Slides for the public – contains no ACIC or CPAS information

Efgartigimod for treating generalised myasthenia gravis [ID4003]

Technology appraisal committee D [16 November 2023]

Chair: Megan John

External assessment group: Southampton Health Technologies Assessment Centre

Technical team: Ross Wilkinson, Alan Moore, Jasdeep Hayre

Company: Argenx

Key issues from ACM1

Recommendation: Efgartigimod is not recommended, within its MA, as an add-on to standard treatment for gMG in adults who test positive for anti-AChR antibodies

Table Key issues

Issue	Committee's considerations	Updated?
Population	Further input needed from clinical experts to help define an appropriate population	Yes
Maintenance IVIg	Maintenance IVIg use should be estimated in the population in which efgartigimod would be used	Yes
Utility values	The same utility values should be used for the 2 arms	Yes
Carer disutilities	Impact would be taken into account qualitatively	Yes
Corticosteroid complication costs	Studies identified were not suitable for decision making	Yes
Treatment effect after treatment stops	A residual treatment effect plausible but uncertain would prefer more evidence / clinical expert input	Yes

Abbreviations: AChR, Anti-acetylcholine receptor; ACM, Appraisal committee meeting; gMG, Generalised Myasthenia Gravis; IVIg, Intravenous immunoglobulin; MA, Marketing authorisation

Additional issues

Table 2 Additional issues

Issue	Description
Placebo effect	NICE asked the company to comment on the placebo effect observed in the placebo arm of ADAPT *Company base case assumes:* • After 16 weeks the established clinical management cohort return to the baseline health-state distribution and remain in the same health state unless a crisis or death occurs
Subcutaneous formulation	The committee are asked to consider the availability of a subcutaneous formulation of efgartigimod

Efgartigimod (Vyvgart, Argenx)

Table 3: 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 • The recommended dose is 10 mg/kg as a 1-hour IV infusion administered in cycles of once weekly infusions for 4 weeks • Subsequent treatment cycles are administered according to clinical evaluation → The frequency of treatment cycles may vary by patient
Price	• List price: £6,569.73 per 400 mg vial - Treatment cycle: [redacted] • A simple PAS discount has been agreed for efgartigimod

Abbreviations: AChRs, 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;

Clinical effectiveness recap

NICE National Institute for Health and Care Excellence

Key clinical trial

	ADAPT (Phase 3, n=167)	ADAPT+ (Phase 3, n=151)
Design	Randomised, double-blind, placebo-controlled	Extension of ADAPT, single-arm, open-label
Population	Adults with gMG 129 (77%) were AChR Ab+	Previously enrolled in ADAPT 111 (74%) were AChR Ab+
Intervention	Efgartigimod 10 mg/kg (IV formulation)	Efgartigimod 10 mg/kg (IV formulation)
Comparator	Placebo	N/A
Duration	26-week	156-week
Key outcomes	Proportion of AChR Ab+ patients who were MG-ADL responders in the 1st cycle	Safety and tolerability in the ACHR Ab+ population
Locations	56 sites in 15 countries	-

n.b. Key exclusion criteria included pregnant and lactating people and people with known seropositivity or who tested positive for an active viral infection

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Abbreviations: Ab+, Antibody positive; AChR, Acetylcholine receptor; gMG, Generalised Myasthenia Gravis; IV, Intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living scale;

Other sources of evidence

Early access to medicines scheme (EAMS)

- Efgartigimod was granted promising innovative medicine status in November 2021 and a positive scientific opinion by the MHRA under EAMS in May 2022
  - ↳EAMS made efgartigimod available in the UK from May 2022 until the MHRA MA was granted (March 2023)
  - ↳EAMS+ makes efgartigimod available for existing and new patients from the point the MA was granted until a recommendation is made by NICE about routine commissioning
- According to the company EAMS/EAMS+ aims to…
  - ↳Provide access to patients with high unmet medical need
  - ↳Generate real-world evidence to support HTA discussions and address uncertainty
- <u>EAMS indication:</u> Adults with AChR Ab+ gMG, including patients with refractory gMG who have failed, not tolerated or are ineligible for licensed treatment
- EAMS/EAMS+ data is available for [redacted] patients from [redacted] specialist gMG centres in England

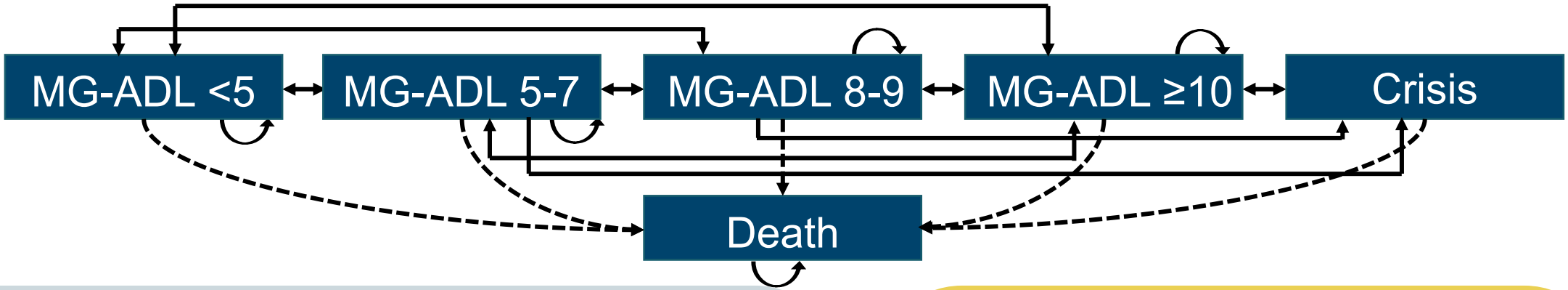
Abbreviations: Ab+, Antibody positive; AChR, Acetylcholine receptor, EAMS, Early access to medicines scheme; gMG, Generalised Myasthenia Gravis; HTA, Health technology assessment; MA, Marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency;

Cost effectiveness recap

NICE National Institute for Health and Care Excellence

Company's model overview

Figure Model structure



- State transition model with a lifetime time-horizon and 28-day cycle length
- Treatment effect modelled through transition probabilities
- After a treatment cycle, patients will have at least one cycle with no efgartigimod
- Patients in the MG-ADL<5 health state do not receive efgartigimod

Health states with lower MG-ADL scores are associated with:

- Lower probability of crisis
- Lower corticosteroid and IVIg use
- Lower monitoring costs
- Better QoL
- Lower caregiver disutility

Abbreviations: IVIg, Intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; Qol, Quality of life;

Response to consultation

NICE National Institute for Health and Care Excellence

Consultation responses summary (1)

Consultation comments

Comments received from:

- Argenx (company – manufacturer of efgartigimod)
- ABN – Neuromuscular Advisory Group (Professional group)
- Joint response from Muscular Dystrophy UK (MDUK) and Myaware (Patient groups)
- 2 Consultant Neurologists

Argenx

- Proposed target population for efgartigimod
- Elicited experts estimates of the proportion of the target population that would receive maintenance IVIg
- Provided alternative corticosteroid complication cost estimate
- Presented analysis on caregiver burden and alternative caregiver disutility values
- Identified alternative utility values from the MyRealWorld-MG study
- Provided a clinical expert statement supporting the residual treatment effect assumption
- Answered questions about modelling the ECM arm and a potential placebo effect

Abbreviations: ABN, Association of British Neurologists; ECM, Established clinical management; IVIg, Intravenous immunoglobulin

Consultation responses summary (2)

ABN – Neuromuscular Advisory Group (endorsed by Royal College of Physicians)

- Stated that clinical trials have shown that efgartigimod is highly efficacious
- Suggested points of use for efgartigimod and EAMS data may inform when efgartigimod should be used / better inform the cost effectiveness estimates than clinical trial data
- Stated that carer support is difficult to evaluate and not appropriate in a MG population

Joint response – MDUK and Myaware (Patient groups)

- Provided responses from patient survey (n=45) on draft guidance
- Concerns: disease burden not fully captured (physical pain, muscle weakness/mobility, steroid side effects, potential development of cataracts, type 2 diabetes, weight gain)
- Some benefits not considered (less travel for treatments, fast acting, novel mechanism)

2 Consultant Neurologists

- Stated that the APADT trial does not reflect who should have efgartigimod on the NHS
- Stated that efgartigimod should be reserved for refractory patients
- Stated that regular IVIg is a relatively uncommon and there is regional variation
- Stated that people with refractory MG often have stopped taking steroids

Abbreviations: ABN, Association of British Neurologists; EAMS, Early access to medicines scheme; IVIg, Intravenous immunoglobulin; MG Myasthenia Gravis;

Key issue: Target population (1)

Committee comments at ACM1

- Input needed from clinical experts to define a population in which efgartigimod is both clinically and cost effective → This population should be clearly defined

Company response to draft guidance

- Delphi panel (6 experts) conducted to gain a consensus on most appropriate NHS target population for efgartigimod
- Proposed target population is easily identifiable in UK specialist centres → Aligns with inclusion criteria for EAMS/EAMS+ and have significant unmet need

EAG comments

- Company proposed target population wording should be revised
  - ↳ People ineligible for standard therapy, appear to fall outside licenced indication unless they are only ineligible for one type of standard therapy but able to receive another standard therapy to which efgartigimod can be added
  - ↳ Proposed alternative population wording – Link to slide 35
- Believe EAMS patient characteristic data should be used – Link to slide 36

Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; EAMS, Early access to medicines scheme

Link to slide 35

Key issue: Target population (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. The company responded to the EAGs comments about the use of the word "ineligible" – Link to slide 35

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 (3)

ABN – Neuromuscular Advisory Group

- EAMS data may be a better source for pathway positions for efgartigimod
- May be sensible to calculate potential cost saving compared to PLEX/IVIg/rituximab usage from EAMS cohort than the whole population
- Efgartigimod could be useful for people with immune-checkpoint therapy-related myasthenia → This would have to be considered in planning at national level

Clinical expert (web comment)

- Efgartigimod should be reserved for refractory patients → Losing the option to prescribe efgartigmod in this population would be detrimental to patient care
- If restricted to people on regular IVIg, a significant cohort would be denied treatment
- ADAPT data does not reflect population who should have efgartigimod in the NHS
  ↳ Many would have done well with standard treatment

- What population should be included in any potential recommendation?

Link to slide 36

Abbreviations: ABN, Association of British Neurologists; CI, Confidence interval; EAG, External assessment group; EAMS, Early access to medicines scheme; IVIg, Intravenous immunoglobulin; PLEX, Plasma exchange;

Key issue: Maintenance IVIg (1)

Committee comments at ACM1

- Proportion of people having maintenance IVIg should reflect the relevant population

Company response to draft guidance

- Used estimates from a Delphi panel (6 experts -from neuromuscular specialist centres)
- Clinicians asked → "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?"
  ↳ *Assumes no supply issues because IVIg supply chain difficulties are transient*

EAG comments

- Accepts Delphi panel results but believes there is still some uncertainty
- Model remains sensitive to IVIg usage estimates
- MG-ADL≥10 health state accrues patients exiting the crisis state
- Delphi panel were not asked what proportion would actually receive IVIg
- Uncertain about the relative percentages that would receive IVIg vs rituximab

Clinical expert (web comment)

- Regular IVIg is relatively uncommon → Many centres use it very infrequently

Abbreviations: ACM, Appraisal committee meeting; IVIg, Intravenous immunoglobulin

Link to slide 37

Key issue: Maintenance IVIg (2)

NICE tech team comments

- Model assumes no QALY benefits of IVIg use
- Concerned IVIg costs are substantially overestimated due to lack of discontinuation

Table Maintenance IVIg utilisation, %

Category	Maintenance IVIg utilisation* %		
	EAMS/EAMS+ (ACM1)	Delphi panel (Company Base Case)	Delphi panel (Scenario)
MG-ADL<5	[redacted]	0.00	0.00
MG-ADL 5–7	[redacted]	50.83	69.17
MG-ADL 8–9	[redacted]	68.70	69.17
MG-ADL ≥10	[redacted]	85.00	69.17
Crisis	63.3	63.3	63.3
Overall	[redacted]	69.17	69.17

*IVIg can also be used as a rescue therapy to manage exacerbations and crisis

- Should IVIg be included as a maintenance therapy?
- If yes in which health states and for what proportion of people?

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Abbreviations: ACM, Appraisal committee meeting; EAMS, Early access to medicines scheme; IVIg, Intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QALY, Quality-adjusted life year;

Key issue: Source of utility values (1)

Committee comments at ACM1

- The same utility values should be used in each treatment arm

Company response to draft guidance

Base case updated to include MyRealWorldMG study utilities, applied to both arms

- MyRealWorldMG study
  - ↳ Removes any confounding treatment effect & produces values with greater differentiation between health states
  - ↳ Reflects current UK care as it included a cohort treated with any treatment in current care (Including Immunoglobulins and rituximab)
- Clinical expert suggests that because people in ADAPT were being monitored, it could have resulted in reporting of higher utility values
- Pooling utility values from ADAPT could include some effect of efgartigimod and would likely underestimate the HR-QoL burden at different severity of gMG

NICE tech team comments

- NICE methods guide infers trial values, where available, are preferred
- Choice of utilities has a significant impact on Incremental QALYs

Abbreviations: ACM, Appraisal committee meeting; gMG, Generalised Myasthenia Gravis; HRQoL, Health-related quality of life

Key issue: Source of utility values (2)

Table Utility values by health state

Category	Old analysis (ACM1)		Pooled utility values	
	Efgartigimod	ECM	ADAPT	MyRealWorldMG
MG-ADL<5	0.828	0.723	**0.781**	**0.802**
MG-ADL 5–7	0.769	0.664	**0.717**	**0.668**
MG-ADL 8–9	0.696	0.591	**0.641**	**0.589**
MG-ADL ≥10	0.618	0.513	**0.557**	**0.465**
Crisis	0.463	0.463	**0.463**	**0.463**

EAG comments

- Both MyRealWorldMG and ADAPT populations are different to the new proposed target population, so neither is suitable
- MyRealWorldMG study is likely to be at high risk of bias
- Utility values from EAMS/EAMS+ or the subgroup of patients in ADAPT that reflect new proposed target population would be more appropriate

- Which utility values should be used for decision making?

Abbreviations: ACM, Appraisal committee meeting; EAMS, Early access to medicines scheme; ECM, Established clinical management; MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Key issue: Caregiver disutility (1)

Committee comments at ACM1

- Carer disutilities contributed substantially to overall modelled QALY gain
- Carer disutilities not appropriate without further evidence → Considered qualitatively

Company response to draft guidance

Base case updated to include alternative caregiver utility decrements

- Caregiver EQ-5D data obtained from MRWMG study and a paper-based survey in France → EQ-5D was valued using a UK value set
- Utility values generally declined with severity of patient's MG; however no linear relationship found
  ↳Likely additional factors are affecting caregiver HR-QoL

EAG comments

- Sample size was small (N=39, 0 from the UK) and people were self-selecting
- Study did not contain a matched control group, so cannot determine if utility decrements are only due to caregiving

Link to slide 38

Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; EQ-5D; EuroQol 5 dimension; gMG, Generalised Myasthenia Gravis; HRQoL, Health-related quality of life; MRWMG, MyRealWorldMG; QALY, Quality-adjusted life year;

Key issue: Caregiver disutility (2)

Table Patient / caregiver utilities and caregiver utility decrements from the new analysis

Category	Mean utility from 2 studies*				Caregiver utility decrements	
	Patient	(n=39)	Caregiver	(n=37)	New analysis	Old analysis (ACM1)
MG-ADL<5	0.786	16	0.812	16	**-0.025**	-0.002
MG-ADL 5–7	0.577	10	0.622**	9	**-0.240** **	-0.045
MG-ADL 8–9	0.597	4	0.725	4	**-0.142**	-0.142
MG-ADL ≥10	0.352	9	0.692	8	**-0.170**	-0.160
Crisis	-	-	-	-	**-0.170** ***	-0.180

* MRWMG & A paper-based survey in France **Excluding one outlier *** Assumed the same as MGADL≥10

NICE tech team comments

- Mean patient utility values from the 2 studies differ from those from ADAPT and MRWMG (E.g. MG-ADL ≥10: 2 studies = 0.352, MRWMG = 0.465 , ADAPT = 0.557)

ABN – Neuromuscular Advisory Group

- Comparison of carer support is difficult to evaluate and not really appropriate in MG

- Should caregivers' utility be included in the QALY calculation?
- If yes are the company's caregiver decrements appropriate for decision making?

Abbreviations: ABN, Association of British Neurologists; ACM, Appraisal committee meeting; EAG, External assessment group; HRQoL, Health-related quality of life; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MRWMG, MyRealWorldMG;

Key issue: Corticosteroid complication costs

Committee comments at ACM1

- None of the studies identified were suitable for decision making

Company response to draft guidance

Base case updated to include updated costs of corticosteroid use complications

- Paper by Lee et al. 2018 provides evidence directly from people with gMG
- Estimated annual cost of corticosteroid related complications was £13,131.60

EAG comments

Base case includes no corticosteroid use complication costs

- Company's estimates are not fit for purpose and lack face and methodology validity
  ↳Has several concerns → Link to slide 40

Clinical expert (web comment)

- People with treatment refractory MG have often stopped taking steroids because they are not effective

- Is the company's approach to estimating corticosteroid complication costs suitable for decision making?

Link to slide 39
Link to slide 41

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

Key issue: Treatment effect after efgartigimod

Committee comments at ACM1

- A residual treatment effect after treatment stops was plausible but uncertain

Company response to draft guidance – base case unchanged

- Asked 1 clinical expert to review available data (additional analysis of ADAPT and ADAPT+ data, real world evidence from U.S.A and other efgartigimod indications)
  - ↳Clinical expert believes assuming a 15% "limited residual effect" is plausible

EAG comments

- Residual effects of efgartigimod after it is discontinued is plausible but uncertain
- Evidence from ADAPT/ADAPT+ may not be generalisable to the proposed population

Clinical expert (web comment)

- Unaware of a residual treatment effect; people report earlier relapsing and so shortening of intervals between treatment doses

NICE tech team comments

- ≈50% of incremental QALY gains come from this assumption

- Is the company's residual treatment effect assumption suitable for decision making?

Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group; QALY, Quality-adjusted life year;

Key issue: Placebo effect

Background

- To model the ECM arm transitions, observations in placebo arm of ADAPT were used up to 16 weeks → Cohort then return towards baseline health-state distribution and remain in the same health state unless a crisis or death occurs
- NICE asked the company to explain why

Company comments

- Model also considers a worsening of disease in efgartigimod arm during the off-treatment period and in cohort who permanently discontinue treatment
- Average duration from disease diagnosis in ADAPT AChR+ patients was 9.3 years
- Possible regression to the mean, a trial effect, or a placebo effect played a role → However, all are specific to a trial setting and are not likely to remain permanently

EAG comments

- Consider company's placebo arm modelling assumptions to be reasonable

NICE tech team comments

- Assuming ECM returns to baseline = higher IVIg use and lower utilities in this arm

- Is the company's approach to modelling the ECM arm suitable for decision making?

Abbreviations: AChR, Anti-acetylcholine receptor; ECM, Established clinical management;

Link to slide 42

Uncaptured benefits

Company comments

- [redacted]
- Subcutaneous formulation enables faster administration and potential for self-administration, reducing burden on patients, caregivers, and healthcare providers
  - Administered as a single dose with no adjustment based on weight or other factors

  ↳Provided scenario (SC:80%, IV:20%) → Link to slide 30

Patient group comments

- Efgartigimod is quicker than conventional therapy to take effect
- There is significant unmet need current treatments are slow to take effect and associated with significant side effects

Clinical expert (web comment)

- Efgartigimod is the first new immunomodulatory treatment and there are few / no other options for some people with refractory MG

- Are all relevant benefits of efgartigimod captured in the model?

NICE

Abbreviations: IV, Intravenous; MG, Myasthenia Gravis; SC, Subcutaneous;

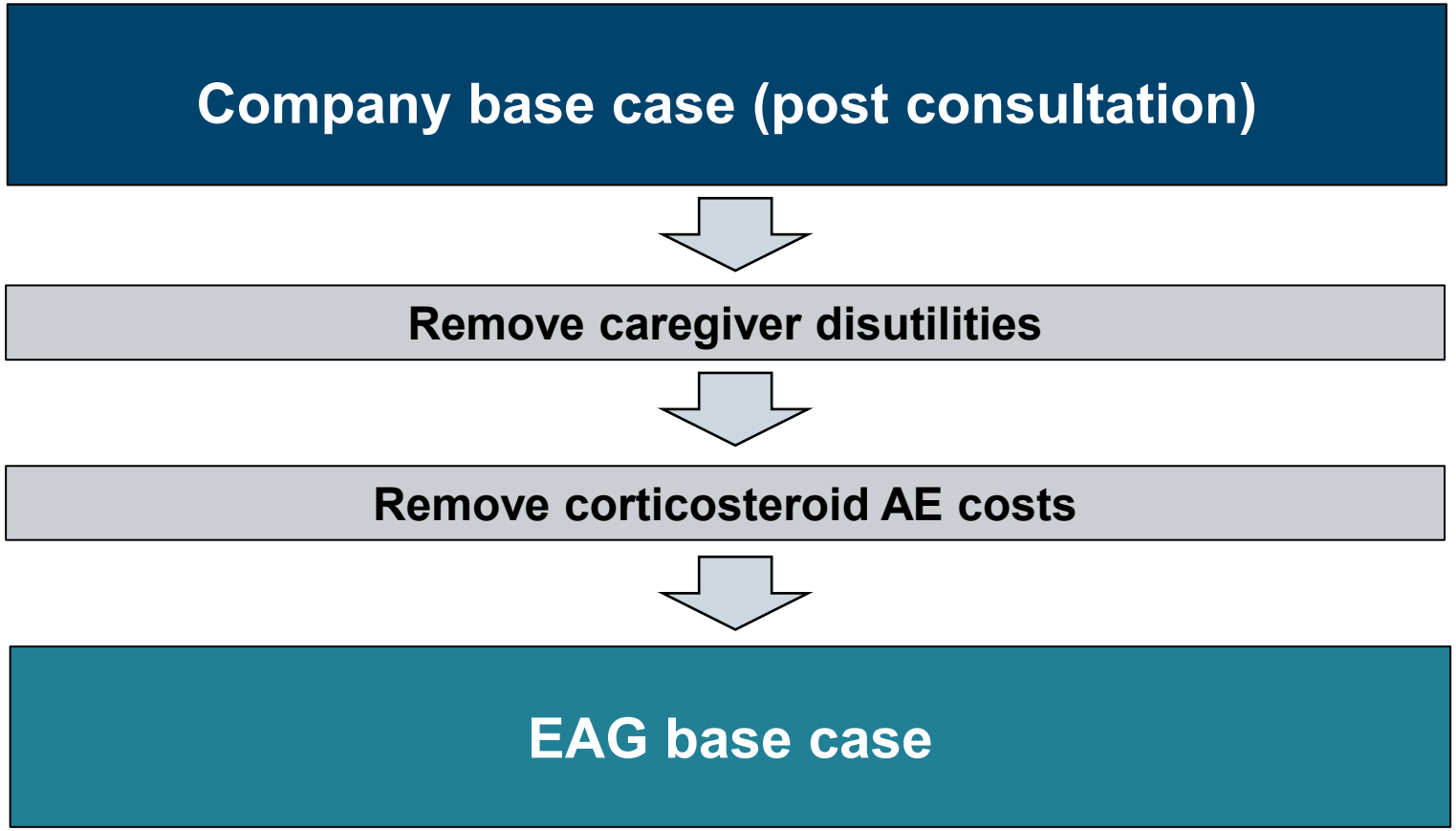
Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

PAS discounts

Cost-effectiveness results and scenarios



Abbreviations: AE, Adverse events; EAG, External assessment group

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Thank you.

Supplementary slides

NICE National Institute for Health and Care Excellence

Efgartigimod subcutaneous formulation

Table Regulatory details

EMA CHMP positive opinion	14th September 2023
Anticipated MHRA approval	November 2023

Table Technology details

Administration	• 1000 mg per week for 4 weeks per cycle • Subsequent treatment cycles are administered according to clinical evaluation → The frequency of treatment cycles may vary by patient
Price	• List price: £15,307.47 per 1000 mg dose

The company suggest that the SC formulation will offer additional benefits such as a faster administration and the potential for self-administration, therefore reducing burden on patients, caregivers, and healthcare providers

The company provided a scenario that assumes 80% of people receive SC efgartigimod and 20% receive IV efgartigimod → The same model and effectiveness inputs are used only the acquisition and administration costs differ

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; IV, Intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; SC, Subcutaneous

Link to slide 25

Trial results ADAPT

ADAPT Primary outcome - MG-ADL responders in cycle 1

MG-ADL is a patient-reported scale developed to assess MG symptoms and their effects on daily activities

- It has an eight-item scale where each item is given a value from 0 (normal) to 3 (severe) → total score can range from 0 to 24 (higher = more severe)

MG-ADL is used to define model health states that capture disease activity levels

Primary outcome: Proportion who were MG-ADL responders in the first treatment cycle

- ≥2-point improvement (reduction) in total MG-ADL score → sustained for ≥4 consecutive weeks → first improvement occurring by week 4 of the cycle

Table 6: Proportion of MG-ADL responders, AChR Ab+ population

	Efgartigimod (n=65)	Placebo (n=64)
Responders % (n)	68% (44)	30% (19)
OR / p value	4.95 (95% CI 2.21, 11.53); p<0.0001	

NICE

Abbreviations: Ab+, Antibody positive; AChR, Acetylcholine receptor; CI, Confidence interval; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; OR, Odds ratio;

Trial results ADAPT+

ADAPT+ efficacy outcome: MG-ADL total score

Mean MG-ADL change from baseline was measured at week 3 of each cycle

- CMIs (≥2-point improvement (reduction) in MG-ADL score) were made in each of cycles 1 to 14 → For all cycles, [redacted] of people with AChR-Ab+ had an improvement of ≥2 points while [redacted] had an improvement of ≥3 points

Figure Mean change from cycle baseline MG-ADL total score (AChR Ab+)

CMI (≥2-point improvement in MG-ADL score)

Abbreviations: Ab+, Antibody positive; AChR, Acetylcholine receptor; CMI, Clinically meaningful improvement; MG-ADL, Myasthenia Gravis Activities of Daily Living scale;

Committee discussion at ACM2 (1)

Parameter	Key question	Scenarios	ICER impact
Population	What population should be included in any potential recommendation?	• The company's new proposed target population	Large
Maintenance IVIg	• Should IVIg be included as a maintenance therapy? • If so, what overall % and what % in each health state should be assumed?	• Not included • EAMS/EAMS+ estimates • Company's updated estimate ↳ Total maintenance IVIg treatment use of [redacted]/ [redacted]	Large
Utility values	Which source should be used for decision making?	• Pooled ADAPT • MyRealWorldMG	Large
Caregiver disutilities	Are the company's caregiver utility decrements appropriate?	• Not included • The company's caregiver utility decrements	Large

Abbreviations: ACM, Appraisal committee meeting; EAMS, Early access to medicines scheme; ICER, Incremental cost-effectiveness ratio; IVIg, Intravenous immunoglobulin

Committee discussion at ACM2 (2)

Parameter	Key question	Scenarios	ICER impact
Corticosteroid complications	Are corticosteroid complication costs estimated using information from Lee et al. 2018 suitable?	• Not included • Costs estimated using Lee et al. 2018 ↳ Costs applied only for patients who found their side effects intolerable (weighted average of 2021-22 costs)	Large
Residual treatment effect	Is the company's efgartigimod residual effect assumption suitable?	• The company's assumption *(15% of people remain in the MG-ADL<5 health state after stopping treatment)*	Large
Placebo effect	Is the company's approach to modelling the ECM arm suitable?	• The company's approach *(After 16 weeks ECM cohort assumed to return towards baseline health-state distribution)*	Large

Abbreviations: ACM, Appraisal committee meeting; ECM, Established clinical management; ICER, Incremental cost-effectiveness ratio; MG-ADL, Myasthenia Gravis Activities of Daily Living scale;

Key issue: Target population (Supplementary slide 1)

Company response to draft guidance

- No changes made to cost effectiveness model
- **Delphi panel results:** Proportion of people estimated to match target population:
  - ↳Mean: 22.1% Median: 20% Range: 10% to 40%
- The word ineligible does not refer to all standard gMG treatments
- Efgartigimod must be used as an add-on to standard therapy, not as a monotherapy
  - ↳In certain situations, clinicians may deem people to be ineligible / not suitable for one of the standard gMG treatments

EAG comments

- Subgroup analysis from ADAPT that the company used to justify making no changes to the model is associated with low certainty, small samples sizes and wide 95% CIs

Proposed alternative population wording

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

NICE

Abbreviations: AChR, Anti-acetylcholine receptor; CI, Confidence interval; EAG, External assessment group; gMG, Generalised Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale;

Link to slide 13

Key issue: Target population (Supplementary slide 2)

Table: Comparison of baseline age and sex characteristics

	ADAPT (AChR+)		UK MRWMG cohort*	EAMS/EAMS+ cohort
	Efgartigimod	Placebo		
Mean age, years	44.7	49.2	45.2	50.7
Male	29%	38%	20%	29.1%
Female	71%	63%	80%	70.9%

*Company and EAG current base cases

ABN – Neuromuscular Advisory Group

- Potential points of use (from an expert clinician's perspective):
  - Resistant to 1st/2nd line treatment BUT responsive to regular IVIg/PLEX (a very small proportion)
  - A lower risk alternative to IVIg/ PLEX/ Rituximab in MG crisis
  - Resistant cases during MG crisis (acknowledge no trial level evidence to support this (non-responsive to PLEX/IVIg/rituximab))

Clinical expert (web comment)

- Efgartigimod could be used as a bridging treatment (until other treatments start to work)

Abbreviations: AChR, Anti-acetylcholine receptor; EAG, External assessment group; EAMS, Early access to medicines scheme; IVIg, Intravenous immunoglobulin; MG, Myasthenia Gravis; MRWMG, MyRealWorldMG; PLEX, Plasma exchange;

Link to slide 13

Key issue: Maintenance IVIg (Supplementary slide)

Company response to draft guidance

- **Delphi panel results**: Proportion of target population eligible/suitable for regular/ maintenance IVIg:
  - ↳Mean: 69.2% Median: 70% Range: 60% to 90%

EAG comments

- Based on Delphi panel results
  - ↳For every 100 people with gMG, 22 (range 10-40) would match target population and be eligible for efgartigimod. Of these, 15 (range 6-36) expected to be prescribed regular/maintenance IVIg

Clinical expert (web comment)

- People on regular long term IVIg could be transferred to efgartigimod

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

Link to slide 16

Key issue: Caregiver disutility (Supplementary slide)

Company response to draft guidance

- Utility decrements obtained by comparing caregiver utility values to age and gender matched UK general population
- This alternative analysis supports previously submitted evidence

Key issue: Corticosteroid complication costs (Supplementary slide 1)

Committee comments at ACM1

- Costs should be generalisable to NHS clinical practice, applicable to gMG and valued using relevant NHS prices

Company response to draft guidance

- TLR developed to capture papers reporting frequency of AEs associated with corticosteroid use
- A weighted average of male and female frequencies of AEs from Lee et al. 2018 was multiplied by unit costs obtained from the national schedule of NHS costs
- Cost applied in model for both high and low dose corticosteroid use
- Could be conservative: calculation assumes events present only once a year

ABN – Neuromuscular Advisory Group

- Costs from asthma or MS populations are not comparable to a MG cohort
  - ↳ A better comparator would be another autoimmune neuromuscular condition where similar doses are used for a similar amount of time

Abbreviations: ABN, Association of British Neurologists; ACM, Appraisal committee meeting; AE, Adverse events; gMG, Generalised Myasthenia Gravis; MG, Myasthenia Gravis; MS, Multiple sclerosis; TLR, Target literature review

Link to slide 22

Key issue: Corticosteroid complication costs (Supplementary slide 2)

EAG comments

- Several concerns;
  - ↳ Lee et al. does not report AEs for people not receiving corticosteroids → Not possible to separate AEs due to corticosteroids from those due to MG
  - ↳ Many AEs reported in Lee et al. may not be severe → NICE appraisals often only cost AEs relating to severe AEs (grade 3+)
  - ↳ Company assume all AEs are treated in a hospital episode
  - ↳ Unit costs calculated using an average of multiple HRG codes → A weighted average should have been used to reflect activity in different codes
  - ↳ Unnecessary to inflate to 2023 costs - cost year in model was 2022
  - ↳ Some NHS codes for AEs are inappropriate and likely overestimate costs
  - ↳ Question using the same AE costs for both high and low dose corticosteroid use

Abbreviations: AE, Adverse events; EAG, External assessment group; HRG, Healthcare resource group; MG, Myasthenia Gravis;

Link to slide 22

Key issue: Corticosteroid complication costs (Supplementary slide 3)

Table: Costs for corticosteroid-related chronic complications

	High dose threshold	Cost per week		Annual cost	
		High dose	Low dose	High dose	Low dose
Company base case ACM2	-	£251.67	£251.67	£13,131.60	£13,131.60
Company base case ACM1	7.5mg/day	£233.74	£110.13	£12,154.33	£5,726.60
EAG base case ACM1	7.5mg/day	£43.99	£6.16	£2,287.48	£320.32

Abbreviations: ACM, Appraisal committee meeting; EAG, External assessment group;

Link to slide 22

Key issue: Placebo effect (Supplementary slide)

Company response to draft guidance

- Average duration from disease diagnosis in ADAPT AChR+ patients was 9.3 years
  - ↳Suggests ECM would likely remain inadequate to improve disease activity
  - ↳Baseline distribution is representative of the expected distribution
- No long-term data on the ECM arm alone is available

EAG comments

- Consider it reasonable that effect observed in the placebo arm may not be long lasting, therefore the placebo arm returning to baseline does not seem unreasonable
- Do not consider it necessary to adjust treatment effect in the placebo arm as it is possible that the additional treatment effect was also present in the efgartigimod arm

Abbreviations: AChR, Anti-acetylcholine receptor; EAG, External assessment group; ECM, Established clinical management;

Link to slide 24