Rozanolixizumab for treating antibody-positive generalised myasthenia gravis ID5092

For meeting – redacted

Technology appraisal committee B, 5 November 2025

Chair: Charles Crawley

External assessment group: Southampton Health Technology Assessments Centre (SHTAC)

Technical team: Emilene Coventry, Catherine Spanswick, Caron Jones, Emily Crowe

Company: UCB

Rozanolixizumab for treating antibody-positive generalised myasthenia gravis

- ✓ **Recap from first appraisal committee meeting**
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ❑ Other considerations
- ❑ Summary

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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: ~7 mg/kg • Date of MHRA approval: 7 March 2024
Administration	• Subcutaneous infusion once-weekly for 6 weeks (1 treatment cycle*), based on weight
Price	• List price: £31.93 per mg • Average cost of £107,285 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; MuSK, muscle specific tyrosine kinase; MHRA, Medicines & Healthcare products Regulatory Agency

Recommendation and key conclusions from ACM1 (1/2)

Recommendation: Rozanolixizumab is not recommended as an add-on to standard treatment for MuSK-Ab+ or AChR-Ab+ generalised myasthenia gravis

Issue	ACM1 preferred assumption/analysis	Company's response
Comparators	• 'Basket' of standard care consistent with NICE scope (IVIg, PLEX, neither) with corticosteroids and immunosuppressants for all, more reflective of NHS practice • Proportion of people having each treatment could be taken from the efgartigimod EAMS cohort dataset	Disagreed; pair-wise comparison with IVIg and PLEX
Rituximab	Uncertainties about where rituximab is used in the treatment pathway, particularly in relation to those with MuSK antibody-positive gMG; committee concluded more information needed	Survey carried out; not included in base case as comparator or subsequent treatment
Relative effectiveness	Improved indirect treatment comparison that: • includes IVIg and PLEX • uses outcomes other than MG-ADL response rate to produce estimates of relative effectiveness • accounts and adjusts for the differential placebo response observed in the trials or adjusts for baseline risks with an informative prior • maintains randomisation	• Updated systematic literature review • Bivariate network meta-analysis • Baseline risk-adjusted network meta-analysis

Abbreviations: ACM, appraisal committee meeting; EAMS, Early Access to Medicines Scheme; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; PLEX, plasma exchange

Recommendation and key conclusions from ACM1 (2/2)

Issue	ACM1 preferred assumption/analysis	Company's response
Long-term treatment effect	• MG0007 designed to evaluate multiple 6-weekly cycles of rozanolixizumab • Committee concluded MG0007 provided some supporting evidence for rozanolixizumab's effectiveness	Provided final results
Subsequent treatment	• Company model did not include IVIg, PLEX or rituximab as subsequent treatments – only corticosteroids and immunosuppressants • Clinical experts would consider using IVIg or PLEX once rozanolixizumab stopped • Committee concluded it would like to see subsequent treatments modelled more appropriately in the economic model	Subsequent treatment modelled as mix of IVIg, PLEX, and standard care with corticosteroids and NSIST
Response assessment timepoint	3 weeks for IVIg and PLEX, 6 weeks for rozanolixizumab	Agreed – updated model but use 12 weeks for standard basket
Costs	Costs of IVIg and PLEX applied every 4 weeks, using NHS reference cost for PLEX administration	Agreed – updated model
Uncaptured benefits	• Committee concluded there may be uncaptured benefits of rozanolixizumab that may affect the utility of people who have it • Asked company to present scenario analyses to incorporate some of these into modelling	Updated base case to include corticosteroid sparing; scenarios for carer and societal costs

Abbreviations: ACM, appraisal committee meeting; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; NSIST, non-steroidal immunosuppressant treatment; PLEX, plasma exchange

Remaining issues for decision making

Issue	ICER impact
Comparators	Large
Indirect treatment comparison	Small
Long-term treatment effect	Unknown
Use of MSE in the model	Unknown
Subsequent treatments	Large

Abbreviations: ICER, incremental cost-effectiveness ratio; MSE, minimum symptom expression

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Consultation comments

- **Also considered in slides on Equality considerations and Uncaptured benefits of rozanolixizumab**

Myaware & Muscular Dystrophy UK (joint submission) and **ABN Neuromuscular Advisory Group**

- **Unmet need** not being recognised. Living with MG is life changing and brings tremendous burden on patients and their families. People are surviving, not thriving
- Treated with blanket approaches, rather than **targeted therapy**, for a long time
- **Few options** for people with MG uncontrolled, or unable to be treated with, current therapies. ABN asks NICE to consider this subgroup, if rozanolixizumab is not cost effective in whole population
- **Careful approach to implementation** would ensure rozanolixizumab used only when likely to have greatest benefit. Commissioners could ask for suitability to be discussed in regional MDT → only 50% of patients discussed would need escalation of treatment, others need improvement of their diagnosis, optimisation of their comorbidities, and better use of standard therapy

Abbreviations: ABN, Association of British Neurologists; IVIg, intravenous immunoglobulin; MDT, multidisciplinary team; MG, myasthenia gravis; PLEX, plasma exchange

Equality considerations

Summary of issues raised at scoping, ACM1 and through DG consultation

Potential equality issue raised		Related considerations
Sex, pregnancy and family	• gMG more prevalent in women than men, women typically younger at disease onset and have higher mortality • Pregnancy may contraindicate some types of treatment (rozanolixizumab SPC: should only be considered if clinical benefit outweighs the risks) • gMG affects decision to have a family	• Differences in prevalence of a disease cannot normally be addressed in a technology appraisal recommendation • Sex and Pregnancy are protected characteristics under the Equality Act 2010 • Human Rights Act 1998 protects right to start a family (Article 12)
Access to treatment, disability, social and economic factors	• Variation in access to IVIg and PLEX across NHS specialist centres • Important to avoid need to travel far for treatment given level of disability • People who can't afford to travel, or have caring responsibilities disadvantaged	• Access to treatments/specialist centres is an implementation issue that cannot be addressed in a technology appraisal recommendation • Disability is a protected characteristic under the Equality Act 2010 • Committee can consider frequency and method of treatment dosing and associated impact on equalities

ACM, appraisal committee meeting; DG, draft guidance; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SPC, summary of product characteristics

Do these or any other equality issues need to be addressed in the guidance?

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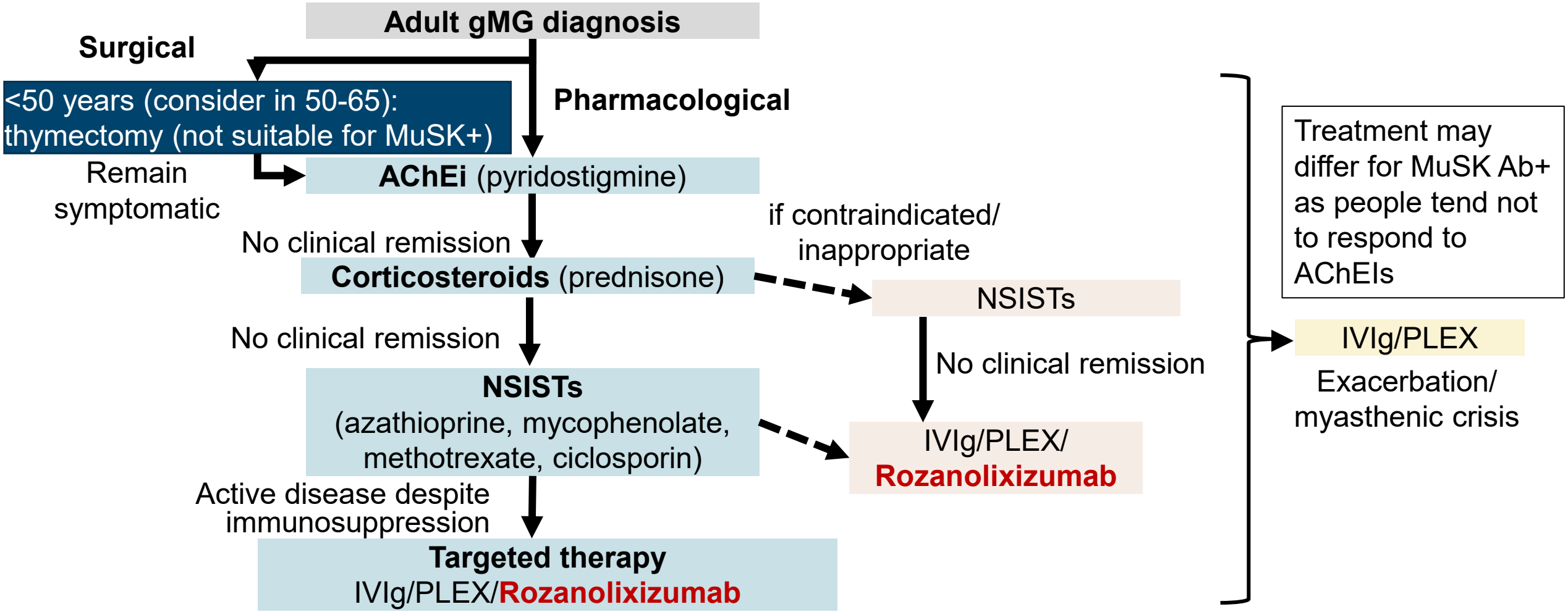
Treatment pathway for generalised myasthenia gravis



Company proposed positioning: Rozanolixizumab as an add-on to standard care (corticosteroids and NSISTs) for refractory AChR+ or MuSK+ gMG

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; SC, standard care

Large impact on ICER

Company response: comparators (1/4)

Company disagrees with basket approach – argues IVIg and PLEX only relevant comparators

ACM1

- IVIg/PLEX/standard care 'basket' consistent with NICE scope, reflects NHS practice more
- Proportion of people having each treatment could be taken from the efgartigimod EAMS cohort dataset

Base case	Preferred comparators
Company ACM1	**Efgartigimod, zilucoplan, IVIg and PLEX** (with corticosteroids and non-steroidal immunosuppressants as background therapy for all treatments)
EAG	**'Basket' of standard care 1) IVIg plus corticosteroids and immunosuppressants 2) PLEX plus corticosteroids and immunosuppressants 3) corticosteroids and immunosuppressants only** in line with efgartigimod EAMS population
Company draft guidance response	**IVIg and PLEX** based on clinical expert opinion, ABN 2025 guidelines, expert elicitation, market data on switches to unapproved targeted therapies, German claims data, information from 30 neuroscience centres (all have access to IVIg, 25 to PLEX) • **People who will never receive IVIg/PLEX:** not target population for rozanolixizumab • **Treatment break:** 2 scenarios modelled for people who may be temporarily off first-line IVIg, PLEX or rozanolixizumab [further company rationale]

Abbreviations: ABN, Association of British Neurologists; ACM, appraisal committee meeting; EAG, external assessment group; EAMS, Early Access to Medicines Scheme; IVIg, intravenous immunoglobulin; PLEX, plasma exchange

Large impact on ICER

Company response: comparators (2/4)

Uncertainty over place of rituximab in treatment pathway

ACM1 Uncertainties about where rituximab is used in the treatment pathway, particularly in relation to MuSK antibody-positive generalised MG; committee concluded more information needed

Company draft guidance response

Rituximab not included in updated base case as a comparator or subsequent treatment; no consensus on use as subsequent treatment in survey of 11 clinical experts from specialist generalised MG centres in the UK

- Rituximab widely used: all experts use it for MuSK-Ab+ generalised MG, and 10 use it for AChR-Ab+ generalised MG; proportion varied across centres
- Typically used before targeted maintenance treatment with IVIg and PLEX where rozanolixizumab is positioned; some would consider rituximab as subsequent treatment but no clear consensus
- Scenarios with rituximab as part of basket comparator and as subsequent treatment

Clinicians who would use rituximab as a second line treatment

First line treatment	AChR Ab+	MuSK Ab+
IVIg	5 of 11	7 of 11
PLEX	5 of 7	6 of 8
FcRn inhibitor	5 of 8	7 of 8

ABN guidelines 2025: Evidence supports early use of rituximab; evidence less robust, but likely to be useful, in established treatment-refractory MG; MuSK-MG often refractory to most conventional MG treatments but highly responsive to rituximab
Consultation comment from MG specialist: Rituximab increasingly used early in treatment pathway, when unable to reduce steroid without relapse; not being used instead of IVIg or PLEX – these are used to keep people out of hospital

Abbreviations: ACM, appraisal committee meeting; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; PLEX, plasma exchange

Large impact on ICER

Company response: comparators (3/4)

Company: EAMS population does not reflect those who would be eligible for rozanolixizumab

Company draft guidance response

- EAMS population includes non-refractory patients and excluded MuSK-positive gMG
- Only 77% (n=37/48) had refractory gMG; 3 had no treatment, 10 on corticosteroids only
- EAG's IVIg and PLEX proportions based on the full cohort, not just refractory patients
- MycarinG trial more representative of real-world refractory gMG patients eligible for rozanolixizumab
- Revised EAMS population (n=37 refractory; 21 IVIg, 7 PLEX, 9 corticosteroids and/or NSISTs only) for scenario with 'basket' comparator including standard care and subsequent treatment proportions

ACM1 EAG: refractory defined slightly differently but comparable to population who would have rozanolixizumab in the NHS

Proportions of people on IVIg, PLEX or standard care only: efgartigimod EAMS population (n=48) vs company's revised population (n=37)

Long-term treatment	EAMS (%)	Revised EAMS (%)
IVIg (+CS and NSIST)	43.8	56.7
PLEX (+CS and NSIST)	14.6	18.9
CS and NSIST only	41.6	24.4

Abbreviations: ACM, appraisal committee meeting; CS, corticosteroid; EAG, external assessment group; EAMS, Early Access to Medicines Scheme; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant treatment; PLEX, plasma exchange

Large impact on ICER

Company response: comparators (4/4)

EAG prefers basket of standard care excluding rituximab as comparator

EAG comments

- Used standard basket, excluding rituximab, as comparator in EAG base case using unrevised EAMS population to inform proportions
- Notes composition of standard basket affects efficacy and cost outcomes because these parameters are calculated as weighted averages based on the treatment composition of the basket
- Scenario varying frequency of PLEX sessions (frequency may vary based on individual needs and treatment response): from 5 sessions every 4 weeks (company and EAG base case) to 4.6 sessions every 4 weeks – **very large effect on the ICER**
- Scenario with 2% of basket on rituximab – based on clinical advice to EAG that 2% in UK are MuSK positive (vs company scenario with 10.5% based on MycarinG)

- Is the basket comparator of IVIg, PLEX, or standard care only appropriate and reflective of NHS practice?
- Is the full or revised EAMS population more relevant to inform the proportion of IVIg, PLEX, and NSISTS + CS only?
- Is rituximab a relevant comparator to be included in the basket? If so, in what proportion?

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Abbreviations: EAG, external assessment group; EAMS, Early Access to Medicines Scheme; ICER, incremental cost effectiveness ratio; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; PLEX, plasma exchange

Small effect on ICER

Company response: indirect treatment comparison (1/4)

Company provided new systematic literature review and NMAs

ACM1

- NMA vs IVIg did not analyse MG-ADL score change or response (outcome used in model); no ITC provided for PLEX; did not adjust for heterogeneity or baseline risk of populations across studies
- Committee concluded that company's ITCs not appropriate for decision making
- Asked for more evidence on IVIg or PLEX and MG-ADL or other outcomes and explore other ITC methods to inform relative treatment effects and adjust for potential placebo effects

Company draft guidance response

- Updated systematic literature review including randomised controlled trials and observational studies
- 2 new indirect treatment comparison methodologies (bivariate NMA and baseline risk-adjusted NMA)
- 2 outcomes:
  - change from baseline in MG-ADL and QMG scores
  - responder rates for MG-ADL (2-point improvement) and QMG (≥3 point improvement)
- Uses correlation between 2 outcomes to 'borrow' information – helps make better use of all available data and reduces uncertainty
- Used patient-level data from MycarinG to measure how closely MG-ADL and QMG outcomes are related
- Used non-informative priors

Abbreviations: ACM, appraisal committee meeting; ICER, incremental cost effectiveness ratio; ITC, indirect treatment comparison; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; NMA, network meta-analysis; PLEX, plasma exchange; QMG, quantitative myasthenia gravis; RCT, randomised controlled trial

Small effect on ICER

Company response: indirect treatment comparison (2/4)

EAG disagrees with new studies included in NMA - response rates same whether observational studies included or not; new studies do not reduce uncertainty

New studies on IVIg and PLEX included in NMAs

Study	Outcomes	Comparators	Used in
Barnett et al., 2017 (prospective, non-RCT, Canada)	MG-ADL CFB QMG CFB	Control (n=54) Prednisone (n=50) IVIg/PLEX (n=45)	Bivariate Baseline risk adjusted NMA
Duan et al., 2023 (retrospective, non-RCT, China)	QMG response QMG CFB	PLEX (n=62) LPE (n=62)	Bivariate
Leng et al., 2024 (retrospective, non-RCT, China)	QMG CFB	PLEX (n=3) Protein A (n=4)	Bivariate

EAG comments on limitations of new studies

Abbreviations: EAG, external assessment group; CFB, change from baseline; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; LPE, lymphoplasmapheresis; MG-ADL, myasthenia gravis activities of daily living; NMA, network meta-analysis; PLEX, plasma exchange; QMG, quantitative myasthenia gravis; RCT, randomised controlled trial

Small effect on ICER

Company response: indirect treatment comparison (3/4)

Bivariate NMA shows rozanolixizumab more effective than IVIg and PLEX

Results from bivariate NMA (used in company model)

Response: ≥2 point improvement in MG-ADL score

Intervention (vs placebo)	Response probability (%)	MG-ADL change from baseline	MG-ADL change from baseline 95% credible interval
Rozanolixizumab 7 mg	[redacted]	[redacted]	[redacted]
IVIg	[redacted]	[redacted] [0 assumed]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]

EAG comments

- Believes all relevant studies for PLEX and IVIg have likely been identified
- **Limitations of the NMAs**
  - Placebo response heterogeneity: bivariate NMAs did not account for differences in placebo response across studies – baseline risk-adjusted NMAs did account for this but no statistically significant results
  - Uncertainty remains about impact of placebo response heterogeneity (although company has investigated as thoroughly as possible)
- **Study quality and bias:** credible intervals for response rates not reported or used in the cost-effectiveness model so uncertainty in response rates not reflected in the economic analysis; PSA drew probabilistic values from beta probability distribution
- **General uncertainty:** all results affected by unclear heterogeneity in study characteristics, unreported or high risk of bias in included studies; scenario analysis (rozanolixizumab response rate = standard care [redacted]) shows that **response rates not a key driver of economic model**

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Abbreviations: ICER, incremental cost effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; NMA, network meta-analysis; PLEX, plasma exchange; RCT, randomised controlled trial; SC, standard care

Small effect on ICER

Company response: indirect treatment comparison (4/4)

NMA results for MG-ADL response

Analysis	MG-ADL response ≥2 points, odds ratio vs placebo (95% CrI)		
	Rozanolixizumab 7 mg	IVIg	PLEX
Original NMA (original submission)	[redacted]	Not done	Not done
Conventional NMA (RCTs)	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs)	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs + non-RCTs; used in updated model)	[redacted]	[redacted]	[redacted]
BLRA NMA (common covariate model)	[redacted]	NA (NA, NA)	NA (NA, NA)
BLRA NMA (exchangeable covariate model)	[redacted]	NA (NA, NA)	NA (NA, NA)

NMA results for MG-ADL change from baseline

Analysis	MG-ADL change from baseline, difference vs placebo (95% CrI)		
	Rozanolixizumab 7 mg	IVIg	PLEX
Original NMA (original submission)	[redacted]	Not done	Not done
Conventional NMA (RCTs)	[redacted]	[redacted]	[redacted]
Conventional NMA (RCTs + non-RCTs)	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs)	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs + non-RCTs)	[redacted]	[redacted]	[redacted]
BLRA NMA (common covariate model)	[redacted]	[redacted]	[redacted]
BLRA NMA (exchangeable covariate model)	[redacted]	[redacted]	[redacted]

- Does the company analysis appropriately adjust for heterogeneity, baseline risk? Has uncertainty been adequately accounted for?
- Are the updated NMAs appropriate for decision making? Does committee have a preference for the bivariate NMA, BLRA NMA or conventional NMA?

Abbreviations: BLRA, baseline risk-adjusted; CrI, credible interval; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; NA, not applicable (no relevant studies); NMA, network meta-analysis; PLEX, plasma exchange; RCT, randomised controlled trial

Unknown effect on ICER

Company response: long-term treatment effect

Company: final results from open-label extension study (MG0007) show consistent efficacy in AChR- and MuSK-positive generalised MG

ACM1 MG0007 (n=[redacted]; [redacted] ~7 mg/kg, [redacted] ~10 mg/kg [unlicensed]); committee conclusion: some supporting evidence for rozanolixizumab's effectiveness

Company draft guidance response

- Final results ([redacted]): meaningful improvements in each treatment cycle
- Responses (≥2-point reduction in MG-ADL score) from day [redacted] of each treatment cycle, with a median time to MG-ADL response of [redacted] in the first [redacted] 6-week treatment cycles; MG-ADL scores plateaued at around [redacted] compared with baseline after repeated cycles (MG0007 long-term results)

EAG comments

Data supports ongoing efficacy of rozanolixizumab; but limitations in study completion and discontinuation:

- [redacted] participants in the 7 mg arm completed the study
- by cycle [redacted], [redacted] participants remained in the 7 mg arm for MSE data
- [redacted] total participants completed the study
- [redacted] discontinued for reasons listed as 'other' - not clearly explained
- important to understand subsequent treatments - gMG is chronic, rozanolixizumab is not curative

Is committee satisfied that the open-label extension study (MG0007) shows rozanolixizumab's long-term efficacy?

For company: why did a substantial proportion of people discontinue treatment?

Abbreviations: ACM, appraisal committee meeting; EAG, external assessment group; gMG, generalised myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; MSE, minimum symptom expression

Company's model overview

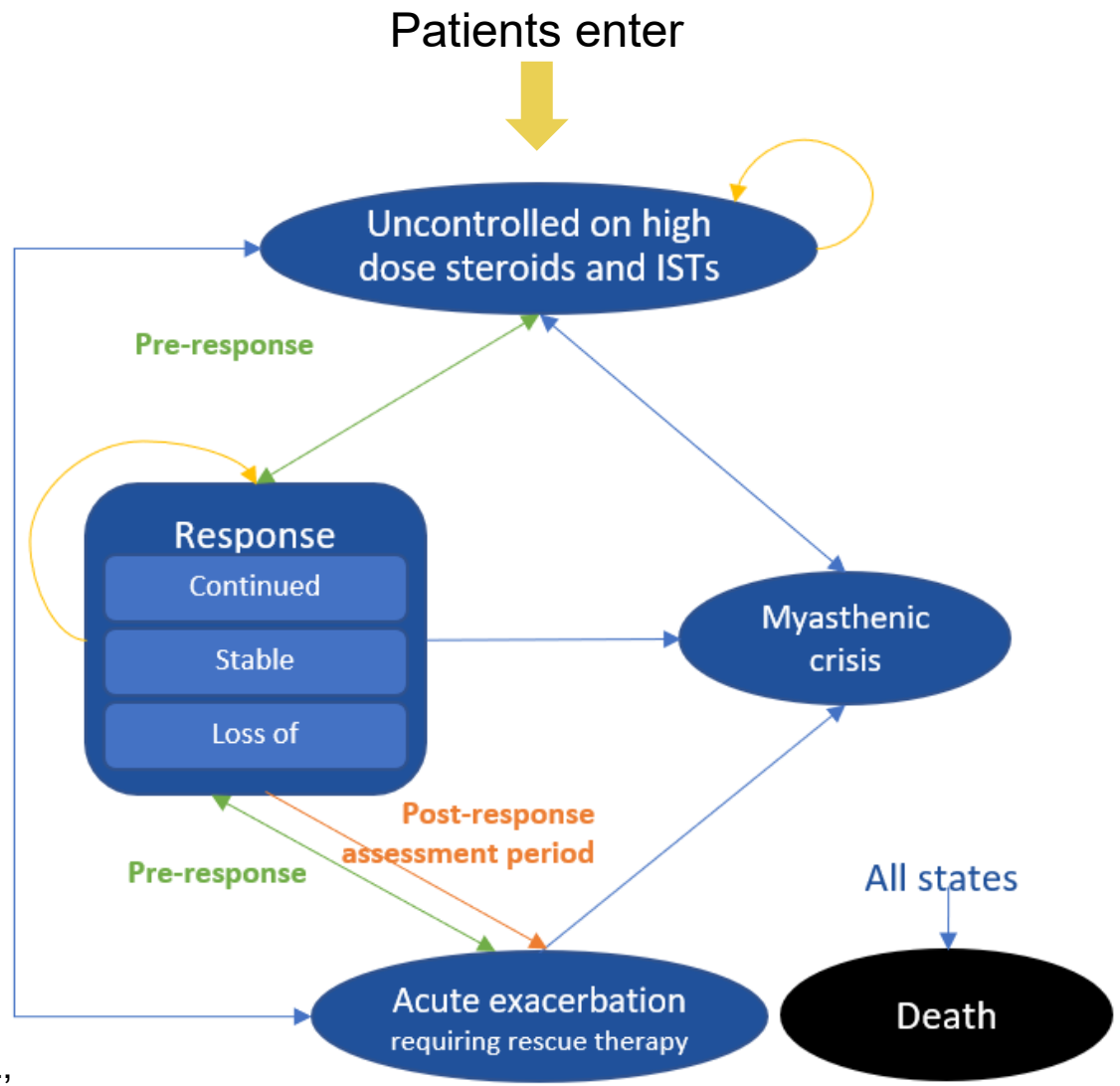
ACM1: Model could be appropriate for decision making if it accounted for subsequent treatment use

- Primary treatment response: decrease of ≥2 in MG-ADL
- Responders separate into 1 of 3 response subgroups at the response assessment timepoint but cannot move between 3 response subgroups

Continued response
Original model: drop of ≥2 points in MG-ADL from baseline, **and ongoing improvement** (≥2 points)
Updated model: patients have reached MSE (MG-ADL score of 0 or 1 – free/nearly free of symptoms)

Stable response
Original model: drop of ≥2 points in MG-ADL from baseline, **no ongoing improvement** (≥2 points)
Updated model: proportion = 1 minus the other 2 states

Loss of response
Original model: drop of ≥2 in MG-ADL from baseline, **and a worsening in score until it returns to baseline**
Updated model: no change



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ACM, appraisal committee meeting; IST, immunosuppressant; MG-ADL, myasthenia gravis activities of daily living; MSE, minimum symptom expression

Unknown effect on ICER

Company response: use of MSE in the updated model (1/2)

Company updated model with data on MSE from MG0007 and MycarinG

Company draft guidance response

- Proportion with MSE from MG0007 used for continued response state: rozanolixizumab average [redacted]% (range [redacted]% to [redacted]%) across all cycles
- Loss of response [redacted]% based on expert opinion
- Stable response is 1 minus the other 2 states
- Other treatment MSE rates based on expert elicitation: IVIg [redacted]% PLEX [redacted]% standard care (scenario only) [redacted]%

EAG comments

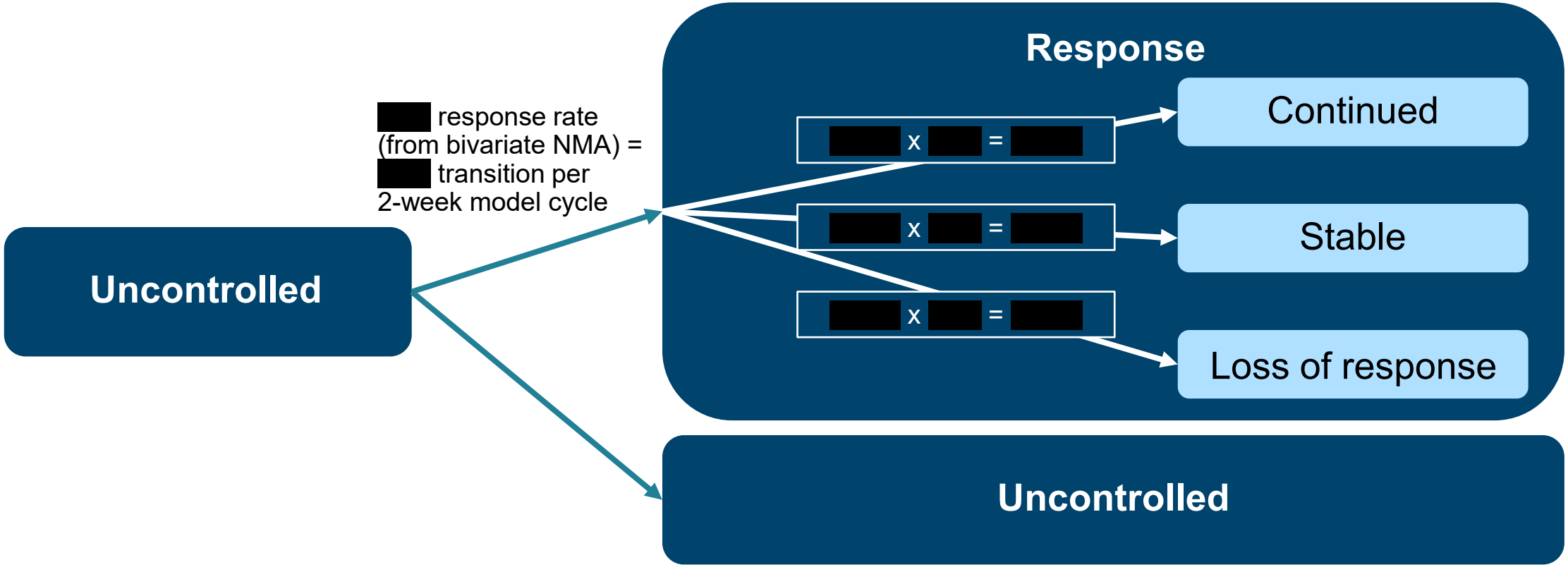
- MSE is a clinically relevant outcome
- Uncertainty in this measure has not been fully reported; for example, response includes people with response in any cycle and proportions with transient or more sustained MSE not known
- More details about distribution of MSE events among patients and treatment cycles would help reduce uncertainty

Abbreviations: ICER, incremental cost effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; MSE, minimum symptom expression; NMA, network meta-analysis; PLEX, plasma exchange

Unknown effect on ICER

Company response: use of MSE in the updated model (2/2)

Distribution of people whose myasthenia gravis responds to first-line treatment with rozanolixizumab



What is committee's view on using MSE to inform the continued response state?
Is it appropriate to use MSE from MG0007 to inform continued response for rozanolixizumab and expert elicitation to inform continued response for IVIg, PLEX, and standard care?

Abbreviations: ICER, incremental cost effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; MSE, minimum symptom expression; NMA, network meta-analysis; PLEX, plasma exchange

Company response: updated model efficacy assumptions and inputs

Bivariate NMA informed updated company model

Primary response rate and response assessment timepoint

Treatment	Response rate used in the model	Response assessment timepoint used in the model (weeks)	Source
Rozanolixizumab	[redacted]	6	Bivariate NMA
IVIg	[redacted]	3	Bivariate NMA
PLEX	[redacted]	3	Bivariate NMA
Standard care basket*	[redacted]	12	Bivariate NMA

Response distribution

Treatment	Continued response	Loss of response	Stable response	Source for proportion in continued response
Rozanolixizumab	[redacted]	[redacted]	[redacted]	MSE rate for rozanolixizumab from MycarinG and MG0007
IVIg	[redacted]	[redacted]	[redacted]	MSE rate estimated by expert elicitation
PLEX	[redacted]	[redacted]	[redacted]	MSE rate estimated by expert elicitation
Standard care basket*	[redacted]	[redacted]	[redacted]	Weighted average of placebo MSE data from MycarinG and IVIg and PLEX from expert elicitation

Treatment-specific MG-ADL score change from baseline (source: bivariate NMA)

Treatment	Continued response	Loss of response	Stable response
Rozanolixizumab	[redacted]	[redacted]	[redacted]
IVIg	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]
Standard care basket*	[redacted]	[redacted]	[redacted]

*Using revised EAMS population; abbreviations: IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; MSE, minimum symptom expression; NMA, network meta-analysis; PLEX, plasma exchange

Large impact on ICER

Company response: subsequent treatments (1/2)

Updated company model includes IVIg, PLEX and standard care in subsequent treatments

ACM1

- Company model did not include IVIg, PLEX or rituximab as subsequent treatments – only corticosteroids and immunosuppressants
- Clinical experts would consider IVIg or PLEX once rozanolixizumab stopped
- Committee concluded it would like to see subsequent treatments in the economic model

Company draft guidance response

- Uncertain how many subsequent treatments lines needed, what follows IVIg/PLEX, and if non-response is a treatment effect modifier
- Updated model included costs and a reduced treatment benefit for subsequent treatments; assumed to be stable but reflects people moving between treatment with IVIg/PLEX and standard care
- Estimates of subsequent treatments informed by Delphi panel and applied to company's revised EAMS cohort standard basket to estimate subsequent treatment proportions in the model
- 4 scenarios, one with rituximab included

NHS England from zilucoplan final draft guidance [ID4008]: using PLEX after IVIg for maintenance treatment is fairly infrequent, and using IVIg after PLEX is also very rare and only for people who are seriously ill

ABN guidelines 2025: role and dose of rituximab beyond 12 months unclear but currently not supported by trial evidence

NICE

Abbreviations: ABN, Association of British Neurologists; ACM, appraisal committee meeting; ICER, incremental cost effectiveness ratio; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; PLEX, plasma exchange

Large impact on ICER

Company response: subsequent treatments (2/2)

EAG preferred to use unrevised EAMS cohort to model subsequent treatments

EAG comments

- Unable to reproduce estimates in model; unclear how Delphi panel data used
- If use unrevised EAMS cohort, around 75% of people on IVIg switch to PLEX and nearly everyone on PLEX switches to IVIg: disagrees with Delphi panel clinical expert estimates
- EAG base case subsequent treatment proportions informed by:
  –unrevised EAMS proportions and Delphi panel estimates (comparator arm)
  –unrevised EAMS basket (rozanolixizumab arm)
- EAG scenario analyses show varying proportions of IVIg and PLEX has a **very large effect on the ICER**

Mean of subsequent treatment proportions from Delphi panel

First treatment	Subs. treatment	Mean
IVIg + SC	PLEX + SC	62%
IVIg + SC	IVIg + SC	6%
PLEX + SC	IVIg + SC	56%
PLEX + SC	PLEX + SC	4%

Note: wide range in clinical expert estimates

EAMS cohort and modelled subsequent treatment proportions

Treatment	Company revised EAMS	Unrevised EAMS	Company subs. treatment	EAG subs. treatment
IVIg	56.7%	48.3%	14.05%	8.2%
PLEX	18.9%	14.6%	35.73%	29.9%
SC (CSs/NSISTs)	24.4%	41.6%	50.22%	61.9%

- Should subsequent treatments be modelled as a basket of IVIG, PLEX and SC? Full or revised EAMS?
- If so, what proportion of switching to IVIG and PLEX and SC is reflective of NHS practice?
- Is rituximab relevant as a subsequent treatment? If so, for what subgroup?

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Abbreviations: CS, corticosteroid; EAMS, Early Access to Medicines Scheme; ICER, incremental cost effectiveness ratio; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant; PLEX, plasma exchange; SC, standard care; subs, subsequent

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Uncaptured benefits

Stakeholder* submissions on uncaptured benefits and new evidence presented by company	
SC administration	Quicker, more convenient, and preferred by patients over IVIg and PLEX
Fatigue	Underreported EQ-5D, despite affecting most gMG patients • Key trials showed rozanolixizumab **improves fatigue**
Side effects of steroids and immunosuppression	Reduces steroid burden and long-term impact of steroids • Company used proxy data from lupus and asthma studies to estimate utility decrement and costs for corticosteroid-related AEs; **incorporated into model** to reflect benefits of corticosteroid sparing
Travel and administration time	Reduces hospital time for patients and carers, improving work-life balance and reducing caregiver burden • Company **micro-costing exercise** showed substantially less admin time for rozanolixizumab than IVIg and PLEX
Healthcare costs	Reduced hospital/critical care admission associated with delayed IVIg/PLEX access
Carer costs and disutilities	• Company included time caring for someone with gMG by MG-ADL range including costs and disutilities, as **option in updated model and as a scenario**
Societal benefits	• Company included societal costs for patients (work time lost) by MG-ADL range as an **option in updated model**

*Includes submissions from company, Myaware and MDUK, ABN and web comments

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Abbreviations: AEs, adverse events; EQ-5D, EuroQol-5 dimension; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis-activities of daily living; PLEX, plasma exchange; QoL, quality of life; SC, subcutaneous

Rozanolixizumab for treating antibody-positive generalised myasthenia gravis

- ❑ Recap from first appraisal committee meeting
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ❑ Other considerations
- ✓ **Summary**

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Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Key drivers of the ICER:

- using the revised or full EAMS population to inform the comparator basket
- number of infusions of rozanolixizumab
- number of PLEX sessions
- proportions of IVIg and PLEX in subsequent treatments basket

Summary of company and EAG base case assumptions at ACM2 (1/2)

Assumption	Company base case ACM1	Revised company base case	Revised EAG base case
Comparator	IVIg and PLEX	IVIg and PLEX; standard care basket as scenario	Standard care basket
Rituximab included as comparator	No	No – scenario	No – scenario
EAMS cohort	N/A	Revised	Unrevised
Source of data for response	MG-ADL change from baseline from NMAs	bvNMA; MSE from MG0007 to inform continued response state	bvNMA; MSE from MG0007 to inform continued response state
Response assessment time point for standard basket	N/A	12 weeks	3 weeks
IVIg and PLEX admin costs frequency	IVIg every 3 weeks PLEX every 4 weeks	Both every 4 weeks PLEX cost set to £0 in model	Both every 4 weeks PLEX cost of £2,482.50 per model cycle included

EAG, external assessment group; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; MSE, minimum symptom expression; N/A, not applicable; PLEX, plasma exchange

Summary of company and EAG base case assumptions at ACM2 (2/2)

Assumption	Company base case ACM1	Revised company base case	Revised EAG base case
Subsequent treatments	No subsequent treatment with IVIg or PLEX – standard care only	Revised EAMS cohort Delphi panel used to inform subsequent treatment proportions of IVIg, PLEX and standard care	Unrevised EAMS cohort EAG-calculated treatment proportions used to inform subsequent treatment proportions of IVIg, PLEX and standard care
MSE proportion used to inform 'uncontrolled off initial treatment' health state	N/A	Standard basket	Use standard care (CSs and NSISTs only) MSE proportion
CS disutility	Not included	Included	Not included (in line with ID4008)
CS resource use costs	N/A	Costs from Stirnadel-Farrant et al. (2023) – systemic lupus erythematosus Costs of managing CS **differ** for IVIg and PLEX, and rozanolixizumab MSE/continued response health states	Costs from Lee et al. (2018) – gMG, as per ID4008 Costs of managing CS **same** for IVIg and PLEX, and rozanolixizumab MSE/continued response health states (Source of corticosteroid management costs)

Abbreviations: ACM, appraisal committee meeting; CS, corticosteroid; EAG, external assessment group; IVIg, intravenous immunoglobulin; gMG, generalised myasthenia gravis; MSE, minimum symptom expression; N/A, not applicable; NSIST, non-steroidal immunosuppressant; PLEX, plasma exchange

Effect on ICER of EAG preferred model assumptions

Greatest impact on ICER: response assessment time point 3 weeks for standard basket; 6 weeks for rozanolixizumab

Deterministic cumulative ICERs

No.	Scenario (applied to company base case)	Effect on incremental cost	Incremental QALY	ICER (£/QALY) vs standard care basket
0	**Company updated base case (using scenario vs revised EAMS population standard basket as comparator)**	–	0.127	Under £20,000
1	Exclude the disutility associated with corticosteroid use	No change	0.119	Under £20,000
2	Use the original EAMS cohort for the standard basket comparator (43.8% IVIg, 14.6% PLEX, 41.6% SC)	Increased	0.130	Over £30,000
3	Use a response assessment time point of 3 weeks for the standard basket; 6 weeks for rozanolixizumab	Increased	0.136	Over £30,000
4	Apply PLEX admin and treatment costs for 5 PLEX sessions every 4 weeks	Decreased	0.136	Under £20,000
5	Subsequent treatment: unrevised EAMS cohort post-rozanolixizumab	Decreased	0.136	Under £20,000
6	Subsequent treatment: EAG-calculated proportions for the standard basket	Increased	0.168	Under £20,000
7	Costs for corticosteroid management from Lee et al.	Decreased	0.168	Under £20,000
8	Use the same corticosteroid resource use costs for MSE in both arms	Decreased	0.168	Under £20,000
9	Use SC MSE proportion to inform the 'Uncontrolled off initial treatment' health state	No change	0.190	Under £20,000
10	**EAG base case**	No change	0.190	Under £20,000

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; MSE, minimum symptom expression; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; SC, standard care

EAG base case: EAG deterministic scenario analyses – effect on ICER

Deterministic scenarios on EAG base case, rozanolixizumab vs unrevised standard basket

No.	Scenario	ICER (£/QALY)
1	Company's revised EAMS cohort as standard basket in comparator arm	No change
2	Include rituximab (2% of patients) in EAG standard basket	No change
3	Response assessment timepoint for standard basket = 12 weeks	No change
4	Apply PLEX admin and treatment costs for 4.6 PLEX sessions every 4 weeks	Increased
5	Subsq Tx: Company's base case proportions, for both arms	Increased
6	Subsq Tx basket, rozanolixizumab: ↑ proportion on IVIg (44.8%) and PLEX (15.6%)	Increased
7	Subsq Tx, standard basket: ↓ proportion on IVIg (7.2%) and PLEX (28.9%)	Increased
8	Use annualised number of cycles for rozanolixizumab treatment	Increased
9	Use IVIg change from baseline in MG-ADL score from bvNMA	No change
10	Set rozanolixizumab response rate same as SC (CS and NSISTs)	No change

Abbreviations: bvNMA, bivariate network meta-analysis; CS, corticosteroid; EAG, external assessment group; EAMS, Early Access to Medicines Scheme; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis-activities of daily living; NSIST, non-steroidal immunosuppressant; QALY: quality adjusted life year; SC, standard care; subsq Tx, subsequent treatment;

Remaining issues for decision making

- Comparators
- Indirect treatment comparison
- Long-term treatment effect
- Use of MSE in the model
- Subsequent treatments

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Thank you

Supplementary appendix

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Company response: comparators

Company provided further rationale for why it considers standard care-only treatment option inappropriate

Company draft guidance response

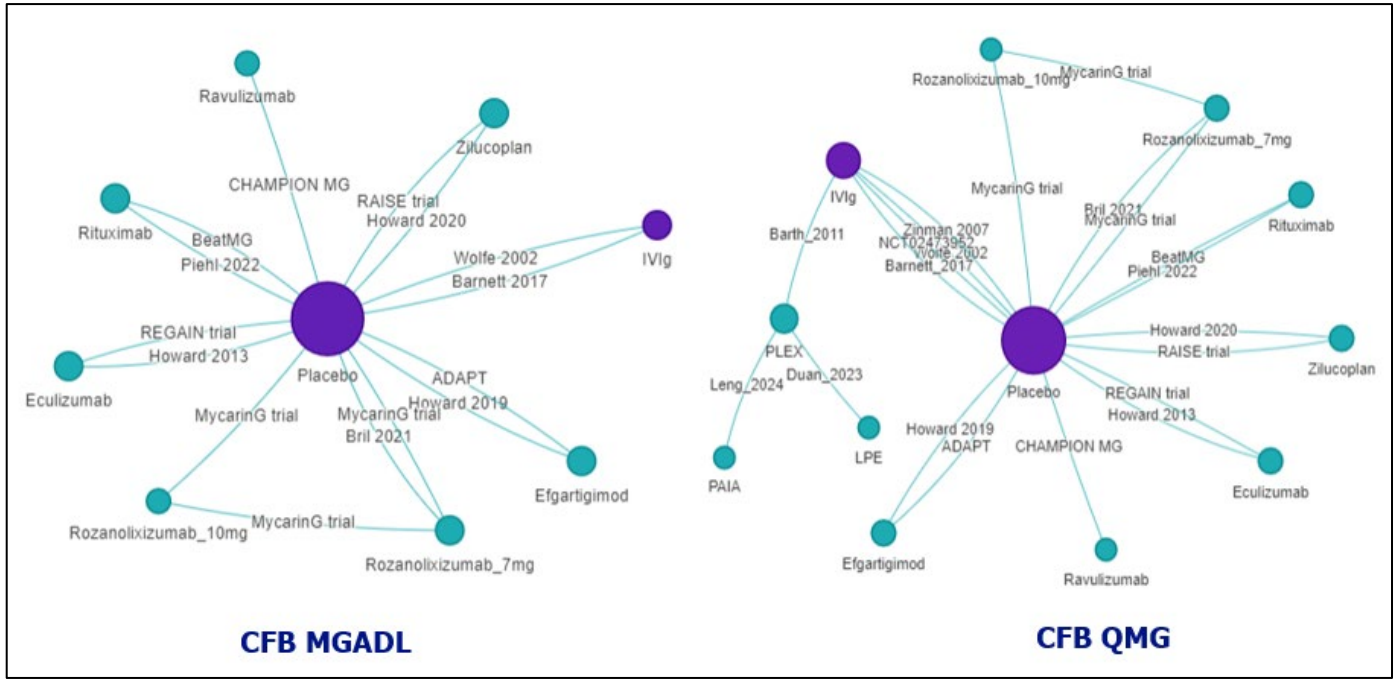
- **Marketing authorisation:** add on to standard care with corticosteroids and immunosuppressants (not with IVIg or PLEX); people on IVIg or PLEX usually also have standard therapy, so fair to compare rozanolixizumab with IVIg or PLEX as alternative add-on options when standard care alone not enough
- **People who will never receive IVIg/PLEX:** not target population for rozanolixizumab
- **Treatment break:** 2 scenarios modelled for people who may be temporarily off first-line IVIg, PLEX or rozanolixizumab
- **Analysis to show perversity of outcomes vs blended basket comparator:** scenario with hypothetical IVIg or PLEX (10% cheaper and 10% more effective) still results in ICERs above NICE thresholds – better treatments could be rejected, leaving patients with less effective, more costly options

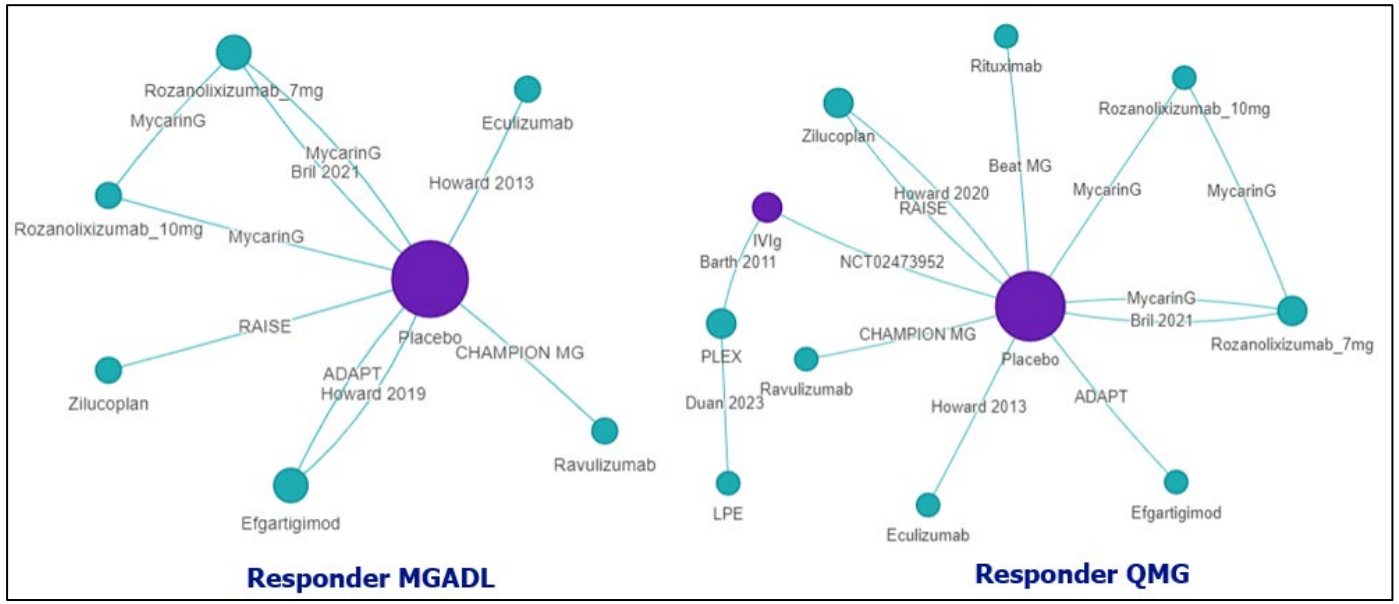
Company response: comparators

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange

Bivariate NMA outcome network

Change from baseline MG-ADL and QMG





Responder MG-ADL and QMG

[Company response: indirect treatment comparison]

MG-ADL, myasthenia gravis activities of daily living; QMG, quantitative myasthenia gravis

Time on treatment

Intervention	Time on treatment (years)
Rozanolixizumab	[redacted]
IVIg	[redacted]
PLEX	[redacted]
Standard basket	[redacted] ([redacted] in company base case)

- Inclusion of MSE to inform the proportion of patients in the continued response state does not affect time on treatment → proportion in 'loss of response' state remains the same ([redacted]), proportions in 'continued' and 'stable' response states are on treatment
- The time on treatment is only dependent on the overall response rate and response assessment timepoint
- The model calculates costs/utilities for 100% of patients who stay in their response state until a clinical event (exacerbation/crisis)
  – changing the initial proportions in the continued and stable response states affects costs and utilities but not time on treatment

Abbreviations: IVIg, intravenous immunoglobulin; MSE, minimum symptom expression; PLEX, plasma exchange

Company response: indirect treatment comparison

New studies on IVIg and PLEX included in NMAs

Study	Outcomes	Comparators	Used in	EAG comments
Barnett et al., 2017 (prospective, non-RCT, Canada)	MG-ADL CFB QMG CFB	Control (n=54) Prednisone (n=50) IVIg/PLEX (n=45)	Bivariate Baseline risk adjusted NMA	No outcomes reported for control group, so can't be used Prednisone treated as placebo in evidence network but appropriateness uncertain because study does not report background treatments for each group IVIg and PLEX combined into 1 group – impossible to assess individual effects IVIg/PLEX group treated as IVIg only in NMA – adds uncertainty
Duan et al., 2023 (retrospective, non-RCT, China)	QMG response QMG CFB	PLEX (n=62) LPE (n=62)	Bivariate	No discussion on how treatment groups selected – concerns about bias Includes PLEX arm but no common comparator to link PLEX to rest of evidence network, instead adds LPE – not relevant to this appraisal
Leng et al., 2024 (retrospective, non-RCT, China)	QMG CFB	PLEX (n=3) Protein A (n=4)	Bivariate	Only 3 patients with gMG in PLEX group No common comparator to link PLEX to rest of network – instead adds Protein A immunoadsorption (PAIA) – not relevant to this appraisal May share patients or data with the Duan study

Company response: indirect treatment comparison

EAG, external assessment group; CFB, change from baseline; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; LPE, lymphoplasmapheresis; MG-ADL, myasthenia gravis activities of daily living; NMA, network meta-analysis; PLEX, plasma exchange; QMG, quantitative myasthenia gravis; RCT, randomised controlled trial

Company response: long-term treatment effect

MG0007 efficacy outcomes

Change from baseline to day 43 in MG-ADL score during each treatment cycle

[redacted]

Abbreviations: BL, baseline; MG-ADL, myasthenia gravis activities of daily living; RLZ, rozanolixizumab

MG0007 long-term results

MG-ADL score stabilised at around -3 compared with baseline

Company response: long-term treatment effect

MG-ADL, myasthenia gravis activities of daily living; RLZ, rozanolixizumab; TRT, treatment

Delphi survey report subsequent treatment proportions

Subsequent treatment proportions based on clinical expert survey used to inform model

Subsequent treatment	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Expert 6	Expert 7	Expert 8	Expert 9	Mean
After IVIg + SC failed: **PLEX + SC**	25%	0%	100%	33%	84%	43%	89%	80%	100%	**62%**
After IVIg + SC failed: **IVIg + PLEX**	0%	0%	0%	33%	0%	21%	0%	0%	0%	**6%**
After PLEX + SC failed: **IVIg + SC**	14%	50%	90%	33%	83%	74%	0%	60%	100%	**56%**
After PLEX + SC failed: **PLEX + SC**	0%	0%	0%	33%	0%	5%	0%	0%	0%	**4%**

Company response: subsequent treatments

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Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SC, standard care (corticosteroids and non-steroidal immunosuppressants)

Small impact on ICER

Source of corticosteroid management costs

EAG preferred alternative source of costs for the model

[Summary of company and EAG base case assumptions at ACM2]

Source of corticosteroid management costs

Health state	Company base case: Stirnadel-Farrant et al. 2023	EAG base case: Lee et al. 2018
Uncontrolled	[redacted]	[redacted]
Stable response	[redacted]	[redacted]
MSE/continued response – rozanolixizumab	[redacted]	[redacted]
MSE/continued response – IVIg and PLEX	[redacted]	[redacted]

Company draft guidance response

Limitations of Lee et al:

- no data on adverse events for people not having corticosteroids
- does not specify severity of AEs
- costs according to dose not included

EAG comments

- Lee et al. accepted by committee in zilucoplan appraisal ID4008
- Study in generalised myasthenia gravis – Stirnadel-Farrant is in systemic lupus erythematosus
- Costs of managing corticosteroids differ for IVIg and PLEX, and rozanolixizumab MSE/continued response health states – costs should be the same

Which is more appropriate source of corticosteroid management costs: Stirnadel-Farrant et al. or Lee et al.? Should costs for CS management be the same for the rozanolixizumab and IVIg and PLEX model arms?

Abbreviations: CS, corticosteroid; ICER, incremental cost effectiveness ratio; IVIg, intravenous immunoglobulin; MSE; minimal symptom expression; PLEX, plasma exchange