Zilucoplan for treating antibody-positive generalised myasthenia gravis [ID4008]

For projector – confidential information redacted

Technology appraisal committee B [13 June 2024]

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Company: UCB

Zilucoplan for treating antibody-positive generalised myasthenia gravis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background: generalised myasthenia gravis (gMG)

Causes of myasthenia gravis:

- An autoimmune disorder caused by Immunoglobulin G autoantibodies targeting acetylcholine receptors (AChRs) and other parts of neuromuscular junction which impairs neuromuscular transmission and causes muscle weakness and fatigue
    - ↳ When muscle groups other than eye muscles affected, the condition is known as generalised MG (gMG)

Epidemiology

- MG affects about 15 in every 100,000 people in the UK → Around 80% progress to gMG
- About 80 to 90% of people with gMG have detectable antibodies against AChRs
- More common in women; in women incidence peaks between 30 and 50 and in men increases with age
- Around 15% people with gMG are refractory to standard therapy (see appendix for refractory definitions)

Diagnosis, symptoms and prognosis of gMG

- Diagnosis: via physical examination, blood tests and MRI and CT scans;
- Symptoms: difficulties with swallowing, vision, speech, breathing, mobility, and persistent fatigue, may relapse and remit over time
- Up to 20% of people with gMG experience a myasthenic crisis at least once, where muscles that control breathing affected, which requires intensive care support and is main cause of MG-related deaths

Abbreviations: AChR, acetylcholine receptor; CT, computerised tomography; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; MG, myasthenia gravis; MRI, magnetic resonance imaging; NMJ, neuromuscular junction

Patient and clinical perspectives

See appendix – patient and clinical perspectives

Substantial unmet need for people with refractory gMG

Joint submission from Muscular Dystrophy UK and Myaware

gMG and the side effects of treatment have physical, emotional and financial impacts

People with gMG struggle to balance treatments, symptom management, side effects and undertaking their day-to-day activities

Zilucoplan may offer better prognosis for people in whom symptoms are not well controlled with current treatment options, and may have fewer side effects

I am unable to do the majority of the things I used to do due to my extreme weakness, breathlessness and fatigue. I have had to reduce my working hours."

Submission from the Association of British Neurologists

Main aim of treatment is to reduce symptoms while minimising side effects

Mild to moderate gMG typically treated with pyridostigmine, corticosteroids and steroid-sparing agents

Care for patients with refractory gMG is less well defined, with IVIg and PLEX used variably across different centres

Significant unmet need for gMG → significant proportion of patients on steroids remain symptomatic; steroid sparing agents limited by tolerance issues

"There is a need to develop new therapies for severe myasthenia given the constrained supply of immunoglobulin and difficulty ensuring provision of plasma exchange in England."

Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; PLEX, plasma exchange.

Other considerations

Equality

- Access to specialist centres: there is regional variation in access to specialist centres for gMG care
- gMG is more prevalent in women than in men, women are typically younger at disease onset, and women typically have higher mortality. Furthermore, pregnancy may contraindicate some types of treatment

Abbreviations: gMG, generalised myasthenia gravis.

Zilucoplan (ZILBRYSQ®, UCB)

Marketing authorisation	• Zilucoplan is indicated as an **add-on to standard therapy** for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. • Date of MHRA approval: 15 January 2024
Mechanism of action	• Zilucoplan inhibits complement protein C5, thereby downregulating activity of the membrane attack complex (MAC), allowing for improved neuromuscular junction signalling

Administration	• Subcutaneous injection once daily from prefilled syringe based on weight:
	  • <56 kg: 16.6 mg dose
	  • ≥56 to <77 kg: 23 mg dose
	  • ≥77 kg: 32.4 mg dose

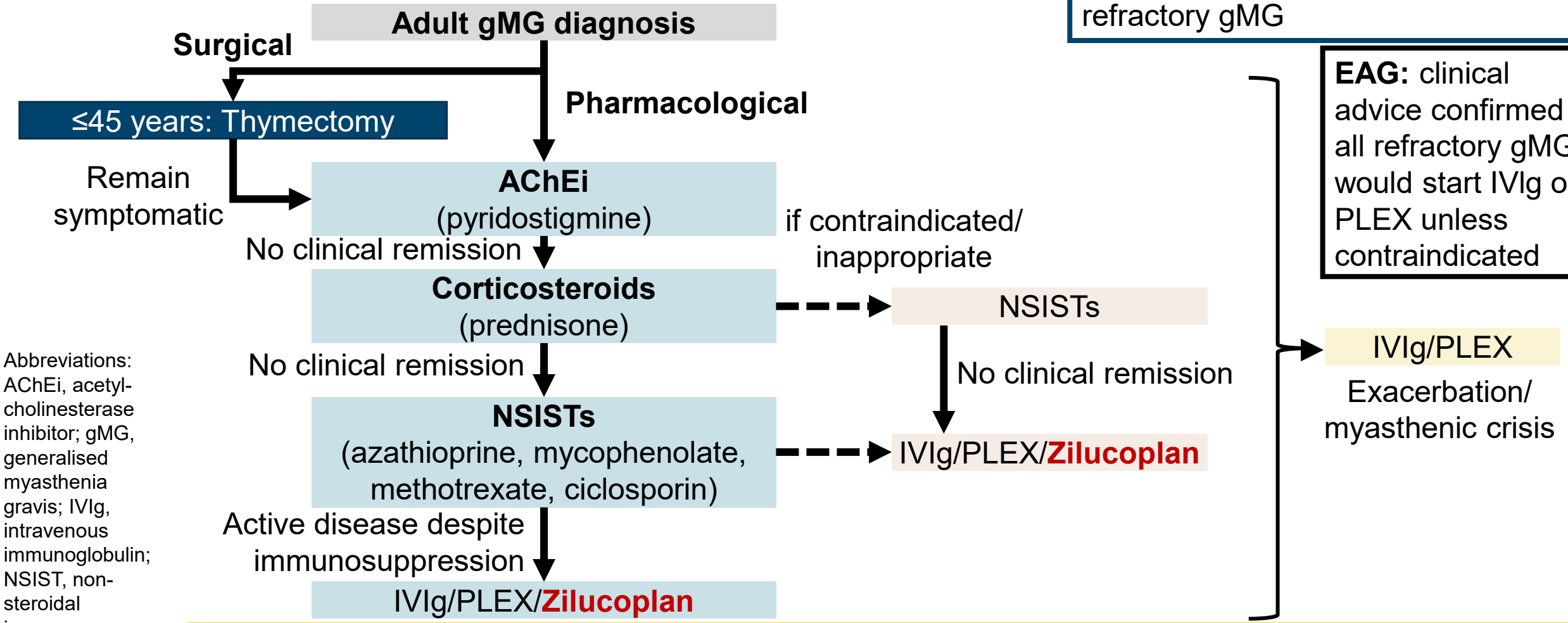
Price	• List price (sold in packs of 7):
	  • 16.6 mg pre-filled syringe x 7: £3,653.97
	  • 23 mg pre-filled syringe x 7: £5,041.78
	  • 32.4 mg pre-filled syringe x 7: £7,114.70
	• There is a confidential patient access scheme for zilucoplan

NICE Abbreviations: AChR, acetylcholine receptor; gMG, generalised myasthenia gravis; MAC, membrane attack complex.

Treatment pathway for gMG

Company proposed positioning: zilucoplan as an add-on to SoC for refractory gMG

EAG: clinical advice confirmed all refractory gMG would start IVIg or PLEX unless contraindicated



Abbreviations: AChEi, acetylcholinesterase inhibitor; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange; SoC, standard of care.

- Does the company's description of the treatment pathway represent NHS practice?
- Is rituximab established care in NHS for gMG? If so, where is it used in the treatment pathway?
- Among NHS patients with refractory gMG, how many are on IVIg, PLEX, or neither?
- What are the subsequent treatment options after IVIg or PLEX for refractory gMG in the NHS?
- Is the proposed positioning for zilucoplan appropriate?

Population: refractory gMG

Company has positioned zilucoplan for refractory gMG, narrower than market authorisation, defined based on criteria from RAISE trial:

- the disease has not responded to other systemic treatments, including pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate and ciclosporin, or these options are contraindicated or not tolerated, **and**
- the disease is uncontrolled, as defined by a MG-ADL ≥ 6 or a QMG ≥ 12, (see appendix) **and**
- an additional therapy such as IVIg or PLEX is being considered, or patients are being treated chronically with IVIg/PLEX **and/or**
- as an alternative option to efgartigimod (subject to NICE approval – appraisal ongoing as of now)

Does the company's definition of refractory gMG align with how it is defined in the NHS?
Do these criteria specify the group of patients in whom zilucoplan would be used in the NHS?

Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis-Activities of Daily Living; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis.

Key issues

Key issues from the EAG report	ICER impact
Decision problem issues	
Exclusion of standard of care as a comparator	High
Clinical effectiveness issues	
Uncertain relevance of the clinical efficacy evidence to patients with refractory generalised myasthenia gravis	Unknown
Uncertainty in network meta-analysis results – heterogeneity and placebo response adjustment	Unknown
Cost-effectiveness issues	
Treatment response rates	High
Response timepoint for all treatments	Low
Resource use for chronic IVIg and PLEX therapy	High
Other issues	
Subsequent treatments	Unknown

NICE Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange.

Decision problem – comparators

	NICE final scope	Decision problem addressed	Company rationale	EAG comments
Comparator	• Standard of care without zilucoplan (including steroids and NSISTs, **with or without** IVIg or PLEX) • Efgartigimod (subject to NICE evaluation)	Modelled comparators separately, excluding steroids and NSISTs: • Efgartigimod • IVIg • PLEX	• Anticipate NICE will approve efgartigimod for refractory gMG • IVIg and PLEX are current SoC in patients who are refractory to treatment	• Zilucoplan, IVIg, PLEX, and efgartigimod all typically added-on to steroids and NSISTs • Need to include steroids and NSISTs in model • Separate modelling of IVIg and PLEX does not reflect usage in practice • Prefer to model overall 'basket' of care (see next)

Note

- Efgartigimod appraisal (ID4003) is ongoing (ACM3 was 9th May; publication date TBC)
- To be considered as comparators, treatments must be established practice in the NHS

What is(are) the relevant comparator(s) for zilucoplan?

Abbreviations: ACM3, appraisal committee meeting; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange; SoC, standard of care; TBC, to be confirmed.

Key issue: Excluding SoC as a comparator for patients with refractory generalised myasthenia gravis

Company

- Excluded steroids and NSISTs from zilucoplan and SoC arms
- Modelled pairwise comparisons with IVIg, PLEX, efgartigimod

EAG

- Zilucoplan, IVIg, and PLEX used as an add-on to steroids and NSISTs
- Efgartigimod EAMS (n=48), patients starting efgartigimod:
  - ↳ 43.8% chronic IVIg
  - ↳ 14.6% chronic PLEX
  - ↳ 41.6% steroids and NSISTs only
- EAG considers EAMS cohort (see box) comparable with likely cohort who would have zilucoplan in the NHS
- EAG prefers to model a blended comparator of SoC treatments based on distribution received in EAMS
- ID4003 (efgartigimod) appraisal similarly used a blended comparator

Efgartigimod EAMS cohort
(see appendix for appraisal comparison)

- AChR ab-positive gMG
- Average age 49.2 years
- 66.7% disease duration >10 years
- Average MG-ADL at baseline 11.2
- ≥1 past non-steroidal immunosuppressant (average 2.6)
- Restricted efgartigimod to patients who were:
  - ↳ Refractory (≥2 NSISTs), or
  - ↳ Intolerant/ineligible to NSISTs, or
  - ↳ Dependent on IVIg/PLEX

- Are patients in the efgartigimod EAMS similar to the patients who would get zilucoplan in the NHS?
- Should SoC be modelled as a blended comparator, or does the committee prefer pairwise comparisons?
- Should steroids and NSISTs be included in both arms?

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Clinical evidence – trial summary

	RAISE (completed)	**RAISE-XT** (ongoing)
Design	Randomised, double-blind, placebo-controlled study	Open label extension (OLE) study
Intervention(s)	• Zilucoplan 0.3 mg/kg/day, SC injection + SoC (n=86)	Zilucoplan 0.3 mg/kg/day, SC injection + SoC (n=200)
Population	Inclusion criteria: • gMG (MGFA Class II–IV) (see appendix) • Positive serology for anti-AChR autoantibodies • MG-ADL score ≥6 (see appendix) • QMG score ≥12 (see appendix) • No change in NSISTs for ≥30 days prior to treatment or anticipated to occur during study • No requirement to have failed multiple prior therapies	Completion of the RAISE Phase III or Phase II study
Comparator	• Placebo + SoC (n=88)	N/A
Pre-planned subgroups	Patients who are treatment refractory, as defined in RAISE	Patients who are treatment refractory, as defined in RAISE
Outcomes	Change from baseline up to week 12 in MG-ADL	Safety and tolerability at extension week 12 Long-term data up to extension week 84
Locations	North America, Europe (including UK), and Japan	North America, Europe (including UK), and Japan

Abbreviations: AChR, acetylcholine receptor; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SC subcutaneous; SoC, standard of care.

RAISE: results

MG-ADL: higher scores indicate more severe symptoms; MCID of ≥2 points

MG-ADL change from baseline (mITT population)

EAG: improvement also observed in placebo arm

MG-ADL CfB and response (≥3 point improvement) by refractory status at week 12

	Placebo, n=88		Zilucoplan, n=86	
	n	Mean CfB [95%CI] (SD)	n	Mean CfB [95%CI] (SD)
mITT	88	-2.30 [-3.17, -1.43]	86	-4.39 [-5.28, -3.50]
Refractory	[redacted]	[redacted]	[redacted]	[redacted]
	n	**Response (n/N)**	n	**Response (n/N)**
mITT	88	46.1% (NR)	86	73.1% (NR)
Refractory	[redacted]	[redacted]	[redacted]	[redacted]

What is the committee's view on:

- zilucoplan's treatment effect at week 12?
- the observed placebo response rate?

RAISE-XT: results

MG-ADL: higher scores indicate more severe symptoms; MCID of ≥2 points

MG-ADL change from baseline (mITT population)

EAG: higher drop out from placebo/ zilucoplan group (treatment switchers)

MG-ADL CfB by refractory status at extension week 12

	Placebo, n=90		Zilucoplan, n=92	
	n	Mean CfB (SD)	n	Mean CfB (SD)
Refractory	[redacted]	[redacted]	[redacted]	[redacted]
Not refractory	[redacted]	[redacted]	[redacted]	[redacted]

What is the committee's view on:

- zilucoplan's long-term treatment effect?
- the observed placebo response rate?

Clinical evidence – baseline characteristics

	RAISE	
	Refractory subgroup (n=88)	Whole population (n=174)
Age (years), mean (SD)	[redacted]	53.0 (15.1)
Female	[redacted]	99 (56.9)
White	[redacted]	128 (73.6)
BMI, mean (SD)	[redacted]	31.0 (7.63)
MGFA class at screening, n (%)		
Class II	[redacted]	49 (28.2)
Class III	[redacted]	117 (67.2)
Class IV	[redacted]	8 (4.6)
Duration of disease, years	[redacted]	9.2 (9.9)
Symptoms at onset, n (%)	[redacted]	112 (64.4)
Prior thymectomy, n (%)	[redacted]	82 (47.1)
Time since most recent crisis (months)	[redacted]	73.9 (100.5)
Baseline MG-ADL	[redacted]	10.6 (3.0)
Baseline QMG	[redacted]	19.1 (4.1)
Concomitant treatments, n (%)	[redacted]	169 (97.1)
Pyridostigmine	[redacted]	144 (82.8)
Prednisone	[redacted]	72 (41.4)
Prednisolone	[redacted]	36 (20.7)
Mycophenolate mofetil	[redacted]	33 (19.0)
Azathioprine	[redacted]	31 (17.8)

EAG:

- Clinical advice: whole trial population reflects a refractory population
- Unclear that this generalisability assumption holds for comparisons with IVIg, PLEX, and efgartigimod

NICE

Is the whole trial population representative of patients with refractory gMG in the NHS?
Is concomitant treatment use similar to that expected in the NHS?

Key issue: Uncertain relevance of the clinical evidence to patients with refractory gMG

Background

- Company positioned zilucoplan for refractory patients (see slide 8)
- RAISE refractory subgroup (n=88) smaller than whole population (n=174)

EAG

- Similarities in outcomes between RAISE refractory subgroup and whole population
- However, assumption that whole trial populations are generalisable to refractory NHS patients may not hold
- In the model, response rates for IVIg and PLEX sourced from trials without defined refractory subgroups
- Of studies included in NMA, only RAISE contained explicitly defined refractory subgroup
  - ↳ Efgartigimod trial had 63% refractory patients (vs. zilucoplan 51%), but refractory not defined in precisely the same way

Are data from the whole trial population in RAISE, and from other trials without explicitly defined refractory subgroups, sufficient for decision making for refractory patients?

Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; NMA, network meta-analysis; PLEX, plasma exchange.

Note, if efgartigimod is excluded as a comparator, neither company nor EAG use NMA in model

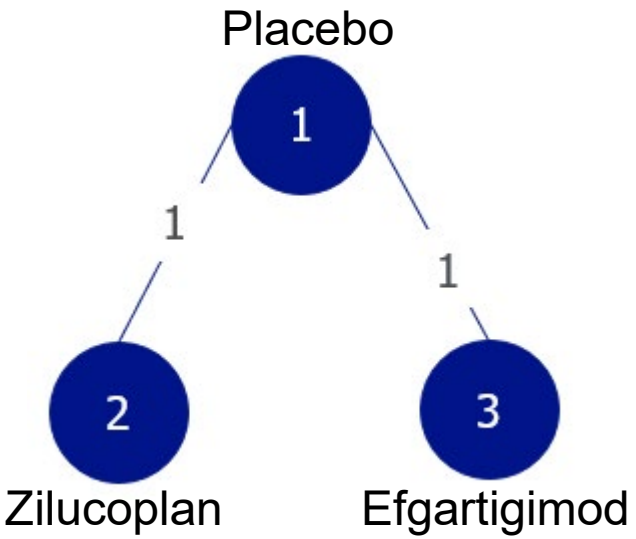
Network meta-analysis

NMA for MG-ADL response was only possible versus efgartigimod

Company:

- Economic model is informed by MG-ADL response rate outcome
  - ↳ NMA for MG-ADL response was only possible versus efgartigimod
  - ↳ No IVIg studies with MG-ADL response outcome
  - ↳ No appropriate PLEX studies
- NMA found [redacted] MG-ADL response when comparing zilucoplan with efgartigimod
- NMAs versus IVIg were possible for other outcomes (see appendix) but were not used in the model

Network diagram
(MG-ADL response rate)



Results (MG-ADL response rate)

Comparator	Analysis approach	Odds ratio (95% CrI)
Efgartigimod	Primary (Phase 3 only)	[redacted]
	Scenario 1 (Phase 2+3)	[redacted]

How company used the NMA in the model (see appendix):

- First, odds ratios for zilucoplan versus efgartigimod were converted to relative risks
- Relative risks were then applied to the referent response rate (calculated as the average response rate across the studies used in the NMA, which was [redacted] to estimate each treatment's response rate)

Abbreviations: CrI, credible interval; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis-Activities of Daily Living; NMA, network meta-analysis; PLEX, plasma exchange

Key issue: Uncertainty in NMA

Note, if efgartigimod is excluded as a comparator, neither company nor EAG use NMA in model

EAG:

- Uncertainties included:
  1. Heterogeneity: unclear whether whole trial population rather than refractory gMG from RAISE included in NMA; differences in baseline characteristics of RAISE and efgartigimod trial not accounted for (see appendix)
  2. Different placebo responses: as noted by company, placebo response higher in zilucoplan trials, but this was not adjusted for
  3. Uncertainty in NMA not propagated into modelling – relative efficacy estimate incorporated into the model as a point estimate with no confidence interval
  4. Anchored matching-adjusted indirect comparison (MAIC) should be feasible, but company did not provide

Due to this, EAG chose to use unadjusted, non-randomised response rates directly from trial arms to inform efficacy in model

Company:

- MAIC limited due to heterogeneity in reporting across trials
- Sample size may be too small after population matching
- Results of sensitivity analyses show results robust to phase of study used and to timepoint of MG-ADL analysis

Is the NMA on MG-ADL response rate versus efgartigimod informative for decision making?

Abbreviations: gMG, generalised myasthenia gravis; MAIC, matching-adjusted indirect comparison; MG-ADL, Myasthenia Gravis-Activities of Daily Living; NMA, network meta-analysis

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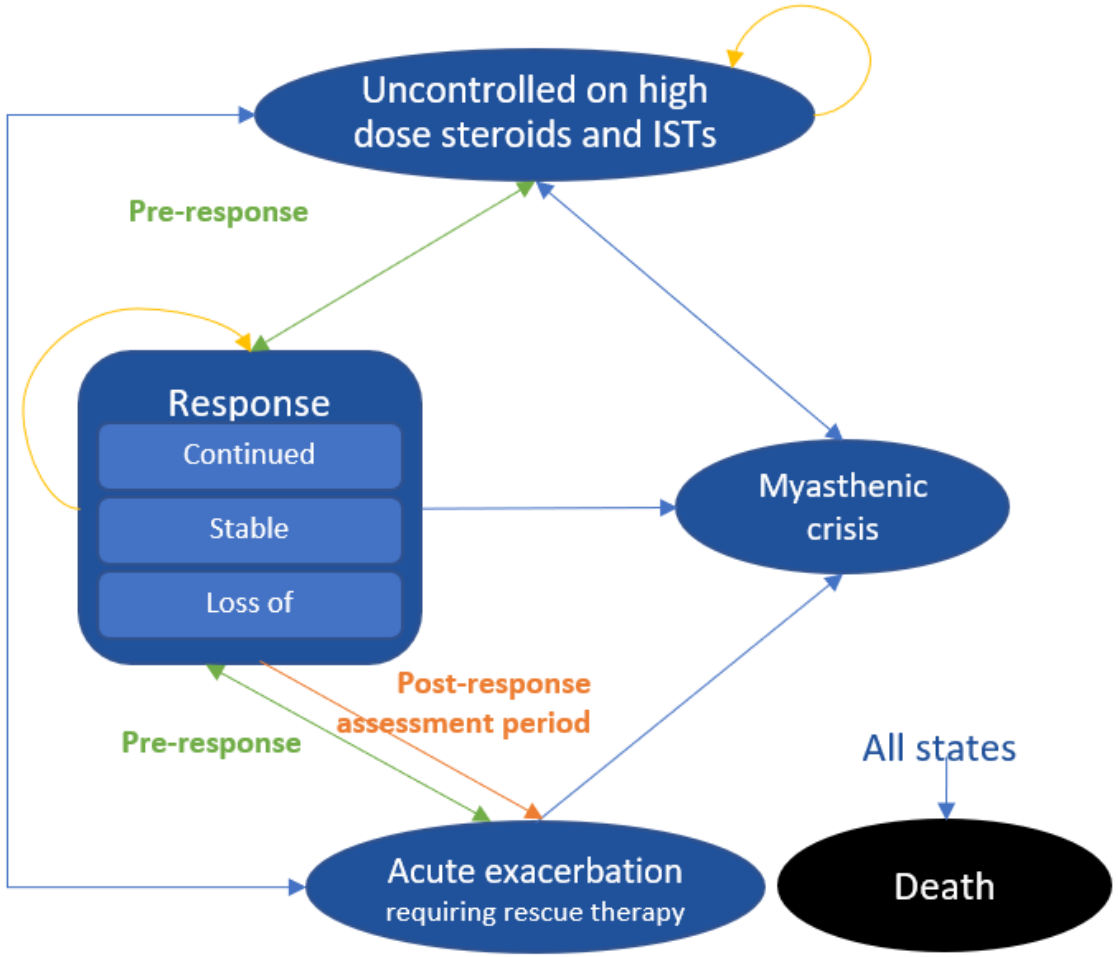
Company's model overview

Model structure

- Cohort state-transition model with 7 health states (see appendix for health state descriptions)
- Cycle length: 2 weeks; time horizon: 52.5 years
- Patients enter model in uncontrolled health state and transition to response health state if they meet treatment response criteria (decrease of ≥3 in MG-ADL) at response assessment timepoint (represents the waiting period to see if a patient responds)
- Responders separate into one of 3 response sub-groups (continued, loss or stable response) at the response assessment timepoint:
  - ↳ [redacted] assumed to be stable
  - ↳ [redacted] assumed to lose response
  - ↳ [redacted] assumed to have a continued response
- Within each health state (except death), patients are at risk of 'exacerbation', 'crisis' or 'death'



EAG: model structure appropriate, reflects patient pathway based on clinical advice

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

Company and EAG base cases – key differences

Model inputs	Company source/assumption	EAG source/assumption
Population	Baseline characteristics of refractory patients in RAISE	Same; scenario analyses conducted for whole RAISE population and RAISE extension study
Comparator	3 separate comparators, without steroids/NSISTs: • Efgartigimod, • IVIg, • PLEX	Blended SoC comparator, using % from efgartigmod EAMS: • 43.8% IVIg + steroids + NSISTs, • 14.6% PLEX + steroids + NSISTs, • 41.6% steroids + NSISTs only
Treatment response rates	• Zilucoplan and efgartigimod: NMA* • IVIg/PLEX: Barth 2011	• Zilucoplan: RAISE arm data • Efgartigimod: ADAPT arm data • IVIg/PLEX: clinical opinion
Response assessment timepoint	• Zilucoplan: RAISE • Efgartigimod: ADAPT • IVIg/PLEX: assumption	• Zilucoplan: clinical opinion • Efgartigimod: clinical opinion • IVIg/PLEX: clinical opinion
Resource use	• PLEX admin costs equal to subcutaneous admin costs • IVIg costs applied every 3 weeks • PLEX costs applied every 4 weeks	• NHS reference cost for PLEX used • IVIg/PLEX costs applied every 6 weeks, based on clinical advice

*Company stated results based on its 2024 NMA, but EAG could not confirm this.
Abbreviations: EAMS, early access to medicines scheme; IVIg, intravenous immunoglobulin; NMA, network meta-analysis; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange; SoC, standard of care.

Key issues: Treatment response rates and timepoints

Company

- Odds ratios from NMA converted to relative risks, then applied to referent response rate to calculate response for zilucoplan and efgartigimod
- IVIg and PLEX from Barth et al, a Canadian RCT (n=84), converted using referent response rate

EAG

- Uncertainty with NMA (slide 19) and Barth et al. study
- Clinical advice: IVIg/PLEX response is too low
- Used unadjusted response rates from the trial arms for zilucoplan and efgartigimod, and clinical opinion for IVIg/PLEX
- Response assessment time of 3 weeks reflects clinical advice

Company's response rate inputs

Treatment	Response rate	Source	Response assessment time point (weeks)	Source
Zilucoplan	[redacted]	NMA	12	RAISE
Efgartigimod	[redacted]	NMA	10	ADAPT
IVIg	51.00%	Barth 2011	6	Assumption
PLEX	57.00%			

EAG's response rate inputs

Treatment	Response rate	Source	Response assessment time point (weeks)	Source
Zilucoplan	73.10%	RAISE	3	Clinical advice
Efgartigimod	73.00%	ADAPT		
IVIg	70%	Clinical advice		
PLEX				

NICE Which are the committee's preferred sources to estimate treatment effects in the model? Which assumptions about treatment response rate and time point are more clinically plausible?

Key issue: Resource use for chronic IVIg and PLEX therapy

Company

- Model applies treatment costs for IVIg every 3 weeks and costs for PLEX every 4 weeks
- PLEX administration cost assumed equal to subcutaneous administration cost

EAG

- Clinical advice:
  - ↳ IVIg usually administered every 4 to 8 weeks, occasionally up to 12 weeks and even up to 16 weeks
  - ↳ PLEX usually administered every 4 to 8 weeks
- Updated administration of IVIg and PLEX to every 6 weeks to reflect this
- Use NHS reference cost SA44A – Single Plasma Exchange (£910), applied every 6 weeks, for PLEX administration cost

Which assumptions around resource use reflect NHS practice?

 Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange.

Additional issue: subsequent treatments

- Refractory gMG is a condition that requires lifelong management
- Over time, patients transition from the response health state to the 'uncontrolled – off treatment' health state
- However, the model does not account for any subsequent treatments that patients may have after stopping zilucoplan or comparators

Zilucoplan graphs – company base case assumptions

- After stopping zilucoplan, would patients be eligible for chronic IVIg/PLEX?
- After stopping IVIg, would patients be eligible for PLEX? And vice versa?
- Would the rate at which discontinuers in each arm have subsequent IVIg/PLEX be similar?

 Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; PLEX, plasma exchange.

Company base case results

Due to confidential prices, exact ICERs will be provided in part 2

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Zilucoplan	See Part 2				-
Efgartigimod					Below £20,000
IVIg					Above £30,000
PLEX					Below £20,000

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Zilucoplan	See Part 2				-
Efgartigimod					Below £20,000
IVIg					Above £30,000
PLEX					Below £20,000

NICE Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year.

EAG base case results

No	Scenario (applied to company base case)	Cumulative ICER (£/QALY) versus SoC
	Company base case (for blended SoC comparator)	Over £30,000
1	Include IVIg and PLEX in SoC	Over £30,000
2	Adapting the proportions of SoC therapies	Over £30,000
3	Include SoC costs in targeted therapies	Over £30,000
4	Different response rates for targeted treatments	Over £30,000
5	Using the change in MG-ADL score from the RAISE trial refractory subgroup	Over £30,000
6	Using a response time point of 3 weeks for all treatments	Over £30,000
7	Applying chronic IVIg costs every 6 weeks	Over £30,000
8	Using NHS reference cost applied every 6 weeks, for PLEX administration	Over £30,000
9	Applying chronic PLEX costs every 6 weeks	Over £30,000
10	Increasing the duration of a myasthenic crisis to 21 days	Over £30,000
11	Increasing the resource use for ICU time due to a myasthenic crisis to 21 days	Over £30,000
	EAG base case	Over £30,000

Abbreviations: ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis-Activities of Daily Living; PLEX, plasma exchange; QALY, quality-adjusted life year; SoC, standard of care.

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Key issues

Key issues from the EAG report	ICER impact
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Clinical effectiveness issues	
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Uncertainty in network meta-analysis results – heterogeneity and placebo response adjustment	Unknown
Cost-effectiveness issues	
Treatment response rates	High
Response timepoint for all treatments	Low
Resource use for chronic IVIg and PLEX therapy	High
Other issues	
Subsequent treatments	Unknown

NICE Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange.

Committee decision making slides (1)

Assumption	Question for committee
Decision problem	Does the company's description of the treatment pathway represent NHS practice?
	Is rituximab established care in NHS for gMG? If so, where is it used in the treatment pathway?
	Among NHS patients with refractory gMG, how many are on IVIg, PLEX, or neither?
	What are the subsequent treatment options after IVIg/PLEX for refractory gMG in the NHS?
	Is the proposed positioning for zilucoplan appropriate?
	Does the company's definition of refractory gMG align with how it is defined in the NHS?
	Do these criteria specify the group of patients in whom zilucoplan would be used in the NHS?
	What is(are) the relevant comparator(s) for zilucoplan?
	Are patients in the efgartigimod EAMS similar to the patients who would get zilucoplan in the NHS?
	Should SoC be modelled as a blended comparator, or does the committee prefer pairwise comparisons?
	Should corticosteroids and NSISTs be included in both arms?

NICE Abbreviations: EAMS, Early Access to Medicines Scheme; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SoC, standard of care.

Committee decision making slides (2)

Assumption	Question for committee
Clinical effectiveness	What is the committee's view on: • zilucoplan's treatment effect at week 12? • zilucoplan's long-term treatment effect? • the observed placebo response rate?
	Is the whole trial population representative of patients with refractory gMG in the NHS?
	Is concomitant treatment use similar to that expected in the NHS?
	Are data from the whole trial population in RAISE, and from other trials without explicitly defined refractory subgroups, sufficient for decision making for refractory patients?
	Is the NMA on MG-ADL response rate versus efgartigimod informative for decision making?
Cost-effectiveness	What is the committee's view on the sources used to estimate treatment effects in the model?
	Which assumptions about treatment response rate and time point are more clinically plausible?
	Which assumptions around resource use reflect NHS practice?
	• After stopping zilucoplan, would patients be eligible for chronic IVIg/PLEX? • After stopping IVIg, would patients be eligible for PLEX? And vice versa? • Would the rate at which discontinuers in each arm have subsequent IVIg/PLEX be similar?

Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis-Activities of Daily Living; NMA, network meta-analysis; PLEX, plasma exchange.

Committee decision making slides (3)

Assumption	Question for committee
Severity/threshold modifiers	Are there any benefits of zilucoplan which are not captured in the QALY calculations? Are there any equality considerations that need to be accounted for?
ICER threshold	What is the committee's preferred ICER threshold?
Preferred ICER	What is the committee's preferred ICER?

NICE Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Supplementary appendix

NICE National Institute for Health and Care Excellence

Clinical classification of MG using MGFA (Myasthenia Gravis Foundation of America)

Class	Description
I	Any ocular muscle weakness.
II	**Mild** weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
IIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
III	**Moderate** weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
IIIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
IV	**Severe** weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
IVa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Background: refractory gMG

No standardised definition of refractory gMG

- Variety of definitions, can be summarised into 5 categories:
    1. failure to respond adequately to conventional treatment
    2. severe adverse effects from conventional treatment
    3. inability to reduce immunosuppressive treatment without relapse or need ongoing rescue therapy
    4. comorbidities restricting use of conventional therapies
    5. frequent myasthenic crises even with conventional treatment

NICE Abbreviations: gMG, generalised myasthenia gravis.

Patient perspectives

Joint submission from Muscular Dystrophy UK and Myaware

People suffer from fatigue, and problems with breathing, speaking, seeing and concentrating – significantly impacting their ability to work or keep the same role

MG and the side effects of some treatments impact individuals physically, emotionally and financially

People with gMG struggle to balance treatments, symptom management, side effects and undertaking their day-to-day activities

People worry about side effects of steroids and steroid sparing treatment options

Similar impact on families and carers – in a survey*, 90% of carers said that caring for someone with MG impacted their ability to undertake their usual activities, and 67% said it caused anxiety/depression

Zilucoplan may offer better prognosis for people in whom symptoms are not well controlled with current treatment options, and may have fewer side effects

"I am unable to do the majority of the things I used to do due to my extreme weakness, breathlessness and fatigue. I have had to reduce my working hours. I can't do much around the house or garden"

"*I have hated prednisolone since the day they put me on it.*"

"My husband has been my carer since diagnosis. He gave up work to care for me full-time. It is both physically and mentally demanding"

NICE

*Survey of 21 carers of people with gMG.
gMG, Generalised Myasthenia Gravis; MG, Myasthenia Gravis

Clinical perspectives

Submission from the Association of British Neurologists

Main aim of treatment is to reduce symptoms while minimising side effects

Several validated patient outcome rating scales including the MG–ADL, QMG, MGC, and MG–QoL15r

Well-defined pathway of care for patients with MG. Mild to moderate MG typically treated with pyridostigmine, corticosteroids and steroid-sparing agents

Care for patients with refractory gMG is less well defined, with IVIg and PLEX used variably across different centres

Zilucoplan suitable for anti-AChR antibody-positive gMG refractory to, or intolerant of, standard therapies

Significant unmet need for gMG → significant proportion of patients on steroids remain symptomatic; steroid sparing agents limited by tolerance issues

"Development of biological terminal complement inhibitors are an important advance in the management of patients with treatment resistant antibody positive myasthenia gravis."

"There is a need to develop new therapies for severe myasthenia given the constrained supply of immunoglobulin and difficulty ensuring provision of plasma exchange in England."

NICE

AChR, Acetylcholine receptor; gMG, Generalised Myasthenia Gravis; IVIg, Intravenous immunoglobulin; MG, Myasthenia Gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL, Myasthenia Gravis quality of life; NSIST, Nonsteroidal immunosuppressive therapy; PLEX, Plasma exchange QMG, Quantitative Myasthenia Gravis

Decision problem – population

	Final scope	Decision problem addressed	Rationale if different from the final NICE scope	EAG comments
Population	Adults with antibody-positive generalised myasthenia gravis	Adults with **refractory** AChR antibody-positive generalised myasthenia gravis, if: • the disease has not responded to other systemic treatments, or these options are contraindicated or not tolerated, and • the disease is uncontrolled, and • an alternative option to efgartigimod (subject to NICE approval), and/or • an additional therapy such as immunoglobulin or PLEX is being considered, or patients are being treated chronically with Ig/PLEX	• High unmet need in refractory population • Limited evidence for standard of care treatments IVIg and PLEX • Clinical evidence from the RAISE trial contained significant subgroup of refractory patients	• Narrower than scope • Clinical advice agrees that full ITT population of RAISE trial adequately represents patients with refractory gMG in the NHS • Definition of a refractory population is appropriate and broadly consistent with published definitions
Subgroups	None specified	-	-	• Company focused on **refractory** gMG, a pre-specified subgroup in pivotal trial RAISE

Decision problem – outcomes

	Final scope	Decision problem addressed	Rationale if different from the final NICE scope	EAG comments
Outcomes	• Improvement in MG • Time to clinically meaningful improvement • Mortality • Number of hospitalisations • Adverse effects of treatment • Health-related quality of life	• Improvement in MG (MG-ADL responder) • Time to clinically meaningful improvement • Mortality • Number of hospitalisations • Adverse effects of treatment • Health-related quality of life (in patients and carers)	Carer's disutility addressed in submission	• Company's economic model does not include carer's disutility

Outcome measures description

Myasthenia Gravis Activities of Daily Living (MG-ADL)

- 8-item patient-reported scale
- Each item scored 0 (normal) to 3 (severe disease), total score 0–24, MCID 2 points
- Items cover talking, chewing, swallowing, breathing, ability to brush teeth or comb hair, ability to stand from chair, double vision, eyelid droop

Quantitative Myasthenia Gravis scale (QMG)

- 13-item clinician-assessed scale
- Each item scored 0 to 3 (higher scores indicate greater severity), total score 0–39, MCID 2 or 3 points
- Items cover endurance or fatiguability. Requires dynamometer or spirometer, so typically only used in research

Myasthenia Gravis Composite score (MGC)

- 10-item scale of patient-reported (for speech, chewing, swallowing and respiratory function) and physician measured (quantitative tests and spirometry to evaluate ocular, neck and proximal limb muscles) outcomes
- Higher scores indicate more severe disease, total score 0–50, MCID 3 points, items weighted so that the max. score for worst respiratory function is worth more points than the max. score for worst eyelid strength

Myasthenia Gravis Quality of Life 15 revised version (MG-QoL15r)

- 15-item patient-reported scale
- Each item scored 0 to 2 (higher scores indicating worse quality of life), total score 0–30, MCID not established
- Items cover mobility (9 items), symptoms (3 items), and contentment and emotional wellbeing (3 items)

RAISE results: secondary outcomes

CfB in QMG score at week 12 (mITT population)

CfB in MGC score at week 12 (mITT population)

CfB in MG-QoL15r score at week 12 (mITT population)

CfB in subscores at week 12 (mITT population)

Network meta-analysis – other results

QMG response rate

Comparator	Analysis approach	OR (95% CrI)
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	[redacted]
IVIg	Primary	No data
	Scenario 1	No data
	Scenario 2	[redacted]

QMG change from baseline

Comparator	Analysis approach	CfB (95% CrI)
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	[redacted]
IVIg	Primary	No data
	Scenario 1	No data
	Scenario 2	[redacted]

Analysis	For the MG-ADL and QMG response outcomes	For the change from baseline outcomes (MG-ADL, QMG, MGC, MG-QoL15r)
Primary	Phase III trials only, primary study endpoint	Phase III trials only, week 12±2
Scenario 1	Phase II & III trials, primary study endpoint	Phase II & III trials, week 12±2
Scenario 2	Conducted for QMG response only. As scenario 1, but included QMG ≥3 point threshold for IVIg trials (other trials ≥5 point)	Phase II & III trials, week 12±2 or primary study endpoint if different

MG-ADL change from baseline

Comparator	Analysis approach	CfB (95% CrI)
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	[redacted]
IVIg	Primary	No data
	Scenario 1	No data
	Scenario 2	[redacted]

MGC change from baseline

Comparator	Analysis approach	CfB (95% CrI)
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	[redacted]

MG-QoL15r change from baseline

Comparator	Analysis approach	CfB (95% CrI)
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	[redacted]

Link back to NMA

How NMA results were transformed for the model

Treatment response rates were calculated based on the odds ratio output from the NMA, applied to a referent response rate

1. Odds ratios converted to relative risks due to difficulties associated with the interpretation of odds ratios

$$RR[t] = \frac{OR_t}{(1 - ReferentResponse) + (ReferentResponse \times OR_t)}$$

Where *t* is the comparator treatment with known odds ratio versus the referent treatment

2. Then, the relative risk was applied to the referent response rate in order to determine each treatment's response rate:

$$Response\ rate[t] = ReferentResponse \times RR_t$$

Referent response calculated as the simple average response across the NMA studies ([redacted])

Baseline characteristics differences in RAISE and ADAPT

Baseline characteristic	RAISE zilucoplan	ADAPT efgartigimod
Female	57%	71%
Age	53 y	47 y
MGFA class 2	28%	39%
Prior thymectomy	47%	57%
MG-ADL score	10.6	9.0
QMG score	19.1	15.9

Barth et al. 2011, baseline characteristics

Table 1 **Baseline demographic data**[a]

Clinical characteristics	IVIg (n = 41)	PLEX (n = 43)	*p* Value[b]
Age, y			
Mean ± SD	57 ± 18	58 ± 17	0.75
Range	19-84	20-84	
Female sex	24 (58)	24 (55)	0.89
MG duration, mo			
Mean ± SD	71 ± 90	64 ± 89	0.75
Range	3-450	5-456	
Previous IVIg treatment	9 (21)	6 (13)	0.33
Previous PLEX treatment	4 10)	8 (20)	0.15
History of thymectomy	13 (31)	19 (44)	0.40
History of thymoma	11 (27)	14 (32)	0.78
Current pyridostigmine	32 (78)	32 (74)	0.69
Current prednisone	14 (34)	21 (48)	0.17
Current azathioprine	6 (14)	7 (16)	0.83
Current mycophenolate mofetil	2 (5)	4 (10)	0.42
Baseline QMGS[c]			
Mean ± SD	14.26 ± 4.0	14.44 ± 3.8	0.83
Range	11-29	11-30	
MGFA classification			
Grade 2	22 (53)	26 (60)	
Grade 3	17 (41)	15 (34)	0.60
Grade 5	0 (0)	1 (2.3)	
AChRAb (positive)	28 (70)	34 (79)	0.34
Baseline AChRAb, nmol/L			
Mean ± SD	149 ± 142	198 ± 132	0.11
Range	0-429	0-457	
Anti-MuSK AB (positive)	2 (5)	2 (4)	0.94
Seronegative	10 (25)	7 (19)	0.32
Decrement at baseline, %			
Mean ± SD	13.8 ± 14.6	17.2 ± 18.5	0.38
Range	0-61	0-63	
Baseline SFEMG jitter, μs			
Mean ± SD	110 ± 52	118 ± 39	0.47
Range	29-247	40-233	
Baseline SFEMG abnormal pairs, %			
Mean ± SD	66 ± 27	77 ± 21	0.06
Range	10-100	19-100	
Baseline SFEMG blocking pairs, %			
Mean ± SD	15.4 ± 13.1	20.8 ± 13.2	0.09
Range	0-60	0-60	

Health state descriptions defined by company

Health state	Definition
Uncontrolled on high dose steroids and ISTs	Patients with MG who do not achieve an adequate response or are intolerant to conventional treatment.
Continued (improved) response	A minimum of 3-point reduction from baseline (responder rate) in MG-ADL total score after time of response assessment AND **ongoing improvement** in MG-ADL score compared with baseline after time of response assessment.
Stable response	A minimum of 3-point reduction from baseline (responder rate) in MG-ADL total score at time of response assessment AND **no change** in MG-ADL after time of response assessment.
Loss of response	A minimum of 3-point reduction from baseline (responder rate) in MG-ADL total score at time of response assessment AND an **increase (worsening)** in MG-ADL score after time of response assessment, with a return to the baseline MG-ADL score
Exacerbation	New worsening of symptoms reported by the patient accompanied by at least one of: • New weakness quantified by the medical research council (MRC) muscle power grade as 4 or less in more than one muscle group in more than one limb • Dysarthria with nasal or incomprehensible speech • Dysphagia associated with daily coughing and choking • Any exacerbation that had required hospital admission • Worsening of symptoms that prompted the use of PLEX or IVIg as a rescue therapy
Myasthenic crisis	Exacerbation requiring intubation
Death	Death health state

Comparison with efgartigimod appraisal (ID4003) (1)

Assumption/input	Committee conclusions in ID4003	Zilucoplan (ID4008)
Population	Company positioned efgartigimod for: • people with active, refractory disease, with a MG-ADL score of 5 or more, AND • who cannot tolerate or are ineligible for standard treatment, or in whom standard treatment has failed "Committee concluded that the company's target population description broadly described the most suitable population to have add-on treatment with efgartigimod"	Company positioned zilucoplan for: • Patients are on treatment for 1 year or more with 2 or more standard treatments, OR • History of treatment with at least 1 standard treatment for 1 year or more, and required chronic PLEX, IVIg, or SCIg, AND • the disease has not responded to systemic treatments, or they are contraindicated or not tolerated, AND • the disease is uncontrolled, as defined by a MG-ADL of 6 or more or a QMG of 12 or more • an additional therapy such as IVIg or PLEX is being considered, or patients are being treated chronically with IVIg/PLEX

Comparison with efgartigimod appraisal (ID4003) (2)

Assumption/input	Committee conclusions in ID4003	Zilucoplan (ID4008)
Comparator	As of ACM3 (9th May) the company's base case included a blended SoC comparator, with 43.8% of patients on maintenance IVIg (as per the EAMS), and a scenario analysis with 14.6% of patients on PLEX	The company have modelled each comparator separately. The EAG's approach of using a blended comparator is similar to the approach in ID4003
Follow up time in pivotal trial	26 weeks	12 weeks
Model structure	State transition model, 4 health states defined based MG-ADL total score, and death. Uncertainty in how closely MG-ADL inform disease severity, limitation noted.	State transition model, 7 health states including death; health states defined by response status (stable, lose response, continued response)
Key assumptions in model		
Treatment effect after stopping treatment	Limited evidence, committee noted: • Modelling a residual treatment effect after stopping efgartigimod highly uncertain; • Treatment effect after permanent stopping may be linked to placebo effect	Not identified as an issue or directly addressed by company or EAG; response in the longer term may partly and indirectly addressed treatment effect in longer term

Comparison with efgartigimod appraisal (ID4003) (3)

Assumption/input	Committee conclusions in ID4003	Zilucoplan (ID4008)
Key assumptions in model (continued)		
Placebo effect	• Benefit observed in placebo arm should be maintained over time-horizon of model	EAG noted placebo effect in response rate outcome, but not an issue addressed either in company or EAG's modelling
Carer's QoL	• Consider carer's QoL qualitatively	EAG noted that company had stated carer's disutilties addressed in submission, but company's model did not include it
Subsequent treatment	• As of ACM3, an issue being discussed; committee concluded that model should include subsequent post treatments being appraised, in particular IVIg	Not identified as an issue by either company or EAG; an issue identified by NICE technical team

Efgartigimod EAMS inclusion criteria

EAMS criteria:

- Efgartigimod was indicated for the treatment of adult patients with AChR antibody-positive gMG including those who had failed, did not tolerate or were ineligible for licensed treatment
- Patients could not have received rituximab within 6 months or IVIg within 4 weeks and IgG levels had to be ≥ 6g/L prior to starting Efgartigimod
- The consensus achieved before the introduction of the scheme with UK MG clinicians was that it would be reserved for patients with refractory disease who had not responded to ≥ 2 non-steroidal immunosuppressant agents who were intolerant or ineligible for such therapies and those patients who were dependent on IVIg and TPE

Efgartigimod's target pop. (ID4003)

Draft guidance 2 (December 2023)

- active, refractory disease, with MG-ADL ≥5, and
- cannot tolerate or ineligible for standard treatment†, or standard treatment has failed

†Standard treatment defined as a maximal dose of steroids, and at least 2 additional treatments, such as non-steroidal immunosuppressants and rituximab, for an adequate time, at an adequate dose.