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:

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 **Draft Guidance Document (DG)** as issued to consultees and commentators

2. **Comments on the Draft Guidance from** Argenx
   a. Response form
   b. Summary of new evidence
   c. Appendices

3. **Consultee and commentator comments on the Draft Guidance** from:
   a. Association of British Neurologists – endorsed by Royal College of Physicians
   b. Muscular Dystrophy UK & myaware

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 **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company response to the DG**

6. **Company response to query from NICE technical team**

7. **External Assessment Group response to query from NICE technical team and response to company response to query from NICE technical team (document 6)**

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Draft guidance consultation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: September 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: 22 September 2023
- Second evaluation committee meeting: 16 November 2023
- 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.

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 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 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 have 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 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 immunosuppressive agent 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.

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 established clinical management. 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 therapy has been started. The committee also noted that the company used efficacy data from the ADAPT trial in its model (see section 3.5). 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 from clinical experts to help define a population in which efgartigimod is both clinically and cost effective is needed. It considered that the characteristics of this population should be clearly defined to enable use in the NHS.

Maintenance IVIg

3.4 The company considered that maintenance IVIg is part of established clinical management in the NHS and that it is received 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 restricts maintenance use. 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 Early Access to Medicines Scheme (EAMS) (see section 3.6; this data is confidential so cannot reported here). A commissioning expert explained that the NHS England commissioning criteria policy for the use of therapeutic immunoglobulin limits the use of maintenance IVIg to rare circumstances. They also provided an estimate of the proportion of people with gMG that have maintenance IVIg (this data is deemed 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 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 and

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 the difference in 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). The committee concluded that the company should estimate the proportion of people having maintenance IVIg in the population in which efgartigimod would be used. If possible, it should use an explicit, valid, and replicable method to estimate the proportion having maintenance IVIg.

Clinical effectiveness

ADAPT and ADAPT+

3.5 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 a Myasthenia Gravis Activities of Daily Living (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+

3.6 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. 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. The committee concluded that the population included in the EAMS and EAMS+ indication was not generalisable to the population outlined in the company's economic model or the population that clinical experts said efgartigimod may be used in.

Economic model

Company's modelling approach

3.7 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 and be included in the least severe health state, but a person could score 1 for all 8 activities and be included in the second-worst health state. 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 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 concluded that the company's model structure was appropriate for decision making.

Treatment effect after stopping efgartigimod

3.8 The EAG noted that in the company's original base case, the transition probabilities for people that 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. The EAG therefore provided updated transition probabilities assuming that 1% of people remain in the MG-ADL below 5 health state after stopping efgartigimod treatment. At technical engagement, the company provided evidence from additional analysis of ADPAT and ADAPT+ data, real world evidence from the US and evidence from efgartigimod in other indications that it believed supported a residual treatment effect for efgartigimod after treatment had stopped. 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. It concluded that a residual treatment effect after treatment stops was plausible but uncertain. The

committee would have preferred more evidence about the possible residual treatment effect, which should include clinical expert input.

Utility values

Source of utility values

3.9 Health-related quality of life data was collected in ADAPT using the EQ-5D-5L and was mapped to the EQ-5D-3L. The company estimated the utility values for the MG-ADL health states using a regression model that contained a treatment effect coefficient. The company explained that the treatment effect coefficient was statistically significant. It therefore included a treatment effect in the MG-ADL health states in the efgartigimod arm, using utility values 0.105 higher 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 including a treatment effect 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 treatment effect 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 treatment effect was applied in 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 assumption of a treatment effect explained by 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 people in the MG-ADL below 5 health state were assumed not to use corticosteroids in the model. 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.

Carer disutilities

3.10 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 and the company did not identify any studies that reported carer disutility in gMG. Instead, 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 did 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 considered 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 quality-adjusted life year (QALY) gain associated with efgartigimod in the company's model. The committee considered that the 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.

Costs

Corticosteroid complications

3.11 The company said that the published literature shows that higher doses of corticosteroids are associated with higher costs from treating complications. 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 a study identified by the company in people with asthma done in the UK (Voorham et al. 2019) and believed

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 as 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, as 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, and that corticosteroid complication costs should be generalisable to NHS clinical practice, applicable to gMG and valued using prices relevant to the NHS.

Cost-effectiveness estimates

3.12 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.

The EAG's preferred assumptions included:

- not including costs for maintenance IVIg (see section 3.4)
- 15% of people remaining in the MG-ADL below 5 health state 6 months after permanently stopping efgartigimod (see section 3.8)
- using different utility values for the efgartigimod and established clinical management arms (see section 3.9)
- not including carer disutilities (see section 3.10)
- using costs from Voorham et al. to model corticosteroid complication costs (see section 3.11).

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 above the range normally considered a cost-effective use of NHS resources.

The committees' preferred assumptions included:

- using the same utility values for the efgartigimod and established clinical management arms (see section 3.9)
- not including carer disutilities (see section 3.10).

There was uncertainty about the population that would have efgartigimod in the NHS if it was recommended in line with the marketing authorisation. The population considered would likely impact the proportion of people expected to have maintenance IVIg. So the committee considered that none of the IVIg maintenance use scenarios considered by the company and EAG were suitable for decision making (see section 3.4). It also considered that both the company's and EAG's corticosteroid complication analyses were not suitable for decision making (see section 3.11). The committee explained that it would prefer to see an analysis that addresses these issues and included:

- clearly identifying and defining the characteristics of the population who would have efgartigimod (see section 3.3)
- estimating the proportion of people having maintenance IVIg in the population who would have efgartigimod (see section 3.4)
- identifying more evidence about the possible residual treatment effect when treatment with efgartigimod is stopped, which should include clinical expert input (see section 3.8)
- using corticosteroid complication costs that are:
  - generalisable to NHS clinical practice
  - applicable to gMG, and
  - valued using prices relevant to the NHS (see section 3.11).

Other factors

Equality

3.13 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

3.14 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

3.15 The committee agreed that further information was needed to address the uncertainties. It 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 normally 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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 22 September 2023. 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.

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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.Describe clearly the population for whom treatment may offer greatest value *(Relevant section from DG) 3.3 The committee highlighted that the clinical and cost effectiveness of efgartigimod would change for different populations. It concluded that further input from clinical experts to help define a population in which efgartigimod is both clinically and cost effective is needed. It considered that the characteristics of this population should be clearly defined to enable use in the NHS.*	The company acknowledged that further input was required from clinical experts to define the population in which efgartigimod would be used in clinical practice (Section 3.3). The proposed target patient population, for treatment with efgartigimod, was defined accordingly and validated by UK clinical experts. See further details in the New Evidence Submission document and in Appendix A.
2. Quantify existing burden of regular rescue treatments in eligible population *(Relevant section from DG) 3.4 The committee concluded that the company should estimate the proportion of people having maintenance*	According to the committee's request in Section 3.4, the company estimated the proportion of people eligible for maintenance IVIg in the target patient population in which efgartigimod would be used. This was defined via an

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intravenous immunoglobulin (IVIg) in the population in which efgartigimod would be used. If possible, it should use an explicit, valid, and replicable method to estimate the proportion having maintenance IVIg. 3.12 So the committee considered that none of the IVIg maintenance use scenarios considered by the company and External Assessment Group (EAG) were suitable for decision making.	explicit and replicable process of expert elicitation (i.e., Delphi). The full report, including survey methodology is included in Appendix A.
3.Explore costs associated with corticosteroid administration *(Relevant section from DG) 3.11 The committee concluded that none of the studies identified by the company were suitable for decision making, and that corticosteroid complication costs should be generalisable to NHS clinical practice, applicable to generalised Myasthenia Gravis (gMG) and valued using prices relevant to the NHS.*	According to the committee's request for further evidence in Section 3.11, a targeted literature review (TLR) was conducted to determine corticosteroid-associated adverse events in the target patient population. The results were used to estimate the annual cost of these complications. Full details of the TLR and analysis are provided in Appendix B.
4.Validate assumptions regarding residual effects of efgartigimod treatment *(Relevant section from DG) 3.8 The committee noted that this assumption had a substantial effect on the cost-effectiveness results. It concluded that a residual treatment effect after treatment stops was plausible but uncertain. The committee would have preferred more evidence about the possible residual treatment effect, which should include clinical expert input.*	The committee requested more evidence about the possible residual treatment effect of efgartigimod, including clinical input (Section 3.8). Therefore, the Company sought clinical expert validation of the available clinical data. See the New Evidence Submission document and Appendix C for full details.
5. Further validating importance of caregiver disutility *(Relevant section from DG) 3.10 The committee noted that carer disutilities contributed substantially to the overall quality-adjusted life year (QALY) gain associated with efgartigimod in the company's model. The committee considered that the 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. However, the committee noted that the disutilities used in the company's model were not appropriate for decision making without further evidence.*	The committee highlighted a need for additional evidence on caregiver burden in section 3.10, so an additional analysis was conducted using previously collected data on gMG patients and their caregivers. Patient and caregiver utilities were compared against the UK general population using a UK value set. Full details can be found in the New Evidence Submission document and in Appendix D.
6.Exploring the appropriate source of utilities for inclusion in the model *(Relevant section from DG)3.9 Health-related quality of life data was collected in ADAPT using the EQ-5D-5L and was mapped to the EQ-5D-3L.*	The committee discussed that there was uncertainty in the most appropriate utility values to use for both treatment arms (Section 3.9). The company was able to source utility data at different levels of natural disease activity from a more representative population. Full details can be found in the New Evidence Submission document.
7.Revised economic analyses *(Relevant section from DG)3.12 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.*	Following the publication of draft guidance, the company updated its base case cost-effectiveness model to reduce uncertainty in the cost-effectiveness estimates. Details of the updated model parameters can be found in the executive summary. The updated economic model is attached with detailed base case and scenario analyses (Appendix E).

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Efgartigimod for treating generalised myasthenia gravis [ID4003]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 22 September 2023. Please submit via NICE Docs.

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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

6th Oct 2023

File name	Version	Contains confidential information	Date
ID4003 Efgartigimod for treating generalised myasthenia gravis (gMG)_summary of new evidence	1.0	Yes	06/10/2023

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NICE National Institute for Health and Care Excellence

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

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

Summary of additional evidence

Further to the first Appraisal Committee Meeting (ACM) regarding efgartigimod for treating gMG held on 10th August 2023 and the subsequent publication of draft guidance, several areas of uncertainty were highlighted (NICE, 2023).[1]

The Company have aimed to provide further evidence to reduce this residual uncertainty, summarised below under six separate headings:

1. **Describing clearly the target patient population for whom treatment may offer the greatest value**
2. **Quantifying the existing burden of regular rescue treatments (e.g., maintenance IVIg) in this population**
3. **Exploring the costs of corticosteroid administration in this population**
4. **Validating assumptions regarding the residual effects of efgartigimod treatment following permanent discontinuation of efgartigimod**
5. **Further validating the importance of caregiver disutility for patients affected by gMG in the population considered eligible for treatment**
6. **Exploring the appropriate source of utilities for inclusion in the economic model**

Revised economic analyses are provided which take into account the new evidence presented (1-6) and consider the availability of a subcutaneous formulation which is expected to be approved by the Medicines & Healthcare Products Regulatory Agency (MHRA) in November 2023. Further details of the revised economic analyses are presented in Appendix E.

In summary, the Company believe that the areas of uncertainty raised at the ACM can be appropriately addressed by the clinical expert validation provided here. Where appropriate, an additional literature search has been conducted to ensure that the most relevant information has been considered for decision making.

Given the rarity of gMG and the paucity of evidence surrounding some current standard of care treatments there are aspects of uncertainty that cannot be addressed with the data, literature, and time available.

The Company have aimed to address and reduce uncertainty wherever possible and remain committed to offering a 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.

NICE National Institute for Health and Care Excellence

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

1. Describing clearly the population for whom treatment may offer the greatest value

Efgartigimod is indicated as an add-on to standard therapy for the treatment of adult gMG patients who are anti-acetylcholine receptor (AChR) antibody positive. Clinical experts noted that the product could be positioned at several points in the clinical pathway. As such, the Committee identified the target patient population as an area of uncertainty as the cost-effectiveness of efgartigimod would change for different populations and requested further input from clinical experts to help clearly define the population for use in the NHS.

The proposed target patient population for treatment on the NHS is as follows:

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 (simplified):

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) and rituximab, for an adequate period of time, at an adequate dose.

This target patient population aligns closely 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 with over (‘academic / commercial in confidence information removed’) enrolled to date. This confirms that this population is easily identifiable in UK specialist centres.

This is a patient population with significant unmet need; patients will have received maximal doses of steroids, and at least 2 additional therapies which could include any NSISTs or rituximab. As a result, patients have few remaining options other than the use of regular rescue therapies (intravenous immunoglobulin [IVIg] or plasma exchange [PLEX]).

To obtain clinical expert validation that this population was appropriately optimised toward those who may benefit most from efgartigimod in clinical practice, a Delphi panel was conducted which narrowed and simplified the description of the target patient population to achieve full consensus from the panel.

Full details of the Delphi panel conducted, and the process / methodology followed, are provided in Appendix A.
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The cost-effectiveness model is representative of the population outlined above, as demonstrated by post-hoc subgroup analyses from ADAPT which showed that efgartigimod was effective in a broad population of patients. Improvements over placebo were consistent regardless of concomitant treatment, baseline disease activity or prior immunosuppressant exposure. In the Phase 3 **Error! Reference source not found.Error! Reference source not found.**ADAPT study, 167 adult patients with gMG were enrolled, randomly assigned and treated between September 2018 and November 2019. Patient characteristics were representative of the gMG population and well balanced between treatment groups. Most patients were less than 65 years old and receiving immunosuppressive treatment at baseline, with a mean time since diagnosis of approximately 10 years.
No observable differences were noted in response based on baseline demographics or prior lines of treatments, suggesting that the trial results are generalisable to the optimised patient population identified above.

No changes were made to the cost-effectiveness model, since the evidence from ADAPT showed that the efficacy observed in AChR+ population is generalisable to the updated target population.

NICE National Institute for Health and Care Excellence

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

2. Quantifying the existing burden of regular rescue treatments in the eligible patient population

The NICE Committee noted in the draft guidance that they did not feel they had appropriate evidence to quantify how frequently regular rescue therapies (IVIg and PLEX) were utilised in practice for the eligible patient population. Analysis of the EAMS and EAMS+ data collected from participating UK centres demonstrated that ('academic / commercial in confidence information removed') had received either prior regular or intermittent IVIg treatment and this real-world evidence was submitted during technical engagement. However, uncertainty was felt to remain regarding the proportion of patients receiving regular rescue therapies in real-world clinical practice beyond the EAMS cohort, particularly considering the need to provide further clarity regarding the target patient population (section 1 above).

To address this uncertainty, the Company developed and conducted a Delphi panel, designed to confirm the optimisation of the target patient profile and to validate economic modelling assumptions on the administration of regular rescue therapies. A Delphi panel was selected, as the methodology is accredited and accepted for achieving convergence of opinions concerning real-world knowledge solicited from experts, to ensure an explicit, valid, and replicable method was used. Six gMG clinical experts were recruited to participate in the two round Delphi panel. They were chosen to represent a diverse, geographically-representative (covering all major regions of England) sample from across the specialist neuromuscular centres in England.

The Delphi panel confirmed the most appropriate population for treatment with efgartigimod in the NHS. By working through the iterative two round process, with the simplified target patient population (as defined in section 1), the experts provided an appropriate estimate of the proportion of patients who would be considered for treatment with maintenance IVIg. The round 2 survey established that the efgartigimod target patient population represents 22.1% (mean, range 10-40%) of the total gMG population. Furthermore, the percentage of patients who would be considered for maintenance IVIg treatment was estimated as 69.2% (mean, range 60-90%). In summary, the results provide important clarity, using a well-recognised and replicable study methodology, to support the NICE discussions around uncertain parameters regarding the target patient population and the corresponding proportion of patients suitable for maintenance IVIg treatment within this optimised group.

Full details of the Delphi panel result, and the process / methodology followed, are provided in Appendix A.

The maintenance IVIg treatment use in the cost-effectiveness model was updated to reflect the total use of 69.2% in the target population and the information on treatment eligibility obtained from the Delphi Panel. This was phased across the different health states according to external clinical expert feedback and this is described further in the economic analyses provided and varied in scenario analysis.**Error! Reference source not found.Error! Reference source not found.**

3. Exploring the costs of corticosteroid administration in this population

The Committee concluded that none of the studies identified by the Company or the External Assessment Group (EAG) to inform assumptions surrounding the assessment of costs associated with corticosteroids use were suitable for decision making. The Committee noted that corticosteroid complication costs should be generalisable to NHS clinical practice, applicable to gMG and valued using prices relevant to the NHS. This is a key area of uncertainty as costs associated with corticosteroid complications have an important effect on the incremental cost-effectiveness ratio (ICER) in the cost-effectiveness model and initial real-world evidence of efgartigimod use in patients with gMG shows an encouraging reduction of almost one-third in total corticosteroid use.[2]

The original SLR conducted as part of the NICE submission focused only on sources for costs, so a new Targeted Literature Review (TLR) was developed to capture papers reporting the frequency of adverse events (AEs) associated with corticosteroid use (i.e., not necessarily converted into costs). The new TLR identified Lee at al. 2018[3] as a relevant and appropriate literature source with evidence derived directly from gMG patients. This source was also mentioned by the EAG through technical engagement following the Draft Guidance. Costs associated with complications were sourced from the latest published NHS reference costs.

The resulting analysis found that the annual cost of systemic corticosteroid related complications was £13,131.60. The same cost was applied for high-dose and low-dose corticosteroid use in the cost-effectiveness model since the frequency of adverse events reported by Lee et al. 2018 is representative of the entire model population on corticosteroid (dose ranging between 0.5mg and 75mg, with a median of 10mg). This new analysis provides disease-specific data on the cost of AEs associated with corticosteroid use in the gMG population using a robust literature source and NHS published cost data. Unfortunately, as of the time of this submission, we were unable to obtain additional clinical validation of this analysis. A full description of the revised analysis can be found in Appendix B.

The cost estimates derived from Lee et al formed the basis for the assumption in the revised base case analyses provided in Appendix E.

4. Validating assumptions regarding the residual effects of efgartigimod treatment, following permanent discontinuation of efgartigimod

The NICE Committee noted that assumptions regarding the residual treatment effect of efgartigimod, following permanent discontinuation of efgartigimod, had a substantial effect on the cost-effectiveness results. They concluded that a residual treatment effect after treatment ends was plausible but uncertain, and clinical expert input on the possible residual treatment effect was requested. This request was made despite the EAG considering the Company's assumption to be reasonable and updating its base case accordingly prior to ACM1.

Available data on the scientific and clinical plausibility of an efgartigimod residual treatment effect following permanent treatment discontinuation was collated by the Company and reviewed by Dr Channa Hewamadduma, consultant neurologist and honorary senior lecturer at Sheffield Teaching Hospitals NHS Foundation Trust. Dr Hewamadduma was selected based on his leading expertise in clinical research and his portfolio of clinical and basic science research projects in neuro-genetics and neuro-degenerative disorders.

Dr Hewamadduma supported the plausibility of the assumption taken in the model regarding ongoing treatment effect of efgartigimod following permanent treatment discontinuation based on the evidence. Full details of the clinical data shared with Dr Hewamadduma can be found in Appendix C.

No changes were made in the model regarding this exploration since the evidence obtained from the clinical expert confirmed that the current assumption on residual effect was plausible.

5. Further validating the importance of caregiver disutility for patients affected by gMG in the population considered eligible for treatment

As caregiver health-related quality of life (HRQoL) was not captured in the ADAPT trial, the Company used the proxy of multiple sclerosis (MS) for caregiver disutilities, based on the assumption that gMG and MS are both chronic autoimmune diseases with similar symptoms and disease course. 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. However, the Committee also stated that the disutilities in the model required further evidence to support the assumptions made regarding MS as a suitable proxy.

To provide additional evidence of caregiver disutility, an additional analysis was conducted using data from two previous studies of gMG patients and their caregivers; the MyRealWorldMG study and a paper-based survey in France. Caregiver data on HRQoL (EQ-5D-5L) and patient data (Myasthenia Gravis Activities of Daily Living [MG-ADL]) were collected in both studies and were pooled for the analysis. The patients included in the MRWMG study were comparable to those in the ADAPT trial in terms of age and gender. Despite the potential inclusion of patients with MG-ADL < 5 in this study, the severity of disease across the identified group is comparable to ADAPT and the population used in the model.

To demonstrate disutility of the caregivers in the pooled dataset, caregiver's EQ-5D-5L data was valued using the UK value set and compared to UK population norms. Caregiver disutility was then described overall and stratified by the MG-ADL score of the person they care for. Caregivers generally had meaningfully lower utility values than the general population of the same age and gender. Further details of these analyses are presented in Appendix D. The subsequent analysis supports the previously submitted evidence on caregiver burden by providing caregiver disutilities captured directly in the target patient population. This in turn supports the assumptions used in the economic analyses submitted. The caregiver utility decrements assumed in the cost-effectiveness model were changed to reflect the values obtained from the Caregiver Burden Study in gMG described above. Please see Table 1 for a full breakdown of the utility decrements of caregivers by MG-ADL category of the patient.

Table 1. Utility decrements of the caregivers by MG-ADL category of the patient

Category	N (number of patient-caregivers data was based on)	Mean
MG-ADL <5	16	-0.025
MG-ADL 5 to 7	10	-0.323
MG-ADL 8 to 9	4	-0.142
MG-ADL ≥10	8	-0.170

6. Exploring the appropriate source of utilities and treatment effect for inclusion in the economic model

Health-related quality of life data was collected in ADAPT using the EQ-5D-5L and was mapped to the EuroQol-5-dimension-3-level (EQ-5D-3L). The Company estimated the utility values for the MG-ADL health states using a regression model that contained a treatment effect coefficient. The EAG considered that the method the Company used to derive utility values and the premise of including a treatment effect were reasonable, however, based on further consideration the Committee concluded that the same utility values should be used for the two arms.

When removing treatment effect coefficient, the Company believes that the use of utilities from the MRWMG study may be most appropriate as these remove any confounding treatment effect.

EQ-5D-5L data collected in the MRWMG study are expected to represent a more accurate estimation of the HRQoL burden of gMG patients than data collected in a clinical trial setting. In the ADAPT study, patients were monitored more closely, which may result in them valuing their health as better even if they have relatively high MG-ADL scores.[4] This effect is well-recognised and known as the Hawthorne effect, whereby individuals modify an aspect of their behaviour in response to their awareness of being observed (McCarney et al. 2007).[5]

This effect was also suggested by a consulted clinical expert in England and can be clearly observed when comparing the estimated health-state utilities from the MRWMG observations to those from ADAPT.

There is accordingly a greater differentiation between the health states in MRWMG utility values, which better aligns with the burden of gMG at the different levels of disease severity. In addition, the MRWMG EQ-5D data are representative of the HRQoL burden of gMG in a cohort treated with any treatment in current care, including immunoglobulins and rituximab. Therefore, this data reflects established UK clinical management where patients in the comparator arm only receive conventional treatment such as acetylcholinesterase inhibitors, corticosteroids, or nonsteroidal immunosuppressive drugs.

Moreover, if all observations in ADAPT are pooled independently of the treatment arm, the health-state utilities would include some of the effect of efgartigimod treatment. Pooled utility values in ADAPT would likely underestimate the HRQoL burden at different levels of gMG natural disease activity and data from the MRWMG would instead be a more accurate representation.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

The health-state utility values in the base case cost-effectiveness model were changed, considering the utilities obtained from MRWMG, and were applied equally in both treatment arms. For completeness, a scenario analysis is provided which utilises pooled utilities directly from the ADAPT study, recognising the limitations described above.

New information: confirmed CHMP positive opinion of a subcutaneous formulation of efgartigimod and MHRA approval is anticipated in November 2023

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion for a subcutaneous (SC) formulation of efgartigimod on 14th September 2023. The SC dossier was submitted to the United Kingdom (UK) Medicines & Healthcare Products Regulatory Agency (MHRA) on 18th September, via the Decision Reliance Procedure, and approval is anticipated in November 2023. This means that when final NICE guidance on efgartigimod is issued, both SC and intravenous (IV) formulations will be available to UK patients.

The upcoming availability of a subcutaneous formulation of efgartigimod will enhance treatment options for patients with gMG and will offer the following benefits.

- The SC formulation will enable a faster administration of efgartigimod and the potential for self-administration, therefore reducing burden on patients, caregivers, and healthcare providers. The SC formulation will be administered as a single dose with no adjustment based on weight or other factors.
- ‘academic / commercial in confidence information removed

In addition, at time of SC approval, our existing, Company-funded efgartigimod homecare programme will be expanded to include the new SC formulation. The homecare programme operationalised by HealthNet Homecare – one of the UK’s leading home care providers – provides home infusion and patient monitoring for efgartigimod-treated patients. During treatment cycles, HealthNet nurses administer the weekly MG-ADL questionnaire, with results being reported in real-time to the specialist centre. In-between treatment cycles, centres can also subscribe to optional intertreatment monitoring of MG-ADL, administered by HealthNet nurses during weekly telephone calls.

Overall, the efgartigimod homecare programme aims to reduce and minimise burden on the NHS, whilst ensuring optimised patient management, monitoring, and corresponding outcomes.

It is anticipated that most patients will ultimately be treated with a SC formulation. Further work is ongoing to develop an optimised self-administration device to enhance simplicity and convenience for HCPs and patients.

Economic analysis including the subcutaneous formulation is included as a scenario in Appendix E.

Higher utilisation of the SC formulation is associated with directionally positive changes in cost-effectiveness.

Revised economic analyses

The revised base case analysis is summarised in Table 2 below:

Table 2. Revised model base case analysis with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Efgartigimod	‘academic / commercial in confidence information removed’						15,228
Established clinical management	‘academic / commercial in confidence information removed’			-	-	-	-

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Reflecting changes to the assumptions regarding regular IVIg treatment, caregiver disutility, costs of administration of corticosteroids and pooled utilities across both arms leads to a base case ICER of £15,228 (when including a confidential discount), This is within the range considered to be a cost-effective use of NHS resources.

Exploratory scenario analyses and an explanation of all parameters assumed are provided in Appendix E.

Economic analyses following technical team request

Following discussion with the EAG and the NICE technical team after the publication of the draft guidance, the following additional questions were posed:

Question 1) How does the model use the transitions that were observed in the established clinical management arm of the ADAPT trial to inform the transition probabilities for the first four cycles after which people are assumed to return to their baseline health state?

Response: Patients in the placebo arm of the ADAPT study were assigned to a given model health-state based on the MG-ADL at baseline and at 4 week, and every 4 weeks thereafter. The number of patients in ADAPT who shifted to a different health state during each 4-week period starting from baseline was then used to calculate the transition matrices of the first four model cycles in the established clinical management arm. The transition matrices were therefore applied in the model to define the probabilities of entering and exiting a specific MG-ADL health-state during the first four model cycles in the established clinical management arm. Thus, the model represents the placebo effect observed during the trial period. After the fifth model cycle, the cohort is assumed to return towards baseline health-state distribution and remain in the same health state unless a crisis or death occurs.

It should be noted that the model considers a worsening of the disease also in the efgartigimod arm during the off-treatment period which follows the 4-weekly infusion of any treatment cycle and in the cohort who permanently discontinue treatment. Therefore, a maintenance of effect assumption was not applied in either the efgartigimod or the established clinical management arm.

Question 2) Why would the observed effect in the established clinical management arm not persist long term?

Response: The target population of the analysis includes gMG patients with MG-ADL>5 despite receiving established clinical management. The average duration from disease diagnosis in ADAPT AChR+ patients was 9.3 years. This suggests that established clinical management would likely remain inadequate to improve disease activity in the target population of the analysis (otherwise patients would have not remained uncontrolled despite use of established clinical management over the disease duration). Therefore, it is assumed that the distribution between health-states observed at baseline in the ADAPT study is representative of the expected population-level distribution of disease activity in gMG patients with an MG-ADL score of at least 5 despite treatment with established clinical management.

Question 3) Is the observed effect in the established clinical management arm due to regression to the mean, a trial effect, or a placebo effect?

Response: No long-term data on the established clinical management arm alone are available from the open label extension study of the ADAPT since all patients started receiving treatment with efgartigimod. Therefore, there is insufficient evidence available to assess whether the observed effect in the established clinical management arm was due to regression to the mean, a trial effect, or a placebo effect. Most likely, as it is often the case in chronic conditions, the three mechanisms all played a role, with some uncertainty on the degree of impact for each.

Nevertheless, these mechanisms are specific of a trial setting and are not likely to remain permanently in a population of patients with a rather long disease duration, over which the established clinical management showed to be inadequate to improve disease activity. Finally, as also mentioned in the response to Question 1, a maintenance of effect assumption was equally not applied in the efgartigimod arm of the model. The cohort in the efgartigimod arm is assumed to worsen during the off-treatment period following the 4-weekly infusion of each treatment cycle and after a permanent treatment discontinuation.

As requested, a scenario analysis exploring the impact of assuming the maintenance of the effect observed in the placebo arm of the ADAPT trial is included in Appendix E.

Summary

Recognising the complexity of cost-effectiveness decision-making for novel treatments in rare diseases, the Company have made every effort to narrow uncertainty and seek clinical validation on points that remained in question after the first ACM.

Responding to the areas raised and noted in the draft guidance, the Company commissioned a third party to develop and deliver a Delphi panel, involving a significant proportion of the specialist neuromuscular centres & clinical leads in England, which has provided important alignment and clarity on the optimised efgartigimod patient population where data is otherwise scant. Additional literature searching and evidence synthesis – as well as incremental clinical validation – has provided clarity in remaining areas, and exploratory analyses and scenarios have sought to explore a range of possibilities where point estimates remain unclear.

The clinical and patient communities, through their statements, have recognised the significant and urgent unmet need that exists in a condition that has seen little meaningful innovation for decades. The Company hope that the information and context provided can help to address outstanding questions and provide the basis for appropriate access for gMG patients for whom existing treatments have proven insufficient and where the burden of disease for patients and their families remains high.

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

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NICE National Institute for Health and Care Excellence

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Summary of additional evidence

Appendices

Appendix A UK Delphi panel to support efgartigimod for the treatment of generalised Myasthenia Gravis
Appendix B Estimation of the cost associated with systemic corticosteroid related adverse events in myasthenia gravis patients
Appendix C Effect following treatment discontinuation: Permanent treatment discontinuation transition probabilities
Appendix D Analysis of the Caregiver Burden Study: utility values and utility decrements for caregivers of people suffering from MG
Appendix E Economic analyses
Appendix F Confidential information checklist

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Single technology appraisal

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

New evidence submission

6 Oct 2023

File name	Version	Contains confidential information	Date
ID4003_Appendices[redacted ACIC]	1.0	Yes	6 Oct 2023

Appendix A UK Delphi panel to support efgartigimod for the treatment of generalised Myasthenia Gravis

Abbreviations

DVT	Deep Vein Thrombosis
EAMS/EAMS+	Early Access to Medicines Scheme
gMG	generalised Myasthenia Gravis
IVIg	intravenous immunoglobulin
IST	immunosuppressive therapy
NSIST	non-steroidal immunosuppressive therapies
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service

A.1 Executive summary

Introduction: The National Institute for Health and Clinical Excellence (NICE) draft guidance for efgartigimod in generalised Myasthenia Gravis (gMG) concluded efgartigimod, as an add-on to standard therapy, improves symptoms and people's ability to carry out their normal activities compared with standard therapy alone. It also highlighted specific areas of clinical and economic uncertainty, which thereby make the likely cost-effectiveness estimates for efgartigimod uncertain. Two such areas of uncertainty include who, within the National Health Service (NHS), might receive / be treated with efgartigimod, and whether this was reflected in clinical trials, as well as uncertainties concerning cost-effectiveness.

To address these issues, the Committee noted a number of areas for which additional information would be valuable. These include identifying and defining the characteristics of the target population who would be treated with efgartigimod, as well as estimating the proportion of these patients receiving maintenance intravenous immunoglobulin (IVIg).

Objective: The objective of this project was to address these identified areas of uncertainty, in order to gain a consensus on the most appropriate target patient population for treatment with efgartigimod in the NHS, and to establish better quantitative estimates of the proportion of people eligible/suitable for maintenance IVIg in this target population.

Methods: The NICE Committee are looking for explicit, valid and replicable methods of research to address the areas of uncertainty, therefore a Delphi panel was considered an appropriate approach. Delphi panels are accredited and accepted for achieving convergence of opinions concerning real-world knowledge solicited from experts.[1] The strengths of the Delphi method include quasi-anonymity, which avoids dominance of one opinion, and iteration, which allows individuals to change their opinions based on the information and explanations provided by other panellists in previous rounds.[2] It has been noted that the qualitative expressions of expert judgement elicited by the Delphi method can be used to scope economic models, while quantitative expressions can contribute towards defining point estimates of parameters and characterising uncertainty. Six experts, chosen to represent a diverse, geographically-representative (i.e., covering all major regions of England) sample of the specialist neuromuscular centres in England, were recruited to participate in this two round Delphi panel.

Results: The project successfully achieved a consensus on an appropriate target patient population for treatment with efgartigimod in the NHS and, working through the iterative two-round process, derived an informed estimate of the proportion of people eligible/suitable for treatment with maintenance IVIg within this population.

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 additional therapies, including non-steroidal immunosuppressive therapies (NSISTs) and rituximab, for an adequate period of time, at an adequate dose.

The Delphi established that 22.1% (mean, range 10–40%, n=6 responses) of the total gMG population would fit this description (round 1 and 2 results were closely aligned), and of these patients, the proportion eligible/suitable for maintenance IVIg was estimated as 69.2% (mean, range 60–90%; n=6 responses).

Conclusion: The simplified target patient population was confirmed to be appropriate for treatment with efgartigimod in the NHS, as well as the corresponding levels of maintenance IVIg usage within this population. The results of this Delphi provide strong additional information to address the remaining areas of uncertainty from a panel of highly experienced experts using a well-recognised and replicable study methodology.

A.2 Introduction

A.2.1 Background

Efgartigimod is currently being reviewed by NICE in England, and a number of clinical and economic uncertainties have been highlighted. This Delphi panel was conducted to provide further evidence to address these uncertainties and provide additional informed opinions, from gMG clinical experts, to support the final decision of the NICE Committee.

A.2.2 Research objectives

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 there are some remaining uncertainties around the population for which efgartigimod will be used and also uncertainty on elements of current treatment, especially around the use of IVIg. The research objective for this Delphi focuses on these elements as noted in Table 1.

Table 1 Research objectives

Number	Objectives
1	To gather expert opinions on the proposed patient population for treatment with efgartigimod on the NHS
2	To explore how many patients within the identified patient population should be prescribed IVIg on a regular / maintenance basis

Abbreviations: gMG, generalised Myasthenia gravis; IVIg, intravenous immunoglobulin; NHS, National Health Service

A.3 Methodology

A.3.1 Delphi process

The Delphi method is well suited to the aims of this project. It is a widely used, accredited and accepted method for achieving convergence of opinion concerning real-world knowledge solicited from experts.[1] The strengths of the Delphi method include quasi-anonymity, which avoids dominance of one opinion, and iteration, which allows individuals to change their opinions based on the information and explanations provided by other panellists in previous rounds.[2] It has been noted that qualitative expressions of expert judgement elicited by the Delphi method can be used to scope economic models, while quantitative expressions can contribute towards defining point estimates of parameters and characterising uncertainty.[2]

The Delphi process consists of rounds of surveys which can, in theory, be repeated continuously until a consensus is deemed to have been reached. The experts take part anonymously and

individually in sequential questionnaire rounds to avoid the possible domination of the process by one or a few members, thus reducing the potential for participant bias.[1]

In the present Delphi project, two rounds of surveys were conducted. In the development of the survey, the target duration of each round was a maximum of 20 minutes. Both rounds of survey included both open-ended and structured questions requiring both qualitative and quantitative answers related to the research objectives shown in Table 1.

Prior to round 1 dissemination to the Delphi panellists, a pilot was conducted with one Lumanity staff member and the argenx medical lead, to confirm that the questions and language were appropriate for the panellists.

Minor revisions were made to the survey based on the pilot to ensure that the functionality of the survey was as desired and the questions were clear, non-leading and unbiased. The round 1 and round 2 surveys are embedded in Appendix III.

After completion of the first round survey, summary responses were incorporated into a second-round survey which was sent to the same panellists for completion. This second survey presented back the anonymised, collated results of the first round to allow experts to reconsider their responses and to provide additional information that might support their responses to new, follow-on questions.

Both surveys were completed by the panellists via the Survey Monkey online platform. Before the first round, panellists were sent an email invitation by the Lumanity team, with a link to complete the survey, information on the context of the research questions, and instructions on how to complete the questionnaire.

The experts were provided with 2–3 days to complete the survey, which was dictated by the ongoing timelines of the NICE evaluation process.

A.3.2 Expert Panel

argenx was responsible for identification of appropriate experts for this study. Due to the rarity of the disease, experts were approached from the known neuromuscular specialist centres in England. The selection criteria to approach the panellists are provided in Appendix I. Once participation was confirmed, Lumanity were provided with the expert contact details for project follow-up. Six experts were approached and all six agreed to participate in the Delphi panel.

The background information of the participants is summarised in Table 2:

Table 2 Panellist experience

Question	Number of participants
Speciality: neurologist	6
Place of practice: specialist neuromuscular centre treating gMG	6
Experience of managing patients with gMG: > 5 years	6
Number of patients at centre with gMG	
101 – 250	1
251 – 500	4
>501	1

Approximate number of gMG patients under experts care:	
101 – 200	2
201 – 300	2
201 – 400	1
401 - 500	1

Abbreviations: gMG, generalised Myasthenia gravis

A.4 Data analysis

All responses from the panellists remained 'quasi-anonymous' when possible, i.e. they were known to the researchers, but their judgments and opinions remained strictly anonymous.[3] A threshold for consensus was pre-defined as 70% of the intention to treat data. This means that 70% of the initial number of panellists who consent to complete a Delphi round must agree for it to be deemed a consensus opinion. If a panellist consents but does not fully complete a survey round their responses will still be considered in the analysis.

For questions in which panellists were asked to provide numerical estimates, measures of central tendency (means, median) and level of dispersion (minimum and maximum) were used when appropriate. The number of panellists who provided a numerical estimate is also reported for each parameter. If a range was provided, the mid-point of that range was used to calculate the mean value, for example for a range of 15–25% the value of 20% was used to calculate the mean.

Qualitative data, e.g. from open text boxes, were presented in a descriptive manner.

If questions required a specific answer to be selected, the experts were always provided with an option such as 'other', and asked, when appropriate, to provide an explanation for their answer. To ensure that the anonymity of the participants was upheld, only Lumanity researchers were involved in project specific communications.

A.5 Results

A.5.1 Patient population likely to receive efgartigimod in the UK

A.5.1.1 Percentage of gMG patients matching proposed target patient population

In the first round of the survey, panellists were asked, over the past 12 months at their specialist centres, what percentage of patients would match the provided description as noted below.

The round 1 patient population was developed based on clinician input prior to the Delphi panel. Clinician feedback confirmed that this patient population have few alternative treatment options and a corresponding high level of unmet need, and would be considered the most suitable for add-on therapy with efgartigimod.

Table 3 Target patient population round 1 Delphi survey

Adult patients (≥18 years) with generalised Myasthenia gravis (gMG) positive for acetylcholine receptor (AChR) antibodies, and has a MG-ADL score ≥ 5 (>50% of MG-ADL score due to non-ocular symptoms) **with at least one of the following characteristics:** o A score of ≥2 on swallowing or breathing MG-ADL domains

o Have failed, not tolerated or are ineligible for standard therapy (standard therapy consists of adequate trials of steroids and at least 2 non-steroidal Immunosuppressive therapies [NSISTs], used at appropriate dosages and for an appropriate duration) o Non-tolerable side effects/comorbidities that limit or contraindicate the use of immunosuppressants o At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characteristics by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infections or use of drugs that may induce deterioration of gMG) with a need for plasmapheresis or immunoglobulins o Patients whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin

Number of responses	n = 6 (all panellists responded; 100%)
Mean percentage of all patients removed'	'academic / commercial in confidence information
Median percentage of all patients	'academic / commercial in confidence information removed'
Range	'academic / commercial in confidence information removed'

On presentation of the above results in round 2 we did not ask for additional information but did allow space for any comments from the panel. One expert noted that the mean values would be more realistic to use.

The panellists were also asked to estimate the separate elements of the above proposed patient description seen at their specialist centres over the past 12 months:

Description	Mean	Median	Range	Number of responses
A score of ≥2 on swallowing or breathing MG-ADL domains ONLY?	'academic / commercial in confidence information removed'			
Who have failed or not tolerated standard therapy (defined as adequate trials of steroids and at least 2 non-steroidal immunosuppressive therapies, used at appropriate dosages for an appropriate duration) ONLY?	'academic / commercial in confidence information removed'			
With non-tolerable side effects/ comorbidities that limit or contraindicate the use of immuno-suppressants ONLY?	'academic / commercial in confidence information removed'			

At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characterised by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infection or use of drugs that may induce deterioration of gMG) with a need for plasmapheresis or immunoglobulins ONLY?	'academic / commercial in confidence information removed'
Whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin ONLY	'academic / commercial in confidence information removed'
More than one of the above categories	'academic / commercial in confidence information removed'

On presentation of the above results in round 2 we did not ask for additional information but did allow space for any comments from the panel. One expert noted that there were too few responses to draw a conclusion.

A.5.1.2 Appropriate use of efgartigimod

Given the patient population described in Table 3, the panellists were asked if such patients were appropriate for add-on treatment with efgartigimod:

There was full consensus (n = 6; 100%) that the proposed population described would be appropriate for add-on treatment with efgartigimod

In addition, a more simplified version of the target patient population description was provided in round 2 to support the experts in providing a more defined estimate regarding IVIg eligibility.

A.5.1.3 Additional populations

In round 1, additional populations of gMG patients were also identified by the panellists as appropriate for treatment with efgartigimod.

Description	% of patients at centre	Number of responses
Bridging therapy e.g. for patients about to undergo thymectomy for thymic hyperplasia	'academic / commercial in confidence information removed'	1
Patients on maintenance plasma exchange	'academic / commercial in confidence information removed'	1
To reduce the dose of steroids patients are on	'academic / commercial in confidence information removed'	1

As before, we did not ask for additional information on the above descriptions in round 2 but space was provided for any of the panellist to provide additional information. One panellist noted that they agreed with the above suggested additional patient descriptions as suitable for treatment with add - on efgartigimod.

A.5.2 Use of regular/maintenance IVIg

Round 1: The experts were asked what percentage of patients in the proposed patient population (Table 3) should be prescribed regular/maintenance IVIg, regardless of potential supply issues. It should be noted that supply chain difficulties, although cited by the Committee, are transient and NHS utilisation patterns suggest no reduction in IVIg over time. Therefore, the Company believe it was most appropriate to remove supply issues from consideration in order to ensure accuracy regarding future IVIg prescribing.

The results are noted in the table below:

Number of responses	n = 6 (100%)
Mean percentage patients prescribed regular/maintenance IVIg commercial in confidence information removed'	'academic /
Median percentage of patients prescribed regular/maintenance IVIg commercial in confidence information removed'	'academic /
Range commercial in confidence information removed'	'academic /

The range in the responses to this question highlighted substantial differences across the panellists on what percentage of the proposed patient population should be prescribed regular/ maintenance IVIg.

To explore why the range was so diverse, the panellists were asked in round 2 to provide a rationale for their individual responses from round 1. In addition, a simplified patient description was provided and the same question asked although reframed to support added clarity on the question.

Explanations provided by the panel suggested that the original question in round 1 was likely mis-interpreted. Three panellists noted a potential confusion with the question and suggested that the lower percentages likely referred to the use of IVIg in the **total gMG population** rather than in the described proposed patient population.

Two other panellists provided additional explanations:

- Mine was based on my tertiary myasthenia population. Other patient populations are likely to vary in composition

- We offered all patients on regular IVIg with positive AChR antibodies treatment with Rituximab. We have had better than average response. We use plasma exchange rather than IVIg. We only have 1–2 patients on regular plasma exchange now and none on IVIg

Round 2: The panellists were then asked to consider a simplified target patient population description.

The simplified, round 2 population is strongly aligned to the patient eligibility criteria agreed as part of the EAMS/EAMS+ Blueteq form implemented in the UK. Clinician feedback (prior to the Delphi) confirmed that this patient population have few alternative treatment options and a high level of unmet need; enrolment in EAMS/EAMS+ demonstrates the relevance of this population to UK practice and confirms that the criteria can be consistently applied in specialist centres, appropriately and accurately.

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 additional therapies, including non-steroidal immunosuppressive therapies (NSISTs) and rituximab, for an adequate period of time, at an adequate dose.

Considering this population, the percentage of **total gMG population** that this would represent was estimated below:

Number of responses	n = 6 (100%)
Mean percentage total gMG patients	22.1%
Median percentage	20%
Range	10% to 40%

The estimates from this simplified description aligned closely with those of the round 1 survey and reduced the range in responses providing more confidence in the mean and median values.

As per round 1, the follow-up question asked what percentage of the simplified target patient population might be eligible for regular/maintenance IVIg, assuming no supply issues and assuming efgartigimod was not available.

Similar to round 1, IVIg supply chain difficulties were removed from consideration as they are expected to be transient and NHS utilisation patterns suggest no reduction in IVIg over time. Furthermore, potential usage of efgartigimod was also removed from consideration, when answering this question, as it is not yet commissioned for routine use within the NHS.

The resulting estimates are noted below:

Number of responses	n = 6 (100%)
Mean percentage eligible/ suitable for regular/ maintenance IVIg	69.2%

Median percentage	70%
Range	60% to 90%

The simplification of the patient description and the additional context added to the questions reduced the range of responses considerable, providing more confidence in the mean and median percentages.

To ensure a further degree of accuracy regarding prescribing in this simplified target patient population – particularly with regards to rescue therapies – a new question in round 2 was added to explore what percentage of the target patient population who might be eligible for regular/maintenance PLEX, assuming efgartigimod was not available. It was also assumed that there were no issues with the rescue therapy supply chain. The responses are below:

Number of responses	n = 6 (100%)
Mean percentage patients eligible/suitable for regular/maintenance PLEX	'academic / commercial in confidence information removed'
Median percentage	'academic / commercial in confidence information removed'
Range	'academic / commercial in confidence information removed'

To test the logic of the previous responses the panellists were asked to consider what percentage of the target patient population would NOT be eligible/suitable for regular/maintenance IVIg, assuming no supply issues and assuming efgartigimod is not available. The responses are below:

Number of responses	n = 6 (100%)
Mean percentage patients NOT eligible/suitable for regular/maintenance IVIg	'academic / commercial in confidence information removed'
Median percentage	'academic / commercial in confidence information removed'
Range	'academic / commercial in confidence information removed'

It should be noted that, over the three previous responses, the total % add up to approximately 100%, therefore providing further confidence in the numerical results.

Explanations for not being eligible/suitable for regular/maintenance IVIg were provided by each panellist (n = 6) and demonstrated considerable consistency. The explanations are noted below:

- *Thrombotic risk/ aseptic meningitis*
- *Contraindications – risk of thrombosis, renal failure, cardiac dysfunction etc.*

- *Contraindications such as poor IV access, previous DVT/ pulmonary emboli, inability to travel to site, severe complications such as aseptic meningitis from previous IVIg doses*
- *Rare cases of vascular complications on IVIg*
- *Patients' choice, reaction to IVIg, thrombosis, venous access, MG improving with another IST but not yet MG-ADL < 5*
- *Risk of thrombosis with IVIg, poor venous excess, risk of heart failure with IVIg*

For patients NOT eligible/suitable for IVIg or PLEX, the panellists were asked how they would treat these patients considering only currently commissioned treatment options (excluding clinical trials, unapproved/free of charge novel therapies, etc.). Again, this demonstrated considerable consistency and simultaneously highlighted the limited options that would be considered suitable for this target patient population.

Panellist	Option 1 (% of patients)	Option 2
1	Higher dose prednisolone (>80%)	Trials of other oral steroid sparing agents e.g. MTX, ciclosporin
2	Rituximab (10%)	Cyclophosphamide (5%)
3	Maintenance corticosteroids (80%)/ possible combination immunosuppressions (<5%)	No other obvious options
4	Ciclosporin (2%)	Cyclophosphamide – not used personally
5	Other IST and efgartigimod (75%)	Bone marrow transplant or monitoring (25%)
6	No other therapy	None

This completed the new questions asked of the panellists in round 2.

A.5.3 Other treatments

In round 1 the panellists were asked what other treatments would be prescribed for the target patient population at their specialist centres from an available list of products to select as noted in the table below. There was space provided for 'other' treatments of which 2 indicated IVIg.

Treatment	Number of responses
Corticosteroids	'academic / commercial in confidence information removed'
PLEX	
Thymectomy	
Rituximab	
Non-steroidal immunosuppressants (NSISTs)	
Other: IVIg	

One panellist in round 2 noted around these results that 'I would expect thymectomy to be offered to all AChR patients at the outset.'

Finally, within round 1, the panellists were provided with the opportunity to provide any additional comments that might further support the objectives of the project. Two additional comments were provided and written in the round 2 survey for the others to review. These comments were:

- *There are limited options for patients who fail standard immunosuppressive treatment. Typically patients are offered either maintenance IVIg or plasma exchange. This group of patients are likely to benefit from efgartigimod and reduce number of day case hospital admissions each year for treatment once the subcut formulation is made available.*
- *There is a small cohort of patients approximately 10 – 15% who are refractory – these patients are dependent on regular IVIg and PLEX and have frequent unplanned admissions to hospital – this group are likely to benefit from access to FcRN blockers (efgartigimod). NSITs will still be used for most patients but they take time to work (up to 18 months) – during this time patients are either symptomatic with resultant 'ad hoc' IVIg or PLEX treatment or are exposed to high dose steroids – efgartigimod as a 'bridging' treatment for these patients would reduce treatment associated risks. In all patients treated with efgartigimod it would be reasonable to have planned treatment pauses or holidays to determine whether the drug is still required and to re-establish the most suitable treatment frequency.*

From round 2 there was one additional response from a panellist agreeing with the previously made comments plus a further response from one panellist as noted below:

- *The advantage of efgartigimod is that it works very quickly and we can assess the response within days. It would be good to give this on a regular basis rather than only when they start to worsen. It can also be used as an induction therapy, while waiting for other maintenance therapies to work (e.g. Rituximab).*

A.6 Summary

Patient population likely to receive efgartigimod in the UK

There was a full consensus that the round 1 patient description, as found in Table 3, would be appropriate for add-on treatment with efgartigimod. It is logical that this consensus holds for the simplified version of this patient description, as summarised below and utilised in round 2:

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 additional therapies, including non-steroidal immunosuppressive therapies (NSISTs) and rituximab, for an adequate period of time, at an adequate dose.

In round 2, it was confirmed this simplified target patient population represents 22.1% of the **total gMG population** seen in the specialist centres around England.

Use of regular/ maintenance IVIg

The mean percentage of these patients eligible/suitable for regular/maintenance IVIg was estimated as 69.2%.

In addition, a mean of 'academic / commercial in confidence information removed' were noted as eligible for PLEX and 'academic / commercial in confidence information removed' as not suitable for regular/maintenance IVIg.

A.7 References

1. Hsu C-C and Sandford B. The Delphi Technique: Making Sense Of Consensus. Practical Assessment, Research and Evaluation. 2007; 12.

2. Iglesias CP, Thompson A, Rogowski WH and Payne K. Reporting Guidelines for the Use of Expert Judgement in Model-Based Economic Evaluations. PharmacoEconomics. 2016; 34: 1161-72.

3. Hasson F, Keeney S and McKenna H. Research guidelines for the Delphi survey technique. Journal of Advanced Nursing. 2000; 32: 1008-15.

Appendix I. Selection of clinical experts

Selection criteria for the UK experts

- The participant must work in one of the neuromuscular specialist centres commissioned to treat gMG as determined by NHS England.
- The centre should be known to treat at least 100 gMG patients (quantifiable expertise).
- The participant must be known as a neurology expert in the treatment of gMG patients (qualitative expertise), who argenx believes will have the knowledge and capability to answer the questions posed in the Delphi survey.
- The participant must be previously responsive to an argenx invitation, to avoid irritation to any potential expert who would be highly unlikely to engage.
- In recruiting the sample, an adequate geographic spread was sought to ensure differing treatment patterns around the country would be explored.

Appendix II Delphia panel experts

Expert	Affiliation
Dr. Saiju Jacob	Queen Elizabeth Hospital, Birmingham
Dr. Channa Hewamadduma	Sheffield Teaching Hospitals NHS Foundation Trust
Dr. Fiona Norwood	King's College London
Dr. Sivakumar Sathasivam	The Walton Centre NHS Foundation Trust, Liverpool
Dr. Jennifer Spillane	UCL Queens Square, London
Dr. Ashwin Pinto	University Hospital Southampton

Appendix III Delphi surveys

Round 1 Delphi Survey

The Delphi survey presented to the panellist's in round 1 is presented below:

Background

On behalf of argenx and Lumanity, thank you for agreeing to participate in this Delphi Panel research project. The project focuses on generalised Myasthenia Gravis (gMG) in the UK setting primarily to support the ongoing submission for efgartigimod to the National Institute for Health and Care Excellence (NICE) in England.

The Delphi methodology

The Delphi methodology was originally developed by the RAND Corporation in the 1950s as a practical and structured method of obtaining opinions on a given question from a range of experts (Dalkey N and Helmer O. An experimental application of the Delphi method to the use of experts. RAND memorandum,1962). The participants take part anonymously in sequential rounds of surveys, with each round being refined based on the feedback from the previous version. The goal is to reach a consensus on the questions posed. This project will comprise two rounds of surveys, with each round taking no more than 20 minutes. A synthesis of responses will be conducted between each survey round to formulate the subsequent surveys. In this study, a predefined threshold for consensus of 70% will be used. As per the Delphi Process, your responses will remain anonymous to the other Delphi Panel respondents. The final report will acknowledge your participation and centre affiliation, although no statements or responses attributable to you or others will be included in this report. This aspect of the Delphi process is designed to prevent dominance of individual opinions, thus enabling the most robust possible consensus (Iglesias CP, Thompson A, Rogowski WH and Payne K. Reporting guidelines for the use of expert judgement in model-based economic evaluations. Pharmacoeconomics. 2016; 34: 1161-72).

NICE

NICE is an executive non-departmental public body of the Department of Health and Social Services in England. They consider the best available evidence to develop recommendations that guide decisions, and especially for new pharmaceuticals they consider clinical and cost-effectiveness of treatments in the UK to ensure that NHS patients have equitable access to appropriate products. 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 there are some uncertainties around the

population for which efgartigimod will be used and also uncertainty on elements of current treatment, especially around the use of IVIg. The research objective for this Delphi focuses on these elements as noted below:

Number	Objectives
1	To gather expert opinions on the proposed patient population for treatment with efgartigimod on the NHS
2	To explore how many patients within the identified patient population should be prescribed IVIg on a regular / maintenance basis

Round 1 survey

This is the first round of two surveys and should take approximately 20 minutes to complete. We recommend that you complete the survey in one sitting; however, if this is not possible, you can save your answers and complete the survey at a more convenient time. For answers to be saved, you will need to complete the section you are on and press 'Next'.

Your individual responses to this survey will be kept anonymous and will be analysed by Lumanity. Results will be combined and presented back to you in a second survey with the aim of moving towards a consensus.

Adverse event reporting

Although this is an online survey and how you respond will be treated in confidence, should you raise an adverse event and/or product complaint, we will need to report this, even if it has already been reported by you directly to the company or the regulatory authorities. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events with this product should also be reported to reportnow@argenx.com. For further information about this medicine please telephone +44 (0) 20 4532 4016 or email ukmedinfo@argenx.com. If any adverse events are identified during the analysis of responses, we require your permission to include your name and contact information in the report we send to the pharmaceutical company commissioning this market research, so that they can report this and meet their legal obligations. The drug safety department may wish to contact you directly for further information relating directly to the adverse event. Everything else you contribute during the Delphi survey will continue to remain confidential.

* 1. Are you happy to proceed with the survey on this basis?

Yes

No

* 2. What is your name?

Please note that this information will be used for internal tracking purposes only. Your individual responses will remain anonymous, although the final report will acknowledge your participation and centre affiliation.

3. I am a:

Neurologist

Specialist nurse

Other (please specify)

* 4. Do you work at a specialist neuromuscular centre treating patients with gMG?

Yes

No

* 5. How many years of experience do you have in managing patients with gMG?

Less than 1 year

1 to 5 years

More than 5 years

* 6. How many patients with gMG are currently registered in the centre/hospital where you work?

<50

51 - 100

101 - 250

251 - 500

>501

* 7. Approximately how many patients with gMG are currently under your care?

<100

101 - 200

201 - 300

301 - 400

401 - 500

501 or greater

Patient population likely to receive efgartigimod in the UK

Efgartigimod is indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody positive.

It has been noted that the product could be positioned at several points in the clinical pathway.

The proposed target patient population for treatment on the NHS is as follows:

- **As an add-on to standard therapy for the treatment of adult patients (≥18 years) with generalised Myasthenia gravis (gMG) positive for acetylcholine receptor (AChR) antibodies, and has a MG-ADL score ≥ 5 (>50% of MG-ADL score due to non-ocular symptoms) with at least one of the following characteristics:**
- **A score of ≥2 on swallowing or breathing MG-ADL domains**

- **Have failed, not tolerated or are ineligible for standard therapy (standard therapy consists of adequate trials of steroids and at least 2 non-steroids Immunosuppressive therapies [NSISTs], used at appropriate dosages and for an appropriate duration)**
- **Non-tolerable side effects/comorbidities that limit or contraindicate the use of immunosuppressants**
- **At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characteristics by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infections or use of drugs that may induce deterioration of gMG) with a need for plasmapheresis or immunoglobulins**
- **Patients whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin**

* 8. Considering the proposed patient population for treatment as described above, what percentage of your patients with gMG over the past 12 months, meet one or more of these categories?

* 9. Considering the proposed patient population for treatment as described above, do you agree that efgartigimod is an appropriate add-on treatment?

Yes

No

10. Please describe any other populations of gMG patients that you feel will be appropriate for treatment with efgartigimod?

11. Please write-in the associated % of patients at your specialist centre (over the past 12 months) that match the description you have written above?

* 12. For each of the following patient categories please provide your **best estimate** of the percentage of the patients in your specialist centre (over the past 12 months) who match the descriptions. We recognise that there is overlap between some of these categories and it will be impossible to provide an accurate assessment without significant background research. This is not the intention of this question – please simply provide your **'best' estimate based on your personal experience**. Each population should be considered with the following context:

As an add-on to standard therapy for the treatment of adult patients (≥18 years) with generalised Myasthenia gravis (gMG) positive for acetylcholine receptor (AChR) antibodies, and has a MG-ADL score ≥5 (>50% of MG-ADL score due to non-ocular symptoms) AND:

	Of the proposed target population what percentage of patients fall into each category
A score of ≥2 on swallowing or breathing MG-ADL domains ONLY?	
Who have failed or not tolerated standard therapy (defined as adequate trials of steroids and at least 2 non-steroid immunosuppressive therapies, used at appropriate dosages for an appropriate duration) ONLY?	
With non-tolerable side effects/ comorbidities that limit or contraindicate the use of immuno-suppressants ONLY?	
At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characterised by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infection or use of drugs that may induce deterioration of gMG) with a need for plasmapheresis or immunoglobulins ONLY?	
Whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin ONLY	
More than one of the above categories	

Use of regular/ maintenance IVIg

For the proposed patient population described in the previous section we now want to understand what percentage should be prescribed regular/ maintenance IVIg. This questions aims to identify how many patients should get IVIg assuming there are no issues around the supply of IVIg.

* 13. The proposed target patient population for treatment on the NHS is as follows:

- As an add-on to standard therapy for the treatment of adult patients (≥18 years) with generalised Myasthenia gravis (gMG) positive for acetylcholine receptor (AChR) antibodies, and has a MG-ADL score ≥ 5 (>50% of MG-ADL score due to non-ocular symptoms) with at least one of the following characteristics:
    - A score of ≥2 on swallowing or breathing MG-ADL domains Have failed, not tolerated or are ineligible for standard therapy (standard therapy consists of adequate trials of steroids and at least 2 non-steroids Immunosuppressive therapies [NSISTs], used at appropriate dosages and for an appropriate duration)

- Non-tolerable side effects/comorbidities that limit or contraindicate the use of immunosuppressants
- At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characteristics by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infections or use of drugs that may induce deterioration of gMG) with a need for plasmapheresis or immunoglobulins
- Patients whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin

Considering the proposed patient population for treatment what percentage of this **TOTAL**

patient population should be prescribed IVIg?

* 14. For each of the separate patient categories please provide your personal opinion on the percentage who should be prescribed IVIg.

Each population should be considered with the following context:

As an add-on to standard therapy for the treatment of adult patients (≥18 years) with generalised Myasthenia gravis (gMG) positive for acetylcholine receptor (AChR) antibodies, and has a MG-ADL score ≥ 5 (>50% of MG-ADL score due to non-ocular symptoms) AND:

	Percentage patients who should be prescribed IVIg maintenance (%)
A score of ≥2 on swallowing or breathing MG-ADL domains ONLY?	
Who have failed or not tolerated standard therapy (defined as adequate trials of steroids and at least 2 non-steroid immunosuppressive therapies, used at appropriate dosages for an appropriate duration) ONLY?	
With non-tolerable side effects/ comorbidities that limit or contraindicate the use of immuno-suppressants ONLY?	
At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characterised by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infection or use of drugs that may induce deterioration of gMG) with a need for plasmapheresis or immunoglobulins ONLY?	
Whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan	

for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin ONLY	
More than one of the above categories	

15. Are there any other patient populations that should be prescribed regular/ maintenance IVIg in your specialist centre? If yes, please describe / specify.

16. What percentage of this other group of patients at your specialist centre (over the past 12 months) will receive maintenance IVIg?

Other treatments

As noted previously, the proposed target patient population for treatment of efgartigimod on the NHS is as follows:

- **As an add-on to standard therapy for the treatment of adult patients (≥18 years) with generalised Myasthenia gravis (gMG) positive for acetylcholine receptor (AChR) antibodies, and has a MG-ADL score ≥5 (>50% of MG-ADL score due to non-ocular symptoms) with at least one of the following characteristics:**
    - **A score of ≥2 on swallowing or breathing MG-ADL domains Have failed, not tolerated or are ineligible for standard therapy (standard therapy consists of adequate trials of steroids and at least 2 non-steroids Immunosuppressive therapies (NSISTs), used at appropriate dosages and for an appropriate duration)**
    - **Non-tolerable side effects/comorbidities that limit or contraindicate the use of immunosuppressants**
    - **At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characteristics by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infections or use of drugs that may induce deterioration of gMG) with a**
    - **need for plasmapheresis or immunoglobulins**
    - **Patients whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin**

17. Please can you indicate by ticking the relevant boxes below which of the following treatments will likely be prescribed for this patient group at your specialist centre?

Corticosteroids

PLEX

Thymectomy

Rituximab

Non-steroidal immunosuppressants (NSISTs)

Other (please specify)

18. Please note any other treatment options for the patient population prescribed at your centre not listed above

19. Please provide any other comments you feel are appropriate to support the objectives of this project.

Delphi round 2

Background

On behalf of argenx and Lumanity, thank you for your continued participation in this Delphi panel research project. The project focuses on generalised Myasthenia Gravis (gMG) in the UK setting primarily to support the ongoing submission for efgartigimod to the National Institute for Health and Clinical Excellence (NICE). The research objective for this Delphi focuses on these elements as noted below:

Number	Objectives
1	To gather expert opinions on the proposed patient population for treatment with efgartigimod on the NHS
2	To explore how many patients within the identified patient population should be prescribed IVIg on a regular / maintenance basis

Abbreviations: gMG, generalised Myasthenia gravis, IVIg, intravenous immunoglobulin; NHS, National Health Service

Round 2 survey

Your responses to the first survey have been collated and reviewed (six completed surveys were received and analysed). This second round of the Delphi panel focuses on specific

questions for which we are looking to achieve a consensus of opinion (pre-defined as 70% of responses) and also presents the full analysis of the round 1 questions, for your information.

We anticipate that this individual survey should take no more than 20 minutes to complete. We recommend that you complete the survey in one sitting; however, if this is not possible, you can save your answers and complete the survey at a more convenient time. To save your answers, you will need to complete the section you are on and press 'Next'.

Your individual responses to this survey will be kept anonymous and will be analysed by Lumanity. Collated results will be provided to you at the end of the study for your information.

Adverse event reporting

Although this is an online survey and how you respond will be treated in confidence, should you raise an adverse event and/or product complaint, we will need to report this, even if it has already been reported by you directly to the company or the regulatory authorities. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events with this product should also be reported to reportnow@argenx.com. For further information about this medicine please telephone +44 (0) 20 4532 4016 or email ukmedinfo@argenx.com. If any adverse events are identified during the analysis of responses, we require your permission to include your name and contact information in the report we send to the pharmaceutical company commissioning this market research, so that they can report this and meet their legal obligations. The drug safety department may wish to contact you directly for further information relating directly to the adverse event.

Everything else you contribute during the Delphi survey will continue to remain confidential.

* 1. Are you happy to proceed with the survey on this basis?

Yes

No

About you

* 2. What is your name?

Please note that this information will be used for internal tracking purposes only. Your individual responses will remain anonymous, although the final report will acknowledge your participation and centre affiliation.

Focused questions for round 2 consensus:

Background: For the proposed patient population we asked what percentage should be prescribed regular/maintenance IVIg, regardless of potential supply issues (n = 6 responses).

The proposed target population for treatment on the NHS was detailed to you in Round 1.

The panel results are in the table below:

Average percentage of patients prescribed regular/maintenance IVIg	'academic / commercial in confidence information removed'
Median percentage of patients prescribed regular/maintenance IVIg	'academic / commercial in confidence information removed'
Range	'academic / commercial in confidence information removed'

The range in the responses to this question highlights substantial differences across the panellists on what percentage of the proposed patient population should be prescribed regular/maintenance IVIg.

Given this finding we want to explore this question further to understand why such variation might exist and to try to work towards achieving a consensus of opinion.

* 3. Considering the wide range of opinions on the percentage that should be prescribed regular/maintenance IVIg from the panel (15% to 70%), can you provide the rationale for your round 1 response? This is to help us understand why this variation might have arisen?

Considering the group response and the rationale that you have just provided, we would like you to consider the following questions and simplified patient population to support achieving a consensus opinion.

The target patient population has been simplified as follows:

License 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 additional therapies, including non-steroidal immunosuppresive therapies (NSISTs) and rituximab, for an adequate period of time, in an adequate dose.**

* 4. Considering this **target patient population**, what percentage of your **total gMG population** will this represent?

* 5. Considering the **target patient population**, what percentage of these patients would be eligible/suitable for regular/maintenance IVIg, assuming no supply issues, and assuming efgartigimod is not available?

* 6. Considering the **target patient population**, what percentage of these patients would be eligible/suitable for regular/maintenance PLEX, assuming no supply issues, and assuming efgartigimod is not available?

* 7. Considering the **target patient population**, what percentage of these patients would **NOT** be eligible/suitable for regular/maintenance IVIg, assuming no supply issues, and assuming efgartigimod is not available?

* 8. Can you please summarise the reasons that would make these patients **NOT** eligible/suitable for regular/maintenance IVIg?

* 9. Considering only currently commissioned treatment options (i.e. excluding clinical trials, unapproved / free-of-charge novel therapies, etc.) how would you treat patients that are not eligible/suitable for IVIg OR PLEX?

Other therapy, *please specify which therapy* and provide a percentage:

Other therapy, *please specify which therapy* and provide a percentage:

Round 1 recap of results

The following pages recap the panel results from Round 1. There are no required responses in this section, however, you will be able to provide any feedback after reviewing the information.

Patient population likely to receive efgartigimod in the UK

Efgartigimod is indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody positive.

It has been noted that the product could be positioned at several points in the clinical pathway.

10. The proposed target patient population for treatment on the NHS is as follows:

- As an add-on to standard therapy for the treatment of adult patients (≥18 years) with generalised Myasthenia Gravis (gMG) positive for acetylcholine receptor (AChR) antibodies, and has a MG-ADL score ≥ 5 (>50% of MG-ADL score due to non-ocular symptoms) **with at least one of the following characteristics**:
    - A score of ≥2 on swallowing or breathing MG-ADL domains Have failed, not tolerated or are ineligible for standard therapy (standard therapy consists of adequate trials of steroids and at least 2 non-steroids Immunosuppressive therapies [NSISTs], used at appropriate dosages and for an appropriate duration)
    - Non-tolerable side effects/comorbidities that limit or contraindicate the use of immunosuppressants
    - At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characteristics by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infections or use of drugs that may induce deterioration of gMG) with a need for plasmapheresis or immunoglobulins
    - Patients whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin

Of the patients with gMG seen by the panellists over the past 12 months at their specialist centres, the following provides the results of how many are considered to meet one or more of the above categories (n=6 responses):

Average percentage of all patients	‘academic / commercial in confidence information removed’
Median percentage of all patients	‘academic / commercial in confidence information removed’
Range	‘academic / commercial in confidence information removed’

We do not require any further information on this, but if you wish to add any additional information, please do so in the box below:

Patient population likely to receive efgartigimod in the UK

11. In round 1 of the Delphi panel we asked if you thought the population described was appropriate for add-on treatment with efgartigimod.

There was full consensus (n = 6; 100%) that the proposed population described would be appropriate for add-on treatment with efgartigimod

Additional populations of gMG patients were also identified as appropriate for treatment with efgartigimod by the panellists. For your information these additional populations were:

Description	% of patients at centre
Bridging therapy (e.g. for patients about toundergo thymectomy for thymic hyperplasia)	'academic / commercial in confidence information removed'
Patients on maintenance plasma exchange	'academic / commercial in confidence information removed'
To reduce the dose of steroids patients are on	'academic / commercial in confidence information removed'

We do not require any further information on this, but if you wish to add any additional information, please do so in the box below:

12. You were asked to provide your best estimate of the percentage of patients at your specialist centre (over the past 12 months) who matched the description of patients proposed for add-on treatment with efgartigimod. The following table presents the collated results of the panel estimates.

As a reminder, efgartigimod is proposed as an add-on to standard therapy for the treatment of adult patients (≥18 years) with generalised Myasthenia Gravis (gMG) positive for acetylcholine receptor (AChR) antibodies, and has a MG ADL score ≥5 (>50% of MG-ADL score due to non-ocular symptoms) **AND**:

Description	Average % of patients at specialist centre	Median	Range	Number of responses
A score of ≥2 on swallowing or breathing MG-ADL domains ONLY?	'academic / commercial in confidence information removed'			
Who have failed or not tolerated standard therapy (defined as adequate trials of steroids and at least 2 non-steroidal immunosuppressive therapies, used at appropriate dosages for an appropriate duration) ONLY?	'academic / commercial in confidence information removed'			
With non-tolerable side effects/ comorbidities that limit or contraindicate the use of immunosuppressants ONLY?	'academic / commercial in confidence information removed'			

At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characterised by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infection or use of drugs that may induce deterioration of gMG) with a need for	'academic / commercial in confidence information removed'
plasmapheresis or immunoglobulins ONLY? Whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin ONLY	'academic / commercial in confidence information removed'
More than one of the above categories	'academic / commercial in confidence information removed'

We do not require any further information on this, but if you wish to add any additional information, please do so in the box below:

Use of regular/maintenance IVIg

13. Regarding the prescribing of IVIg, we also asked for a breakdown of the % of patients by each specific description of who should be prescribed IVIg. The findings are noted in the table below:

Description	**Average % of patients at specialist centre**	**Median**	**Range**	**Number of responses**
A score of ≥2 on swallowing or breathing MG-ADL domains ONLY?	'academic / commercial in confidence information removed'			
Who have failed or not tolerated standard therapy (defined as adequate trials of steroids and at least 2 non-steroidal immunosuppressive therapies,	'academic / commercial in confidence information removed'			

used at appropriate dosages for an appropriate duration) ONLY?	
With non-tolerable side effects/ comorbidities that limit or contraindicate the use of immunosuppressants ONLY?	‘academic / commercial in confidence information removed’
At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characterised by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infection or use of drugs that may induce deterioration of gMG) with a need for	‘academic / commercial in confidence information removed’
plasmapheresis or immunoglobulins ONLY? Whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin ONLY	‘academic / commercial in confidence information removed’
More than one of the above categories	‘academic / commercial in confidence information removed’

Again the variation across the panellist responses was very wide, however the response rate to this question was generally low suggesting this may have been too challenging to estimate.

No further information will be asked around this question, however if you wish to provide any further information please do so below:

14. We asked if there are any other patient populations that should be prescribed regular/maintenance IVIg and what percentage of this group would receive this. This following table describes the responses.

Description	**% of patients at centre receiving IVIg**

Bridging therapy to thymectomy	‘academic / commercial in confidence information removed’
Those with hypogammaglobulinaemia	‘academic / commercial in confidence information removed’
Those on high dose maintenance steroids	‘academic / commercial in confidence information removed’
Younger than 18, MUSK and zero negative cases	‘academic / commercial in confidence information removed’

No further information will be asked around this question, however if you wish to provide any further information please do so below:

Other treatments

In round 1, the proposed target patient population for treatment of efgartigimod on the NHS is as follows:

- **As an add-on to standard therapy for the treatment of adult patients (≥18 years) with generalised Myasthenia Gravis (gMG) positive for acetylcholine receptor (AChR) antibodies, and has a MG-ADL score ≥5 (>50% of MG-ADL score due to non-ocular symptoms) with at least one of the following characteristics:**
    - **A score of ≥2 on swallowing or breathing MG-ADL domains Have failed, not tolerated or are ineligible for standard therapy (standard therapy consists of adequate trials of steroids and at least 2 non-steroidal Immunosuppressive therapies (NSISTs), used at appropriate dosages and for an appropriate duration)**
    - **Non-tolerable side effects/comorbidities that limit or contraindicate the use of immunosuppressants**
    - **At least one myasthenic crisis, unplanned hospital admission or clinically important exacerbation event per year (events characteristics by respiratory or bulbar weakness or paralysis, unrelated to poor adherence to therapy; infections or use of drugs that may induce deterioration of gMG) with a need for plasmapheresis or immunoglobulins**
    - **Patients whose symptom progression is "explosive", requiring rapid symptom control in order to determine an optimal treatment plan for gMG. These patients would otherwise be treated with plasmapheresis or intravenous immunoglobulin**

15. We wanted to explore what other treatments would likely be prescribed for this patient population at your specialist centres. The results from the panellists are noted in the table below:

Treatment	**Number of responses**

Corticosteroids	‘academic / commercial in confidence information removed’
PLEX	
Thymectomy	
Rituximab	
Non-steroidal immunosuppressants (NSISTs)	
Other: IVIg	

We do not require any further information on this, but if you wish to add any additional information, please do so in the box below:

Additional comments

16. Finally, we asked if there were any additional comments that you felt might support the objectives of this project. Two additional comments were provided as follows:

- There are limited options for patients who fail standard immunosuppressive treatment. Typically patients are offered either maintenance IVIg or plasma exchange. This group of patients are likely to benefit from efgartigimod and reduce number of daycase hospital admissions each year for treatment once the subcut formulation is made available
- There is a small cohort of patients approximately 10 – 15% who are refractory – these patients are dependent on regular IVIg and PLEX and have frequent unplanned admissions to hospital – this group are likely to benefit from access to FcRN blockers (efgartigimod). NSITs will still be used for most patients but they take time to work (up to 18 months) – during this time patients are either symptomatic with resultant ‘ad hoc’ IVIg or PLEX treatment or are exposed to high dose steroids – efgartigimod as a ‘bridging’ treatment for these patients would reduce treatment associated risks. In all patients treated with efgartigimod it would be reasonable to have planned treatment pauses or holidays to determine whether the drug is still required and to re-establish the most suitable treatment frequency.

We would like to thank you for your time and if you have any further comments based on any of the results presented here please do so in the box below:

Disqualification page

Based on your response to one of the questions in this survey, we ask that you please contact ‘academic / commercial in confidence information removed’ to discuss any concerns you have, before continuing this Delphi Panel.

Thank you!

Appendix B Estimation of the cost associated with systemic corticosteroid related adverse events in myasthenia gravis patients

B.1 Introduction

Two Systematic Literature Reviews (SLR) were conducted in 2022 to retrieve the available evidence on the burden of systemic corticosteroid exposure in adult patients with chronic diseases (among which Myasthenia Gravis - MG): a clinical SLR to assess the impact of corticosteroid systemic use on mortality, and an economic SLR which explored the impact on the health-related quality of life (HRQoL) and costs. Studies identified via the searches were included only if they provided estimates of burden in patients on systemic corticosteroid compared with non-corticosteroid users, within the same baseline disease was reported in the publication. Frequency of adverse events (AEs) associated with corticosteroid systemic use were not included as outcome of interest in the clinical and economic SLRs previously conducted and therefore any study reporting only AEs were not included.

Among studies reporting costs identified via the SLR conducted in 2022, none included patients with generalized MG (gMG). To ensure an accurate estimation of costs associated with corticosteroid systemic use in gMG specifically, an additional Target Literature Review (TLR) was performed in September 2023 with the aim to obtain available publications that reported the frequency of systemic corticosteroid related AE in MG patients. The frequency of systemic corticosteroid AEs obtained from the literature was then used as basis to estimate the total annual cost of systemic corticosteroid use.

B.2 Target literature search

A target literature search was performed in September 2023 with the aim to obtain available publications that reported the frequency of systemic corticosteroid related AE in MG patients.

A search strategy in PubMed was built, using the following terms:

("myasthenia gravis"[Title/Abstract] OR "MG"[Title/Abstract] OR "myasthenia gravis"[MeSH Terms])

AND

("corticosteroid"[Title] OR "steroid"[Title] OR "glucocorticoid"[Title] OR "prednisone"[Title] OR "prednisolone"[Title] OR "corticoid"[Title])

AND

("adverse events"[Title/Abstract] OR "side effects"[Title/Abstract] OR "complications"[Title/Abstract] OR "adverse effects"[Title/Abstract])

After obtaining the results from the search, the articles were exported into Microsoft Excel for screening, according to the eligibility criteria for the TLR presented in Table 4.

Table 4 Eligibility criteria for the TLR

	Inclusion criteria	Exclusion criteria

Population	Myasthenia gravis patients	Ocular MG only, MG+ thymectomy patients only
Intervention	Corticosteroids administered as maintenance treatment	Variable doses/administration only in perioperative setting, combined intervention with any other medication (including surgery).
Comparator	Any/None	N/A
Outcomes	Corticosteroid related adverse events frequency, reported at any time from the start of CS treatment and not limited to the study period	CS related AE not reported. CS related AE reported only for the duration of the study
Study design	Observational/RCTs	Case reports less than 5, narrative reviews, in vitro studies, animal studies
Other	Full text in English	Other language

Abbreviations: AE, adverse event; CS, corticosteroids; MG, myasthenia gravis; N/A, not applicable; RCT, randomised controlled trial; TLR, targeted literature review

B.3 Results

A total of 51 publications were retrieved. After an initial screening of the title and abstract of each study, 48 publications were excluded, and 3 papers were considered for full text screening.

The main characteristics of the three studies, and the reasons for inclusion/exclusion for data extraction are presented Table 5.

Table 5 Study characteristics

	Johnson 2021[1]	**Lee 2018[2]**	**Fan 2023[3]**
Study design	Observational / retrospective study	Observational study/ survey collected data	Observational cohort study / retrospective
Population	Data from 39 patients with gMG who were treated with oral corticosteroids for >1 year, aged 18 or more years, who were treated at a single centre in the United States between January 2014 and December 2015	298 patients, of age ≥18 years, with MG who reported current (n.174, 58%) or past (n.288) prednisone intake	116 patients registered from 1 July 2017 to 30 June 2021 in the Myasthenia Gravis Trial Database in Xuanwu Hospital, who received mono-CS as initial treatment
Female	n 21 (53.8%) were female	Prednisone group (n.298): 54% female (n.161)	Female n. 43 (37.1%)
Age	Median age: 60 (21), and 26 (66.7%) patients were aged <65 years	Age at enrolment: 58.3 (12.5)	Mean age 50.1, SD (15.7)
Severity	Disease severity: 60% were categorized as MGFA disease class 2A or 2B. The median (IQR) MG-ADL score was 7	MG-ADL: 5.5, SD (4.1)	MG-ADL at baseline, median (IQR): 5.0 (4.0–6.0)

	Johnson 2021[1]	Lee 2018[2]	Fan 2023[3]
	(1) and the range was 2 to 11.		
Country	United States	United States	China
Inclusion criteria	Diagnosis of gMG. MGFA Classes 2–4. Treated with oral corticosteroids for their gMG symptoms for > 1 year. >1 year of follow-up. Decremental response on low-frequency repetitive nerve stimulation or abnormal jitter on single-fiber electromyograph	Patients age ≥18 years who answered "Yes" to "Has your doctor diagnosed you with MG?". Resided in the United States. Completed the 9th semi-annual follow-up survey before November 29, 2017	Patients who received mono-tacrolimus (mono-TAC group) or mono glucocorticoids (mono-GC group) as initial treatment were included
Outcomes	ASEs reported as being related to corticosteroid treatment, by dose	Prednisone AE related in men and in women. Intolerable AE reported and willingness to accept a dose increase by gender	CS incidence of potential adverse events as a secondary endpoint
CS threshold dose definition	Moderate: <30 mg/day, High: >30 mg/day	Threshold not defined.	Threshold not defined.
AChR antibody + MG population	89.7%	Not reported	Not reported
Mean duration CS treatment	Prednisone treatment: 14.3 months (median, 14 months; IQR, 2 months)	Men: 44.3 (74.6) months, women: 52.0 (85.7) months	Follow-up time after initial CS, mean (SD): 20.9 (14.2) months
Mean CS daily dose	36.0 mg. (median, 40 mg; range 10–50 mg; IQR 15 mg)	Current prednisone dosage varied from 0.5 to 75 mg (median 10 mg, IQR 7–20), dosing frequency was daily in 76% and every other day 18%	The initial dose of oral prednisone in 110 patients was 15 or 20 mg and was increased by 10 mg every one week up to 0.5–1.0 mg/kg of body weight per day for maintenance treatment. In 6 patients, methylprednisolone was given intravenously with an initial daily dose of 500 mg and decreased by half every 3 days to 120 mg for 3 days before switching to prednisone 60 mg per day, and then gradually decreased to the maintenance dose based on the clinical efficacy
Mean number of ASEs per patient	2.3 (median, 2; IQR, 1)	Any AE in men group: 81%. Women group: 95%. Mean number of	Patients with any AE: 48 (41.4%). Total number of adverse events: 62.

	Johnson 2021[1]	Lee 2018[2]	Fan 2023[3]
		AE per patient not reported, no data in the publication	Mean number of AE per patient not reported, no data in the publication
Inclusion for data extraction	No	Yes	No
Reason	CS related AE data recorded during the duration of the study	Data of CS related AE which occurred at any time from the start of treatment with CS	CS related AE data recorded during the duration of the study

Abbreviations: AE, adverse events; ASE, adverse side effect; CS, corticosteroids; gMG, generalised myasthenia gravis; IQR, interquartile range; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; SD, standard deviation, TAC, tacrolimus

One study went into data extraction after the screening. The publication by Lee et al.2018[2] was selected among 51 studies captured from the search strategy, as the only relevant publication that fulfilled the pre-defined inclusion criteria of the TLR.

All the AE reported as CS related for the entire study cohort were collected, with the respective frequency of presentation of each AE by gender. As mentioned in Table 2, in this study, CS related AE of patients with current or previous corticosteroid intake that responded the survey were considered.

B.3.1 Source of AEs unit costs

All costs were obtained from the National schedule of NHS costs - Year 2021/22 - all NHS trusts and NHS foundation trusts - HRG data and inflated to 2023 costs using the July 2023 value provided in the consumer price inflation file from the Office for National Statistics website.

- NHS: (https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/)
- ONS: (https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/d7bt/mm23)

For each of the AE, a code was assigned depending on the description of the pathology. As described in Table 6, if one or more codes considered the same condition, an average cost was calculated. For the conditions where a specific code was lacking (for example obesity, acne, striae), a general code of a disease that affects the same body system was used as a proxy.

Table 6 NHS codes and costs used for each AE

Code	Description	Unit cost 2021-2022
Diabetes		
KB01C	Diabetes with Hypoglycaemic Disorders, with CC Score 8+	£ 2,409
KB01D	Diabetes with Hypoglycaemic Disorders, with CC Score 5-7	£ 1,532
KB01E	Diabetes with Hypoglycaemic Disorders, with CC Score 3-4	£ 1,077
KB01F	Diabetes with Hypoglycaemic Disorders, with CC Score 0-2	£ 795
KB02G	Diabetes with Hyperglycaemic Disorders, with CC Score 8+	£ 2,622

Code	Description	Unit cost 2021-2022
KB02H	Diabetes with Hyperglycaemic Disorders, with CC Score 5-7	£ 1,640
KB02J	Diabetes with Hyperglycaemic Disorders, with CC Score 2-4	£ 1,197
KB02K	Diabetes with Hyperglycaemic Disorders, with CC Score 0-1	£ 861
High blood pressure		
EB04Z	Hypertension	£ 919
Serious infection		
LA04N	Kidney or Urinary Tract Infections, without Interventions, with CC Score 13+	£ 3,598
LA04P	Kidney or Urinary Tract Infections, without Interventions, with CC Score 8-12	£ 2,782
LA04Q	Kidney or Urinary Tract Infections, without Interventions, with CC Score 4-7	£ 2,096
LA04R	Kidney or Urinary Tract Infections, without Interventions, with CC Score 2-3	£ 1,497
LA04S	Kidney or Urinary Tract Infections, without Interventions, with CC Score 0-1	£ 1,004
Sleeplessness		
AA43A	Sleep Disorders, excluding Sleep Apnoea, with CC Score 2+	£ 1,191
AA43B	Sleep Disorders, excluding Sleep Apnoea, with CC Score 0-1	£ 852
Moon face		
KA08A	Other Endocrine Disorders with CC Score 4+	£ 2,283
KA08B	Other Endocrine Disorders with CC Score 2-3	£ 1,094
KA08C	Other Endocrine Disorders with CC Score 0-1	£ 749
Bruising		
SA02G	Coagulation Defect with CC Score 5+	£ 3,225
SA02H	Coagulation Defect with CC Score 2-4	£ 1,006
SA02J	Coagulation Defect with CC Score 0-1	£ 765
Fracture		
HD39D	Pathological Fractures with CC Score 11+	£ 4,448
HD39E	Pathological Fractures with CC Score 8-10	£ 2,826
HD39F	Pathological Fractures with CC Score 6-7	£ 1,957
HD39G	Pathological Fractures with CC Score 3-5	£ 1,263
HD39H	Pathological Fractures with CC Score 0-2	£ 644
Acne		

Code	Description	Unit cost 2021-2022
HD21D	Soft Tissue Disorders with CC Score 12+	£ 2,744
HD21E	Soft Tissue Disorders with CC Score 9-11	£ 1,597
HD21F	Soft Tissue Disorders with CC Score 6-8	£ 1,033
HD21G	Soft Tissue Disorders with CC Score 3-5	£ 723
HD21H	Soft Tissue Disorders with CC Score 0-2	£ 523
Fatigue		
HD26D	Musculoskeletal Signs or Symptoms, with CC Score 12+	£ 2,355
HD26E	Musculoskeletal Signs or Symptoms, with CC Score 8-11	£ 1,625
HD26F	Musculoskeletal Signs or Symptoms, with CC Score 4-7	£ 1,106
HD26G	Musculoskeletal Signs or Symptoms, with CC Score 0-3	£ 569
Irritability		
WD09Z	Other Mental Health Disorders, treated by a Non-Specialist Mental Health Service Provider	£ 1,538
Swollen ankles		
WH10A	Unspecified Oedema with CC Score 2+	£ 1,372
WH10B	Unspecified Oedema with CC Score 0-1	£ 638
Changed appearance / Decreased interest in sex		
WH12A	Signs or Symptoms, Involving Appearance or Behaviour, with CC Score 2+	£ 1,980
WH12B	Signs or Symptoms, Involving Appearance or Behaviour, with CC Score 0-1	£ 897
Painful/inflamed/prominent scar		
JD07E	Skin Disorders without Interventions, with CC Score 19+	£ 4,431
JD07F	Skin Disorders without Interventions, with CC Score 14-18	£ 3,324
JD07G	Skin Disorders without Interventions, with CC Score 10-13	£ 2,545
JD07H	Skin Disorders without Interventions, with CC Score 6-9	£ 1,873
JD07J	Skin Disorders without Interventions, with CC Score 2-5	£ 1,169
JD07K	Skin Disorders without Interventions, with CC Score 0-1	£ 709
Headache		
AA31C	Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 11+	£ 1,544
AA31D	Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 7-10	£ 1,039
AA31E	Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0-6	£ 622
Weight gain/ increased appetite		

Code	Description	Unit cost 2021-2022
FD04C	Nutritional Disorders without Interventions, with CC Score 6+	£ 2,767
FD04D	Nutritional Disorders without Interventions, with CC Score 2-5	£ 1,706
FD04E	Nutritional Disorders without Interventions, with CC Score 0-1	£ 838
Inflammation		
WH05Z	Allergy or Adverse Allergic Reaction	£ 542
Depression		
WD06Z	Mood Affective Disorders, treated by a Non-Specialist Mental Health Service Provider	£ 2,158
Changed taste / poor appetite		
WH13B	Abnormal Findings without Diagnosis, without Interventions, with CC Score 1+	£ 1,011
WH13C	Abnormal Findings without Diagnosis, without Interventions, with CC Score 0	£ 510
Poor vision		
BZ24E	Non-Surgical Ophthalmology without Interventions, with CC Score 5+	£ 2,109
BZ24F	Non-Surgical Ophthalmology without Interventions, with CC Score 2-4	£ 1,361
BZ24G	Non-Surgical Ophthalmology without Interventions, with CC Score 0-1	£ 856
Tremor		
AA26F	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 6-8	£ 1,495
AA26G	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 3-5	£ 1,104
AA26H	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-2	£ 781
Poor concentration		
WH09D	Tendency to Fall, Senility or Other Conditions Affecting Cognitive Functions, without Interventions, with CC Score 6+	£ 3,822
WH09E	Tendency to Fall, Senility or Other Conditions Affecting Cognitive Functions, without Interventions, with CC Score 4-5	£ 2,770
WH09F	Tendency to Fall, Senility or Other Conditions Affecting Cognitive Functions, without Interventions, with CC Score 2-3	£ 2,080
WH09G	Tendency to Fall, Senility or Other Conditions Affecting Cognitive Functions, without Interventions, with CC Score 0-1	£ 1,450

Code	Description	Unit cost 2021-2022
Gingival hyperplasia (gum swelling)		
VB10Z	Emergency Medicine, Dental Care	£ 169
Diarrhea		
FD01F	Gastrointestinal Infections without Interventions, with CC Score 8+	£ 2,866
FD01G	Gastrointestinal Infections without Interventions, with CC Score 5-7	£ 1,997
FD01H	Gastrointestinal Infections without Interventions, with CC Score 2-4	£ 1,471
FD01J	Gastrointestinal Infections without Interventions, with CC Score 0-1	£ 991
Palpitations		
EB07A	Arrhythmia or Conduction Disorders, with CC Score 13+	£ 2,697
EB07B	Arrhythmia or Conduction Disorders, with CC Score 10-12	£ 1,846
EB07C	Arrhythmia or Conduction Disorders, with CC Score 7-9	£ 1,379
EB07D	Arrhythmia or Conduction Disorders, with CC Score 4-6	£ 1,044
EB07E	Arrhythmia or Conduction Disorders, with CC Score 0-3	£ 681
Impotence/painful menstruation		
WH08A	Unspecified Pain with CC Score 1+	£ 1,939
WH08B	Unspecified Pain with CC Score 0	£ 780
Low back pain		
HC32H	Low Back Pain without Interventions, with CC Score 6+	£ 2,060
HC32J	Low Back Pain without Interventions, with CC Score 3-5	£ 1,375
HC32K	Low Back Pain without Interventions, with CC Score 0-2	£ 804
Stomach complaints		
FD05B	Abdominal Pain without Interventions	£ 707
Chest pain		
EB12A	Unspecified Chest Pain with CC Score 11+	£ 1,100
EB12B	Unspecified Chest Pain with CC Score 5-10	£ 662
EB12C	Unspecified Chest Pain with CC Score 0-4	£ 385

Note: * Due to the lack of codes related to some of the conditions, other diseases were used as proxy. See that some general codes for diseases were used in the cases where the name of the AE was not included in the description of the code.

According to the definition of Unit cost in the NHS 2020-2021 source, it is the cost incurred by a provider to produce, store, and sell one unit of a product or service. Unit costs include all fixed costs and all variable costs associated with the production of a product or delivery of a service.

The unit cost was calculated dividing the total cost by the total activity. No data is available that could allow us to estimate the average activity per patient. As a conservative assumption, we

therefore assumed that each event can be presented only once a year, therefore, the unit cost was applied only once. This is likely to result into an underestimation of the annual cost of the adverse events.

B.3.2 Estimation of the annual cost associated with systemic corticosteroid complications in MG patients.

Each unit cost was then multiplied by the frequency of the respective systemic corticosteroid related AE obtained from the study of Lee et al. 2018[2] (Table 7). Since the study by Lee et al.[2] reports frequency of AEs in males and females separately, a weighted average of the frequencies between the two cohorts was estimated considering 80% females, in line with the cohort baseline characteristics in the cost-effectiveness model (sourced from MRMWG UK population). The resulting annual cost of systemic corticosteroid related complications was £13,131.60.

As outlined in Table 7, the dose of corticosteroid in patients included in the study from Lee et al. ranged from 0.5 to 75 mg, administered daily in 76% and every other day in 18% of patients. The median was 10 mg. Therefore, the reported frequency of adverse events can be considered representative of the entire cohort in the cost-effectiveness model, independently of whether they are on low-dose (<10 mg/day) or high dose (>10 mg/day).

Table 7 Prevalence of AE in MG patients (Overall population, n.298) and annual cost estimation

Condition	AE frequency, males (n=137)	AE frequency, females (n=161)	AE frequency, all (average males 20% and females 80%)	Unit cost (inflated) weighted by average frequency
Acne	8.0%	12.5%	11.6%	'academic / commercial in confidence information removed'
Back pain	15.3%	16.3%	16.1%	
Bruises	32.8%	42.5%	40.6%	
Changed appearance	29.2%	56.3%	50.9%	
Changed taste	8.8%	13.1%	12.2%	
Decreased interest in sex	14.6%	21.9%	20.4%	
Depression	16.1%	24.4%	22.7%	
Diabetes mellitus/elevated blood sugar	19.7%	25.0%	23.9%	
Diarrhea	19.7%	18.8%	19.0%	
Fatigue	29.2%	34.4%	33.4%	
Fracture	3.6%	8.8%	7.8%	
Fragile skin	32.1%	33.8%	33.5%	
Gingival hyperplasia (gum swelling)	2.9%	9.4%	8.1%	
Headache	10.9%	20.0%	18.2%	
High blood pressure	20.4%	19.4%	19.6%	
Impotence/painful menstruation	2.9%	3.1%	3.1%	
Increased appetite	39.4%	51.9%	49.4%	

Condition	AE frequency, males (n=137)	AE frequency, females (n=161)	AE frequency, all (average males 20% and females 80%)	Unit cost (inflated) weighted by average frequency
Increased hair loss	3.6%	28.1%	23.2%	
Inflammation	5.1%	11.3%	10.1%	
Mood swings	30.7%	43.1%	40.6%	
Moon face	27.0%	59.4%	52.9%	
Painful/inflamed/prominent scar	0.7%	6.3%	5.2%	
Palpitations	8.8%	21.3%	18.8%	
Persistent chest pain	2.9%	3.8%	3.6%	
Poor appetite	1.5%	5.0%	4.3%	
Poor concentration	10.2%	20.6%	18.5%	
Poor vision	15.3%	16.9%	16.6%	
Serious infection	5.1%	9.4%	8.5%	
Sleeplessness	31.4%	48.1%	44.8%	
Stomach complaint	16.1%	19.4%	18.7%	
Swollen ankles	24.1%	26.9%	26.3%	
Tremor	10.2%	8.1%	8.5%	
Weight gain	56.2%	68.8%	66.3%	

Abbreviations: AE, adverse event; MG, myasthenia gravis

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Appendix C Effect of treatment discontinuation: Permanent treatment discontinuation transition probabilities

C.1 Overview

During Technical engagement, the Company submitted post hoc analysis of data from ADAPT and ADAPT+, demonstrating a residual benefit from treatment with efgartigimod for a significant proportion of discontinued patients 'academic / commercial in confidence information removed'. The Company also presented real-world data from patients in the USA who received efgartigimod in a Patient Support Programme where 'academic / commercial in confidence information removed' of patients who had an MG-ADL score <5 at the time of permanent treatment discontinuation still had an MG-ADL score <5 on average more than four months after their last infusion.

Given that the additional discontinuation data indicated a potential for up to 50–70% of patients to have residual treatment benefits, but recognising the uncertainty associated with the limited evidence, the Company proposed to use a conservative value of 15% for the base case (15% of these patients remain in the MG-ADL <5 health state six months after discontinuation of therapy). The EAG considered the Company's new assumption as reasonable, based on the evidence presented, and changed their base case accordingly.

Subsequently, in the NICE Draft Guidance, The Committee noted that this assumption had a substantial effect on the cost-effectiveness results and concluded that a residual treatment effect after treatment stops was plausible but uncertain, and stated that they would prefer more evidence about the possible residual treatment effect, which should include clinical expert input.

In order to provide expert clinical input on this topic, we collated the available data (duplicated below in section C2 again for ease), together with the associated peer-reviewed publications, and asked Dr Channa Hewamadduma (Consultant neurologist and honorary senior lecturer, Sheffield Teaching Hospitals NHS Foundation Trust) for his clinical expert opinion on the scientific and clinical plausibility of an efgartigimod residual treatment effect following permanent treatment discontinuation. Dr Hewamadduma was selected based on his leading expertise in clinical research, his portfolio of clinical and basic science research projects in neuro-genetics and neuro-degenerative disorders in SITRAN (Sheffield Institute for Translational Neurosciences), his position of co-chair of the South Yorkshire and Humber neuromuscular network, and his role as Investigator in multiple clinical trials in IgG-mediated disease, including gMG.

The data package shared with Dr Hewamadduma and his expert response are provided in section C.2 and C.3 respectively.

C.2 Supporting Evidence Package

C.2.1 ADAPT and ADAPT+[2,3]

When considering the ADAPT+ population, patients that received only one cycle of efgartigimod for the entire three year duration of the study ('academic / commercial in confidence information removed'), the data suggests a long-lasting treatment effect after the first cycle of infusions in these patiets.[3] Therefore, it seems plausible to consider that a similar proportion of long-responders would apply in the cohort of those responding patients who discontinue the treatment

due to adverse events or intolerance. Based on this concept, the Company analysed the available MG-ADL data post-permanent discontinuation in ADAPT and ADAPT+.

In the ADAPT trial, of the 'academic / commercial in confidence information removed' patients who permanently discontinued treatment with efgartigimod, 'academic / commercial in confidence information removed' had an MG-ADL score <5 at the last exposure time point, and 'academic / commercial in confidence information removed' remained at an MG-ADL score <5 after 'academic / commercial in confidence information removed' days (Figure 1).

Figure 1: MG-ADL trajectories following permanent discontinuation for patients discontinuing efgartigimod treatment in ADAPT

'academic / commercial in confidence information removed'

Abbreviation: MG-ADL, Myasthenia Gravis Activities of Daily Living Scale

In the ADAPT+ trial, of the 'academic / commercial in confidence information removed' patients who permanently discontinued treatment with efgartigimod; 'academic / commercial in confidence information removed' had an MG-ADL score <5 at the last exposure time point, and 'academic / commercial in confidence information removed' remained at an MG-ADL score <5 at the last measurement, which was recorded between 'academic / commercial in confidence information removed' days after the last efgartigimod exposure (mean: 'academic / commercial in confidence information removed' days) (Figure 2).

Figure 2: MG-ADL trajectories following permanent discontinuation for patients discontinuing efgartigimod treatment in ADAPT+

'academic / commercial in confidence information removed'

Abbreviation; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale

Table 8 summarises the number of patients who maintained an MG-ADL score <5 after permanent efgartigimod discontinuation based on ADAPT and ADAPT+ trials and the respective mean and range of follow-up.

Table 8: Number of patients maintaining an MG-ADL score below 5 after permanent efgartigimod discontinuation based on ADAPT and ADAPT+ trials

Clinical trial	Number of patients with MG-ADL < 5 after the last infusion	Number of patients with MG-ADL <5 in the last measurement who had MG-ADL <5 after the last infusion	Mean follow-up period; days (range)
ADAPT	'academic / commercial in confidence information removed'		
ADAPT+	'academic / commercial in confidence information removed'		
Total	**'academic / commercial in confidence information removed'**		

Abbreviation; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale

Overall, 'academic / commercial in confidence information removed' of patients who had MG-ADL scores <5 at the time of permanent treatment discontinuation maintained the residual efgartigimod

effect for ‘academic / commercial in confidence information removed ’after the last treatment exposure.

C.2.2 Real-world evidence from US patients who received efgartigimod

In addition to the data from ADAPT and ADAPT+, an additional analysis has been performed, using data from real-world evidence (RWE) from the USA, which confirmed the findings from ADAPT and ADAPT+.[4] In this analysis, 'academic / commercial in confidence information removed' of patients who had an MG-ADL score <5 at time of permanent treatment discontinuation, still had MG-ADL<5 at the time of their latest MG-ADL measure, which was on average 'academic / commercial in confidence information removed' after their last infusion.[4]

C.2.3 Evidence from efgartigimod in other indications

To further supplement the data in gMG from ADAPT/ADAPT+, signals of ongoing efgartigimod treatment effect following permanent discontinuation have also been observed in both our Immune Thrombocytopenic Purpura (ITP) & Pemphigus Vulgaris/ Pemphigus Foliaceus (PV/PF) efgartigimod clinical development programmes.[5,6]

C.2.3.1 Immune Thrombocytopenic Purpura[5]

In the Phase II study of efgartigimod in adult patients with primary immune thrombocytopenia (ITP), patients were randomly assigned in a 1:1:1 ratio to receive four weekly doses of either placebo, efgartigimod at a dose of 5 mg/kg body weight, or efgartigimod at a dose of 10 mg/kg body weight, administered as an intravenous infusion. The patients were then followed for up to 21 weeks.

Whilst most patients who responded to efgartigimod had a transient increase in platelet counts, with counts returning to baseline levels in the treatment-free follow-up period, 3 of 26 (11.5%) efgartigimod-treated patients (two newly diagnosed [defined as within 3 months of diagnosis]; one chronic [defined as more than 12 months since diagnosis) with ITP remained in remission throughout the follow-up period.

C.2.3.2 Pemphigus Vulgaris/ Pemphigus Foliaceus[6]

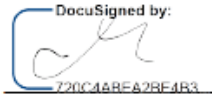
In the Phase II study of efgartigimod in PV/PF, an open-label, multicenter study aimed to determine the optimal dose and posology, efgartigimod as hypothesized, demonstrated a reduction in total IgG levels. However, unlike total IgG, which returned to baseline levels after discontinuation of efgartigimod treatment (with a 10-week treatment-free follow-up), autoreactive antibody levels remained low in several study participants. This suggests a sustained reduction in autoantibody levels during efgartigimod treatment and indicates potential disease modification in peripheral lymphocytes in some patients even after treatment cessation.

'academic / commercial in confidence information removed'

argenx plans to explore this further in Phase III trials, to in part, help us understand if efgartigimod has the potential to modify disease course in certain patients.

C.3 Clinical Expert Review & Statement

I confirm that I have reviewed the available evidence and support the concept of a possible ongoing treatment effect of EFG following permanent treatment discontinuation. This has to be further investigated and proved with robust clinical data. For the sake of the ongoing cost-effectiveness assumption, which necessarily is limited to the data presently available, I believe that the assumption taken (15% limited residual effect) is plausible.

Signed: 

Name: Dr Hewamadduma

Title: Dr

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Appendix D Analysis of the Caregiver Burden Study: utility values and utility decrements for caregivers of people suffering from MG

D.1 Introduction

Informal caregivers play a vital and often unrecognized role in the lives of many patients. In general, this burden consists of a range of physical, emotional, social, and financial problems, impacting their health-related quality of life (HRQoL), and overall functioning. Myasthenia gravis (MG) is a chronic autoimmune disorder affecting the neuromuscular junction disorder of the skeletal muscles. Symptoms of MG, which include eyelid droop, double vision, problems with swallowing, speaking, breathing, dexterity, and mobility, all significantly impact the HRQoL of people suffering from MG and limit their ability to complete activities of daily living independently. In order to cope with these impairments and limitations, many MG patients receive support from an informal caregiver, mostly from their spouse, family members or friends.

D.2 Study design and data collection

This study was a data analyses that assessed the caregiver burden of MG using data from two previously published studies: the first study collected paper-based data in France, the second study was a separate module of an existing digital observational study in Germany, Italy, Spain, and the UK. The data collected in both studies was found to be identical and was pooled for this analysis.

In France, pairs of MG patients and their informal caregivers were recruited through patient advocacy groups. After giving consent, patients and caregivers separately received a paper-based survey, which they sent back after completion. In Germany, Italy, Spain and the UK, pairs of MG patients and their informal caregiver were recruited via the MyRealWorld-MG study; a digital, observational conducted among 1859 adults diagnosed with MG from nine countries. The MyRealWorld-MG study's initial aim was to offer a comprehensive real-world, long-term assessment of the impact of MG in a large, diverse cohort of the impact of MG, from the perspective of those affected by MG. Using a smartphone application developed by Vitaccess Ltd, patients entered data on disease characteristics (diagnosis, disease duration, antibody status, received treatments) as well as monthly data on their experience living with MG during a 2-year period. Participants who reported to have regular help of a caregiver and who gave consent to being approached about future research, were contacted about an additional caregiving burden module in the study. Caregivers were contacted through the MG patients, and both were asked consent for participation in this follow-up study. Caregiver data on HRQoL (EuroQol-5-dimension-5-level [EQ-5D-5L]) and patient data (Myasthenia Gravis Activities of Daily Living [MG-ADL]) were later matched for analysis.

D.3 Methods

To investigate whether caregivers also have a lower quality of life than their peers, their EQ-5D-5L data was firstly valued using the UK value set based on:

- Hernández Alava, M., Pudney, S. & Wailoo, A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. PharmacoEconomics (2022). https://doi.org/10.1007/s40273-022-01218-7.

In a second step we compared the utility values based on the UK value set to UK population norms. The following source was used:

- M Hernández Alava, S Pudney, A Wailoo (2022) Estimating EQ-5D by Age and Sex for the UK (PDF, 428KB). NICE DSU report

Thirdly, we calculated for each caregiver the differences between their own utility value and the population norms for their age and gender ("utility decrement"). As only 10-year age bands were available for the caregivers, the mid-point of this band was used for calculating the age-adjusted utility values and looking up the population norm values.

The distribution of utility values and decrements are presented by MG-ADL category for all observations for which patients and caregivers completed their questionnaire a maximum of 7 days apart (N=39).

D.4 Results

D.4.1 Caregiver and patient characteristics

Baseline characteristics of the patients and caregivers are presented in Table 9.

Table 9 Characteristics of the patients and the caregivers included in this analysis

Proportion of respondents		**All**	
		Caregivers	**Patients**
		N=39	**N=39**
Age	18–40	22%	34%
	40–60	59%	37%
	60+	19%	29%
Age	Mean (SD)	53.1 (15.8)	50.5 (16.4)
Gender	% Female	49%	77%
Countries	Germany	6%	
	Spain	6%	
	France	71%	
	Italy	17%	
	UK	0%	
MG-ADL total score of person diagnosed with MG	Mild: 0–4	41%	
	Moderate: 5–9	36%	
	Severe: 10 and over	23%	
Duration of disease	Mean (SD)	14.1 (11.8)	

Abbreviations: MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; SD, standard deviation

D.4.2 Distribution of utility values

Utility values generally declined with the severity of the patient's MG; however no linear relationship could be found (Table 10). It is likely that additional factors are affecting the health-related quality of life of the caregiver, including the availability of other sources of care, financial strain, family circumstances, whether the caregiver is still in employment, and the age and gender of the caregiver.

One caregiver of a patient in MG-ADL category had an outlying utility value of -0.309 compared to the other caregivers. This was an elderly lady aged 70–79 who cared for her 79-year old husband. She had a VAS score of 50 and indicated having a moderate caregiving burden, but scored herself low on the EQ-5D-5L (health state 53554 for the five dimensions). Excluding this patient resulted in the data from Table 11.

The data presented in Table 10 to Table 12 shows that patients have generally lower utility values than their caregivers.

Table 10 Mean utility values of the caregivers by MG-ADL category of the patient (UK value set)

Category	N	Mean	Std Dev	Median	Lower Quartile	Upper Quartile
MGADL<5	16	0.812	0.111	0.793	0.739	0.883
MGADL 5–7	10	0.529	0.384	0.634	0.393	0.805
MGADL 8–9	4	0.725	0.193	0.791	0.615	0.835
MGADL ≥10	8	0.692	0.343	0.807	0.545	0.939

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; UK, United Kingdom

Table 11 Mean utility values of the caregivers by MG-ADL category of the patient - EXCLUDING one outlier

Category	N	Mean	Std Dev	Median	Lower Quartile	Upper Quartile
MGADL<5	16	0.812	0.111	0.793	0.739	0.883
MGADL 5–7	**9**	**0.622**	**0.261**	**0.704**	**0.458**	**0.805**
MGADL 8–9	4	0.725	0.193	0.791	0.615	0.835
MGADL ≥10	8	0.692	0.343	0.807	0.545	0.939

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living

Table 12 Mean utility values of the patients by MG-ADL category

Category	N	Mean	Std Dev	Median	Lower Quartile	Upper Quartile
MGADL<5	16	0.786	0.129	0.815	0.663	0.904
MGADL 5–7	10	0.577	0.208	0.608	0.483	0.639
MGADL 8–9	4	0.597	0.130	0.610	0.515	0.679
MGADL ≥10	9	0.352	0.307	0.477	0.119	0.575

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living

D.4.3 Distribution of utility decrements

Utility values of the caregivers were compared with those of their peers, and utility decrements were calculated as the difference between these two populations. Generally, caregivers had meaningfully lower utility values than the general population of the same age and gender. The decrements ranged from 0.025 when caring for mildly affected patients to 0.323 for moderately affected patients (Table 13, Table 14). The utility decrements for caregivers of moderate and

severely affected patients were all large and significantly higher than the minimally important difference for the EQ-5D instrument.

Table 13 Mean utility decrements of the caregivers by MG-ADL category of the patient

Category	N	Mean	Std Dev	Median	Lower Quartile	Upper Quartile
MGADL<5	16	-0.025	0.107	-0.031	-0.077	0.037
MGADL 5–7	10	-0.323	0.359	-0.207	-0.458	-0.079
MGADL 8–9	4	-0.142	0.176	-0.062	-0.240	-0.045
MGADL ≥10	8	-0.170	0.328	-0.065	-0.255	0.047

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living

Table 14 Mean utility decrements of the caregivers by MG-ADL category of the patient- EXCLUDING one outlier

Category	N	Mean	Std Dev	Median	Lower Quartile	Upper Quartile
MGADL<5	16	-0.025	0.107	-0.031	-0.077	0.037
MGADL 5–7	**9**	**-0.240**	**0.259**	**-0.132**	**-0.386**	**-0.079**
MGADL 8–9	4	-0.142	0.176	-0.062	-0.240	-0.045
MGADL ≥10	8	-0.170	0.328	-0.065	-0.255	0.047

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living

D.5 Conclusions

Caregivers of MG patients have lower utility values than their peers. Many factors may be influencing the HRQoL of the caregivers, including the patient's disease severity. In general, patients have lower utility values than their caregivers.

Appendix E Economic analyses

E.1 Overview

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

- In line with the additional evidence obtained from the Delphi Panel, a total maintenance IVIg treatment use of 69.17% was considered in the revised model. The total of 69.17% was distributed between the MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health-states weighting by the baseline cohort distribution in the model and considering that patients with worse disease activity would have higher use of IVIg. A maximum use of IVIg treatment equal to 85% was considered for any health-state, to reflect the evidence gathered from the Delphi panel suggesting that about 15% of patients are not eligible for IVIg maintenance treatment. The resulting percentage of cohort on IVIg maintenance treatment by health-state is presented in **Table 1**. An additional scenario was considered where the total of 69.17% is distributed equally between the health-states with MG-ADL of 5 or higher.

Table 15: IVIg use by health-state in the revised cost-effectiveness model (total IVIg use of 'academic / commercial in confidence information removed' from Delphi Panel)

Health-states	IVIg use in revised basecase Total IVIg use of 69.17% weighted by baseline cohort distribution and assigned from worst to better health-states	IVIg use in scenario analysis Total IVIg use of 69.17%: equal distribution between health-states MG-ADL>=5 – Scenario analysis
MG-ADL <5	0.00%	0.00%
MG-ADL 5–7	50.83%	69.17%
MG-ADL 8–9	68.70%	69.17%
MG-ADL ≥10	85.00%	69.17%

.

A description of the calculation of IVIg cost is reported in Section B.3.5.1 of Document B in the original submission (**Table 16**). IVIg was dosed at 1 g/kg, yielding an average of 1 and 8 vials per administration for the 2.5 mg/25 mL and 10 mg/100 mL formulations, respectively. IVIg is administered once every 4 weeks, therefore one administration per model cycle is considered.

To calculate drug costs, the supplied sizes and prices were retrieved from the British National Formulary (BNF). The administration cost for IVIg incorporated both IV administration plus a short-stay hospitalisation for observation.

Table 16 - IVIg drug cost per cycle

Drug	Admin per cycle	Drug cost per vial, £	Drug cost per admin, £	Drug cost per cycle, £	Admin cost per admin, £	Admin cost per cycle, £
IVIg (2.5 mg /25mL)	1.00	172.50	690.00	5,520.00	1,717.92	1,717.92
IVIg (10 mg/100 mL)	1.00	690.00	4,830.00			

Admin, administration; IVIg, intravenous immunoglobulin

- Caregiver disutility values were sourced from the Caregiver Burden Study in gMG. A full description of the approach and values included in the model is provided in **Error! Reference source not found.**.
- The utility values assigned to the MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states were estimated from the mixed model regression on data from the MyRealWorld MG (ARG-MG-2019-01) study, with MG-ADL <5 as the reference (i.e., intercept). These utility values were considered for a scenario analysis in the original submission and therefore a full description of this approach is presented in Section B.3.4.2 of Document B. Specifically, the coefficients for this regression analysis and resulting utility values are reported in Table 41 and Table 42, respectively, in Document B of the Company submission. The resulting utility values by health state were then applied to both the efgartigimod and established clinical management arms of the model.
- The cost of systemic corticosteroid related complications was calculated based on the frequency of corticosteroid related adverse events in MG patients reported in the study by Lee et al. 2018[1] and the associated costs sourced from the latest published NHS Reference Cost. A full description of the method is provided in Appendix B. The resulting annual cost of systemic corticosteroid related complications was 'academic / commercial in confidence information removed' thus a cost per cycle of 'academic / commercial in confidence information removed' The same cost was applied for the cohort on high-dose (>10mg/day) and low-dose corticosteroid use in cost-effectiveness model since the frequency of adverse events reported by Lee et al. 2018[1] is representative of the entire modelled cohort on corticosteroid (dose ranging between 0.5mg and 75mg, with a median of 10mg).
- 20.3% of the cohort in gMG crisis health-state was assumed to experience an extended stay in Intensive Care Unit (ICU). The extended stay was assumed to last 10 days, which represents the maximum reported from the clinicians in the Survey conducted to inform health-care resource use in the model in the original Company submission.

The results of the revised cost-effectiveness model base case analysis are presented in Table 3. The results are based on efgartigimod list price with a 'academic / commercial in confidence information removed' PAS.

Table 17: Revised model basecase analysis with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Efgartigimod	'academic / commercial in confidence information removed'						15,228
Established clinical management							-

E.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, Table 18 and Figure 4.

Figure 3: Incremental cost and QALY cloud in the cost-effectiveness plane with PAS

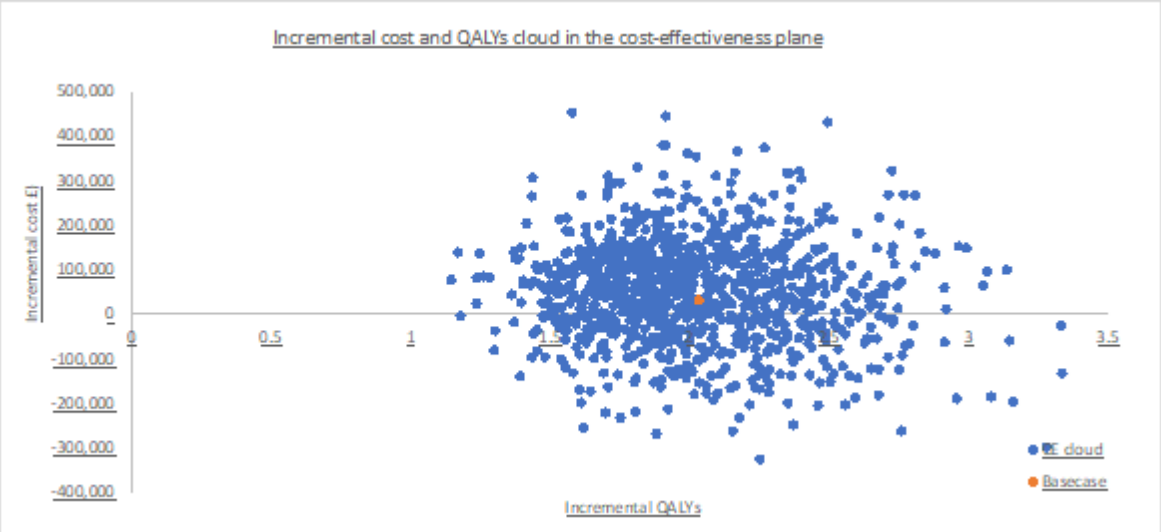
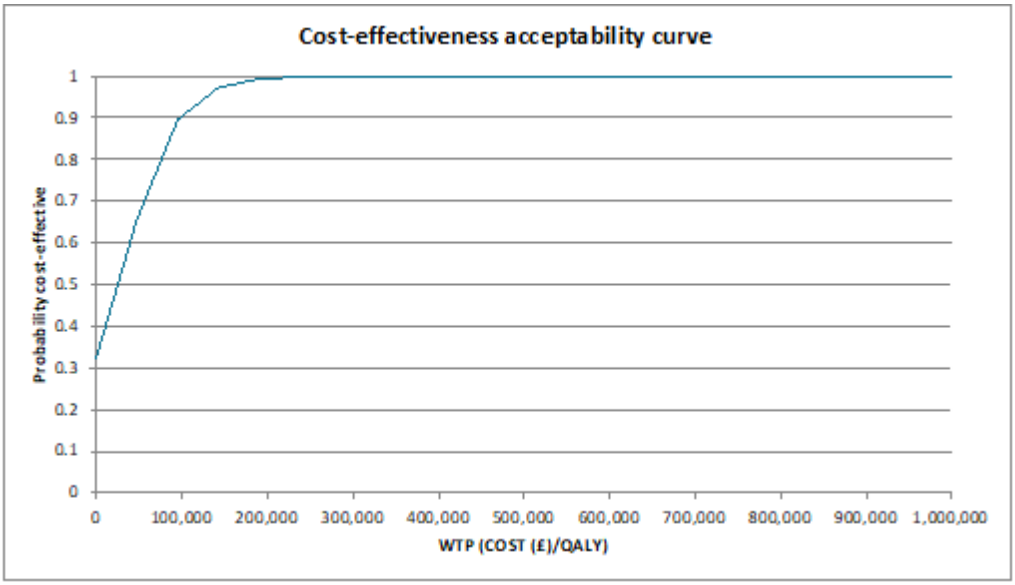


Table 18: Comparison of the base case and PSA results with PAS

	Cost, £			QALYs			ICER (£/QALY)
	Efgartigimod	ECM	Incremental	Efgartigimod	ECM	Incremental	
Base case	'academic / commercial in confidence information removed'						15,228
PSA mean							24,993
PSA 95%CI lower							-83,483
PSA 95%CI upper							143,987

Figure 4: Cost-effectiveness acceptability curve with PAS



E.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 19 and Table 20.

Figure 5: Results of the one-way sensitivity analysis with PAS

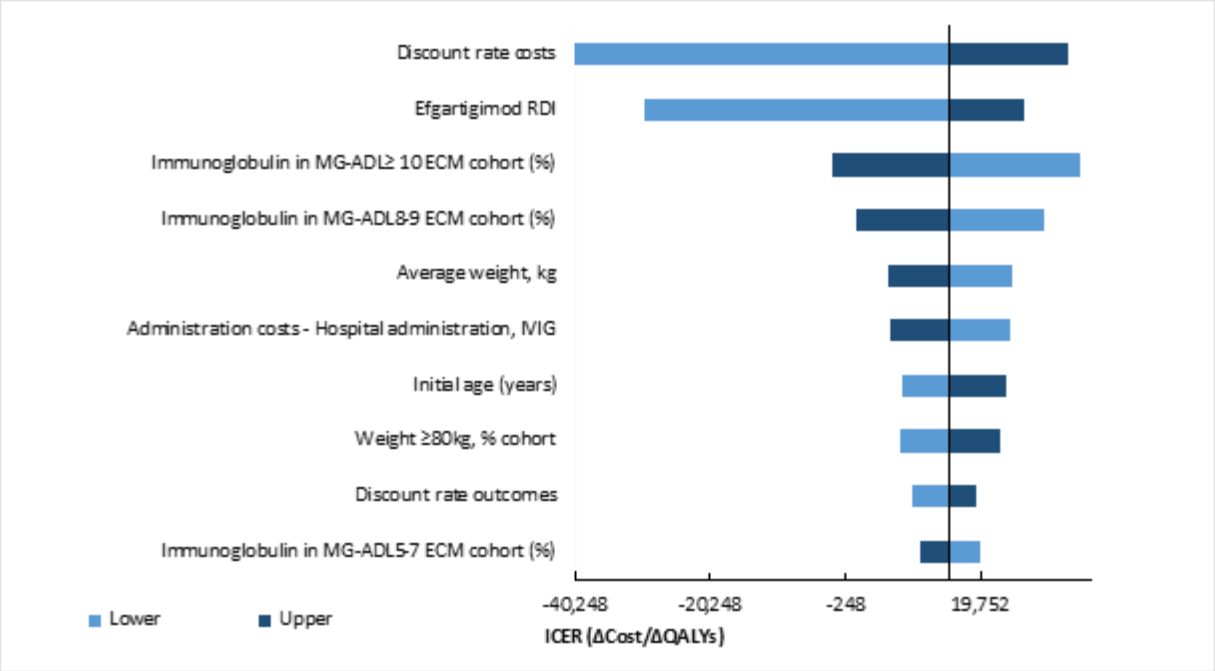


Table 19: Percentage change in base case results with PAS following lower and upper variation in the 10 most influential parameters

Parameter	Lower value	Upper value
Discount rate costs	-378%	115%
Efgartigimod RDI	-297%	72%
Immunoglobulin in MG-ADL≥ 10 ECM cohort (%)	127%	-114%
Immunoglobulin in MG-ADL8-9 ECM cohort (%)	91%	-91%
Average weight, kg	60%	-60%
Administration costs - Hospital administration, IVIG	59%	-59%
Initial age (years)	-47%	54%
Weight ≥80kg, % cohort	-49%	49%
Discount rate outcomes	-37%	26%
Immunoglobulin in MG-ADL5-7 ECM cohort (%)	29%	-29%

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

Table 20: Detailed results of the one-way sensitivity analysis with PAS

Parameter	ICER (£/QALY)	
	Lower	Upper

Discount rate costs	-42,367	32,775
Efgartigimod RDI	-30,073	26,119
Immunoglobulin in MG-ADL≥ 10 ECM cohort (%)	34,525	-2,146
Immunoglobulin in MG-ADL8-9 ECM cohort (%)	29,137	1,319
Average weight, kg	24,380	6,034
Administration costs - Hospital administration, IVIG	24,164	6,292
Initial age (years)	8,127	23,453
Weight ≥80kg, % cohort	7,771	22,685
Discount rate outcomes	9,570	19,220
Immunoglobulin in MG-ADL5-7 ECM cohort (%)	19,670	10,785

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

E.4 Scenario analysis

Results of the scenario analyses are shown in Table 20. The results of all explored scenarios (scenario 1 to 4) 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 'academic / commercial in confidence information removed' PAS for efgartigimod.

Scenario 5 was included to respond to a technical team request to explore a scenario where the placebo effect observed in the placebo arm of the ADAPT trial is not lost beyond the trial follow-up period. Nevertheless, the Company believes this scenario is not representative of natural disease history in gMG patients. In fact, the clinical expert consulted during the model development suggested that some worsening in disease activity would be expected over time. Thus, by assuming that the cohort in the ECM arm remains stable at baseline distribution, the Company is already taking a conservative assumption, i.e. no worsening over time.

Table 21: Scenario analyses for efgartigimod vs Established Clinical Management with PAS

	Scenario description	**Efgartigimod vs Established Clinical Management**			
		Incr Cost, £	**Incr QALYs**	**ICER £/QALY**	**ICER % change vs basecase**
0	Revised base case	'academic / commercial in confidence information removed'			na
1	Efgartigimod formulation: 80% SC and 20% IV				-12%
2	No caregiver disutility				41%
3	Utilities by health-state based on regression on ADAPT data without treatment effect				26%
4	Total IVIg use distributed equally between health-states: 'academic / commercial in confidence information removed' in MG-ADL 5-7, MG-ADL 8-9 and MG-ADL ≥10				64%
5	The effect in the Established Clinical Management arm observed in the placebo arm of ADAPT is maintained				740%

	over the entire time-horizon of the analysis.		

Incr, incremental; ICER, incremental cost-effectiveness ratio; IV, intravenous; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; SC, subcutaneous; PAS, patient access scheme; QALY, quality-adjusted life-years; y, year

Appendix F Confidential information checklist

Not applicable

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 22 September 2023. 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):	Association of British Neurologists – Neuromuscular Advisory Group

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Efgartigimod for treating generalised myasthenia gravis [ID4003]

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

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	The draft consultation has considered all relevant clinical trials, and these consistently show that the Efgartigimod is highly efficacious. • Of note Rozanolixizumab, a very similar molecule, further provides evidence of class efficacy in MG treatment.

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	• Trials in myasthenia gravis are difficult to perform given the heterogeneity of disease manifestations and treatment response and challenges regarding quantitative outcome measurement. It may be that real-world data from EAMS will be an extremely valuable source of information to gauge cost-effectiveness and establish when expert clinicians reaching for this drug, and how impactful this drug is in those circumstances. • In particular the potential for cost saving compared to PLEX/IVIG/Rituximab usage may be more sensible to calculate from the cohort in which it is being applied on EAMS than considering the MG population as a whole.
2	We do not disagree with the points made. • EAMS data may reveal better information as to at which points in the treatment algorithm clinicians could use Efgartigimod. • Efficacy, lifestyle impact and cost effectiveness in the EAMS cohort (treatment refractory, high disease activity or high risk of complication from other treatments) may be more informative than trial data or modelling form the whole MG population. • An asthma population or a multiple sclerosis population are not comparable to a myasthenia gravis cohort. Another autoimmune neuromuscular condition would be a better comparison, for example inflammatory myopathy, where similar treatments and doses for similar amounts of time are used: high doses of steroids for remission induction and long-term steroid sparing immunosuppression/ steroid rescue for relapse • Comparison of carer support is difficult to evaluate and not really appropriate in an MG population. A more appropriate measure may be the cost in terms of days at work lost E.g. IVIG/PLEX and days in hospital / days away from work.
3	EAMS data may reveal better information as to which points in the treatment algorithm clinicians could use Efgartigimod. • Potential points of use (from an expert clinician's perspective): o In individuals resistant to 1st/2nd line treatment BUT responsive to regular/ maintenance IVIG/PLEX. (this will be a very small proportion) o As a lower risk alternative to IVIg/ PLEX/ Rituximab for patients in MG crisis o In resistant cases during MG crisis (we acknowledge there is no trial level evidence to support this (non-responsive to PLEX/IVIG/Rituximab),
4	We do not think that there are any groups that will be differently impacted based on this guidance or this medication.
5	There is potential for this medication to be useful for individuals with immune-checkpoint therapy-related myasthenia, an increasingly common presentation given the exponential increase in application of these drugs in the cancer setting. Mechanistically they should be effective given it is an ACHR ab positive MG, it is safe in patients with multiple comorbidities (less prothrombotic than IVIg/ PLEX) and a lesser immune system suppressing effect than steroids/ steroid sparing agents, which have a potential impact on the anti-cancer effect of these drugs. This would have to be considered in planning at national level so that these patients are not excluded from accessing this drug.
6	

Insert extra rows as needed

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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 [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.
- 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):	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. • £5,500.00 on 23 January 2023 for sponsorship of the MDUK Translational Research Conference 2023. Not ongoing. • £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. • £25,000.00 in August 2023 from Roche as funding for the UK SMA Newborn Screening Alliance. MDUK is co-secretariat of the alliance with responsibility for processing and administering funding requests. A further £25,000 has been pledged for March 2024. Not ongoing beyond that. • £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. Myaware have received no such funding.
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.
Name of commentator person completing form:	[redacted] ([redacted], myaware) [redacted] ([redacted], Muscular Dystrophy UK)

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Efgartigimod for treating generalised myasthenia gravis [ID4003]

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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	To help us prepare this submission, myaware and Muscular Dystrophy UK conducted an online survey of the myasthenia gravis community. The survey received 45 responses. Participants were presented with NICE's description of generalised myasthenia gravis (gMG) and its impact and were asked how accurate they felt this was in relation to their own experience of the condition. They were also asked about the impact that steroids and immunosuppressants have had on their quality of life and the length of time it took for them to take effect. They were asked how important they felt it was that a range of treatments become available for gMG. We are concerned that NICE's description of gMG is not completely accurate and does not fully encompass the impact of living with the condition. The gMG community commented that the description does not address the physical pain of living with gMG; that earlier diagnosis can lead to better treatment management; or that muscle weakness can worsen and lead to a lack of mobility. It also does not identify the additional ailments that come with treating gMG – infections; gut problems; and fragile skin. One respondent to our survey added: *"It is factual but it misses the additional conditions you acquire which you are forced to manage along with their side effects on top of having to manage Myasthenia. Lives are changed for ever following diagnose - Myasthenia is not a solitary condition."*
2	We are concerned that the side effects of long-term steroid use have not been appropriately considered. The gMG community has described the development of cataracts; type 2 diabetes; and rapid weight gain. One survey respondent stated: *"They have totally ruined (my life). I have gone from walking up mountains to being wheelchair bound in no time at all. Both my wife and I had full-time well-paid jobs and now I can no longer work and my wife has had to give up her work to be my full time unpaid carer. So far no medication has worked but as well as myasthenia 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. I have had numerous infections because of my weak immune system. I have had numerous hospital visits and admissions, and I spent almost 7 months in hospital in one go where I had a crisis, sepsis and septic shock. I suffer daily from stomach issues caused by medications and have to take many tablets to counteract the effect my myasthenia medication has had on me. Because of the problems we have needed to have lots of alterations made to the house for instance have the bathroom made into a*

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	wet room, have had the back door widened and ramp fitted for wheelchair access. A stairlift has been installed and I have numerous aids around the house. On top of this we have changed the car so it can accommodate an electric wheelchair and a boot hoist. I now never feel like leaving the house."
3	We are concerned that the time taken for conventional therapy to take effect has not been considered. Some members of the gMG community have shared that pyridostigmine takes 12-18 months to help, steroids 6 months, and immunosuppression 9 months. It has been shown how quickly Efgartigimod can help the symptoms of gMG, which emphasises its importance.
4	We are concerned that the unmet need for effective treatment has not been properly considered. A direct therapeutic that targets the underlying mechanism seen in gMG is something members of the gMG community emphasise is desperately needed, often discussing their desire to return to work and regain their quality of life. Those who have taken part in the Efgartigimod clinical trial have stated they can consider these goals properly now their symptoms have been managed. This in turn would also reduce the intensive need for NHS resources, reduce treatment times, and side effects that dictate the lives of those with gMG. Following the publication of the draft guidance by NICE, one person whose son suffers from gMG said: "*Nobody would choose these treatments and think they're good. They save lives but they take months to work, and the side effects are life changing and life harming. We need to be moving to fast acting treatment with minimal side effects, and Efgartigimod seems the first of a few*."
5	Following the publication of the draft guidance by NICE, one person who is currently receiving efgartigimod emailed Muscular Dystrophy UK to share their experience of the treatment and their concern about its possible non-recommendation. *"I have been receiving Efgartigimod since January as part of the EAMS (early access to medication scheme) and it has been life changing for me. So obviously this news is concerning.* *"I was diagnosed achr positive gMG in August 2019. Started on pyridostigmine, prednisolone and methotrexate. In January 2020 I had my first crisis. I was admitted to ITU and received IVIG. In February I was deteriorating again so my consultant admitted me for plasmapheresis. It worked well but unfortunately I developed a DVT which then developed into a massive double pulmonary embolism and I was again admitted to ITU. So plasmapheresis was no longer a treatment option.* *"In may 2020 I had another crisis and again had IVIG. In July 2020 I started 4 weekly IVIG. In December I had a thymectomy. In 2021 I had rituximab; it didn't help. I swapped methotrexate for azathioprine but within weeks I developed neutropenic sepsis and had to stop it.* *"The IVIG was keeping me stable, but still I had daily gMG symptoms that affected my life significantly.*

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 22 September 2023. Please submit via NICE Docs.

	"The prednisolone caused severe osteoporosis with 4 wedged vertebrae, prediabetes, Cushing's syndrome etc etc but I couldn't get below 30mg. *"Then in January I started efgartigimod and the improvement was immediate. I'm now down to 11mg of prednisolone and still tapering. My ADL scores are often 0 until I'm due for my next cycle. My scores previously were always above 10.* *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".* A second person currently receiving efgartigimod also contacted Muscular Dystrophy UK to share their experience. *"I was diagnosed with gMG 25 years ago when I was 22. I've tried many different drugs which some made a little difference & some not at all.* *Up until November last year I was having plasma exchanges twice a month at [location given]. I had been doing this regime for 7 years.* *The treatment began to not work so well, and the whole process of the treatment including the journey which took 3 hours each way & 3 children at home started to exhaust me.* *[Clinician's name provided] put me forward for Efgartigimod and I began by first set of 4 infusions in December.* *These were done at the hospital but now I have at home.* *I can't begin to tell you what difference it has made not just to me health wise but mentally too.* *I no longer have plasma exchanges, azathioprine is slowly being reduced and to be able to have it at home each time is just amazing.* *Not having to arrange childcare, or cope with the journey is fab. My gMG is currently under control and I feel like I have some quality of life back after such a long time".*
6	

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 [redacted] and information

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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 22 September 2023. Please submit via NICE Docs.

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.
- 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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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	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: The QoL data doesn't use the most common assessment MG-QoL15.
There has not been any consideration of potential side effects of oral immunosuppressant agents such as hepatitis, increased risk of skin malignancies

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

Answer: I would agree with the committees conclusions that regular IVIG is a relatively uncommon treatment in the management of MG, though there is significant regional variation around the UK.
It is also worth pointing out that many patients with refractory MG are not on high dose steroids because they don't work for these individuals therefore these costs are not relevant.
I am unaware of the evidence that efgartigimod can be withdrawn in some patients without a relapse and more data on this would be useful. To date most patients seem to be dependent on 7 to 8 week cycle to maintain benefit and become rapidly symptomatic once treatment is stopped / postponed.
I would also agree that if used this drug should be reserved for refractory patients, not all, as many patients with MG do well on standard treatment.

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

Answer: I agree that it is difficult to argue that efgartigimod will reduce regular use of IVIG, steroid side effects or carer burden to the degree that the current costs are justified. However there is clearly a small cohort of patients in whom the benefits are very significant and who were either refractory to or intolerant of current treatment options. Losing the option to prescribe efgartigmod in this patient population would be detrimental to patient care.

Question: 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?

Answer: It should be noted that people with refractory MG are generally women in their 30s

Comment on section 2.1, Marketing authorisation indication

It is a shame that people with anti-MuSK associated MG are not included in this submission as some remain very symptomatic despite optimal treatment.

Comment on section 3.1, The condition

While it is true that there are treatment refractory patients where there is a high treatment burden, many patients do well on a regime of low dose steroids -/+ oral immunosuppressant drugs. Generally early onset gMG in young women is more likely to be disease resistant.

Comment on section 3.3, Population

I don't agree with the comment that MG gets worse over time. For most patients the reverse is the case: they have a difficult time for a year or two and then their condition settles generally on a combination of steroids -/+ oral immunosuppressants.
Some patients do remain refractory to treatment but these are a minority.
I agree that the APADT trial inclusion data does not reflect the cohort who should have efgartigimod on the NHS as many of these patients would have done well with standard treatment.

Comment on section 3.4, Maintenance IVIg

There seems to be a wide variety of practice in the use of regular IVIG for maintenance treatment of MG. Many centres in the UK use it very infrequently so this would not be an offset cost. Moreover peripheral plasma exchange would be an alternative treatment.
It is reasonable to conclude that people on regular long term IVIG could reasonably be transfered to efgartigimod but if it is limited to this patient population there is a significant cohort of patients who could benefit and who would be denied treatment.

Comment on section 3.7, Company's modelling approach

It would be unusual for a person with MG to have a high (ie bad) score for a single activity as it is generally a condition that affects multiple functions.

Comment on section 3.8, Treatment effect after stopping efgartigimod

I am unaware of a residual treatment effect of efgartigimod. Indeed the reverse seem to be the case in that patients report earlier relapsing resulting in a shortening of intervals between treatment doses. However no-one in the UK has probably been on the treatment long enough to determine the long term response.

Comment on section 3.9, Source of utility values

The standard QoL assessment used in the UK for MG is the QoL15 or QoL15R. This provides a comprehensive view of the patient's perspective and it is clear that for many people efgartigimod results in a significant improvement in QoL.
Regarding the use of steroids between the two arms of the trial, in my experience people with refractory MG are often not on steroids because they don't work.

Comment on section 3.11, Corticosteroid complications

Patients with treatment refractory MG tend to be younger and often have stopped taking steroids because of they are not effective. Therefore while some people might avoid steroid side effects with efgartigimod, most people won't.
That said, there is an argument that it could be used as a bridging treatment while waiting for steroids to work, avoiding particularly high doses, or while waiting for oral immunosuppressant drugs to work. Surveying colleagues around the country suggest that this is indeed the case though they have not yet tried to stop the efgartigimod in these patients and there is a possibility that they might not be able to do so.

Comment on 3.14, Innovation

I would emphasise that this is the first new immunomodulatory treatment for MG potentially available for treatment resistant patients with MG on the NHS (as eculizumab is not approved for use). There are few / no other options for some people with refractory MG.

Name	[redacted]
Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: Contact me if you are interested in getting the relevant info

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

Answer: Contact me if you are interested in getting the relevant info

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

Answer: Contact me if you are interested in getting the relevant info

Question: 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?

Answer: Contact me if you are interested in getting the relevant info

Comment on draft guidance document

Efgartigimod is extremely effective and definitely should be approved by NICE.

I am the Consultant Neurologist who was the first in the UK, so I have patients who are most advanced in terms of the number of cycles patients have been on.

If NICE is genuinely interested in getting the relevant info to make the correct decision, then you should speak to me, rather than the other experts you spoke to who have far less experience in using the drug. I'm guessing this will be a (simple) step too far for NICE.

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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 appraisal consultation document.

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
Authors	Fay Chinnery, Research Fellow, Health Economics, SHTAC Keith Cooper, Senior Research Fellow, Health Economics, SHTAC Joanna Picot, Senior Research Fellow, Evidence Synthesis, SHTAC
Correspondence to	Dr. J. Picot Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House, Enterprise Road, University of Southampton Science Park, Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	18/10/2023

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LIST OF ABBREVIATIONS

AChR	Acetylcholine receptor
AE	Adverse event
AIC	Academic in confidence
CIC	Commercial in confidence
CS	Company submission
EAG	External Assessment Group
ECM	Established clinical management
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
gMG	Generalised myasthenia gravis
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IVIg	Intravenous immunoglobulin
MG	Myasthenia gravis
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
QoL	Quality of life
RCT	Randomised controlled trial
TA	Technology appraisal
UK	United Kingdom
US	United States

1 Introduction

This document is the External Assessment Group's (EAG's) critique of the response by the company, argenx, to the NICE draft guidance consultation (issue date 1st September 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 9th October 2023.

The company's draft guidance response contains the following documents:

- The draft guidance response form
- A summary of new evidence presented under six separate headings:
    - Describing clearly the target patient population for whom treatment may offer the greatest value
    - Quantifying the existing burden of regular rescue treatments (e.g. maintenance IVIg) in this population
    - Exploring the costs of corticosteroid administration in this population
    - Validating assumptions regarding the residual effects of efgartigimod treatment following permanent discontinuation of efgartigimod
    - Further validating the importance of caregiver disutility for patients affected by gMG in the population considered eligible for treatment
    - Exploring the appropriate source of utilities for inclusion in the economic model

  The summary of new evidence also contains the results from the revised base case analysis and the answers to three questions that were posted by the NICE technical team.
    - Appendices A to F in support of the company's new evidence

In this report we present the following:

- Our critique of the company's draft guidance response and new evidence (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis (Section 3)
- The results of EAG scenario analyses (Section 4)

2 CRITIQUE OF THE COMPANY'S RESPONSE TO THE ACD

2.1 The target population for whom treatment may offer the greatest value

The company proposes that efgartigimod is provided within the licenced indication: "As an add-on to standard therapy, adult patients (≥18 years) with generalised Myasthenia Gravis (gMG) positive for acetylcholine receptor (AChR) antibodies" AND is further targeted to the treatment of NHS 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 states that standard therapy includes maximal dose of steroids, and at least two additional therapies, such as non-steroidal immunosuppressive therapies (NSISTs) and rituximab, for an adequate period of time, at an adequate dose.

The EAG believes that whilst the company has obtained clinical input and identified a population for whom treatment may offer the greatest value, the wording used to describe this population in a succinct manner should be revised. In particular, the group of patients who are ineligible for standard therapy, appear to fall outside the licenced indication for efgartigimod unless they are only ineligible for one type of standard therapy but still able to receive another type of standard therapy to which efgartigimod can be added. It is the EAG's understanding that it is not possible to add efgartigimod to intravenous immunoglobulin (IVIg) or rituximab because the action of efgartigimod would reduce the circulating levels of these and it is not possible to add efgartigimod to plasma exchange (PLEX) because this treatment could reduce the circulating levels of efgartigimod.

The company used a two-round Delphi survey to gather opinion from six clinicians drawn from six different specialist neuromuscular centres (Company response Appendix A Table 2 and Appendix II) in different geographical locations (two in London and one each from Birmingham, Sheffield, Liverpool and Southampton). As the company does not indicate how many specialist neuromuscular centres there are in total, the proportion of specialist centres represented is unknown. In the first round of the Delphi survey, clinicians were presented with a detailed target population definition (provided in Appendix A of the company's response) and in the second round they were presented with the simplified version of the company's definition reproduced above. There was a full consensus (n=6, 100%) from the clinicians surveyed in both round 1 and round 2 of the Delphi survey that the proposed target population would be appropriate for add-on treatment with efgartigimod.

The Delphi survey also asked the six clinicians to estimate, for the past 12 months at their specialist centres, what percentage of patients would match the provided description. The results are shown in Table 1 below.

Table 1 Proportion of patients estimated to match the targeted population description

	Delphi round 1 (detailed patient description [a])	**Delphi round 2 (simplified patient description [b])**
Number of responses	N=6 (100%)	N=6 (100%)
Mean percentage of all patients	[redacted]	22.1%
Median percentage of all patients	[redacted]	20%
Range	[redacted]	10% to 40%

Source: Company response Appendix A.5.1 and A.5.2
[a] The detailed patient description is presented in Company response Appendix A.5.1.1 Table 3
[b] The simplified patient description is presented in the company's New evidence submission document, section 1 and the company response Appendix A.5.2 and is reproduced at the beginning of this section of our critique.

The company states that the existing cost-effectiveness model is representative of the more targeted population because post-hoc subgroup analyses from the ADAPT clinical trial in the AChR antibody positive population showed consistently higher proportions of MG-ADL and Quantitative Myasthenia Gravis scale (QMG) responders among efgartigimod treated participants in comparison to placebo treated participant in all subgroups (original CS Appendix E). As we stated in our original EAG report (section 3.3.7) the level of certainty around these results is low due to small sample sizes of each subgroup and wide 95% confidence intervals. The cost-effectiveness model models a patient cohort with characteristics for age and gender that were taken from UK patients (n=25) who fulfilled the ADAPT trial inclusion criteria and who provided data to the MyRealWorld MG study (further details are in our EAG report section 4.2.3). Ideally, we would like to know what the age and gender characteristics are for the [redacted] enrolled in the Early Access to Medicines Scheme (EAMS/EAMS+), but this information has not been provided by the company. It would be helpful to know if the characteristics of the EAMS/EAMS+ patients are in line with the baseline model cohort characteristics because the company states that their target population closely aligns with the EAMS/EAMS+ population.

2.2 Quantifying the existing burden of regular rescue treatments

The company also used their two-round Delphi survey to gather opinion from six clinicians on the proportion of patients within their targeted population who would be considered for treatment with maintenance IVIg. The results from the two rounds are summarised below (Table 2). The wide range of estimates in response to round 1 was explored by asking the panellists to provide a rationale for their round 1 response when round 2 took place. The company states (Company response Appendix A.5.2) that three of the six panellists noted a potential confusion with the question and lower percentages may have referred to IVIg use in the total gMG population, rather than in the proposed targeted population. We believe that, had time allowed, a third round could have been conducted in order to see if the estimates for regular/maintenance IVIg in the proposed population were stable or if the range of estimates could have been reduced further.

Taking the estimate for the proportion of gMG patients who would match the target population description (mean 22.1%, range 10% to 40%) and the estimate for the proportion of this population who would be prescribed regular/maintenance IVIg (mean 69.2%, range 60% to 90%) we would expect that for every 100 gMG patients, 22 (range 10 to 40) would match the target population description and be eligible for add-on efgartigimod treatment and of these 22 patients, 15 (range 6 to 36) might be expected to be prescribed regular/maintenance IVIg.

Table 2 Quantifying the proportion of the proposed population prescribed regular/maintenance IVIg

	Delphi round 1 (detailed patient description [a])	**Delphi round 2 (simplified patient description)**
Number of responses	N=6 (100%)	N=6 (100%)
Mean percentage of patients in the proposed patient population prescribed regular/maintenance IVIg	[redacted]	69.2%
Median percentage of patients in the proposed patient population prescribed regular/maintenance IVIg	[redacted]	70%
Range	[redacted]	60% to 90%

Source: Company response Appendix A.5.2
[a] The detailed patient description is presented in Company response Appendix A.5.1.1 Table 3
[b] The simplified patient description is presented in the company's New evidence submission document, section 1 and the company response Appendix A.5.2

2.3 Exploring the costs of corticosteroid administration in the target population

The company explored the costs of corticosteroid administration by conducting a targeted literature review. Of the three studies identified, they preferred the study by Lee et al.[1] Details of this study are shown in the company response Appendix B Table 5. For all the adverse events (AEs) reported in that study, the company estimated the average costs to treat them using NHS reference costs (2021/22), shown in the company response Appendix B Table 6. These costs were also inflated to 2023 costs using the CPI price inflation file from ONS. The study by Lee et al. presents survey results of AEs from patients with MG in the MG registry in the US who are receiving corticosteroids (AE frequency shown in Company response Appendix B Table 7). Median prednisone dosage in the study was 10mg per day (range 0.5 to 75mg). The company assumes the same frequency of AEs for patients on high or low doses of corticosteroids.

The EAG has several concerns with the approach taken by the company to estimate complication costs related to corticosteroid use. The study by Lee et al. does not report AEs for patients not receiving corticosteroids, therefore it is not possible to separate AEs due to corticosteroids from those due to MG. It also does not specify the severity of AEs. We note that for NICE appraisals, it is usual to only cost AEs relating to severe AEs (grade 3+). We suggest that many of these AEs would not be severe AEs and therefore should not be costed. There is also an assumption that all AEs are treated with a hospital episode, although some of the AEs may be treated with a GP visit or outpatient consultation etc. such as for acne, for example. We also question whether it is appropriate to use the same AE costs for all patients, regardless of dose.

With regard to the calculations of the AEs costs, there are a number of issues. Firstly, the unit costs have been calculated using the average of multiple Healthcare Resource Group (HRG) codes, whereas the unit costs should be calculated using a weighted average to reflect the activity in different codes. We also consider that is unnecessary to inflate costs as the cost year in the original model was 2022. Further, we consider that some of NHS codes for the AEs are inappropriate and likely overestimate the costs to treat the AE.

Considering the above, the EAG believes that the company's estimates of AE costs are not fit for purpose and lack face and methodology validity and we have therefore included a scenario that does not include corticosteroid AE costs.

The study by Lee et al. also included information for the proportion of AEs that were intolerable. We conducted a scenario using these data with the weighted average cost of each AE (Table 4). We note the company uses unit costs from the National Schedule of NHS Costs Year - 2020-21 and inflates them to 2023. However, the latest version of the Schedule is 2021-22 and the EAG prefers to use the costs from the most recent Schedule without inflation, as the costing year in the rest of the model is 2022.

2.4 Validating assumptions regarding residual effects of efgartigimod treatment following permanent discontinuation of efgartigimod

The company asked Dr Channa Hewamadduma to review the available data on the scientific and clinical plausibility of an efgartigimod residual treatment effect following permanent efgartigimod discontinuation. The data are presented in Appendix C of the company's response to the draft guidance. Dr Hewamadduma supports the plausibility of an ongoing efgartigimod treatment effect and consequently no changes were made to the model which uses an estimate of 15% residual treatment effect in the base case (i.e. 15% of these patients remain in the MG-ADL <5 health state six months after discontinuation of therapy).

We note that the data which have been reviewed come from the ADAPT trial and its open-label extension ADAPT+. This is a broader patient group than the targeted population group the company has identified for whom treatment may offer the greatest value. Our concern is that there are no data to indicate whether the company's proposed targeted population group would be equally likely as the overall ADAPT/ADAPT+ population to contain some patients who would be long responders when efgartigimod is discontinued. We still view the residual effects of efgartigimod after the drug is discontinued as plausible but uncertain. Anecdotally, the first response in the Web comments submitted regarding the draft guidance state that the respondent is "*unaware of a residual treatment effect of efgartigimod. Indeed the reverse seem to be the case in that patients report earlier relapsing resulting in a shortening of intervals between treatment doses. However no-one in the UK has probably been on the treatment long enough to determine the long term response.*" As the EAMS/EAMS+ population closely aligns with the company's proposed target population this might be a future source of data to help address this uncertainty.

2.5 Further validating the importance of caregiver disutility for patients in the target population

The company used data from the digital MyRealWorldMG study, collected via a smartphone app, to elicit EQ-5D-5L data for caregivers and patient MG-ADL scores for matched pairs of caregivers and patients from Germany, Italy, Spain and the UK. These data were pooled for

analysis with caregiver EQ-5D-5L data and patient MG-ADL data collected from a similar paper-based survey conducted in France. Results are reported in the company response (Section 5) and more fully in Appendix D, and the caregiver utility decrements are used in the revised version of the model.

The EAG notes that the study was small: data are presented for 39 caregivers and patients, none of whom are from the UK (Company response Appendix D Table 1). There is not a linear relationship between the mean utility decrements of the caregivers and patient MG-ADL scores (Company response Section 5 Table 1). This may be due to the sample size being small, and also because "*additional factors are affecting the health-related quality of life of the caregiver, including the availability of other sources of care, financial strain, family circumstances, whether the caregiver is still in employment, and the age and gender of the caregiver*" (Company response Appendix D.4.2). This study did not include a matched-control group, so the EAG cannot determine if the utility decrements are only due to caregiving. We also note that this study was observational; caregivers and patients taking part were self-selecting, potentially leading to selection bias.

In addition, caregiver health-related quality of life (HRQoL) data were collected via EQ-5D-5L and have not been mapped to EQ-5D-3L values before being used in the model. During consultation on the draft guidance, members of the Association of British Neurologists (Neuromuscular Advisory Group) commented that carer support would be difficult to evaluate and not appropriate in a gMG population. The EAG recalls the Committee preferred to exclude caregiver disutilities from the model and to consider these qualitatively, in order to standardise decision-making with other treatments for gMG. The EAG does not agree with including caregiver disutilities in the model and notes the company's scenario that excluded caregiver disutilities results in an ICER of £21,497 per QALY (Company response Appendix E Table 7).

2.6 Exploring the appropriate source of utilities for the economic model

The company's utility values in the CS were taken from the ADAPT trial and were different in the two treatment arms. However, the Committee concluded the same utilities should be used for both treatment arms. In this case, the company prefers to use utilities from the MyRealWorldMG study, stating that it removes any confounding treatment effect and that EQ-5D data collected from MyRealWorldMG is likely to better represent the HRQoL burden of gMG than patients with gMG in a clinical trial setting.

The EAG considers that both the MyRealWorldMG study population and ADAPT trial population are different to the new proposed target population, so neither source of utilities is

suitable. We consider that utility values from the EAMS/EAMS+ patient cohort, or the subgroup of patients in the ADAPT trial that reflects the new proposed patient population would be more appropriate.

We also note that the MyRealWorldMG study is likely to be at high risk of bias (see EAG report section 3.5) and the utility data from this study was collected using the EQ-5D-5L, rather than EQ-5D-3L. We believe there remains significant uncertainty around this issue.

2.7 The subcutaneous formulation of efgartigimod

The company expects the subcutaneous formulation of efgartigimod to be approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) in November 2023. A scenario analysis with the assumption that 80% of efgartigimod is administered subcutaneously and 20% intravenously is presented in the company's Appendix E.4 Table 7 showing a 12% decrease in the ICER in comparison to the base case ICER.

2.8 Economic analyses in response to the NICE technical team requests

The NICE technical team posted three questions:

- Question 1: How does the model use the transitions that were observed in the established clinical management arm of the ADAPT trial to inform the transition probabilities for the first four cycles after which people are assumed to return to their baseline health state?
- Question 2: Why would the observed effect in the established clinical management arm not persist long term?
- Question 3: Is the observed effect in the established clinical management arm due to regression to the mean, a trial effect, or a placebo effect?

The company answers each of these questions in their response. In general, the EAG considers the company's responses to be reasonable and does not disagree with them. We consider that the company's assumptions with regard to the modelling of the effect on the placebo arm to be reasonable. Whilst there is some uncertainty around the true incremental effect of efgartigimod vs placebo, we consider the company approach to model the treatment arms as observed in the trial to be reasonable and we do not consider it is necessary to adjust the treatment effect in the placebo arm because it is possible that the additional treatment effect in the placebo arm was also present in the efgartigimod arm. Further, we consider it reasonable that the effect observed in the placebo arm may not be long lasting and therefore the company's approach for the placebo arm to return to baseline also does not seem unreasonable.

3 VALIDATION OF THE COMPANY'S REVISED COST-EFFECTIVENESS RESULTS

3.1 Company's revised base case cost-effectiveness results

The results of the company's changes to their previous base case, including the new PAS discount price, are shown in Table 3. These changes decrease the company base case ICER from £29,976 to £15,228 per QALY.

Table 3 Cumulative results for the company's changes to their original base case

Scenario	Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company base case at technical engagement	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£29,976
	ECM	[redacted]	[redacted]	-	-	
Total maintenance IVIg use of 69.17%, distributed between the MG-ADL ≥5 health-states weighted by the baseline cohort distribution	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£32,335
	ECM	[redacted]	[redacted]	-	-	
Using caregiver disutility values from the Caregiver Burden Study in gMG	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£33,561
	ECM	[redacted]	[redacted]	-	-	
MG-ADL-derived utilities estimated from MyRealWorldMG	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£32,228
	ECM	[redacted]	[redacted]	-	-	
Cost of corticosteroid-related complications calculated from Lee et al. (2018)[1] and NHS reference costs	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£27,899
	ECM	[redacted]	[redacted]	-	-	
20.3% of the cohort in crisis assumed to experience an extended stay in ICU	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£27,835
	ECM	[redacted]	[redacted]	-	-	
PAS discount increased to [redacted]	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£15,228
	ECM	[redacted]	[redacted]	-	-	
Company revised base case	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£15,228
	ECM	[redacted]	[redacted]	-	-	

ECM, established clinical management; ICER, incremental cost-effectiveness ratio; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; PAS, patient access scheme; QALYs, quality-adjusted life years

The company presents the results of their probabilistic sensitivity analysis (PSA) in Company response Appendix E Table 4.

4 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. The EAG does not agree with including caregiver disutilities (discussed in section 2.5) and scenario 1 in Table 4 reproduces the company's scenario analysis (Company response Appendix E Table 7 scenario 2).

We also disagree with the way the costs of adverse events related to corticosteroids are applied in the company's base case (discussed in section 2.3). Removing these costs from the model increases the ICER to £37,126 per QALY (scenario 2). Combining scenarios 1 and 2 increases the ICER to £52,411 per QALY (scenario 3; **EAG base case**).

Applying corticosteroid adverse event costs only to patients who found their side effects intolerable and using the weighted average 2021-22 NHS reference costs increased the ICER to £28,374 per QALY (scenario 4). Removing caregiver disutilities as well as only applying costs for intolerable AEs (combining scenarios 1 and 4; scenario 5) increases the ICER to £41,081 per QALY.

The EAG does not consider the MyRealWorldMG utilities best represent the new proposed target population, but nor do the utilities from the ADAPT trial (discussed in section 2.6). The company scenario using the utilities from the ADAPT trial without treatment as a covariate is included in Table 4 (scenario 6). This change increases the ICER to £19,131 per QALY.

The EAG accepts the additional evidence obtained from the Delphi Panel (i.e. a total maintenance IVIg treatment use of 69.17% distributed between the MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health-states weighting by the baseline cohort distribution in the model), is appropriate for the revised target population. The model remains sensitive to IVIg usage. Reducing total maintenance IVIg treatment use to [redacted] (weighted by baseline cohort distribution) increased the ICER to £35,595 per QALY (scenario 7); efgartigimod dominates ECM if total maintenance IVIg treatment use is increased to [redacted] (scenario 8).

The model is not sensitive to including additional costs for the extended stay in the ICU for 20.3% of patients, which has a negligible effect on the ICER (scenario 9).

NICE requested that the EAG run a scenario (Scenario 10) that excludes:

- Maintenance IVIg use
- Corticosteroid complication costs

- Caregiver disutility
- The treatment effect after treatment discontinuation (i.e. 1% patients in MG-ADL<5 after permanent treatment discontinuation)

In this case, the ICER is substantially increased to £529,635 per QALY. They also requested that we retained the placebo effect for the ECM arm over the time horizon. We were not able to include this assumption in this scenario, because this setting changes results in both the efgartigimod arm and in the ECM arm of the model, rather than the ECM arm only. Consequently, we do not believe this aspect of the model is working correctly. In addition, we cannot run a scenario that retains the placebo effect for the ECM arm over the time horizon and excludes the treatment effect after treatment discontinuation, because the two options are mutually exclusive in the model. As a result, the ICER in scenario 10 is likely to be an underestimate.

Table 4 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]	£15,228
		ECM	[redacted]	[redacted]	-	-	
1	Care giver disutilities removed	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£21,497
		ECM	[redacted]	[redacted]	-	-	
2	Corticosteroid AE costs removed	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£37,126
		ECM	[redacted]	[redacted]			
3	Both caregiver disutilities and corticosteroid AE costs removed (**EAG base case**)	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£52,411
		ECM	[redacted]	[redacted]	-	-	
4	Corticosteroid AE costs applied only for patients who found their side effects intolerable (Lee et al. 2018),[1] using a weighted average of 2021-22 NHS reference costs	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£29,100
		ECM	[redacted]	[redacted]	-	-	

Scenario		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
5	Care giver disutilities removed and corticosteroid AE costs applied only for patients who found their side effects intolerable (Lee et al. 2018),[1] using a weighted average of 2021-22 NHS reference costs	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£41,081
		ECM	[redacted]	[redacted]	-	-	
6	Utilities by health-state based on regression on ADAPT data without treatment effect	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£19,131
		ECM	[redacted]	[redacted]			
7	Total maintenance IVIg treatment use of [redacted] distributed between the MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health-states weighting by the baseline cohort distribution in the model	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£35,595
		ECM	[redacted]	[redacted]	-	-	
8	Total maintenance IVIg treatment use of [redacted] distributed between the MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health-states weighting by the baseline cohort distribution in the model	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
		ECM	[redacted]	[redacted]	-	-	
9	Remove extended stay in the ICU for 20.3% of patients	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£15,292
		ECM	[redacted]	[redacted]	-	-	
10	No maintenance IVIg use; no corticosteroid complication costs; no caregiver disutility in the model; no treatment effect assumed after treatment discontinuation	Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	£529,635
		ECM	[redacted]	[redacted]	-	-	

AE, adverse event; ECM, established clinical management; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; QALYs, quality-adjusted life years

5 EAG CONCLUSION

To quantify the cost-effectiveness of efgartigimod in the company's newly described targeted population of gMG patients, some key model inputs have been revised, but others remain the same:

- The mean proportion of gMG patients who would be prescribed regular/maintenance IVIg has been revised and is specified for the company's new targeted population. A mean value of 69.2% was estimated by the six clinicians the company surveyed, but the values ranged from 60% to 90%. We believe there is still some uncertainty associated with this estimate, but it is good that it is specific for the targeted population.
- The cost of complications related to corticosteroid use have been revised but are not specific for the company's targeted population. We have identified several concerns with the approach taken by the company to estimate complication costs related to corticosteroid use and this is still an area of uncertainty.
- The assumption regarding residual effects of efgartigimod treatment following permanent discontinuation of efgartigimod remains the same and data to support this assumption has been validated by Dr Channa Hewamadduma. We believe the residual effects, which have been observed in a broader patient group than the newly described targeted population, should still be viewed as plausible but uncertain. In particular, this effect is uncertain in the newly described targeted population.
- The company continues to include caregiver disutility in the model and we have identified several concerns with the data source for this. Our preference is for carer disutilities to be taken into account qualitatively by the NICE committee.
- The source of utilities for the economic model has been revised and uses the same utilities for both treatment arms, but we consider that the population from which the utilities are drawn is different to the newly described target population. We believe there remains significant uncertainty around this issue.

Overall, we welcome the identification of a targeted population of people with gMG in which treatment may offer the greatest value. However, we recognise that there are still multiple areas of uncertainty, not all of which we can explore due to an absence of data. The results of the EAG scenario analyses using the company's revised base case range from an ICER (£/QALY) of £15,292 to £529,635 and one scenario (IVIg treatment use increased to 80%) in which efgartigimod dominates established clinical management (is less costly and with better health outcomes).

6 REFERENCES

1. Lee I, Kaminski HJ, McPherson T, Feese M, Cutter G. Gender differences in prednisone adverse effects: Survey result from the MG registry. Neurol Neuroimmunol Neuroinflamm. 2018;5(6):e507.

NICE query to argenx on 03/11/23

Dear David,

Hope you are well.

In advance of the upcoming committee meeting for efgartigimod for treating generalised myasthenia gravis, the NICE technical team would like to request some additional information.

Could the company please provide;

- Further data from the efgartigimod EAMS data;
    - Please provide population characteristics for this population and a short summary of how this compares to your proposed target population
    - Could the company also provide the number and types of prior treatments which the patients in the EAMS population have had/are currently receiving?

- Further clarification on the proposed target population;
    - What is meant by "ineligible" for standard treatment? (your proposed wording states "who have failed, are intolerant or ineligible for standard treatment")
    - We note EAG concerns that the proposed wording appears to go against the marketing authorisation for efgartigimod (which is an add-on treatment) – would you like to comment on this?
    - Could the company comment on the EAMS indication wording in regard to "licensed treatments" – we are aware there are no treatments with a marketing authorisation for MG (not including newer treatments coming through)

Please provide this information via NICE docs, a quick response would be appreciated given the time left before the second committee meeting.

https://appraisals.nice.org.uk/request/186916

Best wishes,

Celia

Celia Mayers (she/her)

Project Manager, Technology Appraisals & HST

National Institute for Health and Care Excellence

Level 1A | City Tower | Piccadilly Plaza | Manchester M1 4BT | United Kingdom

Tel: +44 (0) 161 413 4116

Web: http://nice.org.uk

Response to NICE queries (received 3 November 2023)

Efgartigimod EAMS data

- **Please provide population characteristics for this population and a short summary of how this compares to your proposed target population.**

- **Could the company also provide the number and types of prior treatments which the patients in the EAMS population have had/are currently receiving?**

Summary:
The proposed target patient population aligns closely with the EAMS / EAMS+ cohort, as summarised in **Table 1** below, and represents a group of patients in England who have received ongoing treatment in a real-world setting.

The Company have collected baseline demographic information for each patient through the EAMS / EAMS+ process, which includes age and sex. Details regarding the number or type of prior treatments were NOT collected routinely. This follows guidance from the MHRA that data collection during EAMS (and, by extension, EAMS+) should be "minimal and should not be an extra burden for clinicians".

However, for the purposes of an argenx-sponsored scientific symposium at the Association of British Neurologists (ABN) conference on 11th May 2023, the Company worked with Dr Jennifer Spillane (Consultant Neurologist, Guy's and St Thomas' NHS Foundation Trust, University College London Hospitals NHS Foundation Trust, London) to collect information on prior treatments for the first 25 patients in the efgartigimod EAMS / EAMS+. These data are summarised in **Table 4**, demonstrating full alignment with the EAMS / EAMS+ Blueteq form criteria and, by extension, the optimised efgartigimod patient population proposed following the Delphi process conducted in October 2023.

The ADAPT trial has been used to estimate the **clinical effectiveness** of efgartigimod to treat generalised myasthenia gravis. As seen in **Tables 2 and 3** below, the baseline demographics of ADAPT participants who were AChR+ and had treatment with efgartigimod align closely with the demographics of the EAMS / EAMS+ population.

Finally, the **cost-effectiveness model** draws data from more than one source. Efgartigimod efficacy and safety data is based on ADAPT and ADAPT+, whereas the model uses distribution of initial age and sex for the simulated population and utility values of participants from the MRWMG study who received treatment for gMG in a real-world setting. The baseline characteristics of UK gMG patients in MRWMG are also similar to those in EAMS / EAMS+ and are appropriate for use in the cost-effectiveness model.

Table 1. Comparison of EAMS / EAMS+ and NICE Target Patient Population

	Blueteq (EAMS / EAMS+)	NICE Target Patient Pop.
Diagnosis	Adult ≥ 18 years of age with a definite diagnosis of AChR+ gMG	Adult ≥ 18 years of age with a definite diagnosis of AChR+ gMG

MG-ADL	MG-ADL total score of ≥ 5	MG-ADL score ≥5 (>50% of MG-ADL score due to non-ocular symptoms)
Criteria	Have failed, not tolerated or are not suitable for standard therapy* for gMG	Have failed, not tolerated or are ineligible for standard therapy*
*** Standard Therapy**	Standard therapy consists of adequate trials of steroids and at least 2 non-steroidal Immunosuppressive therapies (NSISTs), given in sufficient dose and for sufficient duration	Standard therapy includes maximal dose of steroids, and at least 2 additional therapies, such as non-steroidal immunosuppressive therapies (NSISTs) and rituximab, for an adequate period of time, at an adequate dose.

Table 2. Baseline characteristics of EAMS / EAMS+ cohort

Sex	**n**	**% of cohort**	**Mean age (years)**
Male	23	29.1	58.3**
Female	56	70.9	48.2**
Unknown	1	*	25
Total	80	100	50.7 (median 49.0)

* As the sex of one participant was unknown, the percentage distribution of male and female participants was calculated by removing this datapoint so the total distribution equals 100% of the cohort
** Age data was not available for two male participants and one female participant, so the mean age was calculated by removing these datapoints

For comparison, the baseline age and sex characteristics of participants included in the ADAPT trial have been outlined in Table 3. The ADAPT trial has been used to estimate the clinical effectiveness of efgartigimod to treat generalised myasthenia gravis.

Table 3. Baseline age and sex characteristics for the ADAPT population

	AChR+ patients (n=129)	
	Efgartigimod group (n=65)	**Placebo group (n=64)**
Mean age	44.7	49.2
Male	19 (29%)	24 (38%)
Female	46 (71%)	40 (63%)
Total	65	64

Distribution of sex characteristics in ADAPT participants who were AChR+ and had treatment with efgartigimod, align closely with the demographics of the EAMS / EAMS+ population. Of the AChR+ patients in ADAPT, 71% were female and 29% were male, while 70.9% and 29.1% of the AChR+ EAMS / EAMS+ population were female and male, respectively. The mean age of 44.7 in the specified ADAPT group is similar to the mean age of 50.7 in the EAMS population.

The cost-effectiveness model uses distribution of initial age and sex for the simulated population and utility values of participants from the MRWMG study who received treatment for gMG in a real-world setting. The patients that were included from the MRWMG cohort were from the UK and had gMG as per the criteria from the ADAPT trial. The mean age in this population is 45.2 years and the sex distribution is 80% female and 20% male. These baseline characteristics are also similar to those in EAMS / EAMS+ as presented above and are therefore appropriate to be applied in the cost-effectiveness model.

Prior treatments for the first 25 patients in the efgartigimod EAMS / EAMS+ (collected for the purpose of an argenx-sponsored symposium at ABN 2023) are summarised in **Table 4** below, reflecting a heavily pre-treated patient population, which aligns to both the EAMS / EAMS+ Blueteq criteria and the optimised efgartigimod patient population resulting from the Delphi survey.

Table 4. Prior treatments from the first 25 patients enrolled into Efgartigimod EAMS

Treatments	n (%)
All†	
Corticosteroid	18 (72.0)
NSIST (any prior)	21 (84.0)
1 prior	*9 (36.0)*
2 prior	*8 (32.0)*
3 prior	*4 (16.0)*
Rituximab	14 (56.0)
IVIg/PLEX	19 (76.0)
Baseline	
Corticosteroid	18 (72.0)
NSIST	19 (76.0)
*Corticosteroid **and** NSIST*	12 (48.0)

*Although data were not collected, it is assumed that patients would have received prior pyridostigmine;
†Patients may have received more than one treatment.
IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange.
1. argenx Data on File.

Proposed target population

- **What is meant by "ineligible" for standard treatment? (your proposed wording states "who have failed, are intolerant or ineligible for standard treatment")**

  The word ineligible does not refer to all standard gMG treatments. In line with the marketing authorisation, efgartigimod must be used as an add-on to standard therapy, not as a monotherapy.

  As per the ABN guidelines, in practice, standard gMG therapies (pyridostigmine, corticosteroids or NSISTs) are selected according to patient characteristics, comorbidities and severity of symptoms. Importantly, these may be used alone or in combination. As gMG progresses, the disease may become inadequately controlled, meaning that standard therapies need to be escalated and used in combination. For example, NSISTs may be added to the treatment regimen for a patient already receiving pyridostigmine and/or corticosteroids to improve disease control. Adding NSISTs may enable tapering the dose – or perhaps even discontinuing – pyridostigmine and/or corticosteroids.

In certain clinical situations, clinicians may deem patients ineligible / not suitable for one of the standard gMG treatments. For example, a patient with co-morbid diabetes could be deemed not suitable for high dose corticosteroids. Similarly, patients with inherited deficiency of thiopurine methyltransferase (TMTP) would not be suitable to receive azathioprine immunosuppression. This is the intended meaning behind the use of the word “ineligible” in the target patient population.

In all instances, in line with the marketing authorisation, efgartigimod will used as an add-on to standard therapy. It is simply the mix of these treatments which may differ based on patient presentation.

- **We note EAG concerns that the proposed wording appears to go against the marketing authorisation for efgartigimod (which is an <u>add-on</u> treatment) – would you like to comment on this?**

  The proposed target population is in line with the marketing authorisation for efgartigimod, as it is expected to be used as an adjunct to standard therapy rather than as a monotherapy. Even with the optimised target population and additional evidence provided, argenx is still proposing that efgartigimod be used as an adjunct (add-on) to treatments that are used in current standard care, such as but not limited to corticosteroids and immunosuppressants, while it would replace the use of IVIg or PLEX in these patients. The treatments that are expected to be replaced, are themselves used as add-on therapies.

- **Could the company comment on the EAMS indication wording regarding “licensed treatments” – we are aware there are no treatments with a marketing authorisation for MG (not including newer treatments coming through)**

  To date, there are no published positive reimbursement recommendations for treatments for gMG in the UK. The only approved treatments for gMG are acetylcholinesterase inhibitors, eculizumab (licensed only for anti-AChR antibody positive refractory gMG patients and not reimbursed by NICE), and an oral suspension of azathioprine, which is an immunosuppressant medication. The first treatment option for gMG is usually pyridostigmine, an acetylcholinesterase inhibitor, then corticosteroids and immunosuppressants are offered as second and third line therapies. Although these treatments do not have a marketing authorisation for this indication, they are being routinely used in clinical practice and are specified as comparators for this appraisal. The phrase “licensed treatments’’ was defined by the MHRA as part of the EAMS therapeutic indication but has not been included in the Blueteq form for either EAMS or EAMS+. It was intended to mean treatments that are offered as standard care in NHS clinical practice.

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]

External Assessment Group's response to (i) questions posed by the NICE technical team and (ii) the company's response to questions posed by the NICE technical team.

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
Authors	Fay Chinnery, Research Fellow, Health Economics, SHTAC Keith Cooper, Senior Research Fellow, Health Economics, SHTAC Joanna Picot, Senior Research Fellow, Evidence Synthesis, SHTAC
Correspondence to	Dr. J. Picot Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House, Enterprise Road, University of Southampton Science Park, Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	13/11/2023

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LIST OF TABLES

1 Introduction

This document includes:

1. The External Assessment Group's (EAG's) response to questions that the NICE technical team posed to the EAG in an email of 06 November 2023 about aspects of the IVIg modelling and other key issues in the ID4003 efgartigimod appraisal.
2. The EAG's comments on the company's response to questions that the NICE technical team posed which the EAG received on 09/11/2023.

2 EAG's response to NICE technical team questions

2.1 NICE technical team questions about IVIg

Question 1. IVIg is assumed to provide no QALY benefits – but clinicians would not give IVIg if no benefits were obtained. Is there anything the EAG can comment on this?
EAG response: IVIg has an indirect benefit by affecting transitions to lower (better) MG-ADL health states that have an associated better utility score. But because IVIg is modelled as part of a bundle of SOC/BSC treatment any changes to the bundle doesn't change effectiveness in the model. It is also worth noting that there is a proportion of efgartigimod treated patients who are considered non-responders and they are modelled separately in the same way as the established clinical management (ECM) arm.

Question 2. **More importantly, can we check** – is it the case that there is no discontinuation of IVIg in the model (particularly in the BSC arm)? In the BSC arm the costs of IVIg are >£1 million (discounted) over the lifetime of the model for the average patient – could you comment on this? If no discontinuation of IVIg is modelled, or modelled incorrectly, are IVIg costs inflated unreasonably over time, potentially by many times?
EAG response: There is no explicitly modelled discontinuation of IVIg in the model. However, because the proportion of patients receiving IVIg as part of ECM varies by health state (as shown in CS Table 25) the proportion receiving IVIg does fall with transitions to lower (better) MG-ADL health states. It is worth noting that patients who enter the crisis transitional state exit after one model cycle but can only return to the MG-ADL≥10 health state. When this happens after cycle six, patients stay in MG-ADL≥10 where 100% receive IVIg. As the model runs and crises occur after cycle six, the MG-ADL≥10 health state accrues patients exiting the crisis state and the proportion in this health state therefore rises (after a certain point it begins to fall again which we think may be because of mortality). You would need to ask a clinician on whether, in practice, IVIg would be discontinued and after how long. (You may remember the original EAG base case did not include IVIg). Other

aspects that could be contributing to a potential exaggeration of IVIg costs are i) the Delphi panel were asked about the proportion of patients who were eligible/suitable for IVIg or who should be prescribed IVIg which maybe a greater proportion than those who would actually receive IVIg and ii) we wonder whether more clinical input about the relative percentages of the refractory population who would receive IVIg versus receiving rituximab would be useful? As CS Table 25 shows the proportion receiving rituximab does not alter across the three health states that receive it. Could the model be exaggerating the IVIg costs because the proportion of patients receiving IVIg is too high and in practice some would receive rituximab instead?

2.2 NICE technical team questions about placebo

Question 1. In the EAG base case, the placebo effect is removed in the BSC arm – but the placebo may therefore be retained in the treatment arm. Do the EAG therefore think their base case ICER is an underestimate of the ICER?

EAG response: As we state in our ACD critique, we believe the company's assumptions regarding placebo are reasonable. If the placebo effect was dealt with differently, for example by removing it from both the ECM and efgartigimod arms this would increase the ICER.

Question 2. TA733 FDG section 3.8 – in this appraisal, 3 separate placebo adjustment methods were used – this might require some additional modelling/transition matrices to carry out in this appraisal. Could the EAG comment on these methods as a potential solution for ID4003?

EAG response: We have stated in our ACD that we believe that the company's assumptions are reasonable. A variety of different approaches were explored in TA777 (the link takes us to TA777 not TA733 as written above) and although there may be some logic in using different approaches, we do not believe there is a strong case for using one approach over another. Additionally, we suspect that the company might find it difficult to implement within the confines of their current model structure.

Question 3. The placebo issue links to the IVIg issue: as SoC arm returns to baseline and in the model baseline is >5 MG-ADL (as per ADAPT inclusion criteria), which means everyone in the SoC arm will be in states in which IVIg use is assumed – can you comment on the overlap between the two issues?

EAG response: We are not clear about what you are asking here. Do you mean that if the placebo effect were retained in ECM arm some of the ECM cohort would be in <5 MG-ADL and therefore would not get IVIg?

2.3 NICE technical team question about treatment effect after discontinuation

Question

- This assumption impacts QALYs and costs for a long period over the length of the model (given relatively young starting age and limited mortality)
- Large impact on the ICER – increases EAG base case 3x when treatment effect taken out
- This assumption accounts for ~50% of total QALY gains
- Links into IVIg issue – assuming a substantial % stay in <5 MG-ADL after stopping efgartigimod, means these people will not get IVIg in the intervention arm and significant cost savings will be attributed to efgartigimod – can the EAG comment on this?

EAG response: Yes, benefit partly due to QALY gains and partly due to cost saving for averting use of efgartigimod. As we stated in our critique of the company's ACD response, whilst the ongoing treatment effect for some patients in ADAPT is plausible our concern is that there are no data to indicate whether the company's proposed targeted population group would be equally likely as the overall ADAPT/ADAPT+ population to contain some patients who would be long responders when efgartigimod is discontinued so this is a source of uncertainty.

2.4 NICE technical team question about utility values

Question

- I think NICE methods guide states a preference for utilities from the pivotal clinical trial
- Going from the updated utility source to trial values reduces EAG base case QALYs by >33% - can the EAG comment on this?
- Links to "placebo" and "treatment effect after discontinuation" issues

EAG response: We presume you mean, changing the utility source reduces the incremental QALY by >33%? Our critique response was that neither utility values were particularly appropriate, given the change in population. If pushed, we would probably prefer the utilities from the trial for the reasons you give here.

3 EAG'S COMMENTS ON THE COMPANY'S RESPONSE TO QUESTIONS THAT THE NICE TECHNICAL TEAM POSED

This section should be read in conjunction with the company's response to these questions.

3.1 NICE technical team request for further data from the efgartigimod EAMS data

- Please provide population characteristics for this population and a short summary of how this compares to your proposed target population.
- Could the company also provide the number and types of prior treatments which the patients in the EAMS population have had/are currently receiving?

EAG's comments on the company response

The EAG notes that the EAMS population data show 76% of patients had received IVIg (compared with estimate of 69% of patients who the Delphi panel thought 'should' receive IVIg), but it is unknown if patients in EAMS had received IVIg for maintenance or crisis treatment. In addition, we also note that 72% of the EAMS cohort had used corticosteroids, which aligns with the model population (75%).

The company considers the mean age and sex distribution in the MyRealWorldMG study is similar to the age and sex characteristics of the EAMS population. Consequently, the company believes it is appropriate to use the MyRealWorldMG data in their base case. We present a comparison of the ADAPT trial, EAMS cohort and MyRealWorldMG study population in Table 1.

Table 1 Comparison of baseline age and sex characteristics for the ADAPT trial population, the EAMS cohort and the MyRealWorldMG study

Characteristic	ADAPT trial AChR+ patients		EAMS/EAMS+ cohort ([redacted])	UK MRWMG cohort (n=25)
	Efgartigimod (n=65)	Placebo (n=64)		
Economic analysis	• EAG scenario analysis 12 in Table 24 EAG original report using company original base case • EAG scenario analysis 15 in Table 28 EAG original report using EAG original base case		EAG scenario analyses in Table 2 below using both the company and EAG current base cases	Company and EAG current base cases
Mean age, years	44.7	49.2	Males 58.3[a] Females 48.2[a] Total 50.7	45.2
Male	19 (29%)	24 (38%)	[redacted] (29.1)[b]	20%
Female	46 (71%)	40 (63%)	[redacted] (70.9)[b]	80%

[a] The age of two male and one female participant were unknown so mean age was calculated without these datapoints.
[b] The sex of one participant was unknown so the company excluded this one participant when calculating the percentage distribution of male and female participants.

The EAG conducted a scenario, using both the company's and EAG's base cases, to investigate the effect of using the EAMS population characteristics data (Table 2). This change increases the company's base case ICER by about £12,000 per QALY to [redacted] per QALY. The EAG's base case ICER is increased to [redacted] per QALY.

Given the company's new proposed target population aligns closely with the EAMS/EAMS+ cohort and this cohort is larger than the subset of UK patients in the MyRealWorldMG study, the EAG considers it appropriate to use patient characteristic data from the EAMS cohort, rather than from the ADAPT trial or MyRealWorldMG study.

Table 2 Results for efgartigimod versus established clinical management, CMU costs

No.	Scenario description	ICER (£/QALY)
Company base case		**£15,228**
1	EAMS population characteristics	[redacted]
EAG base case		**£52,411**
2	EAMS population characteristics	[redacted]

EAMS, Early Access To Medicines Scheme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

3.2 NICE technical team request for further clarification on the proposed target population

- What is meant by “ineligible” for standard treatment? (your proposed wording states “who have failed, are intolerant or ineligible for standard treatment”)
- We note EAG concerns that the proposed wording appears to go against the marketing authorisation for efgartigimod (which is an add-on treatment) – would you like to comment on this?
- Could the company comment on the EAMS indication wording in regard to “licensed treatments” – we are aware there are no treatments with a marketing authorisation for MG (not including newer treatments coming through)

EAG’s comments on the company response

The company has clarified the meaning of their proposed wording to describe the target population that would be eligible to receive efgartigimod and we are reassured. However, we also note that the company has not provided an alternative form of words that avoids the potential for misunderstandings to occur. Taking the company’s response into account we suggest that efgartigimod is provided within the licenced indication using revised wording to describe the target group, such as:

- As an add-on to standard therapy for adult patients (≥18 years) with generalised Myasthenia Gravis (gMG) who are positive for acetylcholine receptor (AChR) antibodies AND who have 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 at least one of the standard gMG therapies

The company has also clarified that the phrase “licensed treatments’’ was defined by the MHRA as part of the EAMS therapeutic indication and is intended to mean treatments that are offered as standard care in NHS clinical practice. This phrase is not included in the Blueteq form for either EAMS or EAMS+.