therapies, and there are a lot of side effects.

The disease severity for the EAMS cohort has been mentioned as not representative of the general population. It is important to note that Myasthenia gravis, an unpredictable autoimmune condition, can affect multiple muscle groups. Sometimes, it affects only eye muscles; sometimes, it affects something completely different, like speech. I was once an amateur athlete, but not anymore. When it is not caught in time, it is not a matter of little emergency therapies; it is a disabling condition, and that social cost, perhaps unquantifiable, but not just about the individual's quality of life, must be considered.

Comment on draft guidance consultation:

I am a patient with active, refractory disease who has failed standard therapy for over 30 years. I was first diagnosed with MG at 19 years old, and despite a thymectomy, steroids, mycophenolate and IviG treatments, I developed severe ocular complex ophthalmoplegia and low vision as well as generalized symptoms. This has been, at various times, accompanied by a whole host of comorbidities, including arthritis, gastro challenges, poor mental health, social isolation, weight gain and chronic pain. Some may have been inevitable, but many arise from the difficulty of treating myasthenia, which is inevitably refractory, caused by patients falling through the cracks of different hospitals, centres, doctors, and departments. Some of the decline is often iatrogenic; patients kept on outdated one-size-fits-all treatments for years and years.

I agreed to be enrolled on the trial with much trepidation (and did it despite having some terrible experiences in other areas of the NHS). I went ahead knowing that I had become a carer to an elderly parent, and despite good trial results, there was a risk to her quality of life if I became any more disabled. I enrolled because I admired the passion of neurologists who asked their many patients like me to join. As an older patient, I have seen many changes, and one has been the increase in the number of female neurologists and brilliant researchers who are still trying to investigate treatment options for this old condition. I have had excellent results on this new medication and owe the change in my treatment to this new energy running through the NHS.
he medicine per person is wildly expensive. Anyone would feel guilty using such a costly medicine. If more people were to utilise it, these costs would go down. I know little about drug development, only enough to say that if the people who are supposed to use it cannot, then this would have been a waste of patient and doctor time, scientific research and health, all of which are priceless in the long run.
The long-term potential of Efgartigimod is yet unknown and may be efficacious for other immunological conditions. How much does it cost to have people on prescription medication endlessly, on steroids, for bone scans and arthritis drugs and MRIs and all the other numerous investigations which are de jure for people with immunological conditions, for routine appointments and emergency stays to save life? When doctors sign up to work, they are hoping to make a difference to their patient’s lives,

not to write them off. Efgartigimod has not been recommended because of its cost. How can we bring the cost down?

I am one of the patients who was previously told that Ivig treatment was in short supply. I had to wait years, change hospitals and become severely ill before being able to access it. Once that happened, while grateful, I was incredibly surprised, stunned even, to see that rescue therapies (IVIg and PLEX) were regularly given to some and not to others depending on guidelines. There is a lot of work involved in giving these therapies and there are a lot of side-effects.

The severity of disease for the EAMS cohort has been mentioned as not being representative of the general population. I think it is important to note that Myasthenia gravis, as an unpredictable autoimmune condition, can affect multiple muscle groups. Sometimes it affects only eye muscles, sometimes it affects something completely different like speech. I was once an amateur athlete, not anymore. When it is not caught in time, it is not a matter of little therapies, it is a disabling condition and that future cost, unquantifiable, should somehow be taken into account.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

there are now published studies about real life use of efgartigimod which could be taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

there exists confusion about the use of IVIG in various treatment centres - I work in a centre where we mainly use plasma exchange due to NHS commissioning guidelines for regular IVIG use. However IVIG use in other centres seems to be much higher, probably because they have historically used more IVIG as maintenance therapy and patients continue to be on them.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The treatment refractory subgroup is included within the ADAPT trial group. I cannot see a reason why this group should not benefit from the drug. EAMS data is soon to be published - I would encourage using the available EAMS UK data

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any

group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

no

Comment on section 1.2 (recommendations)

I am unclear about the statement that the trial population is different from the proposed treatment population. Patients with severe disease are included in the tria. I understand that the drug needs to be limited to the treatment refractory population due to cost - from a clinical perspective it would be great if efgartigimod could be used for all patients who meet criteria for the adapt trial, but this is a much larger population that the treatment refractory group (about 5-10 percent of MG patients)

Comment on section 3.2 (Treatment options)

"NHS England considers rituximab, an anti-B-cell monoclonal antibody treatment, to be an equally effective treatment to IVIg. " Rituximab is not equally effective to IVIG - the response rate is at best 50% whereas most patients respond to IVIG (>90%). Rituximab is currently considered as a treatment for patients who depend on IVIG (it is one of the commissioning criteria) - the role of rituximab in MG treatment is likely to change - I would support its earlier use in the disease course

Comment on section 3.3 (Treatment population)

As someone who runs a specialist mysthenia service I want to highlight that drugs like efgartigimod are sorely needed, especially for treatment refractory patients who require regular plasma exchange or IVIG. The only reason to limit the use of efgartigimod to the treatment refractory group is cost - if cost was not an issue I would propose using the adapt trial inclusion criteria for patients who could benefit from this drug. however if the use of this drug has to be limited because of its high cost than NICE should at least allow it for treatment refratory MG patients who have failed other immunosuppressive treatments and are considered for regular IVIG or plasma exchange (similar to current commissioning criteria for rituximab, although rituximab is a very different type of drug)

Comment on section 3.4 (Target population)

I am unclear what this paragraph means. The company considers the use of this drug for patients who meet EAMS eligibility criteria - this population is a subgroup of patients in the ADAPT trial. The reason to limit the indication for this drug to this subgroup is due to cost. There is great need for patients who have failed standard treatments as defined by EAMS criteria to be able to access novel drugs such as efgartigimod.

Comment on section 3.5 (Maintenance IVIg)

With regards to maintenance IVIG, its use seems to vary between specialist centres. About 5-10% of MG patients will be on either IVIG or plasma exchange. I understand that in many centres IVIG is being used as maintenance therapy despite its limited availability. Centres who do not use IVIG as maintenance therapy will use plasma exchange instead. Historically IVIG was used as maintenance therapy hence why there continues to be regular use as a treatment for treatment refractory myasthenia gravis. There are also patients who do not respond to PLEX but respond to IVIG.

Comment on section 3.6 (Maintenance IVIg in target population)

It is difficult to estimate the use of IVIG in the target population as the use of IVIG as maintenance therapy varies between centres. Centres who do not offer IVIG will usually offer plasma exchange. In my opinion the estimation of the Delphi panel (representing a considerable number of specialist centres) should be taken as an approximate figure of IVIG use, but In would maybe reduce the number slightly to account for some centres who use plasma exchange rather than IVIG.
There are also patients who might be eligible for either IVIG or plasma exchange but might have to wait for treatment, referral to specialist centre, or would not be able to have it due to comorbidities, or refuse to have it.

Comment on section 3.21 (The committee's preferred assumptions)

I would support the use of the drug in a population with characteristics similar to ADAPT

Comment on section 3.23 (Additional analysis)

Most patients who are found to benefit from IVIG will continue on IVIG longterm. The proportion of patients stopping IVIG once effectiveness is established is in my opinion low (<5%). Patients who do not receive maintenance IVIG may receive maintenance plasma exchange, this has not been modelled here.

Name	[redacted]
Organisation	Nottingham University Hospitals
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I think that most importantly for efgartigimod, there are patients with generalised myasthenia gravis who have been treated in the EAMS that have failed rituximab. Rituximab is one of our highest efficacy drugs but sometimes with unpredictable responses. The fact that in the real world data from the UK there are 30-40 patients who have tried and failed rituximab speaks volumes for efgartigimod's position in the treatment algorithm for generalised myasthenia gravis in the UK. There are currently

no other drugs licensed after rituximab failure for generalised myasthenia gravis. As a treating physician I know that due to efgartigimod's unique mode of action it will treat patients effectively who have circulating AChR antibodies and active disease despite previous treatments eg failed rituximab. It is the only drug available for generalised myasthenia gravis that has good real world data in the UK, excellent safety profile and was successful in a double blinded RCT. It can be positioned after rituximab. There are patients who are very refractory who need ongoing treatment via regular IVIG or Plasma exchange. I have had one patient in the last 4 years who needed weekly plasma exchange to prevent hospitalisations. An equal alternative in this new era would have been efgartigimod which would have been hugely resource saving eg no need for large vein access, no need for nurses to set up a plasma exchange machine, no need for several hours on the machine. These patients are rare but worth mentioning.

Name	[redacted]
Organisation	Imperial College NHS Trust
Conflict	N/A
Comments on the DG:	

We understand that efgartigimod is still under evaluation to assess both the clinical and cost effectiveness of the drug in AChR antibody positive myasthenia gravis. We have now been able to access and use the drug in six patients with refractory myasthenia in our centre. These include young and older patients previously on long term intravenous immunoglobulin and/or after previous rituximab use with ongoing symptoms. Our experience is extremely positive with significant improvement in MG ADLs. We have also been able to reduce the steroid doses in several cases after 2-3 cycles. Our patient's quality of life have also improved even amongst those who thought they were "treatment resistant".
We appreciate that trying to identify the correct place for efgartigimod in any myasthenia treatment algorithm will be challenging. Patients with refractory MG remain a difficult but relatively small group in most specialist clinics. The response to rituximab remains variable amongst this cohort which often results in the need for ongoing maintenance intravenous immunoglobulin and/or plasma exchange treatment or will culminate in emergency admissions including intensive care unit admissions. These patients also often remain on relatively high/prolonged doses of steroids which results in significant side effects especially in older patients or those with specific medical co-morbidities (e.g diabetes, vascular disease, metabolic bone health). In such cases the use of efgartigimod can be extremely helpful to prevent hospital admissions and reduce long term morbidity from immunosuppressive treatment. Obviously further real world data is needed to evaluate this further but our experience has been positive and we wished to share this with you before any final decision is made.
With best wishes
Yours faithfully

[redacted] (consultant neurologist)
[redacted] (consultant neurologist)

[redacted] (Senior Neurosciences Pharmacist)
Neuromuscular Services
Imperial College Healthcare NHS Trust

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

I have read the report which although very complex, I have found to be very informative.

As a patient who is now having regular Efgartimigod infusions, I have felt it's life changing benefits and am extremely saddened to read that it has not yet been approved for general use.

I was diagnosed with Myasthenia Gravis in 2009. The disease came as a shock as previously I was very fit and healthy. Over the years I have had all the recommended treatments: Pyridogstimine, Prednisolone, Thymus removal, Radiotherapy, Aizathioprine, Mycophenolate, Ivig and Plazma exchange. The only treatment I have not had due to concerns over other health conditions is Rituximab.

Despite the range of medications and treatments, I have still succumbed to three episodes of "Mg Crisis" which were life threatening and extremely scary.

On the first occasion I spent just under 2 weeks in ITU and overall 3 months in hospital. In the 13 to 14 years of having Mg I have seen my once strong muscular frame waste away due to the continuous use of steroids. Aside from muscle waisting the steroids have also caused many side effects, most notably with my eyes and eyesight. I suffer from terrible double vision and constant dry eyes which as forced me to stop driving. I also have Hypertension and have had to stop taking both Aizathioprine and Mycophenolate due to ongoing low Lymphocytes.

My once productive and rewarding working life came to an unplanned halt due to the unpredictable nature of my illness. It has been exchanged for a life of seemingly constant hospital appointments to see consultants in: Ophthalmology, Rheumatology, Urology, Endocrinology, Physiotherapy, Haematology, Gastroenterology, Oncology, Psychology and of course Neurology. I can't be sure whether it's directly related to Mg, but I also have Anaemia, Hypophostemia, and suffer from recurring UTI's, I do suspect that this is due to the many medications I take which compromise my immune system.

I was given IVIG after my 2nd and 3rd Crisis (Type 2 Respiratory failure for which Neostygmine helped to prevent me being induced into a coma).

I was treated with IVIG for just over two years but still the Mg returned with my symptoms fluctuating with alarming unpredictability.

It's difficult to sum up the experience of having Myasthenia Gravis, but one way to describe it is to feel like I'm walking around with two huge shopping bags in each arm that are never empty and can be filled up at any time without my consent, and with other people's shopping! It pulls at my muscles and strangles my breath. … and the medications which do help also cause harm, to not just my physical life but also my emotional and mental wellbeing.

On the very POSITIVE side , I can honestly say that since I have started the Efgartimigod infusions, my symptoms have almost miraculously changed for the better. I feel stronger (from an Mg perspective) I can chew and talk without slurring my words, I can drink without fear of choking, I can brush my teeth and spit out the toothpaste and not have to rest my head on the mirror in front of me, I can hold my head up without my neck giving way… I can prepare meals without having to worry about whether I will be actually able to eat them. I can raise my arms and my legs without them trembling and giving way on me. I can walk further without my muscles seizing up. I actually feel better and despite other health conditions I definitely feel more confident and am able to physically move about without the heaviness and weakness that Myasthenia Gravis brings.

I feel very fortunate to have been given this drug as it seems every thing else had failed. I can testify 100% that if I had not been given this opportunity I would probably have had another crisis by now or at the very least been experiencing episodes of not being able to chew and eat or walk without becoming breathless.

I do hope this testament helps to support the understanding of this illness from my very personal point of view, and that it helps in your decisions in moving forward to allowing access of this treatment to all who could benefit from it, and gain back control from this debilitating disease.

I am so grateful for the wonderful support of my Neurologist and the team of registrars who look after me.

Kind regards

[redacted]

Name	[redacted]
Organisation	University Hospitals Birmingham
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes, but there is more emerging real-life evidence showing efficacy

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

Need to consider the wider impact of newer therapies in myasthenia and how life changing these are to many patients.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Comment on section 1 (recommendations)

There is a clinical need for targeted therapies which are fast acting and safe and that have a novel mechanism of action. There have been no specific targeted therapies for patients with MG since pyridostigmine was first used in the 1930s and efgartigimod represents a major step forward in the management of MG.

Comment on section 1.1 (recommendations)

1. The target group for efgartigimod are refractory MG patients (i.e. those with MG ADL ≥ 5 who have not responded to two or more immunosuppressant agents).

2. Patients who are dependent on regular IVIG and/or PLEX should also be considered as refractory and should be eligible for Efgartigimod.

3. The decision to start Efgartigimod should be made by a consultant neurologist with a special interest in gMG following discussion in MDT

4. There should be clear criteria to assess whether a patient has responded or not – these should include the MG ADL score (with a change of 2 or more being clinically significant) AND another outcome measure that is applicable to a patient with neuromuscular weakness (options include but are not limited to MG composite, MRC sum score, CIDP or MMN RODS score, QMG score) and these outcome measures should be recorded at the end of the 1st and 2nd cycle

5. A patient should have at least 2 cycles of Efgartigimod before a decision is made regarding efficacy

6. The treatment should be stopped if no clear improvement on outcome measures as listed above or if rescue treatment (IVIG or PLEX is required).

7. There should be regular reviews to ensure sustained benefit and safety

8. Once a stable treatment cycle has been established there should be a clear aim to reduce steroid dose and after this there should be a plan to lengthen out the interval between treatment cycles so that patients are being treated in the most efficient way.

The UK MG specialists treating MG patients with Efgartigimod have collected data on the first 49 patients who were treated with Efgartigimod.

Our experience from our centre has been overhwhelmingly positive with one patient coming off regular plex/IVIG.

One of the patients was on 1g/kg IVIG (55g) every 4 weeks for more than 12 months, in addition to multiple attempts with plasma exchange and Rituximab. Since Efgartigimod, she has not needed any rescue therapies.

Comment on section 2 (information about efgartigimod)

The target group for efgartigimod are refractory MG patients (ie those with MG ADL ≥ 5 who have not responded to two or more immunosuppressant agents).
Patients who are dependent on regular IVIG and/or PLEX should also be considered as refractory and should be eligible for Efgartigimod.

Comment on section 3.25 (conclusion)

Efgartigmod has had a significant positive effect in a large number of patients on the EAMS scheme and the paper is being published.

Comment on section 3.4 (Maintenance IVIg)

This is only a very small piece of health economics savings - patients often lead a normal life (more so since the home infusions can be given at their workplaces). The number of hospital admissions saved just for on-going therapy (plex/IVIG etc) is substantial, let alone need for ventilation/ITU stay etc.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? I have been a patient receiving efgartigimod since March 2023. This has shown significant benefits to my Myasthenia symptoms. Prior to starting this medication I was on a high dose of steroids for 2 years and had been unable to reduce them without my Myasthenia symptoms worsening. In almost 12 months I've managed to half my steroid dose and I'm hopeful I'll be able to come off these completely. efgartigimod Has significantly improved my health and hasn't doesn't appear to have the same negative impacts of my general health as other medication. I have tried alternatives to steroids previously and my Myasthenia hasn't responded to any of them. This is the first time I have felt like there is hope to getting my independence back. This medication has been life changing to me. I do fine the administering of this medication to be a little impractical in the sense that I have to arrange for deliveries and have a nurse sit with me for over one hour whilst receiving the infusion. The benefit comepletely outweighs any inconvenience that I may experience. I think if the medication could be administered in an alternative form this would be amazing and may also address concerns relating to cost as I'm aware this is a particularly expensive treatment. One I wouldn't be able to access if it wasn't for the early access scheme. I feel a deep amount of guilt and sympathy for those not on the scheme who may never get to experience the benefits of this drug. I'm very appreciative of the opportunity I have been given.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:
I am an MG patient and am lucky enough to be receiving efgartigimod through the early access to medications scheme, and it has been absolutely life changing for me. I was diagnosed with achr positive generalised myasthenia gravis in 2019. I was started on pyridostigmine, prednisolone and methotrexate.

In January 2020 I had a myasthenic crisis. I was taken to a local hospital and spent over a week in the intensive care unit where I was given ivig.
In February 2020 I was again in a major flare up, heading towards another crisis. I was admitted and given plasmapheresis. The treatment worked well however I was unfortunate to experience a femoral DVT afterwards which developed into a massive double pulmonary embolism, leading to another emergency ambulance being called when I collapsed at home and I was again admitted to intensive care for over a week. I am now on long term warfarin.
In May 2020 another admission to ICU for myasthenic crisis.
After this it was decided I would be started on monthly IVIG maintenance therapy.
By this point I was on long term sick leave from work (assistant practice manager for a GP surgery) I couldn't drive, I couldn't look after my children and my husband had to reduce his working hours to help. I was having to use a wheelchair regularly. My health had deteriorated rapidly.
In October 2020 I had another admission for a severe myasthenic flare up.
In December 2020 I had a thymectomy.
By now I was on high doses of prednisolone which had caused severe osteoporosis, pre diabetes, cataracts, 4 stone weight gain and cushings.
Throughout 2021 things remained the same. I was still requiring monthly ivig but I didn't experience any further crisis.
We decided to change methotrexate to azathioprine in late 2021.
Unfortunately following a UTI I developed neutropenic sepsis and spent a couple of weeks in hospital on various IV antibiotics. I had to stop azathioprine.
Throughout 2022 there was discussion with my consultant about this new treatment that was being trialled, efgartigimod. I couldn't take part in the trial as i would have to stop ivig and it was possible I could receive a placebo. As my MG was fragile we decided it was too much of a risk. However later in the year it became possible to access the treatment through EAMS. I decided to go for it. Nothing else was working well for me after 3 years of trying, and I desperately wanted my life back.
In January 2023 I received my first round of treatment. Before I knew it my MG ADL scores were 0 for the first time since diagnosis! I have had no hospital admissions in 2023. I am able to drive again. I a. working part time as an NHS administrator. I haven't used a wheelchair since I started efgartigimod. I have been able to gradually reduce my steroid dose and am down to 8mg, I was on 30mg for a long time.
I am much more independent and I finally feel like I have got my life back thanks to the efgartigimod treatment.
There is finally a treatment that works well and I feel it would be such a tragedy if it wasn't approved.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	
Has all of the relevant evidence been taken into account?	

Has the real life EAMS data been assessed?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

no

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, as there is no further treatment option for treatment resistant myasthenia

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

no

Comment on section 3.1 (Clinical management)

Our experience with Efgartigimod has allowed stoppage of IVIg and PLEX in treatment resistant/refractory patients. This will result in overall reduction in IVIg and PLEX usage. We have also been able to reduce steroid use in patients who have never been able to reduce their dose previously.

Comment on section 3.2 (Treatment options)

Results with rituximab in AChR positive patients has been disappointing and in my opinion isn't equivalent to IVIg. Additionally the time to onset of action is slow

Efgartigimod has a novel mode of action specifically targeting AchR receptor antibodies

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Maybe an adjustment to the cost can be done

Are the recommendations sound and a suitable basis for guidance to the NHS?

yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

None

Comments on draft guidance consultation

With Myasthenia Gravis being an unpredictable neurological disease. It is vital that this drug can be used as an add-on. It surely helps in reducing the numbers of elderly patients on long term therapy.

Seeing the effect on the life of patients who have improved and are on steroid reduction is very rewarding as a healthcare practitioner.

Treatment options for MG is quite limited. IVIG is used as treatment for patients in crisis. But before these patients go into crisis, PLEX, steroids and immunosuppression are the only options. Rituximab is also an option but it does take time to work in the system.
This will be cost effective if Efgartigimod will be available, because IVIG won't be the only treatment available for maintenance.

The EAMS scheme has been very helpful to MG patients who felt like there was no other option for them. It was an opportunity for the patients to learn about the disease and also the drug. It gave patients a chance to look forward.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

I have a diagnosis of severe refractory gMG. It yas been progressing over the last 20 or so years.

Prior to Efgartigimod I was on Mycphenolate Mofetil (I still am) and an 8 week IVIG cycle. Whilst the IVIG gave a fairly substantial boost at each cycle I was still in an overall decline.

There was little I was able to do efficiently. Carrying anything was extremely difficult as was anything requiring any precision. I needed 2 hands to operate the remote control for my car and both hands to open a door.

I was unable to walk more than about 20 yeards without a rest for a few minutes. Putting things aways was extremely difficult because I couldn't maintain my arms above shoulder height for more than a few seconds. Personal hygiene was extremely difficult to maintain. It also made cooking extremely difficult, to the extent of only really being able to use microwave meals.

The fatigue was terrible. A very brief shopping trip would require considerable rest afterwards, usually most of the next day.

There was no joy left in my life. Even getting treatment was huge burden. A 4 hour train trip was difficult to endure.

I commenced Efgartigimod Dec 22 and have had 6 cycles.

The difference is substantial. Everything is much easier. The fatigue is much more manageable.

I am now back to roughly where I was 2 years ago. Things are still difficult, but increased strength and mobility means I can now carry a bag of shopping and open doors properly.

I don't need a days rest after doing any activity and I can cook a few simple things because I don't keep dropping everything.

Importantly I am much more stable, and the decline is currently arrested. I was able to take a holiday recently for the first time in 5 years.

Whilst I am still very poorly I have purpose and can take joy in my day to day life.

I do not believe an MG-ADL score is any sort of reliable measurement for improvement.

There are two major reasons for this.

- There is a lack of granularity in the scoring. There should be more graduations.

- Whilst the scoring goes from least bad to worst the impact is in no way relative across categories. At an extreme a patient who was ventilated and fed by tube would only improve by 2 points if they became able to breath unaided and eat soft food.

It has been my experience that small changes in mobility make a huge difference in quality of life. This simply does not show up in an ADL score. It is particularly true of diplopia and ptosis too.

Whilst I still suffer to an extent with double vision I can manage much better. I have 2 pairs of glasses now. One with 4 dioptres less prism and one with 8.

Where coping strategies have been evolved these don't show up in an ADL score. I used a chair in shower, this is very rarely used now. I changed my diet because I had problems chewing and limited dexterity to use a knife anyway.

I can now manage a large grip knife and not tire eating.

Thank you for considering my comments.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

No, see my open comments.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, see my open comments

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, see my open comments

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Comments on draft guidance consultation

It is important for NICE to approve use of Efgartigimod in anti-acetylcholine receptor antibody positive (AChR Ab+ve) Myasthenia Gravis (MG) for several reasons:

1. It is much more effective with much less side effects than currently available treatments.

2. The use of Efgartigimod can be limited to those is the refractory group. By refractory I mean patients who:

(A) have failed to respond to 2 non-steroidal immunosuppressant treatments (NSISTs); or
(B) are on regular intravenous immunoglobulin (IVIG) or Plasma Exchange (PLEX)

Please note the above two are separate groups of patients

3. In refractory patients (defined in Point 2 (A) and (B)), there are 3 options of treatment: IVIG, PLEX or Efgartigimod. It is crucial to understand that of the 3 options, it is just not a matter of choosing one or the other. It is important to appreciate that of the 3 options, Efgartigimod is the BEST option because it is a clean drug with better targeted efficacy and less side effects than either IVIG or PLEX.

4. Rituximab is largely ineffective in the treatment of AChR Ab +ve MG and takes a long time of several months to work.

5. Efgartigimod is the first drug since Pyridostigmine which has a targeted effect on the pathophysiology of MG; thus it is very effective, works very quickly (in 1-4 weeks usually) and has few side effects.

I was the first neurologist in the UK to use Efgartigimod in MG under the EAMS. Therefore I have the longest experience of Efgartigimod use in the UK. In addition, currently I have 9 refractory patients on Efgartigimod (the second highest in the UK). Let me explain my experience of Efgartigimod use briefly:

1. In all 9 of these patients, the response has been positive and in some cases, extraordinary.

2. The key here is to carefully choose patients who are experiencing exacerbation of MG, not patients who are symptomatic because of the fatigue of MG: there are ways of distinguishing between these two groups. I'm happy to discuss this further with you if you want. This point is not always appreciated by neurologists. So, patient selection is crucial.

3. One patient in her early 30s had tried 5 NSISTs, was on high dose steroids, failed PLEX in the past, failed Rituximab in the past, had a PEG tube and was walking with a walker while receiving regular IVIG to treat her refractory MG: with Efgartigimod, she has reduced her steroids to a third of her dose pre-Efgartigimod (still on a reducing regime as I write), has had her PEG tube removed, no longer uses a walker, no longer receives IVIG and recently went skiing!

4. Another refractory patient told me she 'cooked the Christmas dinner in December 2023 for the first time in years.'

5. In all 9 patients, I have been able to considerably reduce their steroid doses, which I was unable to do to this level with either IVIG or PLEX. This is very important because the side effects of Prednisolone are severe and devastating.

6. Thus far, in 2 of these patients, I have managed to reduce their NSIST dose; I expect to be able to this in more patients as time passes because in these patients, I have first tried to reduce the steroid doses, so in time I will be expecting to do the same for the NSISTs.

7. The cumulative effect of using Efgartigimod has allowed me to reduce the dose of steroids in these refractory patients, and in time, I will expect to reduce the NSIST doses in these patients too.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

I am [redacted] and I am 55 years old.
I was diagnosed with myasthenia gravis in 1990, at the age of 20; but I suffered from this illness since 1988 and was only diagnosed 2 years later by a neurologist.

I fell on the stairs, because I missed the steps due to double vision which prevented me from seeing correctly the things and objects placed in front of me.

In addition to seeing double, fatigue and eyelids drooping diplopia and ptosis, severely limited my ability to read.

The increased fatigue, specific to the disease, forced me to leave my school and professional activities due to regular absences.

In addition to double vision, I was unable to hold a spoon or an object without it falling, I was so weak.

I had difficulty closing my eyelids, raising my head, due to fatigue and weakness in my neck muscles and loss of all strength in my limbs.

The muscle weakness for me gets worse after each small activity; my facial muscles, particularly the mouth and tongue were so weak and causing me slurred speech.

My MG also affected my other muscles ,so that, when I move my arms and legs, it causing me difficulty walking and getting up from a chair.

The difficulty swallowing caused me many choking,

I also had difficulty chewing solid foods, eating normal foods due to the false routes that food took,

I also had difficulty drinking because water sometimes come out and pass through my nose

I drooled regularly due to the fact that I could not swallow my saliva.

Slowness in eating, and difficulty articulating and fluctuating and unpredictable symptoms have affected my social life ; I couldn't go out in public.

My mobility and my movements have been reduced and have become obstacles; for standing longer, taking the stairs, walking passages without something to grab to help me have my balance, the repeated gestures were a real burden for me.

My generalized myasthenia and its unpredictability and its fluctuations has strongly impacted my life and the life of my loved ones.

The fact that my symptoms could occur at any time of the day limits the professional/social activities of my loved ones too.

The risks of respiratory decompensation in my case were frequent, especially in the evenings, leading to sleep apnea and severe insomnia due to very high and long doses of Steroid intake and which in my case also caused me high blood pressure and osteoporosis, panic attacks, anxiety and emotional stress.

The impacts of this illness are difficult to manage ;it has generated and weakened my self-confidence and has become a difficult burden for those close to me.

The simple gestures of lifelike changing myself during my periods were torture for myself. .

Monthly periods were the times when the symptoms were increased due to fatigue and weakness in the aggravation of each effort.

The gestures of life such as washing, brushing my teeth, my hair, dressing myself, eating normally, preparing a meal, taking a walk, going out to get some fresh air, were impossible because they required repeated gestures that were too difficult for myself to do.

Likewise the heaviness and regularity of the treatments, even hospitalizations, and the limitations imposed on me by the fatigue and the

intensity of the symptoms rendered me invalid and because of the reduction in walking, speaking, and diplopia, I was obliged to lie on my bed all day.

All these things led me to shut myself away.

I saw my life crumble and deteriorate day after day despite all the numerous treatments I received which in my case I didn't respond so well.

My breathing difficulty due to Myasthenia was getting very, very difficult; I couldn't breathe after each effort or exertion.

I ended up receiving the CPAP machine because of severe respiratory insufficiency caused by myasthenia gravis in order to breathe better and help me sleep because without sleep the fatigue was unbearable .

I felt like I was slowly dying..
It's so difficult to say all in a few words the pain, the frustration and all the things the side effects of the treatments have occurred in my case.

I have had treatments that could be given to generalized myasthenic, but mine was very refractory; none of the treatments worked properly.

I got Prednisolone treatment at very high doses every day for 34 years now, including all kinds of immunosuppressants such as Azathioprine, Cyclosporine, Mycophenolate, Methotrexate,
with their side effects which in my case were very complicated.

I had many myasthenic crisis.

I have been intubated and admitted to intensive care more than 5 times.

I also underwent a Thymectomy in 1996(the surgical removal of my thymus) to treat my myasthenia gravis but without amelioration.

I have had plasma exchange [plasmapheresis] several times without success for almost 5 years

I also had immunoglobulin [IVIG] treatments from 1996 until February 2023 which ended up causing me severe migraines due to side effects.

I was also treated with Rituximab which I received for 3 to 4 years.

All these treatments were without much success in my case..

I lived with this emotional stress my whole life.
I didn't think I could one day hope to smile until I received this miracle because for me it is a MIRACLE this new treatment which I called “MIRACLE WATER”

It's EFGARTIGIMOD.

Thank God since I taking Efgartigimod I was able for the first time to reduce the dose of my steroids and even the dose of Methotrexate without the strong fatigue and weakness that I had every time the Doctor tried to reduce them because I had been for too long on high doses without success.

The severe migraines from which I suffered the most during IVIG have drastically reduced.

My fingers, my feet, my shoulders, my neck which slackened and fell easily have regained strength.

Today I can get up from my chair without helping myself with my hands.
I can wash myself alone, brush my teeth, comb my hair without taking many breaks, I can eat normally without mishaps, and go shopping, cook certain dishes, clean my room.

My symptoms have seriously diminished.

My quality of life has become much more normal day after day and quite better for me compared to the months, years when I received the other treatments I listed on top.

My myasthenia gravis is under control, the respiratory failures are less and the tolerance to Efgartigimod is far better for me, without adverse effects,because I do not suffer from migraines like during the IVIG course which I received for 30 years and whose i did not respond too well
and the side effects were so bad.

Efgartigimod is by far the most effective for the case of my generalized and refractory myasthenia from which I suffer.

In addition, the results are instantaneous from the first day, I began to see the effects and an action on my vision; double vision has decreased, I can read for quite a long time without my eyelids drooping, my articulation is much easier, my voice is stronger, my muscular strength is improved ,I see it in repeated gestures like brushing my teeth, taking a shower, typing on my computer, walking without catching or gripping the walls or a person.
I am on my third cycle now.

I see its impact on my quality of life because there is an improvement. And that is very, very reassuring, and means a lot to a person suffering every single day for years from Generalized myasthenia gravis symptoms.

I told myself ,"for you the treatment options are exhausted." Do not expect any further and better treatment."

And when this new medication became available, my generalized myasthenia gravis was able to be managed much better in order to lead such a normal life.

I am so happy and satisfied with my Efgartigimod treatment!.

To help patients with generalized myasthenia gravis, who need more options in their treatment in order to receive the most immediate results and control their symptoms for a long time, without adverse effects and also have a good quality of life, I can say with my experience that Efgartigimod is the treatment that really gives good and better results in this group of patients suffering from generalized myasthenia gravis.

Thanks a lot for putting a smile on our face and taking away the burden and misery on the lives of many of the patients suffering from Generalized Myasthenia gravis despair as well as their families and whose other treatments failed .

I strongly recommend Efgartigimod by giving many stars if I can note that.

Sincerely

[redacted]

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

I've had myasthenia gravis for 26 years
I have been on efgartimoid now for 12 months
This is the only treatment which has improved my quality of life.
I have managed to reduce my azarthprine and prednisone and also before starting this treatment was having plasma twice a month for 7 years I am no longer having to have this for the past 11 months. Not having to go into hospital due to relapses has been amaxing
This drug has not only improved my pysical health but also my mental health

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I dont believe the patient experience and evidence of the EAMS and EAMS+ has been taken into account

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I wouldnt feel educated enough on this subject to comment. The cost effectiveness I dont believe is looking at the bigger picture especially with

those cases of refractory gMg and the years/decades of treatment, medicines, services, resource and hospital beds that add up for not managing a condition effectively and meeting a need that is not being met.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I dont believe so.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No comment

Comment on draft guidance consultation

I have been fortunate enough to receive Efgartigimod through the EAMS and I had my first infusion in December 2022. I continue to have regular infusions and I feel compelled to provide my comments and experience of the treatment having had generalised myasthenia gravis since the age of 15 (I am now 39) and having experienced almost every 'standard' and advanced treatment available for the condition over these years.

I had, up until commencing Egartigimod infusions in November 2022, been having 4 weekly Plasma Exchanges over 3-4 days as an inpatient initially and then as an outpatient for over 6 years. This involved 3-4 days of hospital attendance on a unit, for 4 years peripheral access to insert both access and return lines in to each of my arms and remaining still often for 3-5 hours a day (depending on access success and sufficient pressure for the machine to continue exchanging). The over use of my veins resulted in lines only being able to be inserted by a vascular access team, eventually requiring mid-lines and central lines. I finally got a Vortex port fitted in 2020 to enable better access and completion of my plasma exchanges.

This treatment would mean I was missing 4 days of work a month and I was also having to spend money on travel to and from the hospital as well as other associated costs for food etc, as well as my mother attending treatment with me. Whilst this treatment was usually reserved for 'emergencies' and 'crises' my refractory gMg at this stage was having to be maintained with this highly invasive and taxing regime. It of course impacted my social life, home life, career, mood and overall quality of life. Despite being a fairly stoic person, even I had difficult and desperate times which my family and friends quite often had to support me with.

It not only affected my work, social and home life, it also caused other side effects as a result of the constant removing and re-giving of my blood and new plasma. I became aneamic, I would quite often have highs and lows

with various levels such as potassium having to be supplemented and then causing stomach issues. I also experienced allergic reactions to the donated and man made replacement therapy.
On top of this, the treatment itself perhaps improved my gMg symptoms for 2 or so weeks (taking a few days to take effect) and then I would start a decline and be going in to the next exchange unable to eat for a number of days, losing weight, having trouble swallowing and choking as well as having to take time off of work.

Prior to this I had received Rituximab twice, once paying for this privately as I was unable to access it through my hospital trust at the time, however both times it had little effect. Prior to that I was having regular IVIG infusions, which at first improved my gMg symptoms, but after 1-2 years this also became ineffective in managing my condition.

Before this I was taking Azathioprine and pyridostigmine as well as starting Steroids. My diagnosis at the age of 15 affected my schooling, my opportunity to further my education like my friends and ultimately did impact my progression into higher education and the career path I would have likely taken if it were not for gMg.

I currently feel like I don't have gMg, this is the effectiveness of Efgartigimod for me and what was extremely refractory gMg. I am the strongest I have been since before I was diagnosed and the emotions felt by myself and close family and friends who have known me since I have had the condition, to see me now and how much 'better' and 'well' I look has been quite remarkable to see. To say there have been many tears (of joy) is an understatement.

I felt the effectiveness of the first infusion of cycle 1 within a day or two and my ADL and QoL scores have been reduced to 0. I have very little 'wearing off' of the effectiveness in between cycles and any that I do are in no way comparable to what I have experienced before. I am attending a day unit as an outpatient to have a 1 hour infusion and a 1 hour flush, in comaprison to the burden I was or felt I was on the NHS with the treatments I had to undergo before this 'life changing' treatment is really quite unbeleivable.

I have also been able to reduce both my immunosupressant medication and steroids asa result of the efficacy.

For this treatment to not be made available to others in the same refractory state I was in with my gMg, or even for those who are struggling with standard treatment effectiveness, side effects and daily quality of life would be a real shame and genuinely disappointing. To know what this has done for me, given me in essence my life back and allowed me to do things I have been restricted in doing for 24 years and that not be afforded to someone else in my position and others affected by this under researched and under funded/under represented population really doesn't sit right.

I would urge the guidance and decision to make this treatment not available on the NHS to others be reviewed, re-evaluated and changed to allow others who are struggling and living with this condition to be able to have a real, evidence based opportunity to have their condition managed in such a better way, to the point that it feels as though you are in remission.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Comment on section 1.2 (Recommendations), text "Clinical trial evidence suggests that efgartigimod plus standard treatment improves symptoms and people's ability to carry out their normal activities compared with standard treatment alone. But it is uncertain if the people in the trial reflect the people who would have efgartigimod in the NHS because the company have proposed a target population with more severe disease."

As an MG patient who falls into the 'more severe' category of the disease, it is profoundly distressing to know that I will potentially be denied a treatment which could benefit me.

For me, 'standard treatment' hasn't prevented two spells in hospital for IVIG and plasmapheresis in a six week period; it hasn't restored any of the vitality I used to enjoy; and it has done little to improve my symptoms.

For the benefit of those reading this who have not experienced MG, here is a synopsis of the changes in my life and where I currently sit with the benefit of 'standard treatment':-

Work - Although I am retired, I had maintained roles in three companies which gave me non-domestic focus.
I have been forced to give up each of these roles.

Exercise - Pre MG I was active and walked our dog two miles or more every morning; today fifty metres is at times challenging, as are the stairs, a trip to the supermarket, and even getting out of a chair.

Hobbies - Pre MG I was intensely practical, and capable of most skills involved with metalwork, woodwork and building. I was looking forward to taking on a new project (we built our current house from scratch).
Today I can't use any of my practical skills because, even if I make it to my workshop, my muscles will start to give up cutting through a 2cm piece of timber.
Our plans of a 'new project' are gone.

Travel - In retirement, we planned to travel.
We have now cancelled all of our travel plans and are focused on staying at home.

Supporting family - We have a twenty-six-year-old son with special needs. Suffice to say, our roles have changed.

Generally - It is difficult to explain how it feels to go from being active, looking ahead, driving a car, and filling every day - to struggling to walk, get out of a chair, chew and even at times take a breath.
I find it hard to think that I, and others like me, might be denied a treatment which could restore some of their abilities.

Name	[redacted]
Organisation	Association of British Neurologists Neuromuscular Advisory Group
Conflict	N/A
Comments on the DG:	

ABN neuromuscular advisory group: response to NICE decision on Efgartigimod in gMG

The Association of British Neurologists would like to support the consensus opinion of the myasthenia clinical experts in our membership and the suggestions that efgartigimod should be considered in the treatment algorithm of patients with generalised MG in the following groups:

- Those dependent on regular IVIg or PLEX
- Those with refractory gMG ie. MG ADL> or =5 who have failed treatment despite 2 immunosuppressant agents

We appreciate that the introduction of novel therapeutics into NHS treatment strategies require meaningful evidence from clinical trials as well as robust economic modelling. We agree with the suggestions to accurately represent numbers of gMG patients within the above categories and provide better rationale for corticosteroid and immunosuppressant side effects, disease burden on the individual and their carers but acknowledge the lack of quality baseline information on these areas in this disease in the literature.
However, as clinicians managing the full spectrum of a longterm, autoimmune, relapsing-remitting neurological condition with meaningful morbidity and mortality we in the ABN are very keen to advocate for access to this effective novel treatment in gMG. Efgartigimod has shown clinical efficacy in multi-centre, large scale randomised control trials, represents a step forward in molecule specific therapy in autoimmune disease with strong evidence for tolerance and safety. And importantly, with the evolution of subcutaneous, self-delivery options the drug has untapped potential to revolutionise MG management for some patients with difficult to control disease.

CONFIDENTIAL UNTIL PUBLISHED

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

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Evidence Review Group's critique of the company's response to the second appraisal consultation document.

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AChR	Acetylcholine receptor
AE	Adverse event
CIC	Commercial in confidence
CS	Company submission
EAG	External Assessment Group
ECM	Established clinical management
gMG	Generalised myasthenia gravis
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IVIg	Intravenous immunoglobulin
MG-ADL	Myasthenia Gravis Activities of Daily Living scale
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient access scheme
PLEX	Plasma exchange
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QMG	Quantitative Myasthenia Gravis scale
RCT	Randomised controlled trial
SE	Standard error
UK	United Kingdom

1 Introduction

This document is the External Assessment Group's (EAG's) critique of the response by the company, argenx, to the NICE's second draft guidance consultation (issue date December 2023) for the technology appraisal on efgartigimod for treating generalised myasthenia gravis [ID4003]. The EAG received the company's draft guidance response form, associated documents and revised model on 01 March 2024.

The company's draft guidance response contains the following documents:

- The draft guidance response form (referred to in this report as the company's DG2 response form)
- A summary of new evidence for five areas (referred to in this report as the company DG2 new evidence document):
    - Area 1: Generalisability of data sources to the target patient population
    - Area 2: Maintenance IVIg in the target population: appropriate assumptions regarding level of usage
    - Area 3: Maintenance IVIg in the target population: defining the standard protocol of care
    - Area 4: Maintenance IVIg in the target population: estimating effectiveness
    - Area 5: Handling of placebo effect and extrapolation of post-treatment discontinuation

  The company DG2 new evidence document also contains the results from the company's revised base case analysis.
- Appendices A to F in support of the company's response
- Appendix G which is the company confidential information checklist

In this report we present the following:

- Our critique of the company's response to NICE's draft guidance 2 on efgartigimod for treating generalised myasthenia gravis (gMG) and the company's new evidence (Section 2)
- Our view on another issue that we have identified with the company's model (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis (Section 3)
- The results of the EAG base case and scenario analyses (Section 4)

2 CRITIQUE OF THE COMPANY'S RESPONSE TO THE SECOND APPRAISAL CONSULTATION DOCUMENT

We have aligned our critique of the company's response to the second appraisal consultation document (ACD2) with the numbered comments in the company's DG2 response form.

2.1 Comment 1: Definition of the target patient population and where efgartigimod is expected to be used in clinical practice

The company have confirmed their definition of the target patient population:
"*Patients with active, refractory disease, with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥5 (>50% of MG-ADL score due to non-ocular symptoms), who have failed, not tolerated or are ineligible for standard therapy*"
The company also defines standard therapy: "*Standard therapy includes a maximal dose of steroids and at least two non-steroidal immunosuppressive therapies (NSISTs) for an adequate period of time at an adequate dose*."

The company provides further detail under the heading "Area 1: Generalisability of data sources to the target population" in the company DG2 new evidence document which is supported by information in Appendix A in the accompanying appendices. The company compares the target population with the inclusion criteria for patients entering the Early Access to Medicines Scheme (EAMS) (which was in place prior to Medicines and Healthcare products Regulatory Agency [MHRA] marketing authorisation approval) and EAMS+ (in place since the MHRA marketing authorisation was granted) in Table 3 in the company DG2 new evidence document. The two populations are closely aligned and the EAG considers that as the EAMS/EAMS+ inclusion criteria have already been used to identify patients in the UK to receive efgartigimod the criteria defining the company's target patient population would enable clinicians to identify the appropriate group of patients to receive efgartigimod in the NHS.

2.2 Comment 2: Estimating the level of usage of maintenance IVIg in the target patient population

The company have taken a new approach to estimating the level of maintenance IVIg use in the target patient population for efgartigimod by using real-world evidence from the EAMS/EAMS+ programmes in their base case analysis.

A draft paper[1] (i.e. not yet published or peer-reviewed) describes a retrospective observational study on the use of efgartigimod in 48 patients with acetylcholine receptor

(AChR) antibody-positive gMG who were treated in 12 centres under the EAMS programme in the UK. These 48 patients were all the gMG patients who had completed at least one cycle of treatment as part of the EAMS by 20th July 2023. As noted in section 2.1 above, the inclusion criteria for the EAMS define a population that is very similar to the target population who would be expected to receive efgartigimod in clinical practice defined by the company. When these 48 patients began their treatment with efgartigimod 18 (37.5%) had been receiving regular IVIg with additional NSIST / prednisolone as their gMG treatment and 3 (6.25%) had been receiving regular IVIg only. Therefore, in total 21 patients (43.75%) required regular maintenance therapy with IVIg. There was an additional group of 7 patients (14.58%) who had been receiving regular plasma exchange (PLEX).

The EAG considers that this recent real-world evidence from the EAMS cohort provides evidence of the likely level of maintenance IVIg usage in a population of patients that is a close match to the company's target population that would receive efgartigimod.

In the company's economic model base case a value of 43.8% for maintenance IVIg use in the target population has been used. Sensitivity analyses have been conducted using an upper limit 69% maintenance IVIg use (the value provided for ACM2 which was obtained from UK clinicians in a Delphi panel) and a lower limit of [redacted]% (which has been calculated from the mid-point of the estimates provided by an NHS commissioning expert for the use of IVIg in the total adult gMG patient population and the proportion of that population who would be refractory patients using maintenance IVIg). A further sensitivity analysis includes PLEX as a treatment.

2.3 Comment 3: Appropriately modelling the efficacy of maintenance IVIg

The company has explicitly included IVIg efficacy in its revised base case in response to the NICE Committee's view that it was implausible to include the cost of maintenance IVIg but not any clinical benefits in the company's economic model. The company's approach to including IVIg efficacy is described under the heading "Area 4: Maintenance IVIg in the target population: estimating effectiveness" in the company DG2 new evidence document supported by information in Appendix D in the accompanying appendices.

There are no head-to head studies of efgartigimod versus IVIg so an indirect comparison approach is required to compare the efficacy of the two treatments. The company's feasibility assessment (described in company Appendix D) drew on the company's earlier comprehensive systematic literature review (SLR) (last updated January 2023) which identified 13 publications of 9 studies of IVIg in gMG across the databases searched. After applying their inclusion and exclusion criteria (company Appendix D Table 10), two studies

of IVIg were deemed eligible for the feasibility assessment. Therefore, the feasibility assessment included three studies: the company's placebo-controlled phase III randomised controlled trial (RCT) of efgartigimod, ADAPT (efgartigimod n=, placebo n= in the AChR antibody positive subgroup);[2] an unpublished placebo-controlled phase II RCT of IVIg named by its NCT number, NCT02473952 (IVIg n=30, placebo n=32);[3] a published placebo-controlled RCT of IVIg, Wolfe 2002 (IVIg n=6, placebo n=9).[4] An overview of the studies is provided in the company DG2 new evidence document Table 5.

The company does describe some of the similarities and differences between the efgartigimod and IVIg studies (company Appendix D.1.5) but they do not include an assessment of the risk of bias for either of the IVIg studies. The theory behind ITC approaches is described (company Appendix D.1.4) including noting the risk of residual confounding in a MAIC when few covariates are reported. However, despite stating the decision on the ITC method to be used included considering the availability of the relevant covariates amongst the three trials, the company does not explicitly discuss what the potential treatment effect modifiers and prognostic factors might be in gMG. We note that recent conference abstracts using an indirect comparison approach to compare efgartigimod to ravulizumab or rituximab have included factors such as MG-ADL score at baseline, time from diagnosis, use of prednisone monotherapy, use of prednisone in combination with other non-steroidal immunosuppressive drugs and other non-steroidal immunosuppressive drugs as treatment effect modifiers.[5; 6]

Limited details were available for the two IVIg trials[3; 4] in comparison to the company's efgartigimod trial ADAPT.[2] A comparison of baseline characteristics was hampered by differences in reporting and the absence of some details for the IVIg trials (company Appendix D Table 12). MG-ADL score at baseline was only available for the efgartigimod ADAPT trial[2] and the small Wolfe 2002[4] trial of IVIg in which only 6 participants received IVIg. Neither IVIg trial reported the time from diagnosis or use of steroid or non-steroidal immunosuppressive therapy at baseline. Only one characteristic, age, was reported by all three trials.

There was heterogeneity in the outcomes reported for the three trials (company Appendix D.1.5.4) in terms of the choice of outcome measure, whether they were reported as a dichotomous or continuous outcome (i.e. reporting of percentage achieving a given outcome or reporting change over time from baseline) and the time point for assessing the outcome.

The company's conclusion from their ITC feasibility assessment was that the studies appeared sufficiently similar to include in a network meta-analysis for the outcome of change

from baseline in MG-ADL as this outcome would provide estimates that could be used in the cost-effectiveness analysis. However, the NCT02473952[3] study reported change from the baseline Quantitative Myasthenia Gravis (QMG) score, not change from baseline MG-ADL. Therefore MG-ADL was imputed from QMG using published multivariate meta-analysis methods[7] although the company do not state which of the four models described by Bujkiewicz[7] they used. Furthermore, the time of outcome assessment ranged from 4 to 24 weeks (company appendix D.1.5.4). The company decided to conduct their analyses on the primary timepoints for all included studies (rather than select a common timepoint). Although not explicitly stated, it appears from company Appendix D.1.5.4 that this was to avoid biasing one treatment over the other given that efgartigimod is expected to exert its effects over a shorter timeframe than IVIg.

Although the company present an NMA as their primary analysis they also conducted two separate placebo-anchored MAICs in a sensitivity analysis (i.e. the efgartigimod ADAPT trial[2] versus IVIg Wolfe trial;[4] the efgartigimod ADAPT trial[2] versus IVIg NCT02473952 trial[3]).

NMA (primary analysis)

The company provides a network diagram in company Appendix D.1.6 Figure 10. We have redrawn the figure (Figure 1) to provide additional detail showing how many participants contribute data and with italicised text for study NCT02473952[3] for which MG-ADL was imputed from QMG data.

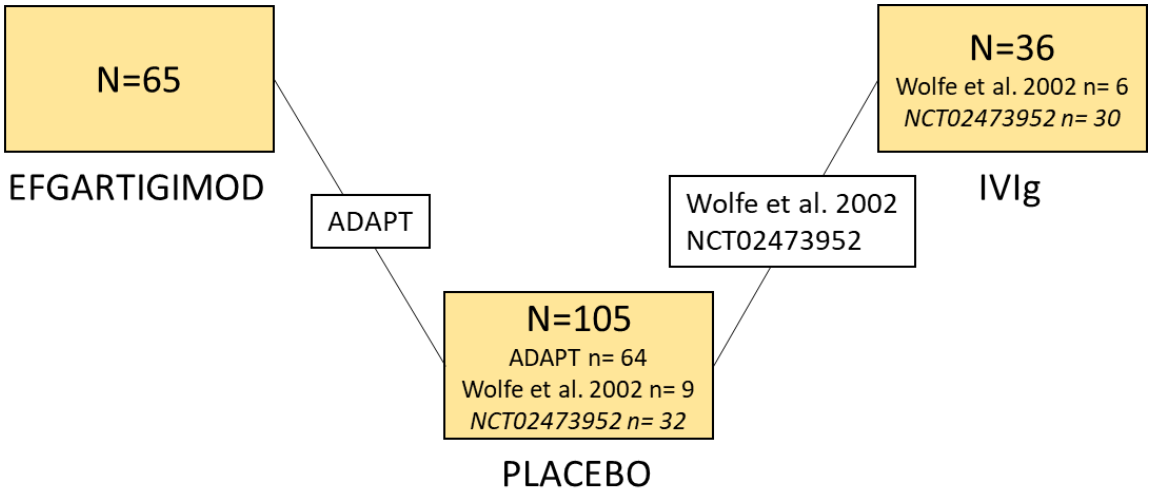

Figure 1 Network diagram for the NMA of MG-ADL change from baseline

Source: Adapted from Figure 10 in company Appendix D.1.6
IVIg, intravenous immunoglobulin

The company presents a summary of the raw outcome data used in the NMA in Appendix D.1.7.1 Table 13. We checked the accuracy of the data from ADAPT[2] and the Wolfe 2002 study[4] and the QMG change from baseline for the NCT02473952 study[3] (but were not able to check the MG-ADL change from baseline that was imputed for the NCT02473952 study). For the ADAPT study, the mean MG-ADL change from baseline values and mean QMG change from baseline values agree with those presented in the original company submission for this appraisal (CS Table 18). To check the standard error (SE) values, we calculated these from the 95% confidence intervals provided and also looked to the CSR for ADAPT (Table 14.2.1.13.1). Neither of these sources provided the identical SEs to those reported by the company in company response Appendix D Table 13 and although the efgartigimod arm SEs we calculated were similar, the placebo arm values were not so we have a concern that the company SE values may be incorrect.

The company state their NMA was performed 'in alignment with the code outlined in the NICE Evidence Synthesis DSU Technical Support Document Series' but because they did not provide their code we have not been able to check this.

The company deemed a random effects NMA to be infeasible and therefore performed fixed effect NMA for all outcomes. Given the lack of data, we agree with the company's use of the fixed effect model whilst noting that it will of course underestimate uncertainty.

We have run our own fixed-effect Bayesian NMA using MetaInsight v.5.2.0[8] and although the results are not identical they are comparable, giving the same treatment ranking with mean differences between treatments of similar magnitude and 95% credible intervals of similar width to those of the company.

MAIC (sensitivity analysis)

As stated above the company conducted two separate placebo-anchored MAICs in a sensitivity analysis:

- the efgartigimod ADAPT trial[2] versus IVIg Wolfe trial[4]
- the efgartigimod ADAPT trial[2] versus IVIg NCT02473952 trial[3]

MAICs use individual patient data from a study of one treatment (in this case data from the ADAPT study of efgartigimod versus placebo) and this is reweighted to match mean baseline characteristics from a target study population for which only aggregate data are available (in this case data from an IVIg trial). This allows treatment outcomes to be compared across balanced study populations.

Company Appendix D.1.8.1 Table 15 shows that only three covariates could be included in each MAIC (the three covariates available differed for the two MAICs). After matching the effective sample size of the efgartigimod ADAPT study fell to [redacted]% of the included sample size in the MAIC versus the NCT02473952 study[3] with the relative weight distributions shown in company Appendix D.1.8.1 Figure 12. The distribution of weights is broadly symmetrical and with no very high weights to skew the results. In contrast after matching for the MAIC versus the small Wolfe 2002 study[4] the effective sample size fell to [redacted] of the included sample size indicating that the results are driven by a few patients. This is supported by the relative weight distributions presented in Appendix D.1.8.1 Figure 13 which are positively skewed. This suggests poor population overlap between the ADAPT and Wolfe 2002 studies.

The results of the company's two anchored MAICs provided in Company Appendix D.1.8.2 Table 16 (efgartigimod ADAPT trial versus IVIg Wolfe trial) and Table 17 (efgartigimod ADAPT trial versus IVIg NCT02473952 trial).

Comparison of the NMA (primary analysis) and MAIC (sensitivity analysis) results is provided in Company Appendix D.1.9 Table 20.

Summary of the EAG's critique of the indirect comparisons

- There is a lack of data for the use of maintenance IVIg in people with gMG but the company have identified two studies and used these to indirectly compare IVIg with efgartigimod in an NMA (primary analysis). The company have also conducted MAICs as sensitivity analyses.
- Indirect comparisons have limitations and can be subject to bias if the underlying assumptions (e.g. of homogeneity and similarity) do not hold. Ideally baseline characteristics, especially those that are potential treatment effect modifiers, would be compared across the trials. In this case, four characteristics could not be compared because they were only reported by the ADAPT trial (history of thymectomy, myasthenia gravis duration, baseline MGFA category and use of steroid or NSIST at baseline).
- The Wolfe IVIg study included 15 participants, six of whom received IVIg. The bulk of the IVIg data comes from the NCT02473952 study which reported on the QMG outcome but not the MG-ADL. Therefore MG-ADL data were imputed from the QMG data using a published multivariate meta-analysis method, although which of four models has been used is not stated. The need for imputation adds another layer of uncertainty to the indirect comparisons.

- The NMA and MAICs enable IVIg treatment effectiveness to be included in the cost-effectiveness model but we consider this to be illustrative and subject to a high degree of uncertainty.

Use of the NMA estimate to model the IVIg treatment effectiveness in the cost-effectiveness model

The company describe how the NMA estimate was used to recalibrate the placebo arm MG-ADL health-states transitions from baseline up to Week 16 in Company Appendix D.1.9.1.

The EAG has checked these calculations and agree with the method used. We note that the transition probabilities are not the same as the established clinical management (ECM) arm, if the effect size for IVIg is zero, as we would expect. However, altering these transition probabilities to correct this makes only a very minor difference to the results so we have not changed this in the EAG base case.

2.4 Comment 4: Appropriately modelling maintenance IVIg dosing and discontinuation

The company investigated the appropriate dosing and discontinuation for maintenance IVIg using a survey of six expert gMG healthcare professionals. They concluded that the most common dosing regimen was 1g/Kg every 4 weeks. They state that this dosing frequency is in line with the Association of British Neurologists (ABN) guidelines[9] and NHS IVIg commissioning Criteria Policy document.[10] The percentage of patients per dosing regimen in the survey are shown in Appendix F Table 31. The company has also provided a scenario where the estimates from the survey on the dosing frequency were used in the model (Company new evidence submission, Scenario 11, Appendix F Table 35) where the ICER increases to £95,499 per QALY.

The EAG considers that the company's assumption of a dosing regimen of 1g/Kg every four weeks is reasonable but notes the variation in use and the sensitivity of the model results to changes in the dosing.

The company's survey on discontinuation concluded that most discontinuations occur during the initial period, defined as any discontinuation after one loading dose and two maintenance doses of IVIg. The weighted average of short-term discontinuations due to non-response was [redacted] (Company new evidence submission, Appendix C.6). The company noted this value aligned with the rate of 19.5% with the discontinuation rate pooled from the studies by Bril et al.[11] and Hellman et al.[12] which is used by the company in their revised model.

The EAG consider these assumptions around short-term discontinuations to be reasonable and appropriate.

For long-term IVIg discontinuation, the company conducted a targeted search of relevant studies and the pooled data is shown in Appendix B, Table 5. Based on the data found, a time to discontinuation curve was conducted and parametric curves were fitted to the curve (Company new evidence submission, Appendix B, Table 6). The exponential function was preferred and then used in the model. The annual rate of discontinuation was [redacted]

The EAG was unable to verify some of the data from Wilf-Yarkoni et al.[13] used to construct the survival function. However, we agree with using the exponential curve and the annual rate of IVIg discontinuation appears reasonable.

2.5 Comment 5: Generalisability of data sources used in the model

To address the concerns of the NICE committee that the clinical evidence for efgartigimod comes from a broader population than the company's intended target population and whether a cost-effectiveness analysis using this clinical evidence would be generalisable to the target population the company has i) compared baseline patient characteristics across different patient populations and ii) presented the results of a post-hoc analysis of efgartigimod efficacy in different patient subgroups. The company's evidence and rationale is provided under the heading "Area 1: Generalisability of data sources to the target population" in the company DG2 new evidence document supported by information in Appendix A in the accompanying appendices.

The company has compared the population characteristics of the following four groups, the first three of which are all from the ADAPT trial:[2]

- ADAPT trial: All patients (n=129) who were AChR antibody positive. This group includes those randomised to receive efgartigimod and those randomised to receive placebo.
- ADAPT trial: Patients who were AChR antibody-positive and who received efgartigimod (n=65).
- ADAPT trial: Patients who were AChR antibody-positive, who received efgartigimod and who were identified in a post-hoc analysis as being refractory to conventional therapy (n=40). These patients had had prior exposure at any time point since diagnosis to ≥2 immunosuppressive therapies (including immunosuppressive therapies being received at the time of screening), or failed treatment with ≥1 immunosuppressive therapy and requiring PLEX or IVIg ≥4times in the preceding year.

- EAMS/EAMS+[1]: 48 patients with AChR antibody-positive gMG who were treated in 12 centres under the EAMS in the UK and completed at least one cycle of treatment by 20th July 2023.

Focusing on potential treatment effect modifiers, the comparison of baseline characteristics presented in Table 4 of the company DG2 new evidence document shows that the EAMS/EAMs+ cohort has a slightly higher (indicating worse disease) baseline MG-ADL score (11.2 compared with 8.8, 9,0 and 9.2 in the three ADAPT subgroups) and a greater proportion have received steroid and NSIST at baseline (56% in the EAMS/EAMS+ group compared with 50%, 52% and not reported in the three ADAPT subgroups). It is difficult to compare time from diagnosis because of differences in reporting between ADAPT and the EAMS cohort. Overall the EAG is reassured that, despite some slight differences, the population characteristics of the EAMS/EAMS+ cohort are relatively similar to the subgroup of ADAPT AChR antibody-positive efgartigimod patients, including those considered refractory to conventional therapy.

The second part of the company's response, concerning the generalisability of data sources used in the model, reports data from a post-hoc analysis of the ADAPT trial where efficacy (in terms of MG-ADL response) was compared for subgroups of AChR antibody-positive patients considered either non-refractory or refractory to conventional prior treatment. These data are presented in company Appendix A.4 Figure 1 and Figure 2 and show that the proportion of MG-ADL responders was consistent (68% in cycle 1 and 75% in cycle 2 among efgartigimod treated non-refractory AChR antibody- positive ADAPT participants compared with 67.5% in cycle 1 and 67.7% in cycle 2 among efgartigimod treated refractory AChR antibody-positive ADAPT participants). Among the EAMS cohort 75% were MG-ADL responders after cycle 1 of efgartigimod (company Appendix A.4 Figure 3). The EAG agrees that these results support the company's case for the generalisability of the efgartigimod treatment effect from the ADAPT whole trial population to the company's intended target population.

The company also presents a comparison of health-related quality of life data for each of the model health states defined by MG-ADL for all the ADAPT AChR antibody-positive participants (n=129) and for the refractory subgroup (n=81) (company Appendix A.5 Table 4). This shows consistency in health-related quality of life between the two populations for each health state again supporting the company's case for the generalisability of the ADAPT whole trial population to the company's intended target population.

2.6 Comment 6: Placebo effect

The committee concluded that the benefit observed in the placebo arm of ADAPT should be maintained over the time-horizon of the model, whilst the treatment effect in the efgartigimod arm should be assumed to worsen during the off-treatment period. In the company's revised model, the benefit observed in the placebo arm of ADAPT is maintained over the time horizon of the model and is applied equally in the efgartigimod arm.

The EAG maintains that the company's original assumptions of modelling the placebo and efgartigimod arms are reasonable. We disagree with the committee's decision to maintain the placebo benefit over the time-horizon. Appendix 1 below (Figure 2 and Figure 3) demonstrates that maintaining the placebo effect in the placebo arm, but assuming no similar benefit in the efgartigimod arm means that the placebo arm performs much better than the efgartigimod arm, which the EAG considers lacks face validity. The company's response is to treat both arms equally. Whilst this seems more realistic to the EAG, we still do not agree with assuming that the placebo effect (or the efgartigimod treatment effect) will persist over the time-horizon. We therefore use the company's original assumptions in our base case analysis.

The EAG reviewed the company's implementation of the placebo effect and agree that it has been implemented correctly. The company applies the transition probabilities observed in the placebo arm of ADAPT up to cycle 4 to the conventional therapy cohort in the ECM arm. After this, the distribution remains as 'last observed' (Company new evidence submission Table 6), rather than returning to baseline as in the initial CS. This 'last observed' distribution is the transition matrix that informs the efgartigimod and IVIg post-discontinuation engines.

2.7 Comment 7: Residual treatment effect after stopping efgartigimod permanently, and link to the placebo effect

The company comments in Company response Appendix E that the residual treatment effect after stopping efgartigimod permanently has been removed from the company's revised analysis. The placebo benefit in ECM is assumed to be maintained over the time horizon and this is applied equally in the efgartigimod arm.

The company conducts two scenarios varying the assumptions on the placebo effect in the ECM and efgartigimod arms (Company response document Appendix F Table 35). In these scenarios, for the residual treatment effect after stopping efgartigimod permanently is set to 7.5%, i.e. the mid-point of 1% and 15%.

The comments on the placebo effect are in section 2.6. We consider it reasonable to use 7.5% for the residual treatment effect after stopping efgartigimod permanently.

2.8 Comment 8: Source of utility values

The company agreed to use the pooled utility values from ADAPT, as preferred by the Committee. The EAG have no further comments on this issue.

2.9 Comment 9: Caregiver disutilities

The company agreed to remove caregiver disutilities from their revised base case and analysis, as preferred by the Committee. The EAG have no further comments on this issue.

2.10 Comment 10: Costs of corticosteroid complications in the model

The company used the costs of corticosteroid complications from Lee et al.[14] based on the frequency of only intolerable adverse events, as preferred by the Committee.

The EAG notes that these costs have been incorrectly calculated as the National Reference unit costs should have been calculated as weighted average by frequency rather than using an average only. The EAG has corrected these costs in section 4.

2.11 Comment 11: Subcutaneous formulation of efgartigimod

The company comments that they have MHRA approval for the subcutaneous formulation of efgartigimod. The company's base case analysis includes a mix of 80% of people receiving the subcutaneous formulation and 20% receiving the intravenous formulation, in line with the Committee's preferred assumption. The EAG have no further comments on this issue.

2.12 Other issues

The EAG notes a significant decrease in the total costs for the efgartigimod arm from [redacted] in the company's previous model to [redacted] in the company's revised base case, and that changing the cost of IVIg does not alter efgartigimod total costs (Table 2). In addition, we note that the company is no longer applying treatment costs or administration costs for IVIg and rituximab in the efgartigimod post-discontinuation engine. The rationale for this is not explained in the company's new evidence or appendices documents.

We understand that rituximab is not an appropriate therapy for the refractory patient cohort efgartigimod is intended for and so ignore these costs. But we consider that patients discontinuing efgartigimod would not be treated with acetylcholinesterase inhibitors (AChEIs), non-steroidal immunosuppressive therapies (NSISTs) and corticosteroids only, and that a proportion would receive active treatment such as maintenance IVIg. Consequently, we have reinstated the treatment and administration costs and QALY gains

for IVIg in the efgartigimod discontinuation engine. The result of this scenario is shown in Table 3.

3 VALIDATION OF THE COMPANY'S REVISED COST-EFFECTIVENESS RESULTS

3.1 Company's revised base case cost-effectiveness results

The company reports their revised base case ICER result in Company response Appendix F Table 32. After submission of their evidence, the company informed NICE of an error in their cost effectiveness model: the percentage figure for patients who discontinue IVIg had been applied incorrectly as 20.7%, whereas it should be 19.51%. This correction, and the cumulative effect of the other changes implemented by the company, results in an ICER of £14,110 per QALY (Table 1).

Table 1 Company revised model base case analysis with PAS

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company revised base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£14,110
	ECM	[redacted]	[redacted]	-	-	

ECM, established clinical management; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years

The EAG reviewed the company's new model, including the implementation of costs and benefits for patients receiving IVIg in the ECM arm, and agree that the changes listed in their Appendices have been implemented appropriately. We attempted to replicate the changes made between the company's previous model (seen at Committee meeting 2) and their current revised base case. Due to the complex coding changes added to the new version of the model and various coding from the previous version of the model that had been removed, we had to start with the company's revised base case and work back to their previous version (rather than vice versa). This analysis required us to:

- Reinsert the costs and QALY benefits into the efgartigimod discontinuation engine,
- Re-enter the costs per cycle for rituximab,
- Recreate the option governing the extrapolation of effect in the original ECM Markov engine,
- Update links to some of the costs and transition matrices used in the model.

It was not possible to exactly recreate the previous company ICER of £15,228 per QALY, instead we calculated an ICER of £22,559 per QALY (Table 1).

Table 2 Cumulative results for the company's changes to their original base case

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)

Company revised base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£14,110
	ECM	[redacted]	[redacted]	-	-	
Source of HRQoL – MyRealWorldMG	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£9,661
	ECM	[redacted]	[redacted]	-	-	
Hospital admin of efgartigimod only	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£18,227
	ECM	[redacted]	[redacted]	-	-	
IVIg and PLEX use – Delphi Panel (69.17%)	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	
Population characteristics – MyRealWorldMG	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	
Caregiver disutilities included	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	
Corticosteroid complication costs – all AEs from Lee at al.	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	
Placebo effect is not maintained and a residual treatment effect applies for 6 months to 15% patients in MG-ADL < 5 after permanent Tx discontinuation	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	
Efgartigimod formulation – 100% intravenous	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	
Use PAS of [redacted]	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	
Use previous IVIg cost	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	
Use previous efgartigimod Markov engine	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£583,641
	ECM	[redacted]	[redacted]	-	-	
Use previous ECM Markov engine	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£22,559
	ECM	[redacted]	[redacted]	-	-	
Company base case at ACM2	**Efgartigimod**	[redacted]	[redacted]	[redacted]	[redacted]	**£15,228**
	ECM	[redacted]	[redacted]	**-**	**-**	

AE, adverse event; ECM, established clinical management; HRQoL; health-related quality of life; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; PAS, patient access scheme; PLEX, plasma exchange; QALYs, quality-adjusted life years; Tx, treatment

The company presents the results of their probabilistic sensitivity analysis (PSA) as a cost-effectiveness plane (Figure 14) and a cost-effectiveness acceptability curve (Figure 15) in Company new evidence submission Appendix F.

4 EAG ANALYSES

4.1 EAG scenario analyses conducted on the company's revised base case

The EAG conducted additional scenario analyses to evaluate the uncertainty around the company assumptions for their new base case (Table 3).

The EAG notes that the company estimates the cost of corticosteroid complications to be £465 per cycle, derived from the intolerable adverse events reported in Lee et al. (2018)[14] and applying the appropriate average NHS reference costs. The EAG prefers to use a weighted average of the NHS reference costs and calculates the cost of complications arising from chronic corticosteroid use to be £386 per cycle. This change increases the ICER to £18,384 per QALY.

Applying treatment and administration costs for IVIg in the efgartigimod discontinuation engine increases the total costs for efgartigimod to [redacted]. Patients receiving IVIg in the efgartigimod post-discontinuation engine would also accrue the benefit from this treatment. However, to model this would require another IVIg engine and the EAG were unable to code this in the limited time available. We attempted to approximate the clinical benefit patients receiving IVIg accrue in the efgartigimod discontinuation engine by calculating the difference in discounted QALYs gained in the ECM arm when maintenance IVIg use is 100% ([redacted] QALYs) and 0% ([redacted] QALYs), using the EAG base case (Table 4). We multiplied this QALY difference by the percentage of patients receiving maintenance IVIg in the efgartigimod discontinuation engine (43.8%), resulting in an ICER of £476,751 per QALY.

The EAG notes that patients in the MG-DL<5 health state receive maintenance IVIg treatment. We are unsure if this would be the case in the NHS and consider further clinical advice would be helpful.

Table 3 EAG scenario analysis results using the company's revised base case

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company's revised base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£14,110
	ECM	[redacted]	[redacted]	-	-	

Scenario		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
1	Use the EAG's calculated cost for cost of corticosteroid complications	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£18,384
		ECM	[redacted]	[redacted]	-	-	
2	Include IVIg costs and benefits in efgartigimod post-discontinuation engine	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£476,751
		ECM	[redacted]	[redacted]	-	-	

ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Incr., incremental; IVIg, intravenous immunoglobulin; QALYs, quality-adjusted life years

4.2 EAG's preferred assumptions

Based on the EAG's critique of the company's model (discussed in section 3) and the scenarios described in section 4.1, we have identified several aspects of the company's revised base case with which we disagree. Our preferred model assumptions are to:

- Use the EAG's calculated cost for cost of corticosteroid complications,
- Include the costs and QALY benefits of IVIg in the efgartigimod post-discontinuation engine,
- Not maintain the placebo effect in the ECM arm and apply a residual treatment effect for 6 months to 7.5 % of patients in MG-ADL < 5 after permanent treatment discontinuation.

Table 4 Cumulative effect of the EAG's preferred model assumptions, efgartigimod versus ECM

Scenario		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company's revised base case		Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£14,110
		ECM	[redacted]	[redacted]	-	-	
1	Use the EAG's calculated cost for cost of corticosteroid complications	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£18,384
		ECM	[redacted]	[redacted]	-	-	
2	Include IVIg costs and benefits in efgartigimod post-discontinuation engine	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£479,229
		ECM	[redacted]	[redacted]	-	-	

Scenario		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
3	Placebo effect is not maintained and residual treatment effect applies for 6 months to 7.5% patients in MG-ADL < 5 after permanent Tx discontinuation	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£463,005
		ECM	[redacted]	[redacted]	-	-	

AE, adverse event; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; QALYs, quality-adjusted life years; Tx, treatment

4.3 Scenario analysis conducted on the EAG's base case

The EAG conducted scenario analyses to evaluate the uncertainty around our assumptions in our base case (Table 5). Excluding the costs and benefits of IVIg treatment from the efgartigimod post-discontinuation engine (scenario 2) had the most significant effect on the ICER, reducing it to £18,887 per QALY, because total costs for the efgartigimod arm are reduced by about [redacted].

Table 5 Scenario analysis results, EAG's base case

Scenario		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
EAG's base case		Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£463,005
		ECM	[redacted]	[redacted]	-	-	
1	Use the company's calculated cost for cost of corticosteroid complications	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£460,410
		ECM	[redacted]	[redacted]	-	-	
2	Exclude IVIg costs and benefits in efgartigimod post-discontinuation engine	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£18,887
		ECM	[redacted]	[redacted]	-	-	
3	Placebo effect is maintained and no residual treatment effect is applied	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£479,229
		ECM	[redacted]	[redacted]	-	-	

Scenario		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
4	The effect in IVIg cohort is based on the MAIC vs NCT024739521	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£557,830
		ECM	[redacted]	[redacted]	-	-	
5	Maintenance IVIg dosing regimen: based on distribution of cohort between dose and frequency alternatives from interview with 6 gMG HCPs	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£487,817
		ECM	[redacted]	[redacted]	-	-	

ECM, established clinical management; HCP, healthcare professional; ICER, incremental cost-effectiveness ratio; Incr., incremental; IVIg, intravenous immunoglobulin; MAIC, matching-adjusted indirect comparison; QALYs, quality-adjusted life years;

5 EAG CONCLUSION

The company has submitted a response to ACD2 to address the issues raised by the NICE evaluation committee after their consideration of the evidence submitted by the company and the views of other stakeholders, clinical experts and patient experts.

- The company has confirmed their definition of the target patient population for efgartigimod which is closely aligned to the EAMS/EAMS+ population. The EAG believes that clinicians would be able to identify the appropriate group of patients to receive efgartigimod in the NHS based on this definition.
- The level of maintenance IVIg use in the target patient population for efgartigimod has been estimated using real-world evidence from the EAMS/EAMS+ cohort and this is incorporated into the company base case economic model (43.8% maintenance IVIg use). Sensitivity analyses have also been conducted for this parameter.
- The efficacy of IVIg has been included in the base case economic model by using an estimate from an NMA (which indirectly compares IVIg and efgartigimod via placebo as a common comparator) to recalibrate the placebo arm MG-ADL health state transitions from baseline up to week 16. We believe the NMA (and MAICs conducted as sensitivity analyses) are subject to a high degree of uncertainty and therefore the IVIg treatment effectiveness should be considered illustrative. As there is a lack of data for the use of maintenance IVIg in people with gMG we are unable to suggest an alternative approach.
- The most common dosing regimen for maintenance IVIg has been identified as 1g/Kg every 4 weeks which we believe is reasonable. We note that the economic model is sensitive to changes in dosing.
- Most IVIg discontinuations occur during the initial period of treatment and the company have calculated a new weighted average of short-term discontinuation due to non-response for IVIg of 19.51% which the EAG believes is reasonable and appropriate.
- A new annual rate for long-term discontinuation of [redacted] is used and, although the EAG was not able to verify all the data that contributed to this value, we think the annual rate of IVIg discontinuation appears reasonable.
- The company has compared patient baseline characteristics for different subgroups of patients and provided the results of a post-hoc analysis of efgartigimod efficacy in different patient subgroups to address concerns about the generalisability of the data sources used in the economic model. Although the EAG identified some slight differences between the EAMS/EAMS+ cohort and the subgroups of the ADAPT trial population we are reassured that these groups are relatively similar and that the

proportions with an MG-ADL response is consistent. The health-related quality of life data is also consistent.

- The company have maintained the placebo effect in the placebo arm and in the efgartigimod arm for the time horizon of their base case model. This results in a greater proportion of patients remaining in beneficial health states over time.
- The company's base case analysis does not include any residual treatment effect after efgartigimod is permanently stopped.
- The company has made other changes to their model that the EAG has no further comments on:
  - Pooled utility values from ADAPT are now used
  - Caregiver disutilities have been removed
  - The costs of corticosteroid complications only include intolerable effects but, as there was an error in the calculations, the EAG has corrected these costs
  - The subcutaneous formulation of efgartigimod has been approved and in the base case 80% of those receiving efgartigimod receive the subcutaneous formulation.

The EAG has identified an important issue with the company's modelling which is not explained in the company's new evidence or appendices documents. Previously, the company model included treatment and administration costs for IVIg or rituximab in the efgartigimod post-discontinuation engine (i.e. a proportion of patients who permanently discontinued efgartigimod were assumed to receive IVIg or rituximab). Although rituximab would not be an appropriate therapy for the company's intended refractory patient cohort, we believe that a proportion would receive active treatment such as maintenance IVIg. The effect of no longer including these costs is a significant decrease in the total costs for the efgartigimod arm. Reinstating the costs and benefits of IVIg treatment in the efgartigimod arm of the company's revised base case increases the ICER to £476,751per QALY (Table 3).

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7 APPENDICES

Appendix 1

[redacted]

Figure 2 Distribution of cohort by health-state over the time-horizon of the analysis, by treatment comparator, company base case: placebo effect is maintained in all arms

Model settings:

- Placebo effect is maintained
- Placebo effect is maintained post-discontinuation

[redacted]

Figure 3 Distribution of cohort by health-state over the time-horizon of the analysis, by treatment comparator: placebo effect is removed from all arms after Cycle 4

Model settings:

- Placebo effect is not maintained
- Placebo effect is removed from active treatment and post-discontinuation a residual effect applies for 6 months
- 7.5% of patients in MG-ADL<5 after permanent treatment discontinuation

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

New evidence submission

13 June 2024

File name	Version	Contains confidential information	Date
Efgartigimod summary of new evidence post-ACM3 [redacted]	1.0	Yes	13 June 2024

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Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

List of Tables

NICE National Institute for Health and Care Excellence

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Executive Summary

The third NICE Appraisal Committee Meeting (ACM3) to evaluate efgartigimod for treating generalised myasthenia gravis (gMG) was held on 9th May 2024.

It has been encouraging that the disease burden, unmet treatment needs and benefits of efgartigimod were recognised during this, and previous, Committee meetings. Furthermore, alignment has been reached on several previously identified areas of uncertainty, including both clinical data and economic parameters, and is further supported throughout by the full repository of available evidence, including real-world UK data.

Following the meeting, the Committee requested additional analyses from the Company on model parameters for which residual uncertainty remained. The Company has conducted all the requested analyses, which are briefly discussed here, and in further detail in the remainder of the document. An updated base case and a fully executable economic model are also included.

In addition to being derived from the best available evidence, the revised base case aligns with NICE methods to inform model assumptions, and correspondingly reduces the level of uncertainty to support an informed decision. A significant increase in the PAS from [redacted] to [redacted] has also been proposed and is incorporated into the base case provided.

This is further supported by the fact that the annual cost of IVIg and efgartigimod per patient becomes similar when the proposed PAS is taken into account. Further erosion of the base case leads to the untenable situation of the cost of this highly effective innovation being less than existing practice with unproven, unlicensed, and less effective treatment.

As part of this revised base case, regular administrations of IVIg have been assumed for a proportion of the refractory cohort who discontinued efgartigimod due to lack of efficacy, in order to explore the full pathway of care.

Scenario analyses are provided (Table 4) to facilitate exploration of further requests from the Committee, including variance of efficacy and dosing parameters for IVIg and consideration of long-term discontinuation assumptions and how these impact total time on treatment.

When considering the long-term time on treatment for efgartigimod compared to IVIg, the Company maintains that the full breadth of available data has been utilised, and NICE methods have been followed to extrapolate beyond evidence appropriately. The request to assume equal time on treatment, across both arms, is not supported by the literature or evidence, and therefore the Company has not incorporated this into the base case analysis presented below, and instead has provided this request as a scenario. Further justification for this decision is contained within this evidence submission.

Table 1 Results of the Company's revised base case cost-effectiveness analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,174

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Established clinical management	[redacted]	[redacted]	[redacted]				

Abbreviations: LYG – life years gained, QALY – Quality Adjusted Life Year, ICER – incremental cost-effectiveness ratio

Moreover, the Company maintains that the above base case is reasonable, as several additional QALY benefits are associated with efgartigimod and could not be captured in the base case or fully represented in the economic analysis. These include reduction in caregiver burden, the convenience of home treatment administration, and a reduced impact on hospital resources. Additionally, efgartigimod has not been shown to have important serious life-threatening adverse events, which are seen in some patients who receive IVIg. The costs to the healthcare system and HRQoL impacts of these AEs have also not been included in the base case model.

In summary, the revised base case demonstrates that efgartigimod can be considered a cost-effective use of NHS resources, even at the lower end of the willingness to pay threshold. The base case strikes an appropriate balance between utilising the best available evidence and following NICE methods, further supplemented with reasonable assumptions (in the patient population identified) to substantiate that efgartigimod can significantly improve the clinical outcomes and quality of life for patients with refractory gMG.

Introduction

gMG is a rare and chronic autoimmune disease with a well-recognised lack of available effective and safe treatment options. This situation is even more critical for patients who have refractory disease, which does not respond adequately to standard treatments. The Committee has acknowledged the particularly high unmet need in this population and concluded that efgartigimod, as an add-on to established clinical management, is a more effective and safer option with a rapid onset of action for improving symptoms of gMG and quality of life than current established clinical management alone.

Throughout the appraisal process, and as emphasised by the many submitted contributions made by clinical experts, patients and carers, it has been clear that there is a significant unmet need in gMG and that effective, safe treatments are especially needed for those patients refractory to standard care.

Following the completion of ACM3, a small number of remaining areas of uncertainty related to the cost-effectiveness modelling and the assumptions that inform it remained. Therefore, the Committee requested that the Company submit additional economic analyses that would be informative for decision-making.

Recap of the ACM3 discussion

After three Committee meetings and the exchange of substantial analysis and evidence, most outstanding uncertainties were addressed successfully. The key areas where agreement was reached at ACM3 include the following:

- Modelling of the placebo effect and exclusion of the residual treatment effect after stopping efgartigimod to align with the placebo effect assumption
- Constituents of standard care or established clinical management

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Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

- The level of IVIg usage in clinical practice, based on real-world evidence from the EAMS/EAMS+ experience in the UK,[1] is the most robust and appropriate data source available for decision-making

The areas of uncertainty remaining are the focus of this new evidence submission:

1. Usage of IVIg in patients who discontinue treatment with efgartigimod
2. Difference in time on treatment between efgartigimod and IVIg
3. Exploration of different parameters for IVIg usage, effectiveness and dosing

Two of these areas (1 & 2) require assumptions to be made beyond any available literature or evidence, as they relate to the real-world usage of efgartigimod beyond the current data. The requested analyses explore the treatment trajectory of patients who fail efgartigimod treatment, how they might be expected to respond to subsequent IVIg therapy, and how time on treatment might differ between efgartigimod and IVIg. The exploration of different parameters for IVIg usage draws on the available evidence and these have previously been included as scenarios. These are repeated here in the context of a new model base case.

Additional analyses

1. Usage of IVIg in patients who discontinue treatment with efgartigimod

Background

The Company recognise the request to consider the total pathway of care for patients with gMG which is refractory to standard treatments and have incorporated the potential use of IVIg as a maintenance therapy for those patients who discontinue efgartigimod.

It is important to note that the use of IVIg in both the ECM arm and post-efgartigimod in the intervention arm has always been included in accordance with its recommended use in guidelines as a rescue treatment for patients experiencing a gMG crisis.

The EAG recognised during ACM3 that the approach they took to modelling IVIg post efgartigimod had technical limitations which confound interpretation. The precise methodology adopted by the EAG in implementing sequential active treatment was not clearly outlined. The EAG noted that patients receiving IVIg in the efgartigimod post-discontinuation engine would also accrue IVIg benefits, but another engine would be required to model this. The EAG also stated that patients in the MG-ADL≤5 health state were assumed to receive maintenance IVIg treatment in their model and were unsure if this would be the case in clinical practice.

Use of a parallel model engine to implement IVIg use post-efgartigimod discontinuation

The Company have incorporated the use of maintenance IVIg following efgartigimod treatment discontinuation by developing a parallel model engine that addresses the technical limitations of the EAG's approach. This revised model permits an exploration of the uncertainties presented by this pathway comparison.

The use of a parallel model engine allows:

- articulation of the costs and benefits of maintenance IVIg treatment post-efgartigimod at the right point in time

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

- imputation of time discounting factors
- addition of considerations on the characteristics of the patients receiving these treatments
- exploration of further aspects associated with the sequential treatment of IVIg post-efgartigimod
- more precise estimates of the costs and effects of each treatment sequence.

Use of maintenance IVIg in patients with an MG-ADL score of 5 or below

The Company base case assumes that only the refractory cohort with MG-ADL ≥5 would start IVIg treatment following discontinuation of efgartigimod. This is considered to be an appropriate use of maintenance IVIg and aligns with the realities of clinical practice. The following elements of clinical practice have been supported consistently by all the clinical experts consulted:

1. Patient symptom control on existing treatment is regularly monitored to include an MG-ADL score
2. An MG-ADL score of <5 signifies adequate symptom control on current treatment with no need for dose adjustment or additional therapy. Furthermore, there could be a consideration of dose reduction of existing treatment(s) to reduce potential side-effects, e.g. maintenance steroid reduction
3. An MG-ADL >5 signifies inadequate symptom control and triggers a review to consider increasing the dose of existing treatment(s) or addition of further treatment to prevent further deterioration, including possible crisis, e.g. IVIg

In line with the approach taken in the ECM arm (conventional therapy +/- maintenance IVIg), only the refractory cohort with MG-ADL ≥5 would start IVIg treatment following discontinuation of efgartigimod. The Company model can track patients from when they discontinued efgartigimod because it incorporates a parallel Markov engine with tunnel states for the cohort discontinuing efgartigimod treatment and starting maintenance IVIg.

While limited evidence exists for patients discontinuing efgartigimod, it is generally accepted that they do not require adjunct active treatment with maintenance IVIg while in a controlled state. Clinical experts at ACM3 supported this and the Company validated it with clinicians during additional discussions.

Exclusion of IVIg non-responders

The Company base case excludes IVIg use after discontinuation of efgartigimod for those patients who previously did not respond to treatment with IVIg. In clinical practice, there are a proportion of patients who do not experience a clinical response or improvement in symptoms following treatment with IVIg or have side effects/complications (e.g. difficulties with venous access). This results in IVIg discontinuation. In a scenario where efgartigimod is available, such patients may receive this alternative treatment, as exemplified by 43.8% of the EAMS cohort who were receiving maintenance IVIg before they started treatment with efgartigimod.

If patients in this refractory cohort do not respond adequately to IVIg and start treatment with efgartigimod, they would not be expected to be retreated with maintenance IVIg post-efgartigimod discontinuation as IVIg has previously been shown to be ineffective. In

accordance with this, 13.7% of the post-efgartigimod cohort is assumed not to restart IVIg. Further detail on the calculation of this percentage is provided in Appendix B.

After excluding the proportion of the cohort who previously did not respond to treatment with maintenance IVIg (13.7%), the cohort starting maintenance IVIg treatment post-efgartigimod discontinuation was 37.7% (43.8% IVIg use from EAMS multiplied by 86.3%).

Treatment outcomes in patients having IVIg after discontinuation of treatment with efgartigimod

Patients discontinuing treatment with efgartigimod in the cost-effectiveness model are a heavily pre-treated refractory population, having failed most, if not all, available options (ECM as well as efgartigimod). Assuming they would have less favourable outcomes than any active adjunctive treatment introduced is reasonable. This would be expected to lead to substantially higher initial discontinuation rates as it is not clinically plausible to assume that outcomes and discontinuation from the total efgartigimod-eligible population would be fully generalisable to this heavily pre-treated, refractory population.

The Company consulted clinical experts to understand how treatment outcomes may present in patients having IVIg after discontinuing treatment with efgartigimod. Clinicians unanimously supported the assumption that initial discontinuations would be higher in this population, though the magnitude is unclear as there is no data available for this cohort.

Therefore, the Company has addressed this by applying a higher initial discontinuation rate (x2 the initial discontinuation rate for maintenance IVIg in a refractory population pre-efgartigimod) for the cohort receiving IVIg post-efgartigimod failure, in recognition of the poorer outcomes anticipated in a highly pre-treated, refractory cohort of patients. This equates to a non-responder discontinuation rate of 39% for the post-efgartigimod refractory cohort, supported by evidence gathered during expert elicitation. Scenario analyses (Scenarios 1 and 2) are provided where this multiplier is varied between 1.5–3x the non-responder discontinuation rate observed in an earlier line of therapy for IVIg.

2. Difference in time on treatment between efgartigimod and IVIg

At ACM3, data was presented to the Committee, highlighting that the average time on treatment for IVIg in the ECM arm of the model was longer than the average estimated time on treatment for efgartigimod. It was commented that this difference appeared to lack face validity given the assumptions of better efficacy and easier administration favouring efgartigimod. In recognition of the Committee's requests, analyses exploring a potential equalising of time on treatment across arms have been provided in full but are not incorporated within the base case.

The Company believes that equalising the time spent on treatment is an unreasonable assumption that deviates from the available data. There is no evidence from the literature or clinical practice to support this. The assumptions incorporated into the base case have been derived from the most robust available evidence for each treatment and extrapolated in accordance with NICE methods. Long-term discontinuation of maintenance IVIg was based on a reconstructed time-to-discontinuation curve, and the choice of parametric function (i.e. exponential) was applied consistently across both arms.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

In clinical practice today, there is no routinely commissioned alternative treatment following the use of IVIg in a refractory patient population. This means that patients may be maintained on IVIg longer as a last resort, even if their response to the treatment is suboptimal. The clinical experts reiterated this during ACM3. Hence, matching time on treatment between efgartigimod and IVIg is not considered reasonable.

In the base case, plasma exchange (PLEX) has not been included in either arm of the analysis, due to uncertainty surrounding its clinical effects and regional variations in access. However, in a hypothetical scenario which equates time on treatment, the Company suggest appropriate implementation would include no further adjunctive treatment in patients who have an MG-ADL score <5 (and are considered "controlled") and use of PLEX as a true last resort for those patients who discontinue IVIg but remain uncontrolled (MG-ADL >5). Since the basis for longer time on treatment for IVIg is that there is no alternative therapy following treatment with IVIg, a hypothetical scenario which reduces time on treatment to equate with efgartigimod should also consider a sequential treatment after IVIg discontinuation. The only possible sequential treatment in current clinical practice is PLEX. Therefore, the Company believes that adding maintenance PLEX after IVIg discontinuation is a logical consequence of this hypothetical setting.

In this scenario (Scenario 4), PLEX is administered to the cohort of patients who discontinue treatment with IVIg in both arms of the analysis. In line with the assumptions made in the new base case analysis, this does not include the cohort with an MG-ADL score <5 at IVIg discontinuation and the same efficacy and discontinuation rate applied for the cohort on IVIg post-efgartigimod discontinuation are applied for PLEX.

Additionally, it should be considered that a number of patients in ADAPT and ADAPT+ discontinued efgartigimod while having an MG-ADL score <5, i.e. clinically well controlled. The Company considers it appropriate to not include this type of discontinuation for IVIg in a scenario where IVIg time on treatment is based on efgartigimod discontinuation data. In this scenario (Scenario 3), a ToT analysis was conducted on efgartigimod observations from ADAPT and ADAPT+, censoring patients that had an MG-ADL score <5 at treatment discontinuation. Details on the method of this analysis and the resulting ToT curve applied to IVIg are provided in Appendix A. An additional scenario analysis (Scenario 5) has been provided to meet the Committee's request without refinement, which equates time on treatment but does not censor patients with controlled symptoms.

3. Parameters related to IVIg use, efficacy and dosing

The Committee has stated that IVIg use of 43.8% in the target patient population was deemed potentially plausible, as the upper end of the range. It is important to state that this figure was collected during EAMS from patients in UK clinical practice that completely align with the target patient population, so it is a reliable indication of real-world usage in a matched population. The Company does not agree that the level of IVIg usage agreed upon is the "upper bound of a plausible range". The previous Company submission presented scenarios using the upper bound estimate from the Delphi panel and the lower bound estimate from the NHSE commissioning database. These parameters are explored in sensitivity analysis (Scenarios 8 and 9) using the revised base case model.

IVIg efficacy in the model was derived via a network meta-analysis (NMA) of the efficacy of maintenance IVIg, which included two relevant randomised controlled trials. The validity of

this method was supported by both the EAG and Committee in the absence of direct head-to-head data. The results of the NMA showed that efgartigimod achieved a reduction in the MG-ADL from baseline that is greater than the reduction achieved with IVIg, and the difference was significant. The results of the NMA were then used to recalibrate the health-state transitions observed in the placebo arm of ADAPT to define the additional benefit of IVIg in the model. An anchored matching-adjusted indirect comparison (MAIC) was conducted to adjust for differences in patient characteristics between the identified studies, which also showed that patients receiving efgartigimod reduced MG-ADL score from baseline, which is greater than the reduction achieved with IVIg. To meet the Committee's request, two scenarios (Scenarios 6 and 7) have been provided where the IVIg efficacy is informed by an MAIC of each available source of IVIg effectiveness.

The Committee has also requested that a scenario be provided where the frequency of IVIg administration is informed by the expert elicitation conducted by the Company on IVIg dosing. The Company confirm that the dosing frequency assumptions applied in the base case model are based on the NHSE IVIg Commissioning Framework[2], the UK ABN gMG guidelines,[3] and expert elicitation. The dosing schedule of 1g/kg IVIg every 4 weeks was supported by the most frequently cited treatment protocol elicited from gMG clinical experts. The studies used to inform the efficacy for maintenance IVIg in the model utilise a higher dosing frequency (i.e. 1g/kg every 3 weeks), which is likely conservative. Scenarios (Scenarios 10 and 11) exploring different assumptions on efficacy and dose have been applied to the new base case.

Overview and results of the updated base case model

Table 2 outlines the Company's base case model assumptions and the revised base case analysis results are provided in Table 3 below. This base case model is aligned with the previous model structure and core assumptions, with additional changes to address the Committee requests.

Table 2 Assumptions applied in the Company's revised base case analysis

Parameter	Description of the assumption applied in the Company's analysis
Population characteristics	Derived from ADAPT
Health-state utilities	ADAPT MMRM, no treatment covariate
Modelling of effect	Placebo effect maintained beyond cycle 4 in conventional therapy cohort and post-discontinuation of IVIg and efgartigimod
Efgartigimod formulation	80% SC, 20% IV
Efgartigimod administration	SC: 100% in hospital for the first 5 infusions, then 80% at home IV: 50% at home and 50% in hospital
Caregiver disutility	Not included
Cost of corticosteroid related complications	Costs were included for intolerable adverse events in MG patients reported in Lee et al. (2018).[4] As requested by the EAG, the costs were based on the weighted average by frequency of the NHS reference costs.
Comparators	Established clinical management, which includes conventional therapy and maintenance IVIg treatment, modelled in separate engines
IVIg use in ECM	43.8% IVIg – from EAMS[1]
IVIg effect	NMA vs Wolfe[5] and NCT02473952[6]

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

IVIg discontinuation	• Initial non-responders' discontinuation of 19.5% was based on the literature and validated with clinical experts. • The per-cycle probability of unplanned discontinuations was based on the reconstructed ToT function from pooled studies identified in the literature. The Exponential parametric curve was selected, in line with efgartigimod ToT.
IVIg dosing frequency	1g/kg every 4 weeks
Treatments post-efgartigimod discontinuation	Maintenance IVIg treatment was included for 37.7% of the cohort with MG-ADL>5 at discontinuation. This percentage excludes patients who previously had no clinical response to IVIg. The cohort not receiving maintenance IVIg was assumed to receive conventional therapy.
Treatments post-IVIg discontinuation	Conventional treatment only.
Maintenance IVIg non-responders post-efgartigimod discontinuation	The cohort receiving maintenance IVIg post-efgartigimod had a higher initial non-responder discontinuation rate (x2) than the IVIg cohort in the ECM arm.
Efgartigimod PAS	[redacted]
IVIg commercial discount	[redacted]The Company is aware that there is a commercial discount in place for IVIg. Based on a range of sources explored, the Company estimated a commercial discount for IVIg of [redacted] and this has been included in the revised base case and can be adjusted in the model as required.

Abbreviations: EAG – External Assessment Group; EAMS – Early Access to Medicines Scheme, IV – intravenous, IVIg – intravenous immunoglobulin, MG – myasthenia gravis, MG-ADL – Myasthenia Gravis Activities for Daily Living, MMRM – mixed model repeated measures, NHS – National Health Service, NMA – network meta-analysis, PAS – Patient Access Scheme, SC – subcutaneous,

Table 3 Revised model base case analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,174
Established clinical management	[redacted]	[redacted]	[redacted]				

Abbreviations: LYG – life years gained, QALY – Quality Adjusted Life Year, ICER – incremental cost-effectiveness ratio

The table of results above demonstrates that despite the most appropriate implementation of IVIg use following discontinuation of treatment with efgartigimod, efgartigimod remains a cost-effective use of NHS resources with an ICER of £21,174/QALY when the PAS is [redacted].

Some parameters have been excluded from the model to reduce uncertainty, although they are plausible when considered individually.

For example, it has been recognised that gMG has a significant effect on carers' quality of life. Adding caregiver disutility to the base case model would substantially reduce the resulting ICER, but the Committee have previously requested that caregiver disutility be considered more qualitatively based on the available evidence. There are also important adverse events associated with the use of IVIg in some cases, which have conservatively

been excluded from the model. The regular use of PLEX as a maintenance treatment, as opposed to a rescue therapy, has not been included in either arm of the base case analysis, given the uncertainty surrounding its clinical effects and regional variations in access. Excluding the use of PLEX in the ECM arm of the model, which would account for an additional 14% of the total cohort as per EAMS data[1], further underestimates the cost associated with ECM.

In line with the Committee's request, the Company have included a treatment sequence for comparison in the base case model. Although this is in line with NICE methods, the Company notes that this type of comparison, whereby the innovative treatment under appraisal is sequenced with the old treatment being replaced, is not always employed in NICE evaluations, which further underlines that the model is conservative.

Scenario analyses

Table 4 below provides an overview and brief description of the company's exploration of various scenario analyses.

Table 4 Results from the scenario analyses conducted by the Company

	Scenario description	Efgartigimod vs established clinical management		
		Incremental cost, £	Incremental QALYs	ICER £/QALY
0	Revised base case	[redacted]	[redacted]	21,174
1	Multiplier applied to non-responders % for the cohort receiving maintenance IVIg post efgartigimod discontinuation = 1.5	[redacted]	[redacted]	54,800
2	Multiplier applied to non-responders % for the cohort receiving maintenance IVIg post efgartigimod discontinuation = 3	[redacted]	[redacted]	Dominant
3	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod after censoring for patients discontinuing with MG-ADL<5. PLEX is applied post-IVIg discontinuation and also post-efgartigimod for the cohort not receiving IVIg because previously did not respond to it.	[redacted]	[redacted]	88,164
4	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod after censoring for patients discontinuing with MG-ADL<5. PLEX not included.	[redacted]	[redacted]	252,751

Summary of additional evidence

5	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod. PLEX not included.	[redacted]	[redacted]	375,457
6	The effect in IVIg cohort was based on the MAIC vs NCT02473952[6]	[redacted]	[redacted]	30,179
7	The effect in IVIg cohort was based on the MAIC vs Wolfe et al. 2002[5]	[redacted]	[redacted]	20,071
8	Maintenance IVIg use in ECM arm: 69.17% based on Delphi Panel	[redacted]	[redacted]	dominant
9	Maintenance IVIg use in ECM arm: [redacted] based on NHS limited data (approximation)	[redacted]	[redacted]	237,040
10	Maintenance IVIg dosing regimen: 1g/kg administered every 3 weeks	[redacted]	[redacted]	dominant
11	Maintenance IVIg dosing regimen: based on a distribution of the cohort across dosing frequency alternatives from interviews with 6 gMG clinical experts	[redacted]	[redacted]	73,951

Abbreviations: ECM – established clinical management; gMG – generalised myasthenia gravis; ICER – incremental cost-effectiveness ratio, IVIg – intravenous immunoglobulin, MAIC – Matching-adjusted indirect comparison, MG-ADL – Myasthenia Gravis Activities of Daily Living, NHS – National Health Service, PLEX – plasma exchange; QALY – Quality Adjusted Life Year

Comparison of efgartigimod and IVIg

IVIg is not an MHRA-approved treatment for gMG, and it has not been subject to the rigor of a HTA process. The robust effectiveness of IVIg is not proven in this indication as a maintenance therapy, and it is only used due to the absence of other alternatives in current clinical practice. IV and SC efgartigimod are MHRA-approved for treating gMG and have demonstrated significantly greater effectiveness than established clinical management, including IVIg. Efgartigimod can be administered in an outpatient setting and ultimately given at home by self-administration, which both reduces the utilisation of NHS resources for in-patient treatment as well as significantly improving the patient's quality of life.

The Company is committed to the significant financing a nurse-led homecare service for all efgartigimod patients, along with training for self-administration as required. The ongoing development of a pre-filled syringe formulation, expected in 2025, will provide additional advantages for patients. The model does not fully capture these benefits, highlighting that the approach used in the revised base case analysis is balanced.

Clinical experts have highlighted the disparity in clinical practice across different treatment centres and explained that this is driven in part by supply constraints for maintenance IVIg and access constraints for PLEX. Therefore, efgartigimod can aid in the standardisation of clinical practice for patients with refractory gMG. To date efgartigimod has not been shown to have important serious adverse events, which are seen in some patients who receive IVIg.

The costs to the healthcare system and HRQoL impacts of these AEs have conservatively not been included in the base case model.

Considering the resulting annual costs of efgartigimod treatment relative to the costs of current practice, efgartigimod is expected to have only a small impact on NHS budgets by displacing the chronic use of rescue treatments.

The annual cost of IVIg and efgartigimod per patient becomes similar when the commercial arrangements proposed are taken into account. Therefore, if efgartigimod was not made available to patients, this would result in a situation where the NHS continues to fund a therapy which is not licensed for gMG and not assessed for cost-effectiveness, at a similar cost to efgartigimod, an innovative licensed therapy for gMG that has demonstrated clinical and cost effectiveness.

Conclusion

The Company recognises the importance of this exchange, has acknowledged the remaining areas of uncertainty highlighted by the Committee and conducted all the requested analyses.

In response to the Committee's request, a revised base case has been provided, which explores the full pathway of care and applies the most realistic assumptions for parameters where uncertainty exists, in line with the best available evidence.

Current established clinical management consists of rescue treatments such as IVIg and PLEX, which are used as a maintenance therapy in gMG outside of their licence and have a substantial budget impact to the NHS with uncertain proven benefit, rare but serious adverse events, potential supply issues and inconsistent accessibility. The use of efgartigimod has the potential to standardise clinical practice for refractory gMG and offer significant benefit for patients and the healthcare system.

As demonstrated throughout this submission, there are benefits associated with efgartigimod that are not fully represented in the economic analysis. The revised base case is conservative and, coupled with an improved commercial offer, demonstrates that efgartigimod can be considered a cost-effective use of NHS resources in an area of significant unmet medical need in patients with refractory gMG.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

New evidence submission

13 June 2024

File name	Version	Contains confidential information	Date
Efgartigimod technical appendix post-ACM3 [redacted]		Yes	13 June 2024

Abbreviations

DG	Draft Guidance
EAG	Evidence Assessment Group
EAMS	Early Access to Medicines Scheme
ECM	established clinical management
gMG	generalised myasthenia gravis
ICER	incremental cost-effectiveness ratio
IVIg	intravenous immunoglobin
ITC	indirect treatment comparison
KM	Kaplan-Meier
LYG	life-years gained
MG-ADL	Myasthenia Gravis Activities of Daily Living
MG	myasthenia gravis
NA	not applicable
NHS	National Health Service
PAS	patient access scheme
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RDI	relative dose intensity
ToT	Time on Treatment

Contents

List of tables

List of figures

Appendix A Long-term discontinuation from maintenance IVIg treatment

To address requests from the NICE Committee, scenarios have been included where the long-term discontinuation of efgartigimod derived from efgartigimod observations in ADAPT[1] and ADAPT+[2] was applied to the cohort on maintenance IVIg treatment. The results are presented in Appendix B of this document. The Company believes the rate of discontinuation extrapolated from efgartigimod observations in ADAPT and ADAPT+ is not representative of discontinuations from maintenance IVIg treatment. This is because some of the discontinuations observed for efgartigimod occurred in patients with an MG-ADL score lower than 5, suggesting the reason for discontinuation may have been improvement in the condition, while there is no evidence to support this type of discontinuation in people receiving maintenance IVIg.

The Company therefore also ran a more plausible scenario analysis using discontinuation data from ADAPT[1] and ADAPT+[2], where patients who discontinued efgartigimod with an MG-ADL<5 (N=5) were censored. Other than this additional censoring, the same method used to derive the Kaplan–Meier (KM) curve of the time-on-treatment (ToT) for the efgartigimod arm used:

- The time between the date of first treatment exposure in ADAPT and the date of the last observation in either ADAPT or ADAPT+ was calculated for each patient and used to produce a KM curve of the ToT.
- Only the AChR+ patients in the efgartigimod arm of ADAPT were considered
- The observations of patients who did not respond to two consecutive cycles were not considered to avoid double counting of patients discontinuing in the model because of no response (as previously described).
- Patients who discontinued because they moved to the subcutaneous trial of efgartigimod (Study 131-2002)[3] were censored.

Parametric fitting of KM curve was performed to extrapolate beyond the observation period using the following distributions: Exponential, Weibull, Log-Normal, Log-Logistic, Gompertz, and Gamma (Figure 1). The parametric function was pre-selected based on Akaike information criterion/Bayesian information criterion (AIC/BIC), visual inspection, and internal and external validity. The Gompertz was the parametric function with the best fit (lowest AIC/BIM values) and it closely overlaps with the Exponential, which was the best fit curve to the KM of ToT applied in the efgartigimod arm. Table 1 summarises the AIC/BIC values associated with each parametric function. The Gompertz curve was therefore selected to estimate the per-cycle probability of discontinuing maintenance IVIg treatment applied a scenario analysis. Figure 2 presents the selected parametric curves extrapolated from the ToT KM with and without censoring for patients with MG-ADL<5 at discontinuation. The median ToT in efgartigimod patients was [redacted] years and the median ToT in efgartigimod patients after censoring for MG-ADL<5 discontinuers was [redacted] years (Figure 2).

Figure 1. Observed ToT data from ADAPT and ADAPT+ censoring for patients with MG-ADL<5 at discontinuation, and parametric extrapolations

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

Table 1. AIC/BIC values of each parametric function

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Gamma
AIC+BIC	133.28	239.40	136.62	136.33	130.65	136.67
AIC	65.65	117.70	66.34	66.19	64.34	66.36
BIC	67.62	121.70	70.28	70.13	66.31	70.30

AIC, Akaike information criterion; BIC, Bayesian information criterion

Figure 2. Best-fit parametric curves extrapolated from observed ToT in ADAPT and ADAPT+ with and without censoring for patients with MG-ADL<5 at discontinuation

MG-ADL, Myasthenia Gravis Activities of Daily Living; ToT, Time on Treatment
Source: argenx, data derived from ADAPT and ADAPT+

Appendix B Economic analyses

B.1 Overview

The revised cost-effectiveness model base case incorporates the following changes:

- Cost of corticosteroid related complications: These were based on the weighted average by frequency of the National Health Service (NHS) reference costs for only intolerable adverse events in myasthenia gravis (MG) patients reported in the study by Lee et al. 2018,[4] per EAG request.
- Maintenance intravenous immunoglobulin (IVIg) post-efgartigimod discontinuation: IVIg treatment for patients who discontinued efgartigimod was modelled via a parallel engine. In line with data used from the EAMS (Dionísio et al. 2024)[5] programme to apply assumptions in the IVIg comparator arm, a proportion of the cohort with a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of ≥5 was assigned to start IVIg treatment post-efgartigimod discontinuation. Maintenance IVIg treatment was not assigned to the cohort previously treated with IVIg and not having responded to treatment.
- Commercial discount for IVIg: The Company is aware that there is a commercial discount in place for IVIg. Based on a range of sources explored, the Company estimated a commercial discount for IVIg of [redacted] The revised base case therefore includes the price of IVIg discounted by [redacted]

Further details of these changes are:

- The costs of corticosteroid related complications were updated based on the suggested tariffs by the EAG. The resulting cost of systemic corticosteroid related intolerable complications was £368.80 per cycle.
- The use of maintenance IVIg following efgartigimod treatment discontinuation was modelled through the development of a parallel model engine, with tunnel states to allow the appropriate simulation of costs and effects of maintenance IVIg from the cycle they start treatment over the time-horizon of the analysis (in line with the approach used in the maintenance IVIg comparator arm):
    i. At discontinuation of efgartigimod treatment, maintenance IVIg treatment is started in 43.8% (EAMS, Dionísio et al. 2024)[5] of the MG-ADL≥5 cohort, excluding patients who previously received maintenance IVIg treatment and did not respond:
        - The proportion of patients who previously received IVIg maintenance treatment (at any point in time) was obtained from EAMS and it is equal to 70.8%.
        - The percentage of maintenance IVIg non-responders reported in the identified literature was 19.5%, as detailed in Appendix B of the summary of new evidence post draft guidance 2 (DG2).
        - In accordance with this, 13.7% (70.5% multiplied by 19.5%) of the post-efgartigimod cohort is assumed not to restart IVIg.
        - After excluding the proportion of the cohort who previously did not respond to treatment with maintenance IVIg (13.7%), the cohort starting maintenance IVIg treatment post-efgartigimod discontinuation was 37.7% (43.8% IVIg use from EAMS multiplied by 86.3%).
    ii. The cohort on IVIg post-efgartigimod discontinuation transitioned between health-states based on the probabilities derived from the indirect treatment comparison (ITC) via network meta-analysis between efgartigimod and maintenance IVIg. Following the same approach as in the IVIg comparator arm, the estimates of IVIg comparative efficacy in terms of MG-ADL change from baseline obtained from the ITC were used to recalibrate the health-states transitions observed in the placebo

arm of ADAPT during each 4-week cycle starting from baseline to Week 16. Beyond cycle four on IVIg, the model assumes the effect is maintained for as long as the cohort remains on IVIg treatment. Full details on the estimation of the transition probabilities in the IVIg cohort are included in Appendix D of the summary of new evidence post DG2, previously submitted.

iii. Both discontinuations due to lack of response and due to unplanned reasons were modelled for the cohort starting IVIg treatment following efgartigimod, in line with how discontinuations are modelled in the IVIg comparator arm. Full detail on the estimation of both the percentage of discontinuation due to lack of response and the cycle probability of unplanned discontinuation is provided in Appendix B of the summary of new evidence post DG2, previously submitted. It is reasonable to assume, as subsequently validated with clinical experts, that patients discontinuing efgartigimod in the cost effectiveness model are a heavily pre-treated, refractory population and would therefore likely have worse outcomes to any active adjunctive therapy introduced at this point. Therefore, the percentage of non-responders in the cohort starting maintenance IVIg after discontinuing efgartigimod was estimated by applying a multiplier of 2 to the proportion of non-responders in IVIg arm, in recognition of the poorer outcomes anticipated in a highly pre-treated, refractory patients.

iv. Patients discontinuing efgartigimod with a maintained low level of symptom activity (MG-ADL < 5) are assumed to not receive IVIg, as their symptoms are sufficiently controlled with the mix of conventional treatments. Therefore, they would not require adjunct active treatment with maintenance IVIg while in this controlled state. This assumption has been confirmed by clinical experts.

v. The cohort discontinuing maintenance IVIg following efgartigimod treatment is assumed to receive conventional therapy and therefore moves to the parallel engine where costs and effects of conventional therapy are applied.

The results of the revised cost-effectiveness model base case analysis are presented in Table 2. The results are based on efgartigimod list price with a [redacted] PAS.

Table 2. Revised model base-case analysis with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER incr (£/QALY)
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,174
ECM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

LYG – life years gained, QALY – Quality Adjusted Life Year, ICER – incremental cost-effectiveness ratio, incr - incremental

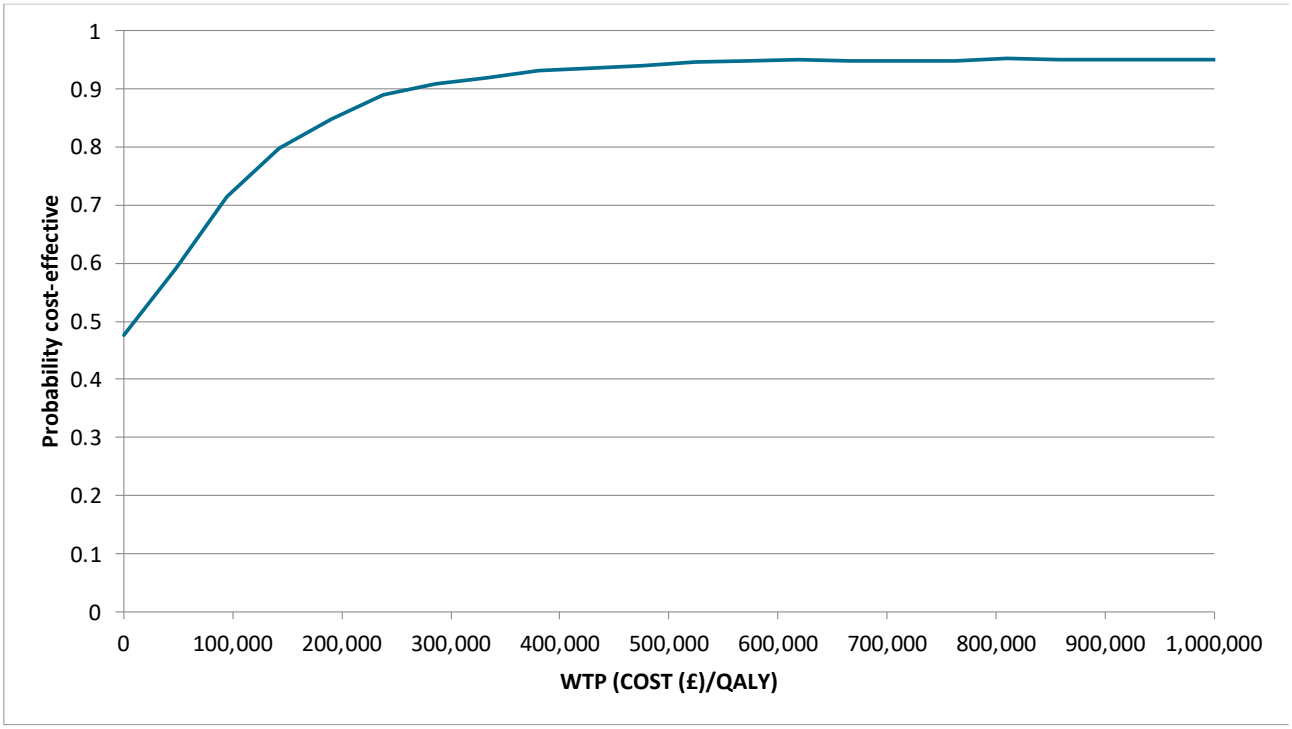
B.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to assess the robustness of the model to parameter uncertainty. In the PSA, 1,000 simulations were performed in which model parameters were varied simultaneously by sampling at random from hypothetical distributions. The distributions used for each variable in the PSA are reported in the model. The results of the PSA are presented in Figure 3 and

Figure 4.

Figure 3. Incremental cost and QALY cloud in the cost-effectiveness plane with PAS

Figure 4. Cost-effectiveness acceptability curve with PAS



B.3 Deterministic sensitivity analysis

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way sensitivity analyses was performed. The results of the deterministic sensitivity analysis are presented in Figure 5, Table 3 and IVIg – intravenous immunoglobulin, ECM – established clinical management, NA – not available, kg – kilograms, RDI – relative dose intensity, MG-ADL – Myasthenia Gravis Activities of Daily Living

Table 4.

Figure 5. Results of the one-way sensitivity analysis with PAS

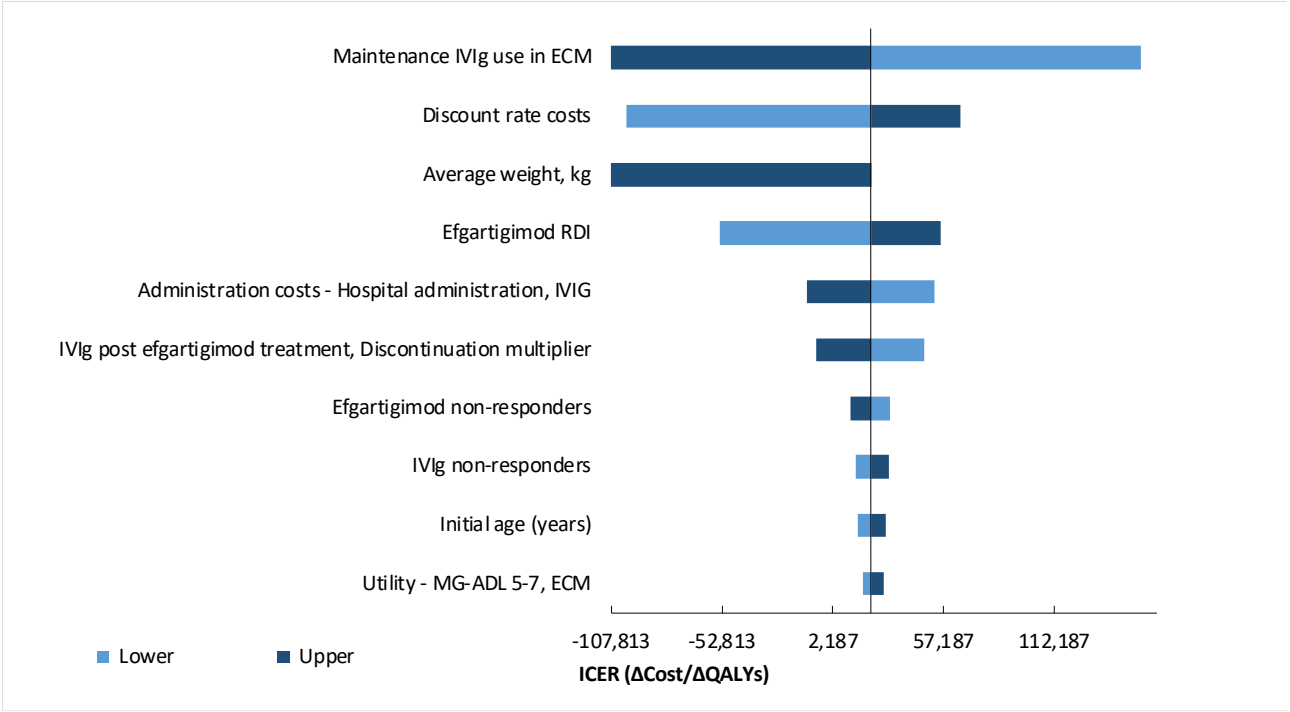


Table 3. Percentage change in base case results with PAS following lower and upper variation in the 10 most influential parameters

Parameter	Lower value	Upper value
Maintenance IVIg use in ECM	635%	NA
Discount rate costs	NA	209%
Average weight, kg	0%	NA
Efgartigimod RDI	NA	163%
Administration costs - Hospital administration, IVIG	149%	NA
IVIg post efgartigimod treatment, Discontinuation multiplier	125%	NA
Efgartigimod non-responders	45%	-49%
IVIg non-responders	-35%	43%
Initial age (years)	-31%	35%
Utility - MG-ADL 5-7, ECM	-19%	30%

IVIg – intravenous immunoglobulin, ECM – established clinical management, NA – not available, kg – kilograms, RDI – relative dose intensity, MG-ADL – Myasthenia Gravis Activities of Daily Living

Table 4. Detailed results of the one-way sensitivity analysis with PAS

Parameter	ICER (£/QALY)	
	Lower	Upper
Maintenance IVIg use in ECM	155,548	Dominant
Discount rate costs	Dominant	65,498
Average weight, kg	21,167	Dominant
Efgartigimod RDI	Dominant	55,726
Administration costs - Hospital administration, IVIG	52,730	Dominant

IVIg post efgartigimod treatment, Discontinuation multiplier	47,605	Dominant
Efgartigimod non-responders	30,681	10,806
IVIg non-responders	13,853	30,314
Initial age (years)	14,705	28,533
Utility - MG-ADL 5-7, ECM	17,181	27,584

IVIg – intravenous immunoglobulin, ECM – established clinical management, kg – kilograms, RDI – relative dose intensity, MG-ADL – Myasthenia Gravis Activities of Daily Living

B.4 Scenario analysis

Results of the scenario analyses are shown in Table 5. As pointed out by a member of the NICE Committee during ACM3, it is expected that the cohort on the IVIg arm would remain on treatment longer considering the limited treatment alternatives available. Nevertheless, to address the request from the Committee, the Company included scenario analyses where the IVIg arm is applied the per-cycle discontinuation probabilities derived from efgartigimod observations in ADAPT and ADAPT+:

- In scenario 3, the probability of discontinuation applied to the IVIg cohort was extrapolated from efgartigimod observations in ADAPT and ADAPT+ after censoring for patients with an MG-ADL<5 at discontinuation, as detailed in Appendix A. In this scenario, the cohort discontinuing IVIg treatment in MG-ADL≥5 health-states was assumed to receive maintenance PLEX, to adequately reflect a scenario of the clinical practice where patients discontinue maintenance IVIg at a large rate. Equally, PLEX was also applied to the cohort excluded from IVIg treatment post-efgartigimod discontinuation, because they previously did not respond to treatment with maintenance IVIg. The method used to apply efficacy and discontinuation for maintenance PLEX was the same method used to model maintenance IVIg post-efgartigimod discontinuation. The Company believes that the results of this scenario would be most representative of the real-world if a higher discontinuation rate was to be observed for maintenance IVIg treatment.
- In scenario 4, the probability of discontinuation applied to the IVIg cohort is the same as in scenario 3. However, this scenario does not include maintenance PLEX after IVIg and efgartigimod discontinuation.
- In scenario 5, the probability of discontinuation applied to the IVIg cohort was extrapolated from efgartigimod observations in ADAPT and ADAPT+ without censoring for patients with an MG-ADL<5 at discontinuation, as modelled for the efgartigimod arm. As scenario 4, this scenario does not include maintenance PLEX after IVIg and efgartigimod discontinuation.

Scenarios 6-11 were included to address the Committee requests to test the impact of alternative data sources available on maintenance IVIg efficacy, use in ECM and dosing schedule, on the revised base case. A full description of the methods for each of these scenarios was provided in Appendix D of the summary of new evidence post DG2, previously submitted.

Scenario 9 was included in response to NICE request to explore a lowest bound for the use of maintenance IVIg in ECM. Nevertheless, the Company believes this scenario is not representative of current clinical practice, given the large uncertainty on the data informing this estimate. In fact, an NHSE commissioning expert confirmed to the Company that these data were obtained from clinical experts consulted for the appraisal, rather than from the National IVIg database. The percentage of IVIg use obtained from prior treatment in EAMS patients is expected to be more robust evidence of real-world IVIg use in gMG patients with active disease despite conventional therapy.

Finally, Scenarios 12 was included to reflect the impact of efgartigimod in resolving some of the burden on caregivers associated with caring relatives with refractory gMG. The Company believes that NICE should consider the burden on caregivers within the scope of this decision-making.

Table 5. Scenario analyses for efgartigimod vs established clinical management with PAS

	Scenario description	Efgartigimod vs established clinical management		
		Incremental Cost, £	Incremental QALYs	ICER £/QALY
0	Revised base case	[redacted]	[redacted]	21,174
1	Multiplier applied to non-responders % for the cohort receiving maintenance IVIg post efgartigimod discontinuation = 1.5	[redacted]	[redacted]	54,800
2	Multiplier applied to non-responders % for the cohort receiving maintenance IVIg post efgartigimod discontinuation = 3	[redacted]	[redacted]	Dominant
3	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod after censoring for patients discontinuing with MG-ADL<5. PLEX is applied post-IVIg discontinuation and also post-efgartigimod for the cohort not receiving IVIg because previously did not respond to it.	[redacted]	[redacted]	88,164
4	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod after censoring for patients discontinuing with MG-ADL<5. PLEX not included	[redacted]	[redacted]	252,751
5	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod. PLEX not included	[redacted]	[redacted]	375,457
6	The effect in IVIg cohort was based on the MAIC vs NCT02473952[6]	[redacted]	[redacted]	30,179
7	The effect in IVIg cohort was based on the MAIC vs Wolfe et al. 2002[7]	[redacted]	[redacted]	20,071
8	Maintenance IVIg use in ECM arm: 69.17% based on Delphi Panel	[redacted]	[redacted]	dominant
9	Maintenance IVIg use in ECM arm: [redacted] based on NHS limited data (approximation)	[redacted]	[redacted]	237,040
10	Maintenance IVIg dosing regimen: 1g/kg administered every 3 weeks (Wolfe et al 2002 and NCT02473952)[6]	[redacted]	[redacted]	dominant
11	Maintenance IVIg dosing regimen: based on distribution of cohort between dose and frequency alternatives from interview with 6 gMG clinical experts	[redacted]	[redacted]	73,951
12	Caregiver disutilities are included based on gMG Caregiver Burden Study	[redacted]	[redacted]	11,839

Results include a confidential PAS of [redacted]
Abbreviations: ECM – established clinical management; gMG – generalised myasthenia gravis; ICER – incremental cost-effectiveness ratio, IVIg – intravenous immunoglobulin, MAIC – Matching-adjusted indirect comparison, MG-ADL – Myasthenia Gravis Activities of Daily Living, NHS – National Health Service, PLEX – plasma exchange; QALY – Quality Adjusted Life Year

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University of Southampton

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

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Evidence Review Group's critique of the company's response to the NICE Appraisal Committee's request for additional cost-effectiveness analyses after the third NICE Appraisal Committee meeting.

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Date completed	03 July 2024

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

CIC	Commercial in confidence
EAG	External Assessment Group
EAMS	Early Access to Medicines Scheme
ECM	Established clinical management
gMG	Generalised myasthenia gravis
ICER	Incremental cost-effectiveness ratio
IVIg	Intravenous immunoglobulin
MG-ADL	Myasthenia Gravis Activities of Daily Living scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient access scheme
PLEX	Plasma exchange
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year

1 INTRODUCTION

This document is the External Assessment Group's (EAG's) critique of the response by the company, argenx, to the NICE Appraisal Committee's request for additional cost-effectiveness analyses on model parameters for which residual uncertainty remained after the third NICE Appraisal Committee meeting (ACM3) to evaluate efgartigimod for treating generalised myasthenia gravis [ID4003]. The EAG received the company's documents and revised model on 14th June 2024.

The company's response to the NICE Appraisal Committee's request consists of the following items:

- A summary of new evidence and additional analyses:
  - Analysis 1: Usage of IVIg in patients who discontinue treatment with efgartigimod
  - Analysis 2: Difference in time on treatment between efgartigimod and IVIg
  - Analysis 3: Parameters related to IVIg use, efficacy and dosing

  The new evidence document also contains an overview and the results of the company's revised base case and scenario analyses
- Appendices A and B in support of the company's response
- Appendix C which is the company confidential information checklist
- The company's revised economic model

In this critique, we present the following:

- Our critique of the company's response to NICE's draft guidance 3 on efgartigimod for treating generalised myasthenia gravis (gMG) and the company's new evidence (Section 2)
- A validation of the results of the company's revised cost-effectiveness analysis (Section 3)
- The results of the EAG base case and scenario analyses (Section 4)

2 CRITIQUE OF THE COMPANY'S RESPONSE

2.1 IVIg use in both arms.

The committee preferred patients who discontinued efgartigimod to have the option of treatment with IVIg.

The company incorporated the use of maintenance IVIg following efgartigimod treatment discontinuation by developing a parallel model engine. In addition, the company changed some of their assumptions relating to the proportions starting IVIg after discontinuing efgartigimod.

The assumptions incorporated for IVIg use in those patients who discontinue efgartigimod are:

- Patients with MG-ADL score < 5 are assumed not to have maintenance IVIg as these patients' symptoms are sufficiently controlled with conventional treatments;
- Higher initial discontinuation rate of 39% vs 19.5% by applying a multiplier of 2 to the initial discontinuation rate as patients discontinuing efgartigimod are a highly pre-treated refractory population and therefore likely to have worse outcomes to any active adjunctive therapy;
- A lower proportion of patients restart IVIg (37.7% vs 43.8%), as 13.7% of the post-efgartigimod cohort are assumed to not restart IVIg (see calculation below).

EAG considers it reasonable that patients with a MG-ADL < 5 would not have maintenance IVIg.

Clinical advice to the company was that initial discontinuations from IVIg would be higher in patients who had first received efgartigimod treatment, compared with patients who had not received prior efgartigimod treatment (Company's summary of new evidence p.7). The company adds that the magnitude of this difference is unclear and that there is no data available for this cohort.

The EAG are uncertain why more patients would discontinue IVIg if they had received prior efgartigimod treatment. It is our understanding that efgartigimod would not detrimentally affect the action of later IVIg therapy. In addition, the two treatments do not have the same mode of action, so not responding to efgartigimod is not an indication that a patient would not respond to IVIg treatment. We consider that more clinical advice on this matter would be beneficial. We explore setting the proportion of IVIg non-responders for the cohort receiving

maintenance IVIg post efgartigimod to be the same as that used elsewhere in the model i.e. 19.5% (scenario 1, Table 4).

The company estimates the cohort starting maintenance IVIg treatment post-efgartigimod discontinuation to be 37.7%. This calculation is described in Appendix B.1, and is summarised here:

- The proportion of patients who previously received IVIg maintenance treatment (at any point in time) from EAMS: 70.5%
- The percentage of maintenance IVIg non-responders reported in the literature: 19.5%
- The post-efgartigimod cohort assumed to not restart IVIg (70.5% multiplied by 19.5%): 13.7%
- The cohort starting maintenance IVIg treatment post-efgartigimod discontinuation (43.8% IVIg use from EAMS multiplied by 100% minus 13.7% i.e. 86.3%): 37.7%

The EAG considers the 43.8% of the EAMS cohort on maintenance IVIg may already exclude the patients who did not respond to chronic IVIg therapy and so we conduct a scenario where 43.8% of patients start maintenance IVIg treatment post-efgartigimod discontinuation (scenario 2, Table 4). Further clinical advice on this matter would be helpful.

2.2 Time on treatment for IVIg and efgartigimod.

While there remains uncertainty, the committee did not consider that the time on treatment for efgartigimod and IVIg would be markedly different and requested a scenario analysis where time on treatment was the same for efgartigimod and IVIg.

In their base case analysis, time on treatment was longer for IVIg, as with the previous version of the company model and the company provided a scenario using the same discontinuation rate for IVIg as for efgartigimod (scenario 5). The results are very sensitive to this assumption (ICER increases to £375,457 per QALY). In the company base case, the time on treatment for efgartigimod is 4.5 years and for IVIg is 10.6 years. In the company scenario analysis with the same time on treatment as efgartigimod, the time on treatment for IVIg is 4.4 years. (Scenario with censoring MG-ADL <5 has a time on treatment of 6.3 years).

The EAG is unclear on correct time on treatment for IVIg, as the evidence available is poor. Further clinical advice on this matter would be helpful.

2.3 New confidential PAS for efgartigimod.

The company increased their confidential PAS from [redacted] to [redacted]

2.4 Other changes to the model.

The company also made the following changes to the model:

- Correcting the costs of corticosteroid related complications as suggested by the EAG at ACM3.
- Including a commercial discount for IVIg of [redacted] The company estimated what they considered the commercial discount to be. As advised by NICE, in the EAG analyses we have removed the estimated discount for IVIg and use the list price. The EAG provide the model results with the actual confidential discount in a confidential addendum.

3 VALIDATION OF THE RESULTS OF THE COMPANY'S ADDITIONAL COST-EFFECTIVENESS ANALYSES

3.1 Company's revised base case cost-effectiveness results

The company reports their revised base case ICER result in Tables 1 and 3 in their Summary of new evidence and in Appendix B.1 Table 2. The cumulative effect of the changes implemented by the company results in an ICER of £21,174 per QALY (Table 1). The EAG notes the company are including an estimated commercial discount of [redacted] for IVIg in their base case. We have removed this discount and recalculated their base case ICER (Table 1).

Table 1 Company revised model base case analysis with PAS

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company revised base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£21,174
	ECM	[redacted]	[redacted]	-	-	
Company revised base case, IVIg commercial discount removed	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	

Source: Partly reproduced from company Summary of evidence Table 1
ECM, established clinical management; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years

The EAG reviewed the company's revised model, including the implementation of costs and benefits for patients receiving IVIg in the efgartigimod post-discontinuation engine, and agree that the changes listed in the Appendices have been implemented appropriately. We were able replicate the changes made between the company's previous base case (seen at Committee meeting 3) and the company's current base case. The incremental results with the changes made to the model are shown in Table 2.

Table 2 Cumulative results for the company's changes to their original base case

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company base case at ACM3	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£14,110
	ECM	[redacted]	[redacted]	-	-	
Include costs and benefits of IVIg in efgartigimod post-discontinuation engine (parallel engine approach)	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£258,282
	ECM	[redacted]	[redacted]	-	-	
Use weighted average by frequency of the NHS reference costs for intolerable adverse events in MG patients reported in Lee et al. (2018).	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£262,536
	ECM	[redacted]	[redacted]	-	-	
Use PAS of [redacted] for efgartigimod	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	
Use commercial discount of [redacted] for IVIg	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£21,174
	ECM	[redacted]	[redacted]	-	-	
Company base case post-ACM3	**Efgartigimod**	[redacted]	[redacted]	[redacted]	[redacted]	**£21,174**
	ECM	[redacted]	[redacted]	**-**	**-**	

ACM3, Appraisal Committee Meeting 3; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; PAS, patient access scheme; QALYs, quality-adjusted life years

The company presents the results of their probabilistic sensitivity analysis (PSA) as a cost-effectiveness plane (Figure 3) and a cost-effectiveness acceptability curve (Figure 4) in Company new evidence submission Appendix B.2.

3.2 Company scenario analyses

The company also conducted scenario analyses on their revised base case (Company new evidence submission Appendix B.2, Table 5). Following ACM3, the Committee requested that IVIg use is modelled in both model arms of the economic model, and asked for a scenario where IVIg time on treatment is equal to efgartigimod time on treatment. The Committee also considered that equivalent time on treatment "should be the basis of an updated analysis"; the EAG notes that the company do not include this in their base case.

We have reproduced the company's scenario analyses below but have removed the estimated commercial discount for IVIg (Table 3).

Table 3 Scenario analyses for efgartigimod vs established clinical management, with PAS, using list price for IVIg

	Scenario description	Efgartigimod vs established clinical management		
		Incremental cost (£)	Incremental QALYs	ICER £/QALY
0	Revised base case, using list price for IVIg	[redacted]	[redacted]	Dominant
1	Multiplier applied to non-responders % for the cohort receiving maintenance IVIg post efgartigimod discontinuation = 1.5	[redacted]	[redacted]	Dominant
2	Multiplier applied to non-responders % for the cohort receiving maintenance IVIg post efgartigimod discontinuation = 3	[redacted]	[redacted]	Dominant
3	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod after censoring for patients discontinuing with MG-ADL<5. PLEX is applied post-IVIg discontinuation and also post-efgartigimod for the cohort not receiving IVIg because previously did not respond to it.	[redacted]	[redacted]	£39,311
4	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod after censoring for patients discontinuing with MG-ADL<5. PLEX not included	[redacted]	[redacted]	£207,142
5	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod. PLEX not included	[redacted]	[redacted]	£341,688
6	The effect in IVIg cohort was based on the MAIC vs NCT02473952	[redacted]	[redacted]	Dominant
7	The effect in IVIg cohort was based on the MAIC vs Wolfe et al. 2002[1]	[redacted]	[redacted]	Dominant
8	Maintenance IVIg use in ECM arm: [redacted] based on Delphi Panel	[redacted]	[redacted]	Dominant
9	Maintenance IVIg use in ECM arm: [redacted] based on NHS limited data (approximation)	[redacted]	[redacted]	£190,870
10	Maintenance IVIg dosing regimen: 1g/kg administered every 3 weeks (Wolfe et al. 2002[1] and NCT02473952)	[redacted]	[redacted]	Dominant
11	Maintenance IVIg dosing regimen: based on distribution of cohort between dose and frequency alternatives from interview with 6 gMG clinical experts	[redacted]	[redacted]	£10,254
12	Caregiver disutilities are included based on gMG Caregiver Burden Study	[redacted]	[redacted]	Dominant

Source: Partly reproduced from Company new evidence submission Appendix B.2, Table 5
Abbreviations: ECM, established clinical management; gMG, generalised myasthenia gravis; ICER, incremental cost-effectiveness ratio, IVIg, intravenous immunoglobulin, MAIC, Matching-adjusted indirect comparison, MG-ADL, Myasthenia Gravis Activities of Daily Living, NHS, National Health Service, PAS, patient access scheme, PLEX, plasma exchange; QALY, Quality Adjusted Life Year

4 EAG ANALYSES

4.1 EAG scenario analyses conducted on the company's revised base case

The EAG conducted additional scenario analyses to evaluate the uncertainty around the company's assumptions in their new base case (Table 4).

We explore setting the proportion of IVIg non-responders for the cohort receiving maintenance IVIg post efgartigimod to be the same as that used elsewhere in the model i.e. 19.5% (scenario 1, Table 4). We conduct a scenario where 43.8% of patients start maintenance IVIg treatment post-efgartigimod discontinuation (scenario 2, Table 4).

Table 4 EAG scenario analysis results using the company's revised base case, with PAS, using list price for IVIg

	Scenario description	Efgartigimod vs established clinical management		
		Incremental cost (£)	Incremental QALYs	ICER £/QALY
0	Revised base case, using list price for IVIg	[redacted]	[redacted]	Dominant
1	Multiplier applied to non-responders percentage for the cohort receiving maintenance IVIg post efgartigimod discontinuation = 1	[redacted]	[redacted]	£28,360
2	43.8% of patients receive IVIg in the cohort starting maintenance IVIg treatment post-efgartigimod discontinuation	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PAS, patient access scheme; QALY, Quality Adjusted Life Year

4.2 EAG's preferred assumptions

Based on the EAG's critique of the company's model (discussed in section 2) and the scenarios described in section 4.1, we have identified several aspects of the company's revised base case with which we disagree. Our preferred model assumptions are:

- Use the list price for IVIg,
- Use the original percentage for non-responders for the cohort receiving maintenance IVIg post efgartigimod discontinuation i.e. 19.5%,
- 43.8% of patients receive IVIg in the cohort starting maintenance IVIg treatment post-efgartigimod discontinuation.

The cumulative effect of these changes resulting in an ICER of £77,362 per QALY for the EAG base case (Table 5).

Table 5 Cumulative effect of the EAG's preferred model assumptions, efgartigimod versus ECM, with PAS, excluding estimated commercial discount for IVIg

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company base case, with list price for IVIg	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£21,174
	ECM	[redacted]	[redacted]	-	-	
+ Use the list price for IVIg	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ECM	[redacted]	[redacted]	-	-	
+ Multiplier applied to percentage of non-responders for the cohort receiving maintenance IVIg post efgartigimod discontinuation = 1	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£28,360
	ECM	[redacted]	[redacted]	-	-	
+ 43.8% of patients receive IVIg in the cohort starting maintenance IVIg treatment post-efgartigimod discontinuation	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£77,362
	ECM	[redacted]	[redacted]	-	-	
EAG base case	**Efgartigimod**	[redacted]	[redacted]	[redacted]	[redacted]	**£77,362**
	ECM	[redacted]	[redacted]	**-**	**-**	

ECM, established clinical management; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PAS, patient access scheme; PLEX, plasma exchange; QALYs, quality-adjusted life years

4.3 Scenario analyses conducted on the EAG's base case

The EAG conducted scenario analyses to evaluate the uncertainty around the assumptions in our base case (Table 6). The model is sensitive to all parameters.

Table 6 Scenario analyses for efgartigimod vs established clinical management, with PAS

	Scenario description	Efgartigimod vs established clinical management		
		Incremental cost (£)	Incremental QALYs	ICER £/QALY
0	EAG base case	[redacted]	[redacted]	£77,362

1	Multiplier applied to percentage of non-responders for the cohort receiving maintenance IVIg post efgartigimod discontinuation = 1.5	[redacted]	[redacted]	£35,804
2	Multiplier applied to percentage of non-responders for the cohort receiving maintenance IVIg post efgartigimod discontinuation = 3	[redacted]	[redacted]	Dominant
3	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod after censoring for patients discontinuing with MG-ADL<5. PLEX is applied post-IVIg discontinuation and also post-efgartigimod for the cohort not receiving IVIg because previously did not respond to it.	[redacted]	[redacted]	£75,181
4	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod after censoring for patients discontinuing with MG-ADL<5. PLEX not included	[redacted]	[redacted]	£284,397
5	Cycle probability of discontinuation in IVIg arm set equal to efgartigimod. PLEX not included	[redacted]	[redacted]	£395,957
6	The effect in IVIg cohort was based on the MAIC vs NCT02473952	[redacted]	[redacted]	£99,474
7	The effect in IVIg cohort was based on the MAIC vs Wolfe et al. 2002[1]	[redacted]	[redacted]	£74,653
8	Maintenance IVIg use in ECM arm: [redacted] based on Delphi Panel	[redacted]	[redacted]	Dominant
9	Maintenance IVIg use in ECM arm: [redacted] based on NHS limited data (approximation)	[redacted]	[redacted]	£370,890
10	Maintenance IVIg dosing regimen: 1g/kg administered every 3 weeks (Wolfe et al. 2002[1] and NCT02473952)	[redacted]	[redacted]	Dominant
11	Maintenance IVIg dosing regimen: based on distribution of cohort between dose and frequency alternatives from interview with 6 gMG clinical experts	[redacted]	[redacted]	£122,530
12	Caregiver disutilities are included based on gMG Caregiver Burden Study	[redacted]	[redacted]	£43,202

Source: Partly reproduced from Company new evidence submission Appendix B.2, Table 5
Abbreviations: ECM, established clinical management; gMG, generalised myasthenia gravis; ICER, incremental cost-effectiveness ratio, IVIg, intravenous immunoglobulin, MAIC, Matching-adjusted indirect comparison, MG-ADL, Myasthenia Gravis Activities of Daily Living, NHS, National Health Service, PAS, patient access scheme, PLEX, plasma exchange; QALY, Quality Adjusted Life Year

5 EAG CONCLUSION

The company presented the results of their revised base case, which includes use of IVIg in both model arms (Table 1). The EAG have reviewed the revised model and conducted extra scenarios to explore the effect of the company's new assumptions (Table 4).

Without evidence to the contrary, we prefer to standardise the percentage of patients starting IVIg treatment and the initial IVIg discontinuation rate throughout the model in our base case (Table 5). However, we consider that further clinical advice would help to resolve the remaining uncertainty concerning:

- The proportion of patients starting IVIg after they discontinue efgartigimod (discussed in section 2.1)
- The initial IVIg discontinuation rate for patients starting IVIg who had received prior efgartigimod treatment (discussed in section 2.1).
- Time on treatment for IVIg compared with efgartigimod (discussed in section 2.2).

6 REFERENCES

1. Wolfe GI, Barohn RJ, Foster BM, et al. Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis. Muscle & Nerve 2002;26(4):549-52. doi: 10.1002/mus.10224

Efgartigimod for treating generalised Myasthenia Gravis (ID4003): Updated proposal for Committee

We appreciate the time, effort and focus that has been invested by all stakeholders in this appraisal, and the recognition that gMG (generalised Myasthenia Gravis) is a rare and chronic autoimmune disease with a notable scarcity of effective and safe treatment options.

We believe that this appraisal effort has shed further light on how important new treatments are for patients with refractory gMG i.e. those who do not respond adequately to standard treatments. In particular, we would like to thank the Committee, who, alongside extensive clinical input and patient/PAG testimony, have recognised and acknowledged the exceptionally high unmet need in this population. This acknowledgement has been well-received by the patient and clinical community.

Furthermore, the appraisal has allowed the patient voice to be heard, highlighting how often refractory gMG patients are required to endure both the uncontrolled effects of the disease, and severe side effects from currently used medications. One such example is the use of chronic corticosteroids – a mainstay of the refractory gMG treatment protocol – which can lead to diabetes, weight gain, depression, and osteoporosis. The negative impact on patients' quality of life is well documented and was raised on numerous occasions throughout the appraisal.

Throughout a detailed review of the clinical data, and reinforced via clinician and patient testimony and real-world UK data (EAMS / EAMS+), we believe that the Committee has been able to assess and confirm how efgartigimod can transform gMG treatment, improve outcomes for refractory patients, and deliver reduction in the use of chronic corticosteroids.

Efgartigimod is an effective and safe option; further advantages include a targeted MOA, rapid onset of action, an approved SC formulation / homecare option to enable out-of-hospital care for suitable patients, and a clear stopping rule. These benefits have been confirmed in multiple trials and in a real-world setting in the UK, where more than 100 patients are currently benefitting from efgartigimod via EAMS. Furthermore, the appropriate use – and placement of – new treatments, such as efgartigimod, has been widely agreed upon by all parties, including the Association of British Neurologists.

Current situation

We acknowledge the complexity and uncertainty inherent in assessing a rare disease like gMG, particularly given the lack of novel treatments and the paucity of data for standard of care. To that end, we appreciate the collective efforts that have gone into finding a solution which minimizes uncertainty and ensures efgartigimod is a cost-effective use of NHS resources.

We believe that the appraisal process has been highly productive in that regard. We have resolved most existing uncertainties, including key clinical data and economic parameters, supported by real-world data generated in the UK.

After the recent Committee meeting on May 9, additional analyses were requested by the Committee. argenx completed these analyses and submitted these on June 13, 2024.

Updated value proposition

To ensure the availability of efgartigimod in England and Wales, we are presenting to the Committee a value proposition closely aligned with the EAG's recommendations and addressing the Committee's principal concerns regarding treatment duration. In the spirit of achieving patient access, this offer contains several adjustments which we hope will help us reach final agreement.

We propose a revised PAS of [redacted] delivering an ICER of £23,181, aligned with EAG scenario 3 in the most recent report. This is significantly higher than the previous offer of [redacted] submitted to ACM3. This upward adjustment is a sign of our commitment to reaching a positive outcome and achieving access for patients with gMG in England and Wales.

This revised proposal is supported by the best available evidence, has been validated by the EAG and reflects UK clinical practice. We would like to highlight that, [redacted] an unproven and less effective treatment with serious side effects, that has never been subject to NICE assessment. [redacted]

The EAG's scenario 3 includes:

- PLEX post-IVIg discontinuation and post-efgartigimod discontinuation for the cohort not receiving IVIg, because they were non-responders.
- Censoring patients discontinuing with MG-ADL < 5.
- Matching the cycle probability of discontinuation between IVIg and efgartigimod.

argenx believes that this proposal recognises the challenges the Committee faced in dealing with perceived uncertainty in assessing efgartigimod in a rare disease. We hope that with this value proposition, a safe and effective long-term pharmacological option for gMG will be available for the first time in the UK.

Clinical and economic rationale

PLEX has been included in EAG scenario 3, aligning with expert neurology opinion and the established gMG treatment pathway. This inclusion meets the request to model a comprehensive care pathway and PLEX use is supported by real-world EAMS data. PLEX is modelled conservatively, used only when patients have failed standard therapy, efgartigimod, and IVIg, leaving no other options.

For the IVIg cohort, censoring patients with MG-ADL < 5 at the time of discontinuation makes the model more clinically plausible and aligns with clinical testimony throughout the appraisal process. This approach, discussed in ACM2 and ACM3, differentiates between discontinuation events in patients with controlled disease and others.

Initially, treatment times were modelled separately for efgartigimod (using trial data) and IVIg (based on available literature). Despite these robust assumptions, argenx has made further adjustments by aligning time-on-treatment estimates for both efgartigimod and IVIg cohorts, as requested by NICE. While using efgartigimod ToT data to model IVIg discontinuations is not supported by current evidence, argenx is accommodating the Committee's request for a pragmatic approach in order to reach a conclusion.

Summary

The updated value proposition is below:

Description	PAS %	ICER
1. Probability of discontinuation in IVIg arm equal to efgartigimod; censoring for pts discontinuing with MG-ADL<5. 2. PLEX applied post-IVIg discontinuation and post-efgartigimod for the cohort not receiving IVIg 3. IVIg price at midpoint of NHS discount range, as provided by NICE	[redacted]	£23,181

We trust that this is received in the spirit in which it is intended: as a thoughtful, balanced and cost-effective solution. argenx is committed to partnering with NICE to deliver efgartigimod to an underserved and vulnerable patient group and we remain open to further dialogue in case of any outstanding questions or concerns.

CONFIDENTIAL UNTIL PUBLISHED

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

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Evidence Review Group's critique of the company's updated value proposition and response to NICE requests for additional comment and analyses

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Date completed	1st November 2024

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

CIC	Commercial in confidence
EAG	External Assessment Group
EAMS	Early Access to Medicines Scheme
ECM	Established clinical management
gMG	Generalised myasthenia gravis
ICER	Incremental cost-effectiveness ratio
IVIg	Intravenous immunoglobulin
MG-ADL	Myasthenia Gravis Activities of Daily Living scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PAS	Patient Access Scheme
PLEX	Plasma exchange
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year

1 INTRODUCTION

This document is the External Assessment Group's (EAG's) critique of the company's (argenx) updated value proposition to NICE on 16th August 2024.

The updated value proposition proposed a revised Patient Access Scheme (PAS) of [redacted]. Their preferred base case was using:

- Probability of discontinuation in intravenous immunoglobulin (IVIg) arm equal to efgartigimod; censoring for patients discontinuing with Myasthenia Gravis Activities of Daily Living scale (MG-ADL) <5.
- Plasma exchange (PLEX) applied post-IVIg discontinuation and post-efgartigimod for the cohort not receiving IVIg because they were non-responders to standard therapy, efgartigimod and IVIg.
- IVIg price at midpoint of NHS discount range ([redacted]), as provided by NICE

The stated value proposition by the company was £23,181 per quality-adjusted life year (QALY).

In this document, we present the following:

- Our critique of the company's new value proposition and the assumptions used to obtain this (Section 2)
- A validation of the results of the company's revised cost-effectiveness analysis (Section 3)
- The results of the EAG base case and scenario analyses (Section 4)
- The EAG's response to NICE requests for additional comment (Section 5)

2 CRITIQUE OF THE COMPANY RESPONSE

2.1 Probability of discontinuation from maintenance IVIg equal to the probability of discontinuation from efgartigimod; censoring for patients discontinuing with MG-ADL<5.

The company provided an explanation of the long-term discontinuation from maintenance IVIg treatment, including censoring for patients discontinuing with MG-ADL<5 in Appendix A of their response to the third NICE appraisal committee meeting.

The company argued that some of the discontinuations observed for efgartigimod occurred in patients with an MG-ADL score lower than 5 and that one potential reason for this was an improvement in the patients' condition. They therefore considered a more plausible scenario where patients who discontinued efgartigimod with an MG-ADL < 5 (n=5) were censored, rather than including all patients.

In an earlier version of the model, the company included the option to set time on treatment to be equal for IVIg and efgartigimod. This was done by making the probability of discontinuing IVIg treatment the same as discontinuing efgartigimod treatment. For the scenario with censoring for patients receiving efgartigimod discontinuing with MG-ADL<5, this was calculated by generating a new time on treatment Kaplan-Meier survival and fitting parametric curves to this. The exponential curve was chosen. Including censoring for patients with MG-ADL<5, the time on treatment with IVIg changes from an average time of 4.4 years (i.e. same as efgartigimod) to 6.3 years for the whole cohort including non-responders.

We maintain our position, given in our critique of the company's response after the third NICE appraisal committee meeting, that it is reasonable that patients with a MG-ADL < 5 would not have maintenance IVIg. However, we note that using this assumption the time on treatment is no longer equal for efgartigimod and IVIg, as preferred by the NICE committee. We note the large uncertainty around the estimation of the IVIg discontinuation rate and time on treatment.

2.2 PLEX applied post-IVIg discontinuation and post-efgartigimod for the cohort not receiving IVIg

The company assume that patients receive PLEX after discontinuing IVIg in the Established clinical management (ECM) cohort. In the efgartigimod cohort after discontinuing efgartigimod, a proportion of the cohort receive IVIg and a proportion receive PLEX.

The company state that PLEX has been included, aligning with expert neurology opinion and the established generalised myasthenia gravis (gMG) treatment pathway. This inclusion meets the request to model a comprehensive care pathway and PLEX use is supported by real-world Early Access to Medicines Scheme (EAMS) data. PLEX is modelled conservatively, used only when patients have failed standard therapy, efgartigimod, and IVIg, leaving no other options.

The EAG notes that the inclusion of PLEX increases the costs for the comparator arm significantly more than for the intervention arm (Table 1). From the model we observe that it appears to be that all patients who discontinue IVIg receive subsequent treatment with PLEX. By contrast in the efgartigimod arm, 6% who do not respond to efgartigimod receive PLEX as a subsequent treatment. Clinical advice regarding the proportion of patients who cannot tolerate or discontinue IVIg and then receive PLEX would be beneficial.

Table 1 Costs for the ECM and efgartigimod arm with and without PLEX as a subsequent treatment

Treatment	Treatment	Total costs	Drug costs
Company base case with PLEX	Efgartigimod	[redacted]	[redacted]
	ECM	[redacted]	[redacted]
Company base case without PLEX	Efgartigimod	[redacted]	[redacted]
	ECM	[redacted]	[redacted]

The EAG notes that PLEX was not included as part of the basket of treatments used for the comparator arm (ECM) being compared with efgartigimod. We are unsure why it would be a relevant subsequent treatment if it was not included as part of the ECM comparator. We also note that the company has not provided full details on how PLEX has been implemented as a subsequent treatment in both treatment arms, such as the proportion receiving treatment and for how long with explanation and justification. Further we do not consider that PLEX has been implemented consistently in both treatment arms and therefore this appears to introduce biases in favour of efgartigimod by including high PLEX costs for the IVIg treatment arm. For these reasons we prefer to remove PLEX as a subsequent treatment.

2.3 IVIg price at midpoint of NHS discount range, as provided by NICE

The company include a price discount of [redacted]% for IVIg. As noted in the EAG's critique of the company's response to the NICE appraisal committee's request for additional analyses after the third NICE Appraisal Committee meeting (3rd July 2024), we were advised by NICE

that they preferred to see the company analyses without any price discount for IVIg. They also advised that they preferred to use the cheaper price for IVIg of £1,380 for vial with 20mg/200ml IVIg. We have used the list price for IVIg in the EAG analyses.

The EAG provide the model results with the actual confidential discount in a confidential addendum.

3 VALIDATION OF THE RESULTS OF THE COMPANY'S ADDITIONAL COST-EFFECTIVENESS ANALYSES

3.1 Company's revised base case cost-effectiveness results

The previous EAG base case is shown in Table 5 of the EAG's critique of the company's response to the NICE appraisal committee's request for additional analyses after the third NICE Appraisal Committee meeting (3rd July 2024).

The company accepted the changes to the previous EAG base case except for including the PLEX and IVIg prices. The cumulative changes for the company's new base case to the previous EAG base case are shown in Table 2. The cumulative effect of the changes implemented by the company results in an incremental cost-effectiveness ratio (ICER) of £23,181 per QALY. The EAG verified the results of the company's new cost-effectiveness analysis.

Table 2 Cumulative effect of the company's preferred model assumptions, efgartigimod versus ECM, with PAS

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
EAG base case (3rd July 2024)	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	**£77,362**
	ECM	[redacted]	[redacted]	-	-	
+ Probability of discontinuation in IVIg arm equal to efgartigimod; censoring for pts discontinuing with MG-ADL<5.	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£284,397
	ECM	[redacted]	[redacted]			
+ PLEX applied post-IVIg discontinuation and post-efgartigimod for the cohort not receiving IVIg	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£75,181
	ECM	[redacted]	[redacted]			
+ IVIg price at midpoint of NHS discount range, as provided by NICE. [redacted]	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£146,999
	ECM	[redacted]	[redacted]			

+ PAS increased to [redacted]	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£23,181
	ECM	[redacted]	[redacted]			
Company's updated cost effectiveness	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	**£23,181**
	ECM	[redacted]	[redacted]			

ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Incr, incremental; IVIg, intravenous immunoglobulin; PAS, patient access scheme; PLEX, plasma exchange; QALYs, quality-adjusted life years

4 EAG RESPONSE TO NICE REQUESTS FOR ANALYSES

4.1 EAG's preferred assumptions

Based on the EAG's critique of the company's model (discussed in section 2), we have identified several aspects of the company's revised base case with which we disagree. Our preferred model assumptions are:

- PLEX is not included as subsequent treatment,
- Use the list price for IVIg with prices of £1,380 for vial with 20mg/200ml IVIg, as requested by NICE.

The cumulative effect of these changes result in an ICER of £212,079 per QALY (Table 3).

Table 3 Cumulative effect of the EAG's preferred model assumptions, efgartigimod versus ECM, with PAS, excluding estimated commercial discount for IVIg

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company revised base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£23,181
	ECM	[redacted]	[redacted]			
+ PLEX not included as subsequent treatment	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£236,830
	ECM	[redacted]	[redacted]			
+ Use the list price for IVIg with prices of £1,380 for vial with 20mg/200ml IVIg	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£212,079
	ECM	[redacted]	[redacted]			
EAG base case	**Efgartigimod**	[redacted]	[redacted]	[redacted]	[redacted]	£212,079
	ECM	[redacted]	[redacted]			

ECM, established clinical management; ICER, incremental cost-effectiveness ratio; Incr, incremental; IVIg, intravenous immunoglobulin; PAS, patient access scheme; PLEX, plasma exchange; QALYs, quality-adjusted life years

4.2 Scenario analyses conducted on the EAG's base case

NICE requested the EAG run scenario analyses for:

- The timepoint of assessing IVIg response (3 weeks)
- The IVIg response rate (70%)
- The dosing frequency of IVIg (6 weekly dosing)
- The population characteristics of the EAMS cohort (Age 49.2 years, 75% female).
- Lower and upper range for uptake of IVIg ([redacted]% - [redacted]%)
- Time on treatment for IVIg equal to that of efgartigimod

Due to the nature of the model, we are unable to run a scenario analysis on the timepoint of assessing IVIg response. The results for the other scenarios requested by NICE are shown in Table 4. The ICERs range from dominant (upper range for uptake of IVIg) to £335,561 per QALY (IVIg dosing 6-weekly).

Table 4 Scenario analyses for efgartigimod vs established clinical management, with PAS

	Scenario description	Efgartigimod vs established clinical management		
		Incremental cost (£)	Incremental QALYs	ICER £/QALY
0	EAG base case	[redacted]	[redacted]	£212,079
1	IVIg response of 70% i.e. non-response of 30% (base case IVIg response of 80.5%; non-response 19.5%)	[redacted]	[redacted]	£259,206
2	IVIg dosing 6 weekly (base case 4 weekly)	[redacted]	[redacted]	£335,561
3	Patient characteristics of the EAMS cohort (Age 49.2 years, 75% female)	[redacted]	[redacted]	£212,302
4	Lower range for uptake of IVIg ([redacted]%)	[redacted]	[redacted]	£330,140
5	Upper range for uptake of IVIg ([redacted]%)	[redacted]	[redacted]	dominant
6	Time on treatment for IVIg equal to that of efgartigimod	[redacted]	[redacted]	£312,132

5 EAG RESPONSE TO NICE REQUESTS FOR ADDITIONAL COMMENT

5.1 Efgartigimod dosing

In the ADAPT trial which underpins the company submission, and as stated in our original EAG report (section 3.2.1), participants received efgartigimod (10mg/kg) in cycles consisting of four IV infusions (one infusion per week) to a maximum of three cycles. 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). To be considered eligible for another efgartigimod treatment cycle patients had to meet these criteria (CS B.2.3.1):

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

As part of the company's response to the second NICE Draft Guidance document a draft paper[1] (i.e. not yet published or peer-reviewed) was provided describing the use of efgartigimod in 48 patients with acetylcholine receptor (AChR) antibody-positive gMG who were treated in 12 centres under the Early Access to Medicine Scheme (EAMS) in the UK. The inclusion criteria for the EAMS define a population that is very similar to the target population who would be expected to receive efgartigimod in clinical practice defined by the company. We note that the objective of this study was to " p*rovide the first real-world experience regarding the Efgartigimod efficacy, safety and tolerability in the UK population*" and that according to the EAMS treatment protocol "*Efgartigimod was given as per the ADAPT trial as a cyclical treatment as an IV infusion weekly for four weeks (10 mg/kg in one-hour intravenous infusion), with subsequent treatment cycles dependent on the patient's symptoms.*"

The mean time interval between completing one cycle of treatment and starting the next decreased slightly with each subsequent cycle as shown in Table 5. We are concerned that the ADAPT trial dosing schedule may not have been fully adhered to in the EAMS cohort. This is because i) with a 4 week treatment period and a minimum of 8 weeks from initiation of the previous cycle before the start of the next cycle we would have expected the lower bound of what we presume to be the range of values for the mean time interval in Table 5 to

be 4 weeks, not 3 weeks; ii) there is evidence from the discussion section of the paper describing real world use of efgartigimod that at least one patient had an MG-ADL score of 4 at the beginning of the 2nd cycle ("*a patient who started the trial with an MG-ADL score of 11, and, after the 1st cycle, the score lowered to 0, reaching a score of 4 at the beginning of the 2nd cycle, and afterwards keeping a score of 2*"); and iii) in the discussion of the paper the authors also state "*The interval between treatments declined after Cycle 1 – likely because the patient and clinician could predict when the symptoms were likely to deteriorate and adjusted the timing of the next cycle to pre-empt the worsening of symptoms*." Therefore, we believe that in real-world clinical practice a proportion of patients may receive efgartigimod more frequently than would occur if the ADAPT trial dosing protocol was strictly adhered to. Additionally, and as stated in the EAG's original report (section 2.2.2) the Summary of Product Characteristics (SmPC)[2] states that "*the earliest time to initiate a subsequent treatment cycle was 7 weeks from the initial infusion of the previous cycle*" so the efgartigimod dosing in EAMS may have been more aligned with this than the ADAPT trial. We note that the frequency of efgartigimod dosing in the economic model is based on the ADAPT trial data.

We are also mindful that clinicians (and potentially patients if they are self-administering subcutaneous efgartigimod at home) may have a lower MG-ADL threshold for initiating the next cycle of treatment if the patient is experiencing severe problems, for example, with swallowing or breathing. The EAG recalls clinical experts' advice that the MG-ADL score is obtained by scoring eight items (talking, chewing, swallowing, breathing, brushing teeth/combing hair, arising from a chair, double vision, eyelid droop) from 0 to 3 giving a score range 0-24. The ways that a score of 5 or more can be achieved are diverse and not everyone with a score of 5 or more will have the same impairments.

Table 5 Real-world evidence on mean time intervals in efgartigimod treatment cycles

Time period considered	Number of patients[a]	Mean time interval[b]
Time between finishing the 1st cycle and starting the 2nd cycle	32	6.4 weeks (3 - 15.7 weeks, SD 2.4).
Time between finishing the 2nd cycle and starting the 3rd cycle	25	5.5 weeks (3 - 10.9 weeks, SD 1.6)
Time between finishing the 3rd cycle and starting the 4th cycle	14	4.6 weeks (3.0 - 6.7 weeks, SD 0.9).

Source: Moniz Dionisio draft paper 2024[1]
SD, standard deviation
[a] Numbers contributing data inferred from the number of patients in Table 2 of the draft paper completing a particular cycle of treatment (i.e.32 patients are listed as completing a 2nd cycle of treatment, so we infer 32 patients started a 2nd cycle of treatment)
[b] Data are believed to be mean, range and SD but the paper does not explicitly state that it is the range that is reported.

5.2 Company updated treatment pathway

Figure 1 describes the logic of the company's model, as we understand it. However, the model is complicated and we recognise that Figure 1 may not fully represent the company's approach.

We disagree with the way PLEX has been included in the model, because its use is applied differently in each arm. PLEX is applied at the same time as IVIg in the efgartigimod arm, but sequentially (i.e. after IVIg) in the ECM arm. We consider that if the company want to bring PLEX into subsequent treatment:

- It should have been included in the basket for ECM (i.e. a proportion of patients should receive IVIg and a proportion of patients should receive PLEX first-line)
- For patients in the EFG arm who need to receive subsequent treatment with IVIg or PLEX second-line, the proportions of patients receiving IVIg and PLEX should be the same as for first-line treatment in the ECM arm

However, the company's model is not designed to include PLEX at first line in ECM.

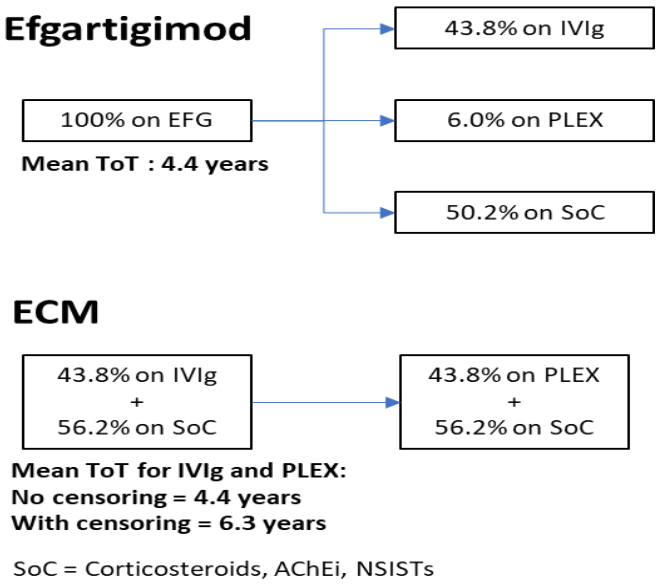

Figure 1 Patient flow in company's updated model

AChEi; acetylcholinesterase inhibitors; EFG, efgartigimod; IVIg, intravenous immunoglobulin; NSISTS, on-steroidal immunosuppressants; SoC, standard of care

6 EAG CONCLUSION

The company presented the results of their revised base case, which includes the use of PLEX in subsequent treatment in both model arms (Table 2). The EAG have reviewed the revised model and we prefer to exclude PLEX from subsequent treatment and to use the list price for IVIg (equivalent to £1,380 for a 20mg/200ml vial) in our base case (Table 3). We conducted the scenarios requested by the NICE Technical Team on our revised base case, to explore the remaining uncertainty when comparing the cost-effectiveness of efgartigimod with ECM (Table 4).

We still consider that it is reasonable that patients with a MG-ADL < 5 would not receive maintenance IVIg. However, we note that this assumption results in different time on treatment for efgartigimod and IVIg, which the NICE committee disagreed with. We judge there to be considerable uncertainty in the estimates of the IVIg discontinuation rate and time on treatment.

Because PLEX was not included as part of the ECM comparator, we do not think it is appropriate to include it in subsequent treatment. Furthermore, we do not consider that PLEX has been implemented consistently as subsequent treatment in both treatment arms, resulting in a higher proportion of patients receiving PLEX in the ECM arm compared with the efgartigimod arm. This causes much higher PLEX costs in the ECM arm and reduces the ICER. Consequently, we prefer to remove PLEX from subsequent treatment. Clinical advice regarding the proportion of patients who cannot tolerate or discontinue IVIg and then receive PLEX would be beneficial.

We note that the frequency of efgartigimod dosing in the economic model is based on the ADAPT trial data. However, there is evidence from the EAMS cohort that, in some cases, the interval between efgartigimod treatment cycles may have been shorter than specified in the ADAPT trial.

7 REFERENCES

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