For Zoom – [noACIC]

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Technology appraisal committee D [9 May 2024]

Chair: Raju Reddy

External assessment group: Southampton Health Technologies Assessment Centre

Technical team: Ross Wilkinson, Alan Moore, Jasdeep Hayre

Company: Argenx

Efgartigimod for treating generalised myasthenia gravis [ID4003]

- ✓ **Recap from ACM2**
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ❑ Cost-effectiveness results
- ❑ Supplementary slides

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Draft guidance: preliminary recommendation

Efgartigimod is not recommended as an add-on to standard treatment for gMG in adults who test positive for anti-acetylcholine receptor antibodies

Why the committee made this decision:

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

However, it is uncertain if the people in the trial reflect the people who would have efgartigimod in the NHS because the company have proposed a target population with more severe disease. There are also uncertainties in the economic model including:

- IVIg use and effect assumptions
- The effect of efgartigimod after treatment is stopped permanently
- How the benefits observed in the placebo arm of ADAPT are included

Consultation responses received from:

Company (Argenx), Clinical experts, Myaware & Muscular Dystrophy UK (joint response), Association of British Neurologists (ABN) advisory group, Web comments (n=34)

Abbreviations: gMG, Generalised Myasthenia Gravis; IVIg, Intravenous immunoglobulin;

Efgartigimod (Vyvgart, Argenx)

Table: Technology details

Marketing authorisation	• Efgartigimod is indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are AChR antibody positive • MHRA MA received March 2023
Mechanism of action	• Efgartigimod is a human IgG1 antibody fragment that binds to the neonatal Fc Receptor, resulting in a reduction in the levels of circulating IgG including pathogenic IgG autoantibodies
Administration	• Efgartigimod is provided as a concentrate for IV infusion and solution for injection • Recommended IV infusion dose is 10 mg/kg as a 1-hour IV infusion administered in cycles of once weekly infusions for 4 weeks • Recommended SC injection dose is 1,000 mg administered in cycles of once weekly injections for 4 weeks • Subsequent treatment cycles are administered according to clinical evaluation → frequency of treatment cycles may vary by patient
Price	• List price: ↳ £6,569.73 per 400 mg vial - treatment cycle: [redacted] ↳ £15,307.47 per 1,000mg SC injection – treatment cycle: [redacted] • A simple confidential PAS discount has been agreed for efgartigimod

Abbreviations: AChR, Anti-acetylcholine receptor; gMG, Generalised Myasthenia Gravis; IgG, Immunoglobulin G; IV, Intravenous; MA, Marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; PAS, Patient access scheme; SC, Subcutaneous.

Unresolved key issues from ACM2

Table: Unresolved key issues

Partially resolved | Requires more in-depth discussion

Issue	Committee's considerations
Target population	• The company's description broadly described the most suitable population, but some uncertainty remained
Generalisability	• Using clinical-effectiveness results from a population broader than the updated target population was a source of uncertainty
Maintenance IVIg	• The evidence from the Delphi panel and the company's approach to modelling IVIg use substantially overestimated the use of maintenance IVIg ↳ *The company's approach to modelling IVIg use did not account for a proportion of people whose disease did not respond to IVIg and did not account for people who would stop IVIg over the lifetime of the model*
Treatment effect after stopping	• Would consider the company's assumption alongside other scenarios, but there was uncertainty associated with these assumptions and required further input • May be linked to placebo effect
Placebo effect	• The benefit observed in the placebo arm of ADAPT should be maintained over the time-horizon of the model

Several issues can be considered resolved as there is agreement between the committee, EAG and company

Abbreviations: ACM, Appraisal committee meeting; IVIg, Intravenous immunoglobulin; * See appendix - Key issues from ACM2 – Agreed between Committee, EAG and Company

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Consultation responses to draft guidance (1/3)

Consultation response: Two clinical experts

- Unlike in other countries, NHS patients lack access to effective fast acting therapies
- Significant % of people in refractory population receive support from a carer (supporting them through ADLs, clinical appointments, transport, monitoring disease and sharing anxiety of a potential crisis)
- Steroids have a high burden. Significant % of refractory population likely on steroids
  - ↳ *"The number of patients who we see in clinics who have become dysmorphic, depressed because of permanent changes to their faces and bodies is heart breaking"*
  - ↳ Listening to the MG patient community and seeking their views is the only fair way to obtain a complete understanding of patients lived experience of steroids
- Committee should consider clinical effectiveness evidence from the EAMS programme

Commented on the committee's assumptions relating to:

- Target population *(see later slides)*
- Maintenance IVIg use *(see later slides)*
- Maintenance IVIg dosing and discontinuation *(see later slides)*
- Residual treatment effect *(see later slides)*

Abbreviations: ADL, Activities of daily living; EAMS, Early access to medicines scheme; IVIg, Intravenous immunoglobulin; MG, Myasthenia Gravis;

Consultation responses to draft guidance (2/3)

Consultation response: Myaware and Muscular Dystrophy UK (patient group)

- Concerned that the recommendation in the draft guidance does not:
  - ↳ Reflect the clear need for access to new treatments for MG
  - ↳ Fully take account of the evidence and insight that has been provided by the patient community
- Concerned that the committee does not view the evidence (e.g carer disutility study) and insight that has come from the patient community as sufficiently robust

Commented on the committee's assumptions relating to:

- Target population *(see later slides)*
- Maintenance IVIg use *(see later slides)*

Consultation response: ABN advisory group (professional group)

- Efgartigimod is an effective novel treatment with the potential to revolutionise MG treatment especially now that the subcutaneous formulation is available
- Acknowledges the lack of information needed to inform key model parameters such as carer quality of life and the impact of efgartigimod on corticosteroid and immunosuppressant side effects

Commented on the committee's assumptions relating to:

- Target population *(see later slides)*

Abbreviations: ABN, Association of British Neurologists; IVIg, Intravenous immunoglobulin; MG, Myasthenia Gravis;

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Consultation responses to draft guidance (3/3)

34 web comments from patients, carers and other commentators, across several themes:

High unmet need

- Lack of options for refractory MG
- Severe impact of condition

Identifiable target population

- Refractory (as in EAMS)
- Dependent on IVIg/PLEX

Benefits of efgartigimod

- Fast acting with option for home use
- Subcutaneous formulation can be administered easily and relieve hospital infusion unit burden
- Effective and steroid sparing

IVIg

- Variability in access
- Higher usage in target population
- Efgartigimod = lower IVIg use

Caregiver Burden

- Should be considered
- Mental health impacted
- Impacts wider family/friends

Abbreviations: EAMS, Early access to medicines scheme; IVIg, Intravenous immunoglobulin; MG, Myasthenia Gravis; PLEX, Plasma exchange;

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Key issue: Target population (1/2)

Background

- Committee concluded company's description broadly described most suitable population; some uncertainty remained
  - ↳ "People with active, refractory disease, with MG-ADL score of 5 or more (over 50% of MG-ADL score from non-ocular symptoms) and who cannot tolerate or are ineligible for standard treatment, or in whom standard treatment has failed. *(Standard treatment includes a maximal dose of steroids, and at least 2 additional treatments, such as non-steroidal immunosuppressants and rituximab, for an adequate period of time, at an adequate dose)*"

Company

- Proposed description consistent with Blueteq, a requirement for the EAMS/EAMS+ programme
- Efgartigimod will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements to provide specialised neurology services
- Efgartigimod will be offered within MG specialist centres as in EAMS/EAMS+ and patients will continue to be registered through Blueteq, to ensure alignment with target population

EAG

- Proposed description closely aligned with EAMS/EAMS+ and would enable clinicians to identify the appropriate group of patients to receive efgartigimod in the NHS

*See appendix - Target population (Supplementary slide 1, Supplementary slide 2)

Abbreviations: EAMS, Early access to medicines scheme; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Key issue: Target population (2/2)

Clinical expert

- Efgartigimod treatment should only be approved for use in specialist centres
- Consensus amongst experts is to use efgartigimod in cohort of patients with biggest unmet need
  - ↳ Defined in EAMS → proposed group would have tried pyridostigmine and prednisolone and two or more other NSISTs in addition to having had a thymectomy
  - ↳ Patients with easy to control gMG are not the intended target population

Myaware and Muscular Dystrophy UK

- A minority of patients are in desperate need of relief of their symptoms and the side effects of standard treatments
- Appreciate it is difficult to robustly define standard treatment pathway - even more reason to encourage these add-on therapies to become options

ABN advisory group

- Supports the consensus opinion of its MG clinical expert memberships and the suggestions that efgartigimod should be considered in the treatment algorithm of patients with gMG in the following groups:
  - Those dependent on regular IVIg or PLEX
  - Those with refractory gMG (ie. MG ADL ≥5) despite 2 immunosuppressant agents

Is the target population appropriate for decision making?

Abbreviations: EAMS, Early access to medicines scheme; gMG, Generalised Myasthenia Gravis; IVIg, Intravenous immunoglobulin; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NSIST, Nonsteroidal immunosuppressive therapy; PLEX, Plasma exchange;

Key issue: Generalisability

Background

- Committee considered the inclusion criteria for ADAPT may not reflect NHS population for efgartigimod
- Using clinical-effectiveness results from a population broader than the proposed target population was a source of uncertainty

Company

Continues to use data from the full ADAPT population

- Baseline characteristics similar across the total ADAPT population, ADAPT AChR-Ab+ subgroup that received efgartigimod, the post-hoc refractory ADAPT AChR-Ab+ subgroup that received efgartigimod and the EAMS/EAMS+ populations
- Post-hoc analysis comparing non-refractory and refractory AChR-Ab+ subgroups showed a similar proportion of patients experienced a significant clinical response after one cycle of efgartigimod
  - ↳ Non-refractory: 17/25 (68%) Refractory: 27/40 (67.5%)
- Response rates in non-refractory/refractory ADAPT AChR-Ab+ subgroups and EAMS/EAMS+ consistent

EAG

- Reassured that characteristics of EAMS/EAMS+ cohort are relatively similar to refractory ADAPT subgroup
- Agrees that the efficacy results support the company's case for the generalisability of the ADAPT data

NICE technical team

- ADAPT data does not include SC administration of efgartigimod - SC use may increase time on treatment for example, but this is uncertain with limited data

NICE How generalisable are the ADAPT outcomes to the target population?

*See appendix – Supplementary Slide 1 and 2

Abbreviations: Ab+, Antibody positive; AChR, Anti-acetylcholine receptor; EAMS, Early access to medicines scheme; SC, Subcutaneous;

Key issue: Maintenance IVIg use (1/2)

Background

- Committee concluded evidence from Delphi panel substantially overestimated use of maintenance IVIg

Company

- **Updated base case**
  - ↳ 43.8% maintenance IVIg usage *(EAMS/EAMS+ 48 patients from 13 specialist centres)*
- **Sensitivity analysis upper/lower bound**
  - ↳ Upper : 69% maintenance IVIg usage *(Delphi panel)*
  - ↳ Lower : [redacted] maintenance IVIg usage *(NHSE commissioning expert estimates applied to Delphi panel estimates of the percentage of the total gMG population represented by the target population)*
- **Scenario analysis**
  - ↳ 14.6% plasma exchange regularly at treatment initiation
- Believe supply issues and commissioning restrictions of IVIg are not relevant considerations

EAG

- Recent RWE from EAMS provides evidence of likely level of maintenance IVIg usage in a population closely matched to company's target population

Clinical experts

- CE1: Maintenance IVIG and PLEX are important for a significant proportion of patients in specialist centres
- CE1: The shortage of IVIg that has now been largely resolved although it should still be used carefully
- CE2: Some centres don't have access to IVIg and PLEX which are used very much as rescue treatments

Abbreviations: CE, Clinical expert; EAMS, Early access to medicines scheme; IVIg, Intravenous immunoglobulin; NHSE, NHS England; PLEX, Plasma exchange; RWE, Real world evidence;

Key issue: Maintenance IVIg use (2/2)

Myaware and Muscular Dystrophy UK

- Do not believe that shortage of supply should be a factor in assessing maintenance IVIg usage → hope that this would be resolved in the future
- Believe the Delphi panel held by the company to estimate maintenance IVIg use is technically robust

What is the most appropriate usage of IVIg in the target population?

Abbreviations: IVIg, Intravenous immunoglobulin;

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Key issue: Maintenance IVIg clinical benefit (1/2)

Background

- Model included cost of IVIg but assumed no clinical benefits
  - ↳ Biased cost-effectiveness results in favour of efgartigimod

Company

Revised base case to include IVIg efficacy using evidence from an NMA

- NMA based on ADAPT and two maintenance IVIg RCTs
  - ↳ NMA results show efgartigimod achieved a reduction in MG-ADL [redacted] points greater vs IVIg
- Scenario analysis presented using two separate placebo-anchored MAICs in a sensitivity analysis
  - ↳ 1) ADAPT Vs IVIg (Wolfe) - MG-ADL change, [redacted] greater for efgartigimod than IVIg
  - ↳ 2) ADAPT Vs IVIg (NCT02473952) - MG-ADL change, [redacted] greater for efgartigimod

EAG

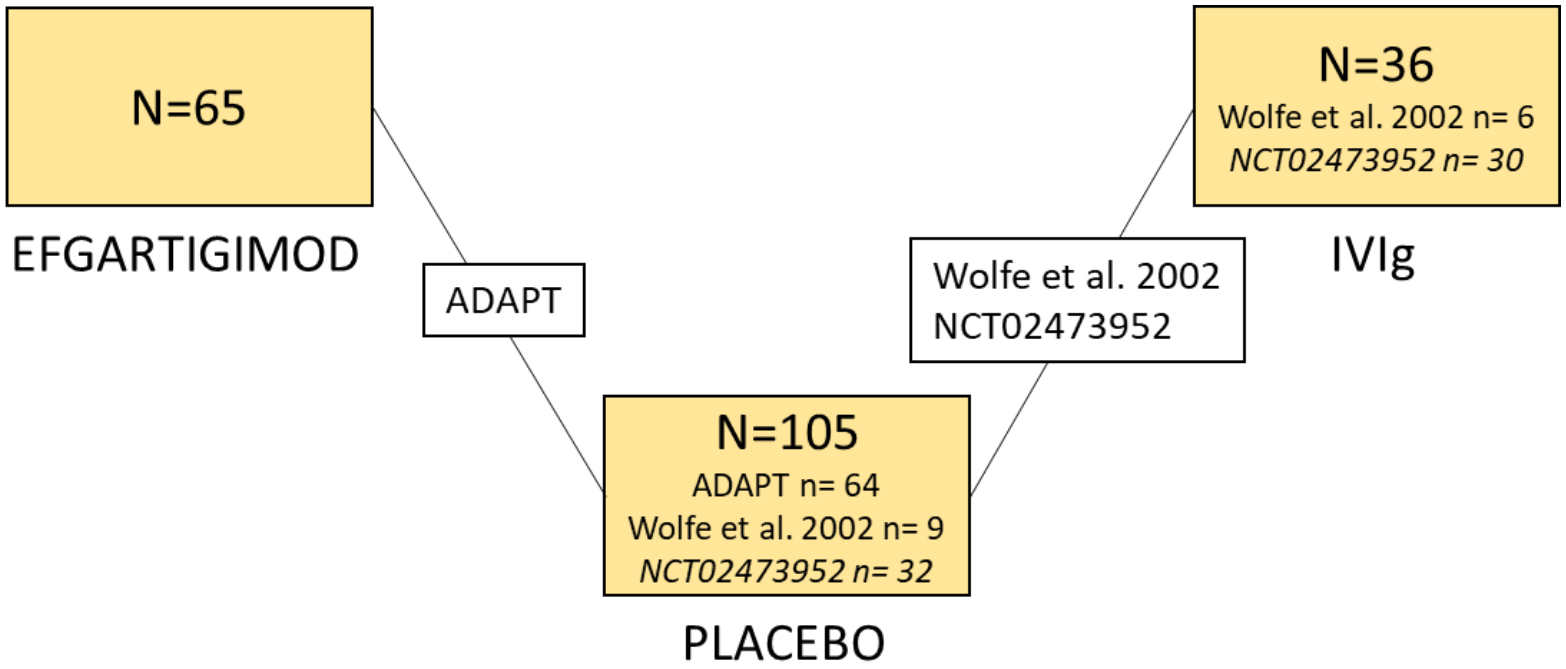
Considers results of NMA and MAICs to be illustrative and highly uncertain

- Not possible to compare baseline characteristics across studies
- The company did not explicitly discuss potential treatment effect modifiers and prognostic factors
- There was heterogeneity in outcomes reported for the studies
- NCT024739523 study provided most of the data on IVIg, but study reported change from baseline QMG score so MG-ADL data had to be imputed, which introduces additional uncertainty
- Agrees with method company used to incorporate the NMA estimates into the model

Abbreviations: IVIg, Intravenous immunoglobulin; MAICs, Matching-adjusted indirect comparisons; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NMA, Network meta-analysis; QMG, Quantitative myasthenia gravis; RCT, Randomised controlled trials;

Key issue: Maintenance IVIg clinical benefit (2/2)

Figure Network diagram for the NMA of MG-ADL change from baseline



How robust is the company's analysis for IVIg clinical benefit?

Abbreviations: IVIg, Intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NMA, Network meta-analysis

Key issue: Maintenance IVIg dosing and discontinuation (1/2)

Background

- Committee noted that the model assumed the maximum dosing for IVIg and did not model discontinuation

Company

Revised base case to include discontinuations due to non-response and unplanned reasons

- Initial discontinuation based on literature data → non-responder IVIg discontinuation rate: 19.5%
- Long term discontinuation based on a reconstructed time to discontinuation curve → exponential curve - assumes constant rate of unplanned discontinuation → annual rate: [redacted]
- Disagree that model assumed maximum dosing frequency for IVIg → model considers:
  - ↳ IVIg dose of 1g/kg per cycle, in line with the relevant NHS Commissioning Policy
  - ↳ IVIg every 4 weeks, in accordance with MG guidelines from ABN, which states IVIg duration of response is ~3-4 weeks → therefore, IVIg every 3 weeks is plausible, and studies have investigated efficacy of IVIg administered every 3 weeks
- Discontinuation rates, dosing regimen and dosing frequency were validated by six gMG clinical experts

EAG

- Assumption of a dosing regimen of 1g/Kg every four weeks is reasonable → but model results are sensitive to changes in dosing
- Assumptions around short-term discontinuations are reasonable and appropriate
- Agree with exponential curve for time to discontinuation curve and annual rate of IVIg discontinuation appears reasonable

Abbreviations: ABN, Association of British Neurologists; gMG, Generalised Myasthenia Gravis; IVIg, Intravenous immunoglobulin; MG, Myasthenia Gravis;

Key issue: Maintenance IVIg dosing and discontinuation (2/2)

Clinical expert

- There are many reasons why maintenance IVIg use may not be continued indefinitely
  - ↳ IVIg use will be subject to annual review if patients are stable, the dose will be reduced or subjected to an IVIg dependence test as per NHSE commissioning guidance

NICE technical team

- Average time on treatment estimated for IVIg in the ECM arm (~[redacted]) is longer than the average estimated time on treatment for efgartigimod (~[redacted]) – appears to lack face validity given assumed better efficacy for efgartigimod and easier administration

*See appendix - Maintenance IVIg dosing and discontinuation (Supplementary slide 1)

How appropriate is the company's assumptions for IVIg dosing and discontinuation?

Abbreviations: ECM, Established clinical management; IVIg, Intravenous immunoglobulin; NHSE, NHS England;

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Key issue: Maintenance IVIg in the efgartigimod arm

Background

- The model at ACM2 included the costs of maintenance IVIg in both arms

Company

Base case no longer contains IVIg and rituximab costs post efgartigimod discontinuation

EAG

Base case contains IVIg costs post efgartigimod discontinuation

- Believe people would receive maintenance IVIg after discontinuing efgartigimod
  - ↳ Reinstated treatment, administration costs and QALY gains for IVIg post efgartigimod discontinuation

NICE technical team

- The clinical pathway should be considered in both arms, therefore IVIg costs/benefits should be included in the efgartigimod arm
- NICE methods guide:
  - *"The care pathway is an important consideration for evaluating the technologies' effectiveness and costs. It includes the entire sequence of tests and treatments relevant to the evaluation."*
  - *"The treatment pathway or range of treatment pathways must be understood for the value of the technology to be assessed." (Section 2.2.16)*

Should IVIg use be assumed in both arms?

Abbreviations: ACM, Appraisal committee meeting; IVIg, Intravenous immunoglobulin; QALY, Quality-adjusted life year;

Key issue: Placebo effect

Background

- Committee concluded that the benefit observed in the placebo arm of ADAPT should be maintained

Company

Revised its base case so that the benefit observed in the placebo arm of ADAPT is maintained

- Benefit observed in placebo arm applied to both arms
- Scenario analyses presented using placebo effect and potential residual treatment effects assumptions

I. Placebo effect removed beyond Cycle 4 in the conventional therapy arm. Post IVIg and efgartigimod discontinuation a residual effect of 7.5% in MG-ADL<5 is considered for 6 months

II. Placebo effect removed from all arms beyond cycle 4. Post IVIg and efgartigimod discontinuation a residual effect of 7.5% in MG-ADL<5 is considered for 6 months

EAG

Base case uses original placebo effect assumptions

- Disagrees with the committee's decision to maintain the placebo benefit over the time-horizon
- Agrees with how placebo effect assumptions were implemented in the company's updated model
- Scenario analysis presented assuming the placebo effect is maintained and no residual treatment effect

Myaware and Muscular Dystrophy UK

- Believes concerns raised by the committee regarding the treatment of the placebo effect appeared to diverge from the assessment provided by the EAG

Has the committee seen any new evidence to change its views that the benefit observed in the placebo arm of ADAPT should be maintained?

Abbreviations: EAG, External assessment group; MG-ADL, Myasthenia Gravis Activities of Daily Living scale;

Key issue: Residual treatment effect

Background

- Committee concluded there was uncertainty with assumptions around treatment effect after stopping treatment permanently and the issue may be linked to placebo effect

Company

Revised its base case removing residual treatment effect post discontinuation of efgartigimod

Residual treatment effect removed because it conflicts with assuming the benefit observed in the placebo arm of ADAPT is maintained

EAG

Base case assumes a 7.5% residual treatment effect

- Reasonable to use 7.5% for the residual treatment effect after stopping efgartigimod permanently

Clinical expert

- Previously stated that an ongoing treatment effect following treatment discontinuation was possible and that a 15% limited residual treatment effect is plausible.
  - ↳ However, this must be further investigated and proved with robust clinical data → given the substantial impact on cost effectiveness estimates the residual treatment effect assumption should be removed or revised

Myaware and Muscular Dystrophy UK

- It may be some time before a residual treatment effect can be efficiently explored

Should any treatment effect be assumed after stopping treatment permanently?

Equality, Innovation and other Issues

Background

- Committee noted that access to specialist centres is an implementation issue that cannot be addressed by a NICE technology appraisal recommendation
- Committee considered that all additional benefits of efgartigimod had already been taken into account

Company

- Adopting the committee's preferred assumptions has generated an ECM profile unlikely to be reflective of UK clinical practice
- By adopting the committees preferred approach to modelling the cost of corticosteroid complication the burden associated with the use of corticosteroids is not fully captured

Web comments

- Because efgartigimod can be given at a patient's home and is now available as a SC injection it could resolve disparities in access to treatment
- The financial costs and mental health problems of carers (who are disproportionately female) should be considered
- Women develop MG when they are young with increased family and work responsibilities
- Efgartigimod seems to be well tolerated in the elderly population who account for the biggest proportion of new gMG diagnoses
  - ↳ The elderly are particularly susceptible to steroid induced side effects and may be more at risk from the thromboembolic complications of IVIg/PLEX

Should the committee consider anything further in respect to equality, innovation & other issues?

Abbreviations: ECM, Established clinical management; SC, Subcutaneous;

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Unresolved key issues – company and EAG base case

Table: Unresolved key issues - company and EAG base case

Issue		Company	EAG*	Scenarios
Maintenance IVIg	Use	43.8% in the ECM arm	43.8% in the ECM arm and after efgartigimod discontinuation	69.17% / [redacted] / Administered every 3 weeks
	Clinical benefit	Estimated using evidence from an NMA		Based on the MAICs
	Dosing & discontinuation	Include discontinuations due to non-response and unplanned reasons: • Non-responder IVIg discontinuation rate 19.5% • Unplanned discontinuation annual rate [redacted]		Non responder disc: [redacted]
Placebo effect		Maintained the benefit observed in the placebo arm of ADAPT	Used original placebo effect assumptions	• Benefit observed in the placebo arm isn't maintained beyond cycle 4 in: I. Conventional therapy cohort II. All arms (Both scenarios assume a 7.5% residual effect for 6 months post IVIg & efgartigimod) • Placebo effect maintained & no residual treatment effect
Treatment effect after stopping efgartigimod		Residual treatment effect removed	7.5% residual treatment effect	

* The EAG has corrected the calculated costs for corticosteroid complications

Abbreviations: ECM, Established clinical management; IVIg, Intravenous immunoglobulin; MAICs, Matching-adjusted indirect comparisons; NMA, Network meta-analysis;

Key questions for ACM3

Table: Questions for committee

Issue	Questions for committee
Target population	• Is the target population appropriate for decision making?
Generalisability	• How generalisable are the ADAPT outcomes to the target population?
Maintenance IVIg	• What is the most appropriate usage of IVIg in the target population? • How appropriate is the company's assumptions for IVIg? (time on treatment, efficacy, dosing) • Should IVIg use be assumed in both arms?
Treatment effect after stopping	• Should any treatment effect be assumed after stopping treatment permanently?
Placebo effect	• Has the committee seen any new evidence to change its views that the placebo effect should be retained in the comparator arm?
Baseline characteristics	• Are the committee happy to use baseline characteristics from ADAPT?

Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; gMG, Generalised Myasthenia Gravis;

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

PAS discounts

- When the company and EAG base case ICERs are calculated using confidential prices both are substantially above what NICE normally considers an acceptable use of NHS resources

NICE

Abbreviations: EAG, External assessment group; ICER, Incremental cost-effectiveness ratio; PAS, Patient access scheme;

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Key issues from ACM2 – Agreed between Committee, EAG and Company

Table: Resolved Key issues

Issue	Committee's considerations
Baseline characteristics	• Age and gender distribution captured in ADAPT should be used in the model
Utility values	• Utility values should align with other baseline characteristics • Pooled utility values from ADAPT should be used in decision making
Caregiver disutility	• Depending on the severity of the condition, gMG could have a substantial impact on carers' lives • The disutility values used by the company were not appropriate for use in the model • The committee would continue to take into account the impact on carers' lives qualitatively in its preferred assumptions for decision making
Corticosteroid complication costs	• The EAG's scenario, in which costs were only applied for people in Lee et al. who found their side effects intolerable, was appropriate for decision making

Abbreviations: Ab+, Antibody positive; AChR, Anti-acetylcholine receptor; EAMS, Early access to medicines scheme; gMG, Generalised Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NSIST, Nonsteroidal immunosuppressive therapy;

Link to - Unresolved key issues from ACM2

Key issue: Target population (Supplementary slide 1/2)

Table: Target population wording

MHRA therapeutic indication	As an add-on to standard therapy for the treatment of adults with gMG who are AChR antibody positive
EAMS therapeutic indication	Adults with AChR-antibody seropositive gMG, including adults with refractory gMG who have failed, not tolerated or are ineligible for licensed treatment
Company proposed target population	Those with active, refractory disease, with a 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 NSISTs and rituximab, for an adequate period of time, at an adequate dose.
ABN advisory group	Patients with gMG in the following groups: • Those dependent on regular IVIg or PLEX • Those with refractory gMG (ie. MG ADL ≥5) who have failed treatment despite 2 immunosuppressant agents

Link to - Key issue: Target population

Abbreviations: AChR, Anti-acetylcholine receptor; EAG, External assessment group; EAMS, Early access to medicines scheme; gMG, Generalised Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MHRA, Medicines and Healthcare products Regulatory Agency; NSIST, Nonsteroidal immunosuppressive therapy;

Key issue: Target population (Supplementary slide 2/2)

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

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

Link to - Key issue: Target population

Abbreviations: Ab+, Antibody positive; AChR, Anti-acetylcholine receptor; EAMS, Early access to medicines scheme; gMG, Generalised Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NSIST, Nonsteroidal immunosuppressive therapy;

Key issue: Generalisability (Supplementary slide 1/2)

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

Link to - Key issue: Generalisability

Abbreviations: Ab+, Antibody positive; AChR, Anti-acetylcholine receptor; EAMS, Early access to medicines scheme; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; NSIST, Nonsteroidal immunosuppressive therapy; SD, Standard deviation;

Key issue: Generalisability (Supplementary slide 2/2)

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

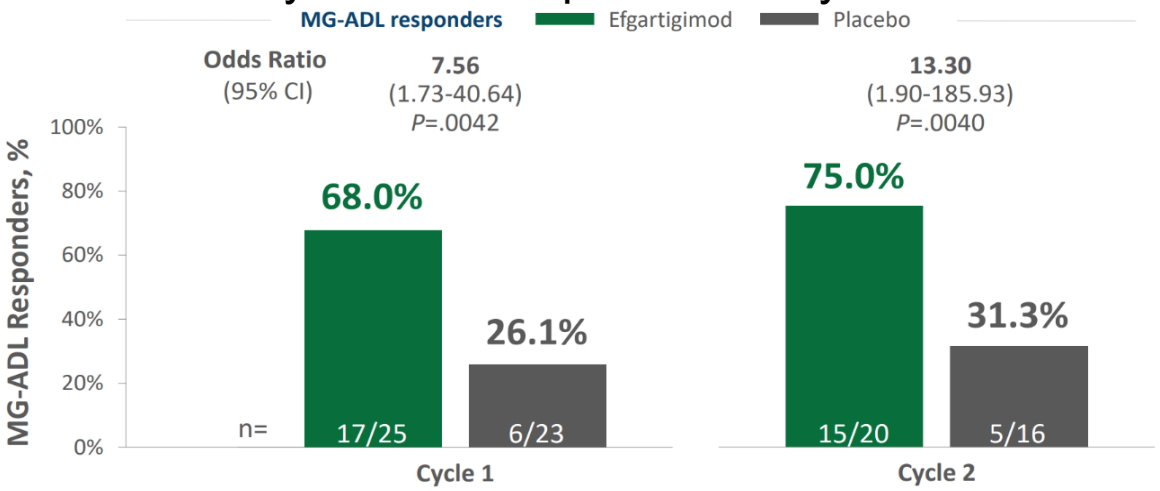


Figure Proportion of MG-ADL responders among ADAPT refractory AChR-Ab+ patients in cycles 1 & 2

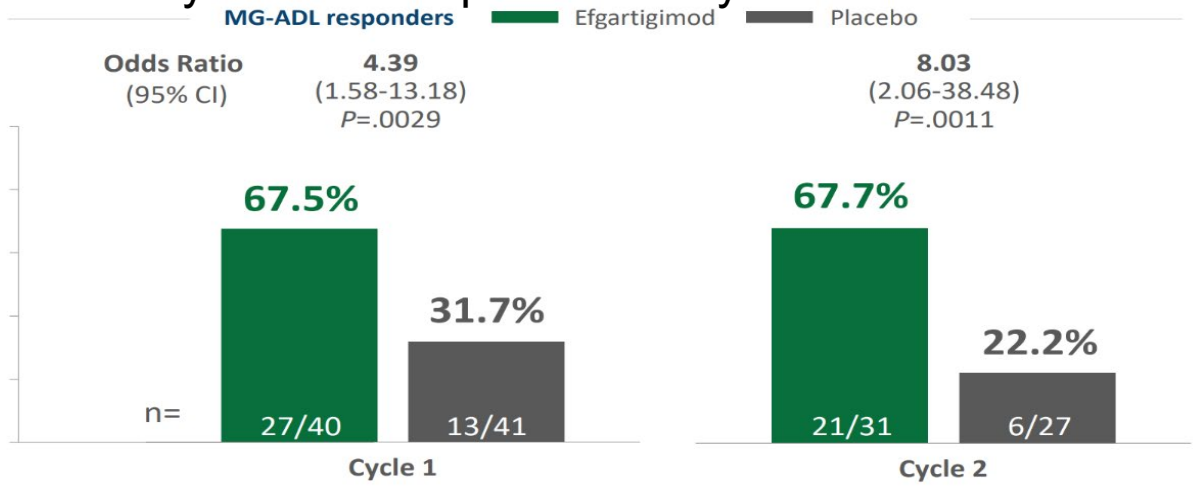
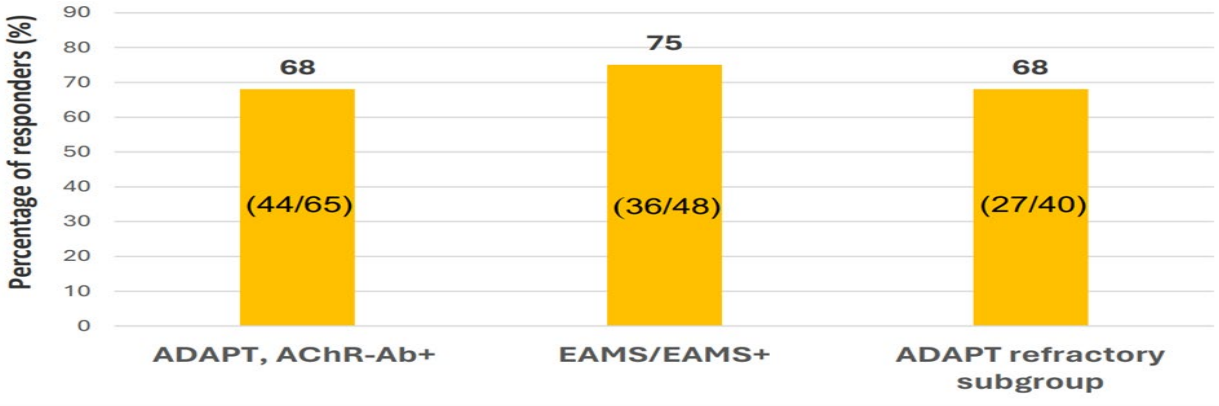


Figure MG-ADL responders after cycle 1 of efgartigimod



Link to - Key issue: Generalisability

Abbreviations: Ab+, Antibody positive; AChR, Anti-acetylcholine receptor; MG-ADL, Myasthenia Gravis Activities of Daily Living scale;

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Key issue: Maintenance IVIg dosing and discontinuation (Supplementary slide 1)

[redacted]

[redacted]

Link to - Key issue: Maintenance IVIg dosing and discontinuation

NICE

Abbreviations: EAG, External assessment group; IVIg, Intravenous immunoglobulin; ToT, Time on treatment;

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