Rozanolixizumab for treating antibody-positive generalised myasthenia gravis [ID5092]

For public release – CON information is redacted

Technology appraisal committee B [14 August 2024]

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Rozanolixizumab 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 antibody-mediated destruction of the 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 AChR; estimated 3% have antibodies against MuSK
- 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

Substantial unmet need for people with refractory gMG

Joint submission from Muscular Dystrophy UK and Myaware

gMG and 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

Subcutaneous administration makes it easier for people to access the therapy from home. If they do attend a clinic, it will take less time compared to IV administration

"Due to fatigue and embarrassment with my slurry speech, I don't feel comfortable going out. I also can't walk long distances which has changed me as a person."

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

New targeted therapies such as Rozanolixizumab allow reduction of other immunotherapies (steroids, immunosuppression and IVIG and PLEX)

"Rozanolixizumab (and similar drugs) is a step change in gMG management. This is a therapy which targets molecules involved in the pathogenic mechanisms of the disease."

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

Other considerations

Equality

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

Abbreviations: gMG, generalised myasthenia gravis.

Rozanolixizumab (RYSTIGGO®, UCB)

Marketing authorisation	• Rozanolixizumab is indicated as an **add-on to standard therapy** for the treatment of generalised myasthenia gravis (gMG) in adult patients who are ***anti-AChR or anti-MuSK* antibody positive**. • Licensed dose: ~ 7mg/kg • Date of MHRA approval: 7 March 2024
Mechanism of action	• Rozanolixizumab decreases the serum IgG concentration by inhibiting the binding of IgG to FcRn. This also decreases the concentration of pathogenic IgG autoantibodies, targeting the core pathophysiology of gMG.

Administration	• Subcutaneous infusion *once-weekly for 6 weeks* (1 treatment cycle*), based on weight:
	  • ≥35–<50 kg: 280 mg
	  • ≥50–<70 kg: 420 mg
	  • ≥70–<100 kg: 560 mg
	  • ≥100 kg: 840 mg

Price	• List price: [redacted] • Average cost of [redacted] for a 6-week treatment cycle • There is a confidential patient access scheme for rozanolixizumab

* 1 dose per week for 6 weeks, further treatment cycles dependent on clinical evaluation and vary by patient

Abbreviations: AChR, acetylcholine receptor; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; MuSK, muscle specific tyrosine kinase; FcRn, neonatal fragment crystallisable receptor; MHRA, Medicines & Healthcare products Regulatory Agency

Treatment pathway for gMG

EAG: Rozanolixizumab positioned as an alternative to IVIg or PLEX for refractory gMG and for when NSISTs contradicted; uncertain whether rituximab a comparator for patients with refractory MuSK+ gMG

Adult gMG diagnosis

Surgical

≤45 years: Thymectomy (not suitable for MuSK+)

Remain symptomatic

Pharmacological

AChEi (pyridostigmine)

No clinical remission

Corticosteroids (prednisone)

if contraindicated/ inappropriate

NSISTs

No clinical remission

IVIg/PLEX/Rituximab/ **Rozanolixizumab**

No clinical remission

NSISTs (azathioprine, mycophenolate, methotrexate, ciclosporin)

Active disease despite immunosuppression

Targeted therapy IVIg/PLEX/Rituximab/**Rozanolixizumab**

Treatment may differ for MuSK Ab+ as people tend not to respond to AChEIs

IVIg/PLEX

Exacerbation/ myasthenic crisis

Abbreviations: AChEi, acetyl-cholinesterase inhibitor; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MuSK, muscle specific tyrosine kinase; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange; SoC, standard of care.

Company proposed positioning: Rozanolixizumab as an add-on to SoC for refractory AChR+ or MuSK+ gMG

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- Is the proposed positioning for rozanolixizumab appropriate?
- Is the treatment pathway different for MuSK+ gMG and AChR+ gMG?
- What is the position of rituximab in the treatment pathway?

Population: refractory gMG

Company has positioned rozanolixizumab for refractory AChR+ or MuSK+ gMG, narrower than market authorisation:

- Refractory is defined as:
  - disease-classified as MGFA class II–IVa ; and
  - uncontrolled after 2 or more prior therapies (excluding acetylcholinesterase inhibitors), and
  - an additional therapy such as IVIg or PLEX is being administered or considered

EAG: clinical advice suggested company's definition of refractory appropriate, although a disease severity score threshold (such as MG-ADL score), which might be expected in clinical practice, is not included

Prior therapies to include the following:

↳ prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, other immunosuppressants

- Do these criteria define the group of patients in whom rozanolixizumab would be used in the NHS?

Abbreviations: AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; PLEX, plasma exchange; MG-ADL, Myasthenia Gravis-Activities of Daily Living

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
Uncertain relevance of the overall trial populations to patients who are AChR antibody-positive and MuSK antibody-positive	Unknown
Cost-effectiveness issues	
Treatment response rates	High
Response timepoint for all treatments	Low
Resource use for chronic IVIg and PLEX therapy	High
Subsequent treatments	Unknown

Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase

Decision problem – comparators

	NICE final scope	Decision problem addressed	Company rationale	EAG comments
Comparator	• Efgartigimod* • Zilucoplan* • Ravulizumab** • Standard of care without rozanolixizumab (including ISTs [including rituximab] with or without IVIg or PLEX)	• Efgartigimod* • Zilucoplan* • IVIg • PLEX	• Anticipated NICE will approve efgartigimod and zilucoplan for refractory gMG • IVIg/PLEX are current SoC in patients who are refractory to treatment	• Separate modelling of IVIg and PLEX does not reflect usage in practice • Prefer to model overall 'basket' of care (see next)

* Subject to NICE evaluation **Appraisal terminated

- Evaluation of zilucoplan (ID4008) concluded that efgartigimod (ID4003) was not a relevant comparator because the evaluation is ongoing and so not considered established NHS practice
- To be considered as comparators, treatments must be established practice in the NHS

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

Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; ISTs, immunosuppressive therapies; CSs, corticosteroids; 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/NSISTs from rozanolixizumab and SoC arms
- Pairwise comparisons with IVIg, PLEX, efgartigimod, zilucoplan
- Rozanolixizumab intended to mainly displace IVIg or PLEX in clinical practice, so these are the most relevant comparators

EAG

- Rozanolixizumab, IVIg, and PLEX used as an add-on to steroids and NSISTs
- Clinical opinion to EAG: both IVIg and PLEX used in people with refractory gMG as part of SoC
- Prefers to model a blended comparator of SoC treatments with distribution sourced from EAMS (as for ID4003 & ID4008)
- Efgartigimod EAMS (n=48), patients starting efgartigimod:
  - 43.8% chronic IVIg (plus steroids and NSISTs)
  - 14.6% chronic PLEX (plus steroids and NSISTs)
  - 41.6% steroids and NSISTs only

- EAG considers EAMS cohort comparable with likely cohort who would have rozanolixizumab in the NHS:

Efgartigimod (ID4003) 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

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- Are people in efgartigimod EAMS similar to those who would have rozanolixizumab in the NHS?
- Which comparator(s) does (do) the committee consider appropriate?

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Clinical evidence – trial summary

	MycarinG/MG0003 (completed)	**MG0007** (completed)
Design	Randomised, double-blind, placebo-controlled Phase III	Open label extension (OLE), randomised observational study
Intervention(s)	6 once-weekly SC doses of rozanolixizumab (either ~7 mg/kg or ~10 mg/kg dose)	6 once-weekly SC doses of rozanolixizumab (repeated as needed), dose switching allowed
Population	Inclusion criteria: • gMG (MGFA Class II–IVa) (see appendix) • Positive serology for AChR or MuSK autoantibodies • MG-ADL score of at least 3 (see appendix) • QMG score of at least 11 (see appendix) • Considered for additional treatment (eg IVIg or PLEX)	• Participants who have entered or completed the observation period of MycarinG or • Required (but did not receive) rescue therapy (except IVIg or PLEX) during the observation period of MycarinG or • Completed at least 6 visits in MG0004 (discontinued)
Comparator	• Placebo + SoC	N/A
Subgroups	• Refractory subgroup (post hoc) defined as uncontrolled disease despite SoC, i.e. ≥2 prior MG therapies • Stratified based on receptor (AChR+/MuSK+)	• None for refractory subgroup; • Stratified based on receptor (AChR+/MuSK+)
Duration	• 6-week treatment period followed by 8-week observation period	Results reported for up to [redacted] treatment cycles
Outcomes	• Change from Baseline to Day 43 in MG-ADL score (*primary, used in economic model)* • Response rates for MG-ADL (*secondary, used in economic model*)	• Primary outcome: occurrence of TEAEs and TEAEs leading to withdrawal of rozanolixizumab; secondary outcome: MG-ADL response to day 43 within 1 treatment cycle (*used in economic model*)
Locations	Multiple sites: North America, Europe and East Asia	Multiple sites: North America, Europe and East Asia

Clinical evidence – baseline characteristics

MycarinG/MG0003 (n=200)	Placebo (n=67)	Rozanolixizumab ~ 7 mg/kg (n=66)	~~Refractory subgroup~~ ~7 mg/kg (n=[redacted])
Age (years), mean (SD)	50.4 (17.7)	53.2 (14.7)	53.8 (14.1)
Female	47 (70.1)	39 (59.1)	19 (67.9)
White	46 (68.7)	41 (62.1)	15 (53.6)
BMI, mean (SD)	28.03 (6.19)	27.38 (6.86)	[redacted]
MGFA class at screening, n (%)			
Class II	23 (34.3)	29 (43.9)	[redacted]
Class III	41 (61.2)	34 (51.5))	
Class IV	3 (4.5)	3 (4.5)	
Duration of disease, years	9.418 (9.348)	6.877 (6.799)	[redacted]
Prior thymectomy, n (%)	31 (46.3)	32 (48.5)	[redacted]
Prior myasthenic crisis, n (%)	23 (34.3)	19 (28.8)	[redacted]
MG-ADL, mean (SD)	8.4 (3.4)	8.4 (3.8)	[redacted]
QMG, mean (SD)	15.8 (3.5)	15.4 (3.7)	[redacted]
AChR+, n (%)	53 (79.1)	56 (84.8)	[redacted]
MuSK+, n (%)	8 (11.9)	4 (6.1)	[redacted]
≥2 prior gMG specific therapies	[redacted]	[redacted]	[redacted]
Prior systemic corticosteroids	38 (56.7)	43 (65.2)	[redacted]
ISTs	33 (49.3)	32 (48.5)	[redacted]
AChEIs	60 (89.6)	55 (83.3)	[redacted]

EAG:
Clinical advice suggests patient characteristics in company's model, based on whole MycarinG trial population, are broadly reflective of people with refractory disease who would have rozanolixizumab in England.

- Are the whole trial population efficacy results likely to be applicable to people with refractory gMG in the NHS?

Primary outcome: MG-ADL score change from baseline

MycarinG trial (baseline to day 43)	Rozanolixizumab ~7 mg/kg (RS N=66; refractory N=[redacted])	Placebo (RS N=67; refractory N=[redacted])	Difference
Randomised set LS mean (SE)	(n=65) -3.370 (0.486)	(n=62) -0.784 (0.488)	LS mean (95% CI) -2.59 (-4.09 to -1.25) p=<0.001
Refractory subgroup [a] Mean [SD]	[redacted]	[redacted]	LS mean (97.5% CI) [redacted]

[a] post-hoc analysis; refractory defined as ≥2 prior treatments (not including AChEis)
RS: randomised set; CI: confidence interval; LS: least squares; SD: standard deviation; SE: standard error

MG0007: up to [redacted] cycles of treatment

- Consistent and clinically meaningful reduction in MG-ADL score (≥2.0) in both arms
- People having ~7 mg/kg dose had mean reduction in MG-ADL between [redacted] points across
- **EAG:** MG-ADL change from baseline from cycle [redacted] of MG0007 contributes to the economic model. This cycle showed [redacted] in MG-ADL total score compared to the other cycles, but it had the smallest sample size of all the cycles (n=[redacted]) with [redacted] participants missing. This is the treatment cycle with the least robust data from a trial at high risk of bias, so should be interpreted with caution.

Secondary outcome: % of MG-ADL response (≥2 points from baseline)

MycarinG (MG0003, baseline to day 43)	Rozanolixizumab ~7 mg/kg (RS N=66; refractory N=[redacted])	Placebo (RS N=67; refractory N=[redacted])	Difference*
Randomised set Responders, n (%)	45/66 (68.2)	19/67 (28.4)	OR (95% CI): 5.77 (2.10 to 14.88); p<0.001
Refractory subgroup Responders, n (%)	[redacted]	[redacted]	[redacted]

*** EAG:** confidence intervals wide for both refractory subgroup and randomised set, but both results statistically significant.

MG0007: at [redacted] cycles of treatment

- Proportion of MG-ADL responders consistent in both rozanolixizumab arms for up to [redacted] cycles
- People having ~7 mg/kg dose had a responder rate of [redacted], [redacted], [redacted] and [redacted] for each of the [redacted] cycles consecutively
- **EAG**: results from MG0007 show [redacted] response compared to MycarinG, but are subject to uncertainty due to high risk of bias in the study design and from dose-switching

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

Background

- Company positioned rozanolixizumab for refractory patients (see slide 8)
- MycarinG refractory subgroup ([redacted], [redacted]) smaller than whole population (n=200)

EAG

- EAG's clinical experts suggested that overall randomised population of the MycarinG trial could be broadly reflective of refractory generalised myasthenia gravis patients in England
- MycarinG eligibility criteria include the participant either having or being considered for IVIg or PLEX, meaning that the overall trial population is likely to reflect a refractory population
- Whole population and refractory subgroup in the trial generally experienced [redacted] treatment effects.

- Does the committee consider the results for the whole trial population in MycarinG applicable to people with refractory gMG in the NHS?

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

Subgroups: People with AChR+ and MuSK+ gMG

MycarinG (MG0003)	Rozanolixizumab ~7 mg/kg (AChR+ [redacted]; MuSK+ [redacted])	Placebo (AChR+ [redacted]; MuSK+ [redacted])	Difference
Primary outcome: MG-ADL score change from baseline at Day 43			
Randomised set LS mean (SE)	(n=65) -3.370 (0.486)	(n=62) -0.784 (0.488)	LS mean (95% CI); p-value -2.59 (-4.09 to -1.25) p<0.001
AChR Ab+ Mean (SD) LS mean (SE)	[redacted] (n=NR) -3.03 (0.89)	[redacted] (n=NR) -1.10 (0.87)	LS mean (97.5% CI) Not tested -1.94 (-3.06 to -0.81)
MuSK Ab+ Mean (SD) LS mean (SE)	[redacted] (n=NR) -7.28 (1.94)	[redacted] (n=NR) 2.28 (1.95)	LS mean (97.5% CI) Not tested -9.56 (-15.25 to -3.87)

AChR Ab+: acetylcholine receptor antibody-positive; CI: confidence interval; MuSK Ab+: muscle-specific kinase antibody-positive; OR: odds ratio; RS: randomised set; SD: standard deviation; SE: standard error.

EAG:

- There was a [redacted] difference in MG-ADL in the MusK+ stratum than in the AChR+ stratum, but the confidence intervals are very wide, reflecting the small numbers

NICE

- Is the efficacy of rozanolixizumab versus placebo likely to be similar across MuSK+ and AChR+ patients?

Subgroups: People with AChR+ and MuSK+ gMG, primary outcome: change in MG-ADL from baseline

MG0007 trial:

- Results generally consistent with those of overall study population
- No evidence for worsening efficacy in MuSK+ compared with overall study population for cycles [redacted]. Explanation for this is unclear
- MuSK+ antibody-positive subgroup has a very small number of participants, it is not clear which dose arm is reported, and this trial is at high risk of bias, so results should be interpreted with caution

- What is the committee's view on rozanolixizumab's treatment effect compared with placebo?
- Is the timing of response assessment likely to have an impact on the treatment effect estimate?
- Does committee consider it appropriate to apply observed treatment effect for the whole MycarinG population to the MuSK + subgroup?

Abbreviations: AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase; MG-ADL, MG-ADL, Myasthenia Gravis-Activities of Daily Living; generalised myasthenia gravis

Key issue: Uncertain relevance of overall trial populations to people who are AChR and MuSK antibody-positive

Background

- MycarinG primarily included patients who were AChR antibody-positive, with only a minority of MuSK + patients (placebo n=8, 11.9% and rozanolixizumab ~7 mg/kg n=5, 7.6%)

EAG

- Uncertainty in response outcome for MuSK + patients because very small subgroup
- Overall trial population approximates the relative proportions of MuSK+ and AChR+ people in NHS
- AChR+ subgroup likely to characterise clinical efficacy for most people seen in NHS, but excludes MuSK+
- Comparator trials vary in whether they include AChR+ overall trial population or AChR+ subgroup
- Comparator trials do not permit any comparisons specifically for MuSK+
- Indirect treatment comparisons (NMA/MAIC) restricted to the AChR+ subgroup of refractory patients in the MycarinG and RAISE trials could reduce uncertainty in results for AChR+ subgroup for comparison of rozanolixizumab against zilucoplan, but company did not provide

- Is the overall MycarinG trial population or the AChR+ subgroup most appropriate for decision making?

Abbreviations: gMG, generalised myasthenia gravis; NMA, network meta-analysis; AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase; MAIC, matching-adjusted indirect comparison

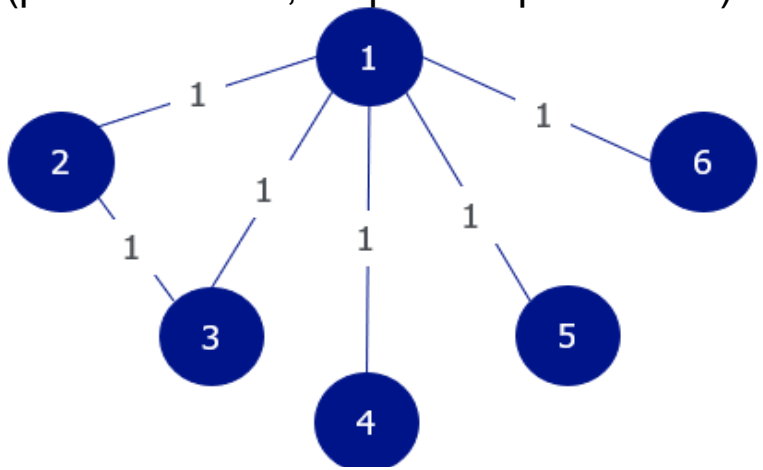
Network meta-analysis and MAIC

EAG: NMAs done on overall populations, do not consider the refractory, AChR+ or MuSK+ subgroups

Rozanolixiz-umab	ITC method	Outcomes: MG-ADL response & MG-ADL score CFB	EAG comments
vs efgartigimod	Fixed-effect NMA/ Anchored MAIC	Yes	Anchored MAIC not informative*
vs zilucoplan	Fixed-effect NMA	Yes	Company did not provide MAIC analysis
vs IVIg	Un-anchored MAIC	No, QMG response & QMG CFB	Agree anchored MAICs not feasible**
vs PLEX	-	-	-

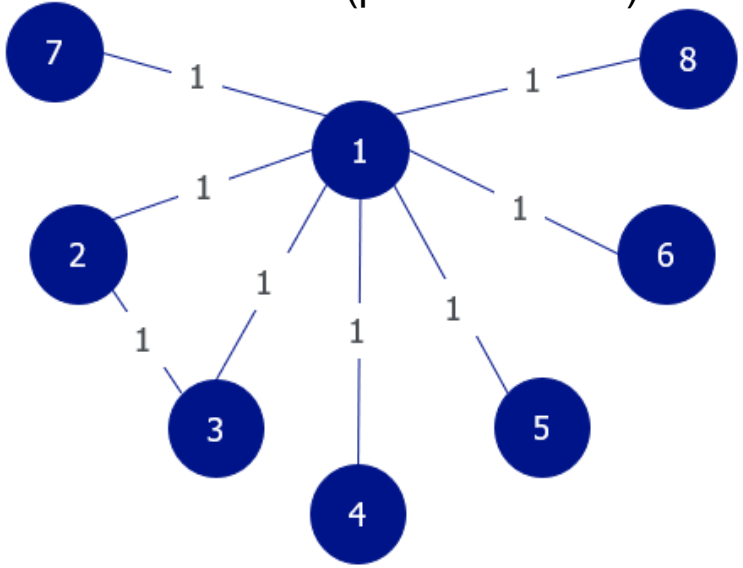
1	Placebo
2	Rozanolixizumab 7 mg
3	Rozanolixizumab 10 mg
4	Zilucoplan
5	Efgartigimod
6	Ravulizumab

MG-ADL response evidence network - (phase III trials; ≥2 point improvement):



Change from baseline in MG-ADL score evidence network (phase III trials):

1	Placebo
2	Rozanolixizumab 7 mg
3	Rozanolixizumab 10 mg
4	Zilucoplan
5	Efgartigimod
6	Ravulizumab
7	Rituximab
8	Eculizumab



* Results not used in model;

** Company did not investigate whether any single-arm studies could be included in unanchored MAIC to enable comparisons against IVIg or PLEX for the MG-ADL outcomes

NMA & MAIC results: MG-ADL response:

NMAs conducted to compare rozanolixizumab against comparators

NMA comparison	Odds ratio (95% CrI) for MG-ADL response rate	
	Response (≥2 point improvement)	Response (≥3 point improvement)
Rozanolixizumab vs efgartigimod [a]	[redacted]	[redacted]
Rozanolixizumab vs zilucoplan [a]	[redacted]	[redacted]
Rozanolixizumab vs placebo [b]	[redacted]	[redacted]
Zilucoplan vs placebo [b]	[redacted]	[redacted]
Efgartigimod vs placebo [b]	[redacted]	[redacted]
Rozanolixizumab vs IVIg/PLEX	No NMAs for IVIg/PLEX	No NMAs for IVIg/PLEX

[a] Not used in company's economic model. Efgartigimod & zilucoplan not currently recommended
[b] Used in company's economic model, response defined as a ≥2 point* improvement in the MG-ADL score.

Anchored MAIC results for rozanolixizumab vs efgartigimod (week 4 assessment)

- Odds ratio (95% CrI) for the rate of responders (≥2 point improvement in the MG-ADL score): [redacted] ([redacted] to [redacted]). This odds ratio is larger than that obtained from the NMA (above). The NMA nor MAIC results are [redacted] significant at the conventional level.

* In ID4008 (zilucoplan) response defined as **≥3 point** improvement in the MG-ADL score

NICE

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

NMA & MAIC results - MG-ADL change from baseline

NMAs conducted to compare rozanolixizumab against comparators

NMA comparison	MG-ADL change from baseline[a],mean difference between treatments (95% CrI)
Rozanolixizumab vs efgartigimod	[redacted]
Rozanolixizumab vs zilucoplan	[redacted]
Rozanolixizumab vs placebo	[redacted]
Zilucoplan vs placebo	[redacted]
Efgartigimod vs placebo	[redacted]
Rozanolixizumab vs IVIg/PLEX	No NMAs provided for IVIg/PLEX

CrI, credible interval.
[a] Change from baseline to the primary assessment timepoint of the study.

Anchored MAIC results for rozanolixizumab vs efgartigimod (week 4 assessment)

- Mean (95% CrI) treatment difference in the change from baseline in MG-ADL score was [redacted] to [redacted]), but the result is [redacted] significant.

- What is the committee's view on the NMAs and MAICs conducted? Are they informative for decision making? Would the committee like to see any additional analyses?

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

Clinical efficacy summary

EAG:

- Rozanolixizumab at the licensed ~7 mg/kg dose is effective versus placebo in both a statistically significant and clinically meaningful way
  - MuSK+ subgroup in MycarinG had a [redacted] response than the whole trial population for all outcomes. But very small sample size make these results uncertain

- NMAs or MAIC scenario analyses limited to AChR+ could more accurately characterise the relative effectiveness of rozanolixizumab in this population, but company did not conduct these

- MG0007 extension study is at high risk of bias because there is no placebo arm, it is open-label, and there is confounding caused by dose-switching, therefore results uncertain
  - This uncertainty carries into economic model because MG0007 informs continued response outcome

- NMAs: subject to several key uncertainties: do not account for between-trial heterogeneity in baseline characteristics or placebo responses
  - Only MAIC comparison relevant to economic model shows no statistically significant difference in odds of MG-ADL response for treatment with rozanolixizumab compared to efgartigimod
  - MAIC analysis does not adjust for the placebo effect and has other uncertainties

Abbreviations: MG-ADL, Myasthenia Gravis-Activities of Daily Living; NMA, network meta-analysis; PLEX, plasma exchange; MAIC, matching-adjusted indirect comparison; AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase

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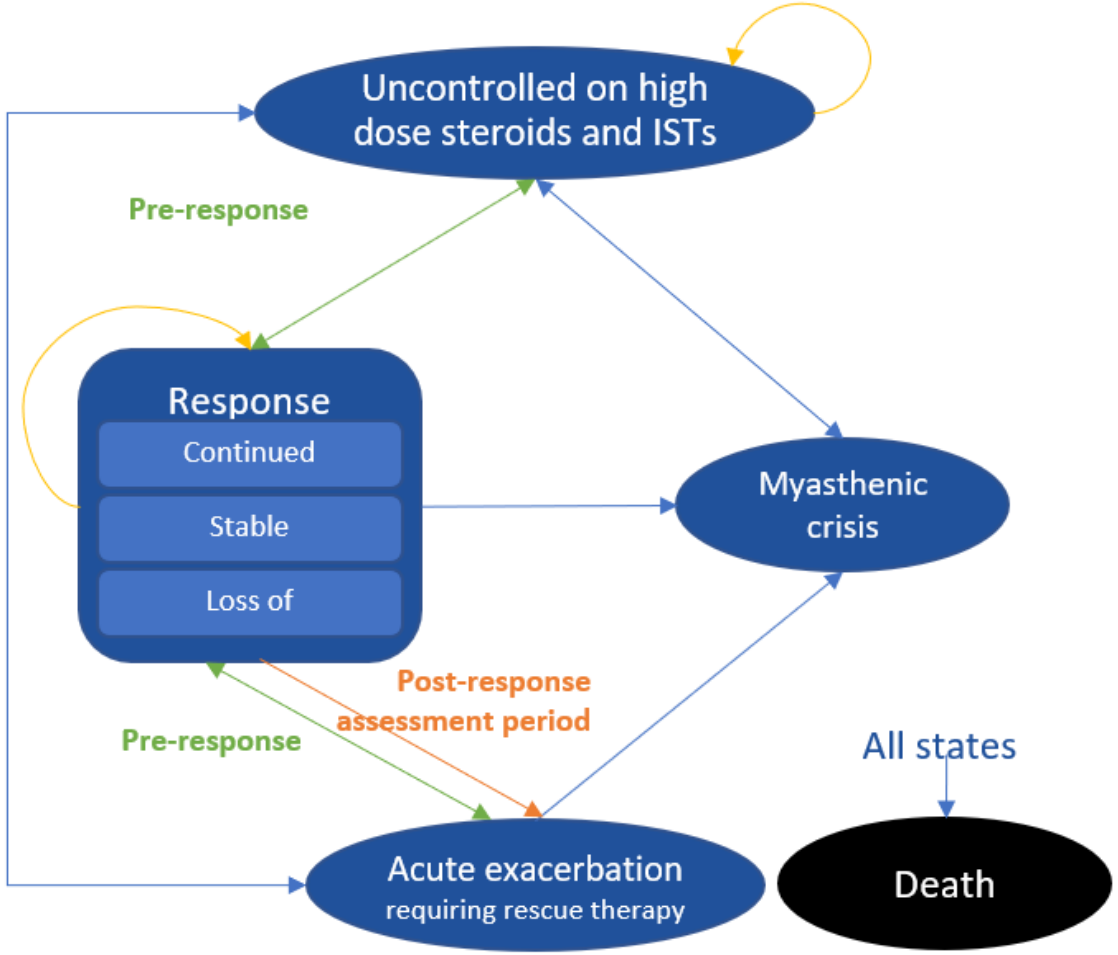
Company's model overview

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 ≥2 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
- 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; however, it does not account for subsequent treatments

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	Full trial population of MycarinG	Same but conducted scenario analysis for AChR+ and MuSK+ subgroups
Comparators	4 separate comparators, without steroids/NSISTs: • Efgartigimod, • Zilucoplan, • IVIg, • PLEX	Blended SoC comparator, using % from efgartigimod 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	• Response rate of 70% for IVIg and PLEX, based on advice to EAG from clinical experts • Trial arm response rates for rozanolixizumab, efgartigimod and zilucoplan
Response assessment timepoint	• Rozanolixizumab: MycarinG • Zilucoplan: RAISE • Efgartigimod: ADAPT • IVIg/PLEX: assumption	• Response assessment timepoint of 6 weeks for all treatments
Resource use	• IVIg costs applied every 3 weeks • PLEX costs applied every 4 weeks	• IVIg and PLEX costs applied every 6 weeks • Correcting PLEX admin cost and removing zilucoplan administration costs after cycle 2

Abbreviations: EAMS, early access to medicines scheme; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange; SoC, standard of care; ; AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase

Treatment response rates in relation to placebo effect and timepoints

Company

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

EAG

- Uncertainty with NMA, MAIC (slide 21) and Barth et al. study
- Referent response rate implausible
- Clinical advice: IVIg/PLEX response too low, assessment time of 6 weeks
- Used unadjusted response rates from the trial arms for rozanolixizumab, zilucoplan and efgartigimod, and clinical opinion for IVIg/PLEX

Company's response rate inputs:

Treatment	Response rate	Source	Response assessment time point (weeks)	Source
Rozanolixizumab	[redacted]	NMA	6	MycarinG
Zilucoplan	[redacted]	NMA	12	RAISE
Efgartigimod	[redacted]	NMA	10	ADAPT
IVIg	51.01%	Barth 2011	6	Assumption
PLEX	57.01%			

EAG's response rate inputs:

Treatment	Response rate	Source	Response assessment time point (weeks)	Source
Rozanolixizumab	72%	MycarinG	6	MycarinG
Zilucoplan	73%	RAISE	6	Clinical advice
Efgartigimod	68%	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 rarely up to 16 weeks
  - ↳ PLEX usually administered every 4 to 8 weeks
- Based on clinical opinion, IVIg and PLEX cost every 6 weeks
- Use NHS reference cost SA44A – Single Plasma Exchange (£910), applied every 6 weeks, for PLEX administration cost

Committee conclusion from ID4008 (zilucoplan):

- IVIg and PLEX costs should be applied every 4 weeks and use the NHS reference cost for PLEX

Which assumptions around resource use for IVIg and PLEX best reflect NHS practice?

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

Key issue: subsequent treatments

Background

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

EAG

- Patients stopping rozanolixizumab, zilucoplan, or efgartigimod may be eligible for chronic IVIg or PLEX
- Applying subsequent treatment costs within economic model likely to impact overall cost-effectiveness
- Further clinical advice regarding potential subsequent treatments is required
- Economic model could include discontinuation engines for each comparator

- After stopping rozanolixizumab, 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 and EAG's exploratory analysis

Company reported base case results for the pairwise comparison, EAG conducted scenarios applied to the company base case

No	Scenario (applied to company base case)
	Company revised base case (SoC only, excluding IVIg and PLEX)
1	+ Use ECM as the comparator: 43.8% of patients receive IVIg; 14.6% of patients receive PLEX; 41.6% of patients receive neither, all patients receive the cheaper standard therapies and include SoC costs
2	+ Using 70% response rates for IVIg and PLEX (giving a 40.88% response rate in the ECM arm) and trial response rates for rozanolixizumab (72%), zilucoplan (73%) and efgartigimod (68%)
3	+ Using a response assessment time point of 6 weeks for all treatments
4	+ Correcting the PLEX administration cost and removing zilucoplan administration costs after cycle 2
5	+ Applying chronic IVIg treatment and administration costs every 6 weeks
6	+ Applying chronic PLEX treatment and administration every 6 weeks

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; ECM, established clinical management

Rozanolixizumab 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

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
Uncertain relevance of the overall trial populations to patients who are AChR antibody-positive and MuSK antibody-positive	Unknown
Cost-effectiveness issues	
Treatment response rates	High
Response timepoint for all treatments	Low
Resource use for chronic IVIg and PLEX therapy	High
Subsequent treatments	Unknown

Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; AChR, acetylcholine receptor; MuSK, muscle specific tyrosine kinase

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.

Decision problem – population

	Final scope	Decision problem addressed	Rationale if different from the final NICE scope	EAG comments
Population	Adults with antibody-positive gMG	Adults with refractory AChR or MuSK antibody-positive gMG, if: • the disease is classified as MGFA class II-IVa, and • the disease is uncontrolled despite standard treatments, as defined by inadequate response to ≥2 prior MG therapies (after AChEIs), and • an additional therapy such as IVIg or PLEX is being administered or considered	High unmet need for novel targeted treatments with an acceptable safety profile that is effective in patients with gMG who: • are AChR Ab+ or MuSK Ab+, and • have uncontrolled or refractory disease, and • are being treated with or considered for IVIg/PLEX	• Narrower than scope • EAG's clinical experts agree that the company's rationale for focusing on refractory patients is appropriate. • Company's network meta-analyses (NMAs) that compared rozanolixizumab against zilucoplan or efgartigimod were based on whole-trial populations which included both refractory and non-refractory patients

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 and duration of hospitalisations • Adverse effects of treatment • Health-related quality of life	• Improvement in MG (MG-ADL responder rate) • Time to clinically meaningful improvement • Signs and symptoms of disease • Mortality • Adverse effects of treatment • Health-related quality of life	The number and duration of hospitalisations were not captured in the clinical trials	The outcomes are generally appropriate and consistent with the NICE scope

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)

How NMA results were transformed for the model

Treatment response rates were calculated based on the odds ratio output from the NMA (rozanolixizumab vs placebo), applied to a referent response rate. Referent response rate is the simple average of placebo response rates across the studies.

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 used 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])

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 2-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 2-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 2-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 ID4003 (efgartigimod) & ID4008 (zilucoplan)

Assumption /input	Efgartigimod (ID4003)	Zilucoplan (ID4008)	Rozanolixizumab (ID5092)
Company's target population	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"	~~Z~~ilucoplan 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, AND • the disease is uncontrolled, • an additional therapy such as IVIg or PLEX is being considered	rozanolixizumab: • as an add-on to SoC for refractory AChR+ or MuSK+ gMG • Refractory is defined as: ○ disease classified as MGFA class II–IVa ; and ○ uncontrolled after 2 or more prior therapies, and ○ an additional therapy such as IVLg or PLEX is being administered or considered

Comparison with ID4003 (efgartigimod) & ID4008 (zilucoplan)

Assumption /input	Efgartigimod (ID4003)	Zilucoplan (ID4008)	Rozanolixizumab (ID5092)
Population and subgroups in trial	ADAPT: adult patients with generalised Myasthenia Gravis (gMG), 77% were anti-acetylcholine receptor (AChR) antibody positive	RAISE: adult patients generalised myasthenia gravis (gMG), all were AChR antibody positive. • Refractory gMG subgroup: (pre-planned in trial)	MycarinG: adult patients with generalised myasthenia gravis (gMG) who are *AChR+ or MuSK+* • AChR (majority) and MuSK subgroup (minority, 13 patients, pre-specified) • Refractory gMG subgroup: (post hoc analysis)
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	Same: • Company: comparators modelled separately; • EAG: a blended comparator as in ID4003 and ID4008
Follow up	26 weeks	12 weeks	6 weeks

Comparison with ID4003 (efgartigimod) & ID4008 (zilucoplan)

Assumption /input	Efgartigimod (ID4003)	Zilucoplan (ID4008)	Rozanolixizumab (ID5092)
Key assumptions in model			
NMAs and MAICs	N/A	Committee would have preferred company to try different methods to obtain estimates of relative differences in those studies so that IVIg and PLEX could be included in NMA. Additional analyses for comparative effectiveness compared with zilucoplan requested	NMAs for comparisons of rozanolixizumab against efgartigimod and zilucoplan (MG-ADL response & MG-ADL change from baseline) No NMA provided for IVIg or PLEX. MAICs for comparison of rozanolixizumab against efgartigimod (anchored) and IVIg (unanchored)
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, limitations noted	State transition model, 7 health states including death; health states defined by response status (stable, lose response, continued response)	Same as ID4008

Comparison with ID4003 (efgartigimod) & ID4008 (zilucoplan)

Assumption /input	Efgartigimod (ID4003)	Zilucoplan (ID4008)	Rozanolixizumab (ID5092)
Key assumptions in model			
Placebo effect/ response rate in relation to placebo effect	• Benefit observed in placebo arm should be maintained over time-horizon of model	Committee: • Limitations in company's approach of estimating specific response rates from the uncertain NMA • EAG's approach not adjusted for placebo response observed in trials; • Prefer response rates based on clinical data rather than expert opinion • Conclusion: accurate estimates of treatment response for any treatments not presented, requested more analysis to clarify	Company and EAG's approaches same as ID4008; • Company: response rates based on NMAs and Barth et al. study; • EAG: response rate from trial arms and clinical opinions for IVIg/PLEX. • Neither company nor EAG's approach fully address uncertainties relating to placebo effect

Comparison with ID4003 (efgartigimod) & ID4008 (zilocoplan)

Assumption /input	Efgartigimod (ID4003)	Zilucoplan (ID4008)	Rozanolixizumab (ID5092)
Key assumptions in model			
Carer's QoL	• Consider carer's QoL qualitatively	Model did not apply disutilities for adverse events or caregiver burden Committee: several uncaptured benefits associated with zilucoplan and asked the company to provide scenarios that consider these	Company's model does not capture disutilities for caregivers EAG: considered it appropriate to not include caregiver's disutilities in the model
Resource use	N/A	Committee: IVIg and PLEX costs should be applied every 4 weeks and use the NHS reference cost for PLEX	Company: apply costs for IVIg every 3 weeks and costs for PLEX every 4 weeks EAG: IVIg and PLEX cost every 6 weeks, based on clinical expert opinion, use NHS reference cost for PLEX

Comparison with ID4003 (efgartigimod) & ID4008 (zilucoplan)

Assumption /input	Efgartigimod (ID4003)	Zilucoplan (ID4008)	Rozanolixizumab (ID5092)
Key assumptions in model			
Subsequent treatment	• As of ACM3, an issue being discussed; committee concluded that model should include subsequent post treatments being appraised, in particular IVIg	Committee: • Noted gMG required lifelong treatment, clinicians would consider IVIg or PLEX after zicucoplan stopping; • Conclusion: would like to see subsequent treatments accounted for in model	Company: Assumes that patients in 'Uncontrolled on high dose steroids and ISTs' health state stop receiving treatment due to lack of efficacy EAG: Questions company assumption. Refractory gMG is a condition that requires lifelong management, so subsequent treatments should be accounted for in model
Treatment effect after stopping treatment	Limited evidence, committee noted that modelling residual treatment effect after stopping efgartigimod highly uncertain	Not identified as an issue or directly addressed by company or EAG	Not identified as an issue or directly addressed by company or EAG

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.

Network meta-analysis and MAIC

Background

- **Company**: reported fixed-effect NMAs comparing rozanolixizumab with efgartigimod and zilucoplan for the outcomes of MG-ADL response and MG-ADL score change from baseline;
- No NMA conducted for IVIg or PLEX given lack of placebo-controlled trials with relevant outcomes

- **EAG**: requested exploring alternative ITC analysis methods such as MAICs to account for the heterogeneity of trial baseline characteristics

- **Company**: provided anchored MAIC comparing rozanolixizumab against efgartigimod for change in MG-ADL from baseline and MG-ADL response, but results not used in model; also provided unanchored MAIC comparing rozanolixizumab against IVIg for QMG outcome, results did not inform model;
- did not conduct a MAIC comparing rozanolixizumab against zilucoplan

EAG

- Agree not feasible to conduct anchored MAICs for comparisons of rozanolixizumab against IVIg, given lack of placebo-controlled trials
- Unanchored MAIC of rozanolixizumab against IVIg not informative because comparator trial did not report MG-ADL response or change from baseline (2 key clinical efficacy parameters that inform model)
- Company did not investigate whether any single-arm studies could be included in unanchored MAIC to enable comparisons against IVIg or PLEX for the MG-ADL outcomes
- NMA and MAIC analyses done on overall trial populations and do not consider the refractory, AChR+ or MuSK+ subgroups

Key issue: Response rates in relation to placebo effect

Company

- Odds ratios for MG-ADL response rates from NMAs to inform transition probabilities from uncontrolled to response health states
- NMAs do not account for heterogeneity of placebo response rates, which were 31% and 30% respectively in trials of rozanolixizumab and efgartigimod and, [redacted]% for zilucoplan
- To account for placebo effect heterogeneity, company applied a calculation to the odds ratios from the NMAs that compared rozanolixizumab against efgartigimod and zilucoplan. The calculation assumes a common overall 'referent' placebo response rate of [redacted]%.
- No NMAs for the MG-ADL response outcome, so response rates for IVIg/PLEX derived from trial by Barth et al.: 51% and 57%, respectively (calculated from a different response outcome: QMG, not MG-ADL)

EAG

- Company 'referent' response rate of [redacted]% inappropriately high relative to range of placebo responses observed
- Company do not explain rationale for this calculation (converting odds ratios to relative risks then multiplying them by the referent placebo response rate)
- Company do not discuss how this calculation models the placebo effect or justify their assumptions
- Response rate estimates when calculation applied in economic model are inconsistent with expected values
- EAG clinical experts provided estimates of response rates to IVIg and PLEX based on their clinical experience, agreeing that about 70% of patients respond to IVIg treatment and about 70% respond to PLEX treatment.
- EAG prefers to use the response rates for rozanolixizumab, efgartigimod and zilucoplan based on results from the MycarinG, ADAPT and RAISE trials, 72%, 68% and 73% respectively
- Neither company's nor EAG's approaches fully address all uncertainties relating to placebo effect

Key issues: Treatment response rate timepoints

Company

- The treatment response assessment timepoints used in model are those for primary outcome assessment in the clinical trials for rozanolixizumab, efgartigimod and zilucoplan; and are assumptions for IVIg and PLEX

EAG

- Economic model does not consider comparative evidence directly but via placebo through referent response rate, which is an average placebo response.
- Because of limitations of outputs from indirect comparisons, EAG prefer to use response rates for rozanolixizumab, zilucoplan and efgartigimod from the MycarinG, RAISE and ADAPT trials respectively
- Clinical experts noted that treatment effects are observed and maintained much earlier, after 1-2 weeks

Treatment	Odds ratio	Company preferred response rate	EAG preferred response rate	Company preferred assessment time point (weeks)	EAG preferred assessment time point (weeks)
Rozanolixizumab	[redacted]	[redacted]	72%	6	6
Zilucoplan	[redacted]	[redacted]	73%	12	6
Efgartigimod	[redacted]	[redacted]	68%	10	6
IVIg/SCIg	1.04	51.01%	70%	6	6
PLEX	1.33	57.01%	70%	6	6

NICE Which are the committee's preferred response assessment timepoints for use in the model?

Subgroups: People with severe gMG

MycarinG (MG0003)	Rozanolixizumab ~7 mg/kg (RS N=66)	Placebo (RS N=67)	Difference
Randomised set LS mean (SE)	(n=65) -3.370 (0.486)	(n=62) -0.784 (0.488)	LS mean (95% CI) -2.586 (-4.091 to -1.249) p=<0.001
Baseline MG-ADL score ≥5 Mean (SD)	[redacted]	[redacted]	Not tested
CI: confidence interval; LS: least squares; RS: randomised set; SD: standard deviation; SE: standard error.			

EAG:

- MG-ADL score change from baseline is reported for a pre-specified subgroup of participants with baseline MG-ADL ≥5
- EAG's clinical experts suggest this subgroup reflects those with moderate to severe gMG
- Rozanolixizumab ~7 mg/kg was [redacted] in the more severe MG group (i.e. MG-ADL ≥5) compared to the overall trial population
- In MG0007, improvements in MG-ADL score generally consistent with results in the randomised set for all subgroups, but no results reported for subgroup with MG-ADL score ≥5