Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from UCB Pharma:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Joint submission from Myaware and Muscular Dystrophy UK
   b. Association of British Neurologists – endorsed by Royal College of Physicians

4. **Expert personal perspective** from Abuk Mabil – patient expert, nominated by Myaware

5. **External Assessment Report** prepared by Southampton Health Technology Assessment Centre (SHTAC)

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Rozanolixizumab for antibody positive generalised myasthenia gravis [ID 5092]

Document B

Company evidence submission

22 March 2024

FINAL

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Document B	2.0	Yes	22nd March 2024

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This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

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Contents

List of Tables

List of Figures

Abbreviations

ABN	Association of British Neurologists
ACh	Acetylcholine
AChEI	Acetylcholinesterase inhibitor
AChR	Acetylcholine receptor
AChR-Ab+	AChR-autoantibody positive
ADA	Antidrug antibody
ADLs	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AWTCC	All Wales Therapeutic and Toxicology Centre
BNF	British National Formulary
CCP	Clinical Commissioning Policy
CE	Conformité Européenne (European conformity)
CFB	Change from baseline
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CRF	Case report form
CS	Corticosteroid
DIC	Deviance information criterion
DSA	Deterministic sensitivity analysis
EAMS	Early Access to Medicines Scheme
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Level Version
ER	Emergency room
ES	Enrolled set
FAS	Full analysis set
Fc	Fragment crystallisable
FcRn	Neonatal Fc receptor
gMG	Generalised myasthenia gravis
GP	General practitioner
HCP	Healthcare professional
HES	Hospital Episode Statistics

HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product
INMB	Incremental net monetary benefit
IQR	Interquartile range
IPD	Important protocol deviation
IST	Immunosuppressive therapy
ITC	Indirect treatment comparison
IVIg	Intravenous immunoglobulin
KOL	Key opinion leader
LFT	Liver function test
LRP4	Low-density lipoprotein receptor-related protein 4
LS	Least square
LYG	Life years gained
MAC	Membrane attack complex
MD	Mean differences
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
MG-ADL	Myasthenia gravis activities of daily living
MG-C	Myasthenia gravis composite
MGFA	Myasthenia Gravis Foundation of America
MGII	Myasthenia Gravis Impairment Index
MG-QOL15r	Myasthenia Gravis Quality of Life 15-item scale
MGSPRO	Myasthenia Gravis Symptoms Patient Reported-Outcome
MHRA	Medicines and Healthcare products Regulatory Agency
MuSK	Muscle-specific tyrosine kinase
MuSK-Ab+	MuSK-autoantibody positive
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSIST	Non-steroidal immunosuppressive therapy
NMA	Network meta-analysis

NMB	Net monetary benefit
NMJ	Neuromuscular junction
oMG	Ocular myasthenia gravis
OR	Odds ratio
PD	Pharmacodynamics
PLEX	Plasma exchange
PK	Pharmacokinetic
PK-PPS	Pharmacokinetic per-protocol set
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QMG	Quantitative myasthenia gravis
QoL	Quality of life
RCT	Randomised controlled trial
RS	Randomised set
SCIg	Subcutaneous immunoglobulin
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality rate
SOC	System organ class
SS	Safety set
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TPMT	Tiopurine methyltransferase
RS	Randomised set
ULN	Upper limit of normal

Executive summary

Burden of generalised myasthenia gravis

Generalised MG (gMG) is a chronic autoimmune disease that causes severe, fluctuating weakness and fatigue in muscles, including those responsible for breathing, swallowing and mobility, and can lead to dependence on others and/or mechanical support for movement and breathing (1-3).

The severe and debilitating symptoms of gMG impose a substantial clinical and humanistic burden on patients and their caregivers (2, 4-18), and a considerable financial burden on patients and the healthcare system (19-27). In addition to lifelong symptoms that impair day-to-day living(4), patients with gMG face the risk of myasthenic crisis (9-12), a life-threatening deterioration of muscle weakness and respiratory failure requiring intensive care with mechanical ventilation (9, 21, 28, 29).

Established clinical management of gMG includes acetylcholinesterase inhibitors (AChEIs) and non-targeted immunosuppressive treatments (ISTs). Currently available treatments are associated with limitations such as burdensome side effects and delayed treatment effect up to 18 months (3, 11, 30-36).

Furthermore, approximately 15% patients with gMG are refractory to standard therapies and continue to experience poor symptom control, severe disease burden and poor quality of life (QoL) (37, 38). These patients are at an increased risk of myasthenic exacerbation and crisis and are more likely to use increased healthcare resources, leading to a high economic burden (19-24, 31, 39, 40).

Unmet need

Currently, the only treatments available for patients with refractory gMG are chronic intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) (19). Supply of IVIg is managed in the UK and PLEX is available only in few specialised centres (41-43). Furthermore, PLEX and IVIg have burdensome side effects and are costly to the healthcare system (20, 36, 41, 43, 44).

Thus, there is an unmet need for licensed targeted treatments with a fast onset of action that minimise symptom burden, reduce the risk of myasthenic exacerbations and crises, and improve QoL for patients who are refractory to available treatments.

Clinical effectiveness

Rozanolixizumab is the first gMG treatment to be licensed in patients with gMG and either acetylcholine receptor (AChR) or muscle-specific kinase (MuSK) auto-antibodies (45). Because of its targeted mechanism of action and fast onset of action, it is expected that rozanolixizumab will reduce the impact of uncontrolled disease on patients and improve QoL for patients and their caregivers. As a short (up to 18 minutes), once-weekly subcutaneous (SC) infusion administered in a 6-week cycle, that is only repeated as needed, rozanolixizumab will avoid the need for frequent intravenous (IV) administration, facilitating access to treatment for all eligible patients.

The clinical outcomes reported in Section B.2 demonstrate that cyclic treatment with rozanolixizumab provides statistically significant and clinically meaningful improvements in the signs and symptoms of disease activity, with a fast onset of action (the treatment effect of rozanolixizumab was observed as early as Day 8 in some patients) and a consistent response over multiple treatment cycles (46, 47).

Rozanolixizumab as an add-on therapy to standard treatment was associated with an acceptable safety profile and was generally well tolerated by patients with gMG in the Phase III trial MycarinG (46). The open-label extension study MG0007 demonstrated the tolerability and acceptable safety profile of repeated cycles of treatment with rozanolixizumab, with no new safety signals identified (47).

Economic value

A state transition Markov model was developed to evaluate the cost effectiveness of rozanolixizumab as a treatment for adult patients with gMG from the perspective of the UK NHS/personal social services (PSS). This structure captures the chronic nature of gMG. The base case compared rozanolixizumab with efgartigimod (subject to NICE evaluation), zilucoplan (subject to NICE evaluation), intravenous/subcutaneous immunoglobulin (IVIg/SCIg), and plasma exchange (PLEX) in adult patients utilising the MycarinG trial as the source of clinical characteristics.

Base case deterministic ICERs for rozanolixizumab compared with efgartigimod, zilucoplan, IVIg/SCIg and PLEX are [redacted] and [redacted], respectively.

The model predicts discounted QALY gains of 0.0175 in comparison with efgartigimod, 0.0913 in comparison with zilucoplan, 0.1588 in comparison with IVIg/SCIg and 0.1018 in comparison with PLEX.

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The marketing authorisation for rozanolixizumab is as an add-on to standard therapy for adult patients with AChR or MuSK antibody-positive (Ab+) gMG (48).

This submission is for rozanolixizumab ≈7 mg/kg as an add-on to standard therapy for the treatment of adult patients with refractory AChR Ab+ or MuSK Ab+ gMG, if:

- the disease is classified as MGFA class II–IVa, and
- the disease is uncontrolled despite standard treatment, as defined by inadequate response to ≥2 prior MG therapies (after acetylcholinesterase inhibitors [AChEIs]), and
- the patient is being treated with or considered for an additional therapy such as intravenous immunoglobulin (IVIg) or plasma exchange (PLEX).

There is a high unmet need for novel effective treatments with a fast onset of action and an acceptable safety profile in patients with gMG who are being considered for IVIg/PLEX, as these treatment options can be a significant burden to the patient and are costly to the healthcare system.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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	There is a 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. Both IVIg and PLEX are a burden to the patient and costly to the healthcare system. Refractory gMG is associated with a substantial clinical and economic burden vs non-refractory disease. In addition, adult patients with AChR or MuSK Ab+ refractory gMG are those who clinicians are expected to prioritise as per the label granted by the EMA and approved by the MHRA.
Intervention	Rozanolixizumab	Rozanolixizumab	-
Comparator(s)	• Efgartigimod (subject to NICE evaluation) • Zilucoplan (subject to NICE evaluation) • Ravulizumab (subject to NICE evaluation) • Standard of care without rozanolixizumab (including ISTs[†] [including rituximab] with or without IVIg or PLEX)	• Efgartigimod (subject to NICE evaluation) • Zilucoplan (subject to NICE evaluation) • IVIg • PLEX	• It is anticipated that efgartigimod and zilucoplan will be approved for use in refractory patients with gMG (subject to NICE evaluation) • IVIg/PLEX (added to CSs and ISTs[‡]) is the current SoC in patients who are refractory to treatment; therefore IVIg and PLEX are relevant comparators for this submission

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			• NICE was unable to make a recommendation on ravulizumab due to withdrawal of the evidence submission by the company • Rituximab was not included as comparator as it is not licensed in the UK for gMG and has not been robustly studied in the target population. Furthermore, NHSE CCP and AWTCC expert opinion recommend its use at different points of the clinical pathway‡ and [redacted]§
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.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or	Cost-utility analysis	-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • adults with autoantibodies against AChR • adults with autoantibodies against MuSK • adults with severe MG needing IVIg or PLEX	None	• The data from the clinical trials included patients with autoantibodies against AChR or MuSK. The population with anti-MuSK antibodies is small in the trial, introducing considerable uncertainty. The clinical results are presented for the individual subgroups in Section B.2.7.4; however, the economic modelling considers the overall trial population. • The overall population in the submission already includes adults with severe MG needing IVIg or PLEX, so it is not treated as a subgroup. When the MycarinG primary efficacy endpoint was assessed in patients with MG-ADL score >5 at Baseline (see Section B.2.7), the results were consistent with the overall population, thus a scenario economic analysis for this subgroup was not performed.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	There is geographic variability in treatment availability and access to specialist centres, which introduces inequality among patients with MG in terms of access to care. The introduction of rozanolixizumab will improve equity of access to treatment, as its administration does not require highly specialised equipment or training. Home administration by a healthcare professional may be considered for patients who have tolerated administration of rozanolixizumab in the clinic.	

† ISTs (including mycophenolate) are not currently licensed for MG in the UK (25, 26, 49, 50). ‡ Sources: NHSE CCP (51) and AWTCC (52) clinical expert opinion on rituximab in gMG; § EAG report on zilucoplan (53).

Abbreviations: AChEI, acetylcholinesterase inhibitor; AChR, acetylcholine receptor; AWTCC, All Wales Therapeutic and Toxicology Centre; CCP, clinical commissioning policy; CS, corticosteroid; EAG, External Assessment Group; EMA, European Medicines Agency; gMG, generalised myasthenia gravis; IST, immunosuppressant therapy, IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MHRA, Medicines and Healthcare products Regulatory Agency; MuSK, muscle-specific kinase; NHSE, National Health Service England; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life years; PLEX, plasma exchange; PSS, Personal Social Service; SoC, standard of care.

B.1.2 *Description of the technology being evaluated*

A summary of the technology being evaluated is provided in Table 2. Further details are provided in Appendix C.

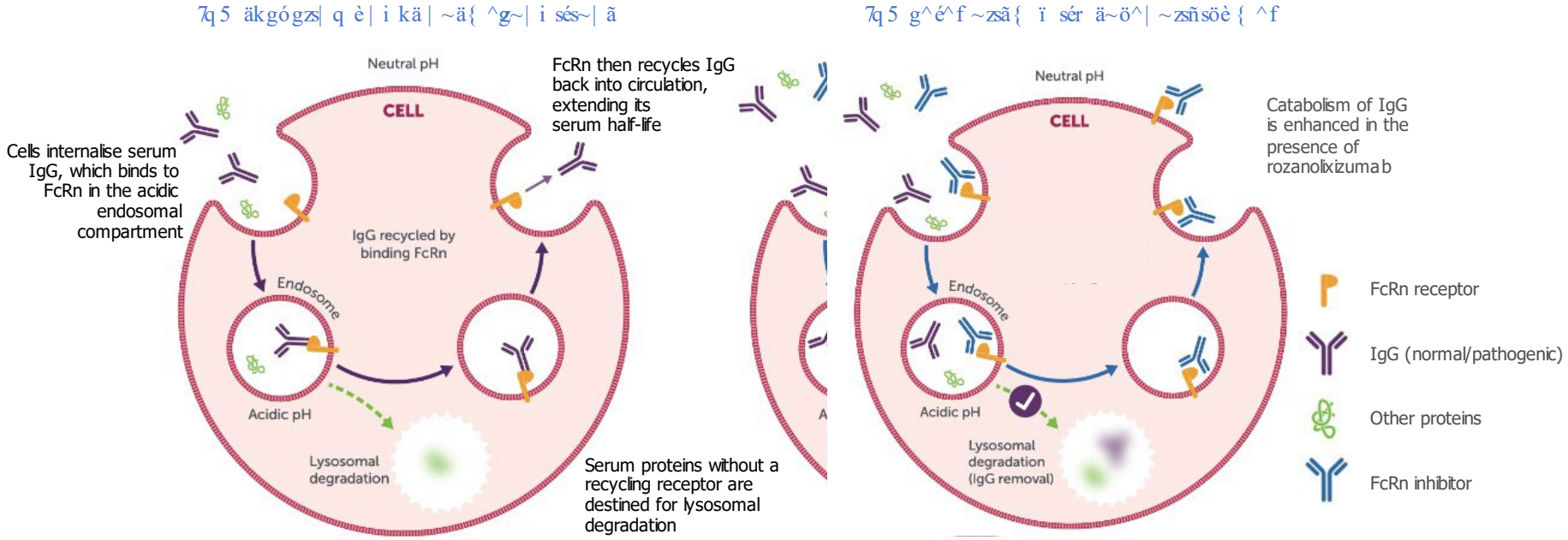
Table 2: Technology being evaluated

UK approved name and brand name	The generic name of the drug is rozanolixizumab. The brand name is Rystiggo®.
Mechanism of action	Rozanolixizumab is a humanised IgG4 monoclonal antibody that decreases the serum IgG concentration by inhibiting the binding of IgG to FcRn, a receptor that, under physiological conditions, protects IgG from intracellular degradation and recycles IgG back to the cell surface (Figure 1) (54, 55). By reducing the concentration of IgG, rozanolixizumab also decreases the concentration of pathogenic IgG autoantibodies, targeting the core pathophysiology of MG.
Marketing authorisation/CE mark status	The EMA granted rozanolixizumab orphan designation in April 2020. CHMP positive opinion was issued in November 2023 for rozanolixizumab (54). EMA granted a marketing authorisation on 5th January 2024 (54). UK MHRA regulatory approval was granted on 7th March 2024 (48). UK orphan drug designation was granted on 12th February 2024 (56).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Rozanolixizumab (Rystiggo®) is indicated as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-AChR or anti-MuSK antibody positive (54).
Method of administration and dosage	• Rozanolixizumab is administered as a short (up to 18 minutes) subcutaneous (SC) infusion once-weekly for six weeks, representing one treatment cycle. Subsequent treatment cycles may be administered according to clinical evaluation and the frequency will vary by patient. Approximately 90% of patients in the clinical trials had treatment-free intervals of 4–13 weeks between cycles, while 10% of patients had a treatment-free interval of less than 4 weeks. Based on the clinical trial program, the average annualised number of cycles per patient was [redacted]. • Rozanolixizumab is administered using a syringe driver at a constant flow rate up to 20 mL/h. • Rozanolixizumab can be administered by a healthcare professional in an outpatient/infusion centre, or in the hospital setting, and is given without pre-medications. Home administration, carried out by a qualified healthcare professional, may be considered for patients who have tolerated previous administration of rozanolixizumab in the clinic, and after evaluation and recommendation from the treating physician. • Rozanolixizumab is administered as a SC infusion, preferably into the lower right or lower left abdomen below the belly button. Infusions should not be given

	into areas where the skin is tender, erythematous, or indurated. • Rozanolixizumab dosing uses a fixed-dose approach based on body weight. In the phase III program this was referred to as (≈)7 mg/kg. The body weight categories and respective weekly doses are: ○ ≥35–<50 kg: 280 mg ○ ≥50–<70 kg: 420 mg ○ ≥70–<100 kg: 560 mg ○ ≥100 kg: 840 mg
Additional tests or investigations	None
List price and average cost of a course of treatment	List price: [redacted] Rozanolixizumab cost will be weight-based. Patient average weight in MycarinG was 81.1 kg, resulting in an average cost of [redacted] (list price) for a 6-week treatment cycle
Patient access scheme (if applicable)	[redacted]

Abbreviations: AChR, acetylcholine receptor; CE, Conformité Européenne (European Conformity); EMA, European Medicines Agency; Fc, fragment crystallisable; FcRn, neonatal fragment crystallisable receptor; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; MuSK, muscle-specific tyrosine kinase; MHRA, Medicines and Healthcare products Regulatory Agency; PAS, patient access scheme; SC, subcutaneous.

Figure 1: Mechanism of action of rozanolixizumab



Left panel: Under physiological conditions cells internalise serum IgGs. In the endosomal compartment, IgGs bind to FcRn and are excreted back into circulation, thus extending the half-life of the immunoglobulin. ***Right panel***: Rozanolixizumab binds to the FcRn in the endosomal compartment, blocking the recycling of IgGs that are instead sent to the lysosome for degradation.
Abbreviations: FcRn, neonatal fragment crystallisable receptor. IgG, immunoglobulin G.
Source adapted from Wolfe GI, et al. 2021 (55).

B.1.3 *Health condition and position of the technology in the treatment pathway*

Disease overview

- Generalised MG is a chronic, autoimmune disease that causes severe, fluctuating weakness and fatigue in muscles, including those responsible for breathing, swallowing and mobility (1-3)
- The severe and debilitating symptoms of gMG impose a substantial clinical and humanistic burden on patients and their caregivers (2, 4-18), and a considerable financial burden on patients and the healthcare system (19-27)
    - In addition to lifelong symptoms that impair day-to-day living (4), patients with gMG face the risk of myasthenic crisis (9-12), a life-threatening deterioration of muscle weakness and respiratory failure requiring intensive care with mechanical ventilation (9, 21, 28, 29)
- It is estimated that there are 19,053 people living with MG in England (57)

Current treatment pathway and position of technology

- Established clinical management of gMG includes AChEIs and non-targeted immunosuppressive treatments (ISTs). Some patients with gMG (15%) are refractory to these standard therapies and continue to experience poor symptom control, a high disease burden and poor quality of life (QoL) (37, 38)
    - Currently available treatments are associated with limitations such as burdensome side effects and a delayed treatment effect that can take up to 18 months (3, 11, 30-36)
    - Patients who are refractory to treatment are also at an increased risk of myasthenic exacerbation and crisis and are more likely to use increased healthcare resources, leading to a high economic burden (19-24, 31, 39, 40)
- There is an unmet need for licensed, targeted treatments with a fast onset of action that minimise the symptom burden, reduce the risk of myasthenic exacerbations and crises, and improve QoL for patients who are refractory to available therapies
- Rozanolixizumab is a targeted add-on therapy to standard of care for adult patients with AChR-Ab+ or MuSK-Ab+ gMG who are refractory to current treatments, such that the disease is uncontrolled (45)
    - Rozanolixizumab is administered via a short subcutaneous infusion (up to 18 minutes) and does not require hospital admission or the use of highly specialist equipment, facilitating patient access to treatment (45)
    - Rozanolixizumab is the first gMG treatment to be licensed in adult patients with AChR Ab+ or MuSK Ab+ gMG (58)
- Clinical outcomes reported in Section B.2.6 demonstrate that cyclic treatment with rozanolixizumab provides statistically significant and clinically meaningful improvements in the signs and symptoms of disease activity, as measured by MG-ADL, QMG, MG-C, and MG symptoms patient-reported outcome (MGSPRO), with a fast onset of action (treatment effect of rozanolixizumab vs placebo was observed as early as Day 8 in some patients) and a consistent response over multiple treatment cycles (46, 47)

B.1.3.1 *Disease overview*

Myasthenia gravis (MG[a]) is a chronic autoimmune disease caused by antibody-mediated destruction of the neuromuscular junction (NMJ) (see Section B.1.3.1.2 for pathophysiology) (1, 59). Patients with generalised MG (gMG) experience debilitating and fluctuating muscle weakness and severe fatigue in muscles, including those responsible for vital functions (e.g. breathing, swallowing and mobility). Symptoms of gMG can considerably impact day-to-day living to such an extent that employment and working hours are affected and caregiver support is needed (3). In addition, patients with gMG experience poor mental health, leading to higher rates of depression and anxiety compared with patients with other chronic illnesses (60-64). Symptoms are relapsing and remitting in nature, and, during severe exacerbations, may lead to respiratory failure and the requirement for mechanical ventilation (myasthenic crisis is described in Section B.1.3.1.3) (65). Approximately 15% of patients are refractory to therapy (66, 67) and experience high disease activity despite maximal immunosuppressive treatment. The clinical classification of MG with a description of symptoms is presented in Table 3.

Table 3. Clinical classification of MG (MGFA)

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.
V	Defined by intubation with or without mechanical ventilation (except when this is employed during routine post-operative management)

Abbreviations: MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America.
Source: The Myasthenia Gravis Foundation of America (68).

[a] MG and gMG patient populations are often not distinguished in the literature. Throughout this document, where discussing specific studies, we use the terminology (MG or gMG) used by each reference. Due to the high proportion of MG patients who experience gMG, it is anticipated that results of studies in patients with MG are also applicable to patients with gMG.

B.1.3.1.1 Epidemiology

Myasthenia gravis is a rare disease with low rates of incidence and prevalence (69, 70). In the UK, the annual incidence of MG is estimated at 25 cases per million people (2015–2019) (57), with an annual incidence rate of 17.6 per million people in England in 2021 (71). The Clinical Practice Research Datalink (CPRD) collected epidemiology data for a range of neuromuscular diseases across the UK from 2000–2019 and reported a lifetime prevalence estimate for MG of 33.7 (95% CI; 32,7, 34.7) per 100,000 people in 2019 (57, 72). Overall, it is estimated that there are 19,053 people living with MG in England (57). Most patients with MG (80–90%) develop gMG, and approximately 15% of patients with gMG are refractory to standard therapy (66, 67, 73). The number of people diagnosed is predicted to increase further, with an absolute annual growth rate of around 1% across the EU5, including England (71, 74).

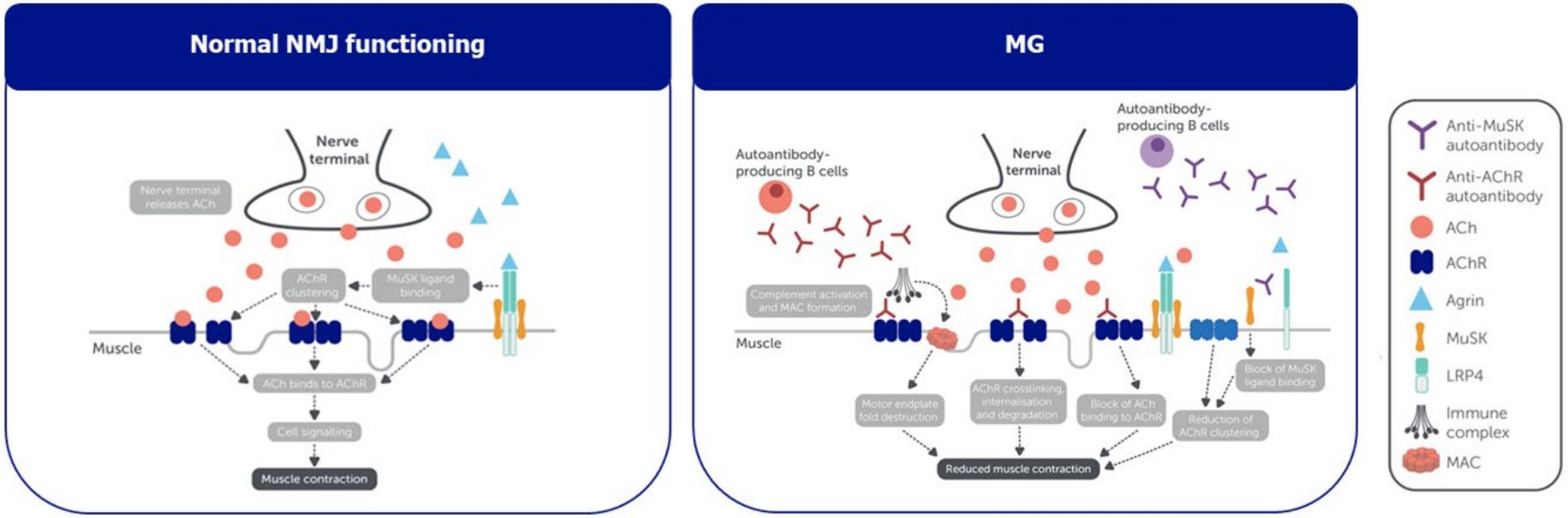
The majority of patients with gMG (80–90%) have autoantibodies against AChR (59, 65, 75, 76); however, an estimated 3% of patients with gMG in England have autoantibodies against MuSK (MuSK-Ab+) (71). In approximately 10% of gMG patients, no autoantibodies for AChR or MuSK are detectable (seronegative MG [SN-MG]) (77).

Myasthenia gravis is more prevalent in female than male patients, with female patients accounting for approximately 60% of the MG population (78, 79) (see Section B.1.4 for equality considerations related to women).

B.1.3.1.2 Pathophysiology

Muscle weakness in MG is caused by defective synaptic transmission at the NMJ (Figure 2) (1, 59). At the healthy NMJ, acetylcholine (ACh) binds to AChRs in the post-synaptic muscle-cell membrane activating the muscle fibre and resulting in muscle contraction (80, 81). In MG, autoantibodies bind to components of the NMJ and either initiate the classical complement cascade (AChR autoantibodies), or prevent clustering of the AChRs (MuSK autoantibodies) (Figure 2). AChR autoantibodies cause the activation of the complement system leading to assembly of the membrane attack complex (MAC). In MuSK-Ab+ MG, binding of auto-antibodies to MuSK leads to blocking of the correct assembly of AChRs, resulting in the loss of AChRs from the motor endplate (3). The activity of these autoantibodies leads to the disruption of normal signalling between nerve fibres and muscles and leading to the unpredictable, fluctuating muscle weakness and fatigue characteristic of MG (59, 73, 80, 82-85) (Figure 2). A treatment directly targeting autoantibodies may minimise the loss of AChRs at the NMJ and the impact on muscle function (see Section B.1.2 for rozanolixizumab mechanism of action).

Figure 2: Pathogenesis of MG



Abbreviations: ACh, acetylcholine; AChR, acetylcholine receptor; LRP4, low-density lipoprotein receptor-related protein 4; MAC, membrane attack complex; MG, myasthenia gravis; MuSK, muscle-specific kinase; NMJ, neuromuscular junction.
Source: Adapted from Howard et al, 2018 (80), Gilhus et al, 2019 (3), Lindstrom et al, 2000 (81) and Kaminski et al, 1997 (83).

B.1.3.1.3 Clinical burden

Myasthenia gravis can be a severe and debilitating disease, characterised by fluctuating and unpredictable muscle weakness which can lead to persistent fatigue and can result in dependence on others and/or mechanical support for movement and breathing (2).

Approximately two-thirds of patients experience muscle weakness confined to extraocular muscles at initial presentation, known as ocular MG (oMG) (86-88). Most (80–90%) patients with oMG will develop gMG within two years (10, 82, 86), which is associated with weakness in the muscles of the head, neck, arms, hands, chest, legs and torso (65). Of 1,518 patients with MG, 75% reported muscle weakness after physical strain, 71% had weakness of upper limbs and 70% had difficulty walking (89). Persistent fatigue is one of the most common symptoms of gMG, occurring in 44–70% of patients and interfering with daily activities such as walking, self-care and going to work (2, 82, 89-94). The debilitating symptoms of gMG reduce patient QoL (see Section B.1.3.1.4).

The symptoms of gMG are unpredictable and fluctuate in intensity. Patients can experience a sudden worsening of their symptoms (exacerbation) that requires urgent intervention to prevent a myasthenic crisis (9-12), a life-threatening deterioration of muscle weakness and respiratory failure requiring treatment in an intensive care unit with mechanical ventilation and hospitalisation (9, 21, 28, 29). The annual rates of exacerbation and myasthenic crisis are estimated at 0.244 and 0.023 per 10,000 person-years, respectively (95). Patients who experience a myasthenic crisis will spend a median of 12–14 days on mechanical ventilation, with 20% of patients still ventilated beyond 1 month (96). Myasthenic crisis carries a mortality rate of 3–8% despite intensive care, intubation, and escalation of immunomodulatory therapy (28).

Many of the symptoms of gMG are similar for the different autoantibody types of gMG; however, patients with MuSK antibodies tend to have more severe bulbar symptoms and generalised weakness, including crises, compared with AChR-Ab+ gMG (97-99). Responses to therapy also differ, as patients with MuSK-Ab+ MG have a lower probability of achieving stable remission compared with AChR-Ab+ patients, and patients with MuSK-Ab+ often do not tolerate treatment with acetylcholinesterase inhibitors (AChEI) (98) (see Section B.1.3.2.2). Patients with MuSK-Ab+ MG are more likely to develop refractory disease compared with AChR-Ab+ MG patients (67).

In addition to the debilitating symptoms associated with gMG, the majority of patients (~75–90%) experience comorbidities such as joint problems, cardiac and thyroid disease, dyslipidaemia, diabetes and other autoimmune conditions (39, 73, 85, 89, 100, 101).

Studies from Denmark, Norway, Sweden, France and Germany report excess mortality among patients with MG compared with the general population (102-104). The standardised mortality rate (SMR) was higher for patients with MG in Denmark (1.42), Finland (1.30) and Sweden (1.21) compared with the respective general population (102). The mortality rate was 5.7% among German patients with MG (n=1,247) in 2019, compared with 1.1% for the general population (105). In France, MG was associated with increased mortality in comparison with an age- and gender-matched control population, with a hazard ratio of 1.82 (95% CI; 1.74, 1.90]) (104).

Mortality is higher among younger female patients compared with the general population. In a Nordic study of patients from Denmark (n=2,248), Finland (n=2,306) and Sweden (n=4,500), SMR was numerically higher in women with MG aged <65 years compared with age- and sex-matched general population controls (102) (see Section B.1.4, Equality considerations).

B.1.3.1.4 Impact on quality of life

Patients with MG experience debilitating symptoms that severely impact all aspects of their lives, including planning for future opportunities (4).

Several studies have demonstrated that QoL is reduced in patients with MG compared with the general population (5-8). Moreover, patients with MuSK antibodies have shown higher disease burden scores (indicating lower health-related quality of life [HRQoL]) compared with patients positive for AChR antibodies (6). In a multicentre study of HRQoL, 86.5% of patients with MG (n=37) reported moderate or severe problems in ≥1 dimension (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) of the European Quality of Life-5 Dimensions-3 Level Version (EQ-5D-3L) scale, and the percentage of patients with moderate or severe problems was substantially higher in patients with MG compared with the general population (5).

In an analysis of the MyRealWorld-MG observational study (1,859 participants with moderate to severe MG), QoL in those with moderate to severe MG was lower than in the general population (8). The mean MG-Activities of Daily Living (MG-ADL) score was higher in the MG group vs the general population (5.8 vs 1.2, respectively, p<0.0001), indicating a higher symptom burden and lower functional status among patients with MG. In addition, EQ-5D-5L utility values were on average 0.165 and 0,361 lower in patients with moderate and severe MG, respectively, compared with the general population and those with severe disease had worse scores than those with mild symptoms (0.511 vs 0.872, respectively, p<0.001). As well as negatively impacting patient QoL, severe disease is also associated with a greater caregiver burden vs mild gMG (estimated marginal means for severe vs mild MG [95% CI]: 0.16 [0.13; 0,19] p≤0.0001) (106).

The utility value for patients with MG (0.688, interquartile range [IQR]: 0.599–0.837), as measured by the EQ-5D-5L (107), is similar to that for patients with chronic heart failure (0.696; standard deviation [SD]: 0.302) (108), highlighting the severity of the disease burden of MG and its impact on patients' QoL (8, 109).

Patients with active disease despite maximal immunosuppressive therapy, or with severe disease, experience particularly poor QoL (93, 110-114). In addition to the symptom burden, QoL is impacted by the limitations of available therapies: long-term corticosteroid (CS) use is associated with multiple side effects (63, 115, 116), whilst IVIg and PLEX therapies are not easily available or accessible, and present high cost and treatment burdens (see Section B.1.3.3) (20, 25, 36).

The impact of muscle weakness on QoL is compounded by the chronic fatigue experienced by many patients (93). Between 44% and 70% of the MG population experience fatigue, and these patients have significantly poorer MG-QoL15 (p<0.001) and functional disability scores (p<0.001) than those without fatigue (91-93). Persistent fatigue may prevent patients with MG from performing daily tasks (2).

The fluctuating, chronic, symptoms of gMG negatively impact patients' mental health, leading to depression, fear, and anxiety (4, 60-62). In a European cross-sectional study (n=55), 64% of patients with MG had depression (assessed using the Beck Depression Inventory [BDI] Scale) and 46% of patients had moderate or severe anxiety (assessed using the State-Trait Anxiety Inventory) (64). Using the Myasthenia Gravis Impairment Index [MGII] score, depression was associated with higher disease severity (p<0.0001) and generalised disease (p=0.02) (63). Fatigue is also associated with increased depressive symptoms (63). Due to the fluctuating nature of the symptoms, anxiety may be worsened by the fear of exacerbation and myasthenic crises, which cannot be predicted (64, 65). The risk of suicide is over four times higher among patients with MG vs the general population (odds ratio [OR] 4.3 [95% CI; 2.0, 9.4], p=0.0003), highlighting the profound impact of gMG on patients' lives (117).

Although the negative effect of living with gMG on QoL is well established, non-disease specific instruments such as the EQ-5D may be insensitive to common symptoms of gMG, such as fatigue, vision impairment, and hand weakness (118). A report by the Office of Health Economics (OHE) suggests that generic measures of HRQoL may fail to reflect what matters to patients by not capturing symptoms such as fatigue (119). In addition, the EQ-5D may miss changes in QoL when patients' symptoms and functioning are unpredictable and fluctuate over time. If the patient is not experiencing symptoms on the day of the questionnaire (the EQ-5D asks respondents to assess their health 'today'), the score may overestimate patient QoL (119). It is likely that widespread use of non-disease-specific instruments, and the insensitivity of these on measuring the detrimental impact of common symptoms of MG on HRQoL, has led to an underestimation of the impact of MG on HRQoL (120, 121).

B.1.3.1.5 Economic burden

Direct costs

Generalised MG is associated with a substantial economic burden related to treatment costs, healthcare resources utilisation (HCRU) and lost productivity for patients and carers (see below for indirect costs) (19-24). Refractory patients with high disease activity incur high healthcare costs due to the higher level of hospitalisation and intensive care for symptom exacerbation and crises compared with non-refractory patients (19, 43).

The annual cost of treating patients with gMG in the UK was estimated to be £217 million (2014/15 costs), based on a cost analysis using data from a cohort study of primary (CPRD) and secondary care (Hospital Episode Statistics [HES]) in the UK (19, 43). Patients with refractory disease accounted for 18.2% (£34.5 million) of the total cost, despite only comprising 5.7% of the patient population in the study (19). The higher annual treatment cost per patient in the refractory population was largely due to the treatment and administration of IVIg and PLEX (76% of the total costs) (19, 43).

Patients with refractory MG spend longer in hospital than non-refractory patients (19). In the cohort study described above, amongst 1,149 patients with MG (from 1997–2016), total number of inpatient days was higher in the refractory MG cohort (median [IQR] = 33 [16–74] days) than in the non-refractory cohort (16 [6–45] days [p <0.0001 vs refractory MG]) (19).

Myasthenic crisis is associated with a substantial cost burden related to admission to ICU and intubation for assisted mechanical ventilation (in 66–90% of cases), provision of a feeding tube, and IVIg or PLEX treatment (21-24). Some patients experiencing myasthenic crisis or exacerbation of symptoms are hospitalised with uncontrolled symptoms for prolonged periods, ranging between 5–92 and 1–30 days in patients who require or do not require intubation, respectively, and incur substantial costs to the healthcare system (25-27, 122). Plasmapheresis was also associated with longer hospital stays, as a course of PLEX to treat a myasthenic exacerbation requires a hospitalisation of at least 10 days (27). The high cost and HCRU burden of managing patients with gMG adds to the growing challenge of limited National Health Service (NHS) resources against a backdrop of increased demand for treatment, staff shortages and long wait times (123).

Indirect costs

Productivity losses

Patients with MG and their caregivers can face economic hardship related to loss of employment or reduced working hours (13-18). Unemployment rates are higher for patients with MG than the general population or matched control groups, and higher compared with other chronic conditions (13-16). Patients with MG, especially those with uncontrolled symptoms, face unemployment (23–59%), long-term sickness absence (19–47%), and the resulting reduced income (36–53%) (13-16). As patients with MG tend to be of working age at diagnosis (mean age at disease onset is 45±18 years for men and 35±18 years for women [p<0.001]) (124), much of their working lives will be affected by MG.

Caregiver disutilities

Many patients with gMG require caregiver support for daily activities, which leads to reduced employment in those caring for gMG patients. A survey of expert physicians across France, Germany, Italy, Spain, the UK, and the US reported that 38% of patients with gMG required a caregiver (14, 17, 18). In total, 25% of caregivers changed their work status or retired as a result of needing to provide care (18).

Hours of work and caregiver time lost, categorised by MG-ADL score, were assessed in a survey as part of the MyRealWorld-MG study (125). Overall, the proportion of patients requiring caregiver help increased with disease severity (higher MG-ADL scores) as did the average number of working hours/week that caregiver lost. While only 10.4% of patient with mild disease (MG-ADL score 2–3) reported having a caregiver, 50% of the patients with MG-ADL scores 8–9 required caregiver help. Caregivers of patients with MG-ADL score 8–9 lost an average of 14.5 hours of work each week, which increased to >34 per week when assisting patients with MG-ADL score >12 (125).

B.1.3.2 *Clinical pathway of care*

There are currently no specific National Institute for Health and Care Excellence (NICE) guidelines for the full clinical pathway of care in MG, and there is limited published information on the care pathway for patients with MG. Recommendations from the Association of British Neurologists (ABN) management guidelines (25) (published in 2015 and updated in 2018) are included in Sections B.1.3.2.1, B.1.3.2.2 and B.1.3.2.4.

Following a diagnosis of MG (Section B.1.3.2.1), a number of treatments are available, depending on disease severity and symptom control (Section B.1.3.3.2).

B.1.3.2.1 Diagnosis

There is no formal diagnostic pathway recommended by NICE, and the diagnosis of MG may be challenging due to fluctuating symptoms (65). In addition, MG is a rare disease and therefore unfamiliar to many HCPs, and an overlap in symptoms with other neurological diseases can result in an MG diagnosis being missed or delayed (86, 126). UK guidelines advise physicians to seek the advice of a specialist neurologist with an interest in MG if the diagnosis is uncertain or when the disease is difficult to manage (25, 127).

The focus of the diagnostic process is to look for the signs and symptoms, neurological findings and laboratory results that are characteristic of MG, while excluding other diagnoses (29, 128, 129). The ABN management guidelines and others recommend that MG is diagnosed through a combination of patient medical history, physical and neurological exams, autoantibody serum testing, and electrophysiological tests (25, 126-128, 130).

B.1.3.2.2 Management of generalised myasthenia gravis

Licensed targeted treatments for gMG are not routinely reimbursed and consequently not available to patients in England and Wales outside of compassionate use, Early Access to Medicines schemes and individual funding requests.

Acetylcholinesterase inhibitors, such as pyridostigmine, are the first-line treatment for gMG (25, 26, 122) (Table 4). If treatment with AChEIs is not effective or only provides short-term relief, CSs such as prednisolone are used (25, 26, 122). Clinical guidelines for the management of gMG recommend a CS starting dose of 10 mg on alternate days, which may be increased to a maximum dose of 100 mg on alternate days or 1.5 mg/kg (127).

Non-steroidal immunosuppressive therapies (NSISTs), such as mycophenolate and azathioprine, are offered in addition to steroids as current standard of care, with the aim of providing additional symptom relief and reducing CS dose over time (25, 26, 122). Azathioprine, although an available option, generally would not be given as the first choice NSIST, because of the increased risk of skin malignancy and slower mechanism of action than mycophenolate (≥12 months vs 6–12 months, respectively). In addition, an enzyme level check is required before initiating azathioprine, as azathioprine is contraindicated in patients who lack thiopurine methyltransferase (TPMT) due to increased risk of liver failure (122).

Alternative NSISTs may be offered, including methotrexate, ciclosporin and rituximab, although these are not currently licensed for gMG in the UK (25, 26, 49, 50, 122, 131). Rituximab has been commissioned for use by NHS England (NHSE) in gMG patients who present active disease despite maximal immunosuppressive therapy, are experiencing a myasthenic crisis, have frequent relapses, experience significant side effects with oral ISTs or are unresponsive to licensed rescue treatments (51). Expert clinical opinion sought by the All Wales Therapeutic and Toxicology Centre (AWTTC) has suggested rituximab may be used as a first-line treatment for newly diagnosed

antibody positive MG in combination with steroids, as opposed to its use for refractory patients (52). However, there is limited evidence of rituximab's effectiveness, up to 12 months of treatment may be needed to observe any clinical benefit and safety concerns have been raised (e.g. increased risk of severe infections) (25, 51, 132-134). International consensus guidelines stated that rituximab has not fulfilled hopes for its use in refractory patients and has not been robustly studied in the population considered in this appraisal; for example, both trials for rituximab in MG were in patients who were relatively early in their disease course (mean time since diagnosis 132.4 days in RINOMAX and 5.5 years in BeatMG compared with 8.6 years in the pivotal trial for rozanolixizumab, MycarinG) (135).

Surgery to remove the thymus (thymectomy) is an option for people age <45 years with mild to moderate disease and antibodies against AChR (25, 26). However, there is little evidence to support the effectiveness of thymectomy in patients with MuSK antibodies (136). Patients are treated before thymectomy to prevent possible ICU admission with respiratory crisis after the procedure. Pre-thymectomy treatments include pyridostigmine, CSs, NSISTs, PLEX, and IVIg, with a preference for treatments with a fast onset of action. Thymectomy is an elective surgery and not an emergency procedure, and it can take at least 12 months for patients to achieve maximum clinical benefit.

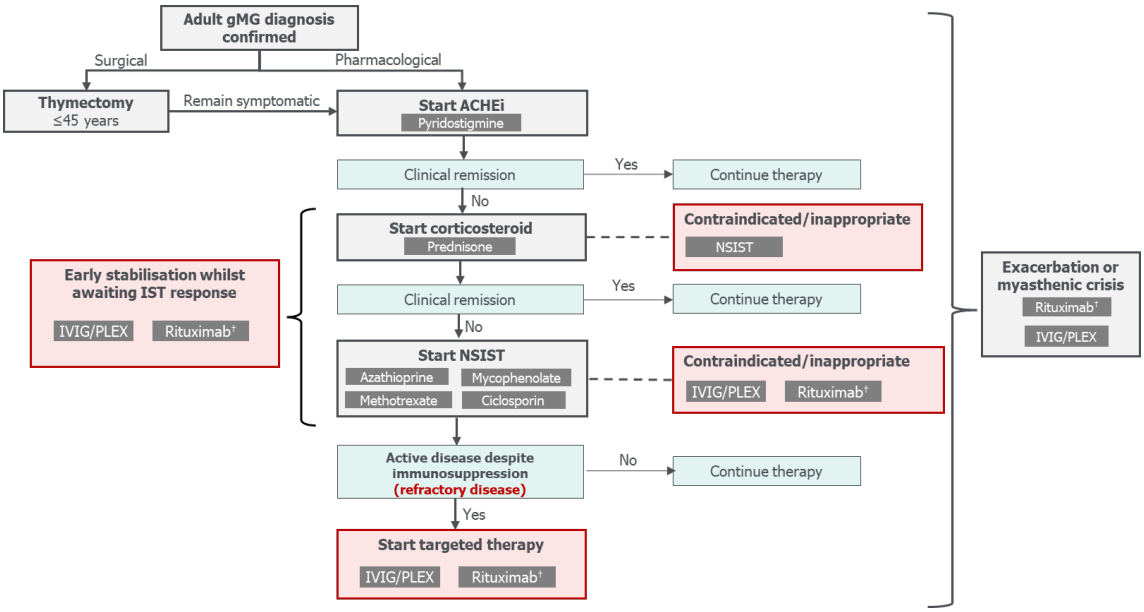
Chronic IVIg or PLEX are used as a maintenance treatment for refractory patients (25, 26, 36, 122, 137). Chronic PLEX can be used following failure on all standard therapies or when CSs and ISTs are contraindicated or inappropriate (25, 26, 36, 137). The IVIg NHSE Clinical Commissioning Policy (CCP) on the use of IVIg states that, where possible, PLEX should be considered before IVIg. In the remaining circumstances, where a patient with gMG has failed all standard treatments (including steroids and immunosuppression) and following authorisation by a specialist in MG from a centre with a specialist neuromuscular service, IVIg maintenance therapy may be considered (138). According to the latest report from the NHSE IVIg database, 666 patients with MG accessed IVIg as a treatment option, although this dataset has limitations, including underreporting (139). The company requested access to anonymised data from MDSAS IVIg database commissioned by NHSE to support the evidence base for this submission. The request was denied. Efgartigimod is currently available for patients with refractory gMG who have failed, not tolerated or are ineligible for current treatments through the Early Access to Medicines Scheme (EAMS) and EAMS PLUS.

While the classes of therapy used in patients with MuSK-Ab+ gMG are generally the same as those for patients with AChR-Ab+ gMG, the responsiveness of patients to specific therapies differs between the two subpopulations (21). Patients with MuSK-Ab+ gMG are less responsive to AChEIs and are frequently intolerant to pyridostigmine at conventional doses (140). They respond to CS and NSISTs but tend to remain dependent on high-dose CS despite concomitant therapy with NSISTs (140). For those patients who are refractory to CS and NSISTs, remaining treatment options include rituximab and PLEX, while IVIg is usually less effective. While not licensed, rituximab is recommended by international MG consensus guidelines and by an NHSE CCP for MuSK-Ab+ MG patients who have an unsatisfactory response to initial immunotherapy (134, 135, 141). This is in contrast to patients with AChR-Ab+ gMG where rituximab is only considered when patients fail on or do not tolerate other immunotherapies (141).

In the event of a myasthenic crisis (see Section B.1.3.1.2), patients are treated in hospital with mechanical ventilation, IVIg and/or PLEX and best supportive care (25, 26, 122). For impending crisis, bulbar or respiratory compromise can be managed using IVIg and PLEX (122).

The current treatment pathway for gMG is presented in Figure 3. Currently available treatments for patients with gMG are listed in Table 4. The limitations associated with the available treatments for gMG are discussed in Section B.1.3.3.

Figure 3: Current treatment pathway for mild-to-severe gMG in the UK



† In the UK, IVIg or PLEX are the first choice to stabilise patients with exacerbation or myasthenic crisis, while rituximab is used for maintenance after stabilisation.
As opposed to for refractory patients (as shown here), expert clinical opinion sought by the All Wales Therapeutic and Toxicology Centre (AWTTC) has suggested rituximab could be used as a first-line treatment for newly diagnosed antibody positive MG with steroids, based on emerging clinical evidence (52). In addition, there is limited evidence of its effectiveness, in clinical trials and the real world, as well as safety concerns, for patients with refractory gMG (25, 132, 133, 135).
Source: Adapted from the ABN management guidelines and validated by UK clinical expert opinion (25, 122, 127).
Abbreviations: ABN, Association of British Neurology Guidelines; gMG, generalised myasthenia gravis; IST, immunosuppressant therapy; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant therapy; PLEX; plasma exchange; UK, United Kingdom.

Table 4: Currently available treatments for MG in the UK

Treatment	Method of administration	Indication	Time to onset of effect	Time to maximal effect	Efficacy	Safety	Other limitations
AChEIs	Oral or IV	All patients with MG	15–30 minutes	2 hours	Limited RCT evidence	Nausea, diarrhoea abdominal cramping, increased salivation	• Most gMG patients cannot be adequately managed with AChEIs alone due to dose-limiting toxicities • MuSK-Ab+ gMG patients are less responsive to and are frequently intolerant to pyridostigmine (at conventional doses)
Low-dose and high-dose CS	Oral or IV	Off-label	2–4 weeks	5–6 months	Limited RCT evidence	Skin atrophy, glaucoma, mood disorders, risk of infection, weight gain, osteoporosis, diabetes (all in relation to dose)	• Significant side effects with chronic treatment. • MuSK-Ab+ gMG patients remain dependent on CS despite concomitant therapy with NSISTs
Non-CS ISTs	Oral or IV	Off-label	up to 18 months	1–2 years	Limited RCT evidence	Bone marrow suppression, leukopenia, hypertension, GI intolerance, infection, hepatoxicity, nephrotoxicity, teratogenicity	Delayed onset of effect
PLEX	IV	Off-label	1–7 days	1–3 weeks	Limited RCT evidence	Allergic reactions, risk of infection, hypotension, nephrotoxicity, thrombosis	• Need for specialised equipment that may not be readily available • Burdensome intervention • Repeated interventions may be necessary due to rapidly declining effect

Treatment	Method of administration	Indication	Time to onset of effect	Time to maximal effect	Efficacy	Safety	Other limitations
IVIg	IV	NHSE CCP	1–2 weeks	1–3 weeks	Limited RCT evidence	Allergic reactions, nausea, hypotension, anaphylactic reactions, nephrotoxicity, thromboembolism	• Burdensome administration (long infusion time) • Specialised setting required for infusions • Repeated interventions may be necessary due to rapidly declining effect • Expected higher risk of AEs such as venous failure and thrombosis with long-term use (142, 143) • IVIg is usually less effective in MuSK-Ab+ gMG patients
CD20-antibodies (rituximab)	IV	Off-label	12 months	12 months	Phase II: no significant difference in CS-sparing effect vs placebo	Risk of fatal infusion reactions, tumour lysis syndrome, severe mucocutaneous reactions and progressive multifocal leukoencephalopathy	• Burdensome infusions • Delayed onset of effect • Infusion reactions

Abbreviations: AChEI, acetylcholinesterase inhibitor; AChR+, acetylcholine receptor-positive; CCP, Clinical Commissioning Policy; CS, corticosteroids; GI, gastrointestinal; gMG, generalised myasthenia gravis; IST, immunosuppressive therapy; IV, intravenous; IVIg, intravenous immunoglobulin; NHSE, National health Service England; PLEX: plasma exchange; RCT, randomised controlled trial.

References: AChEIs: Pyridostigmine Bromide SmPC (144). CS: Sanders 2016, (21); Farmakidis 2018, (31). NSISTs: Farmakidis 2018, (31). PLEX: Osman 2020, (145). IVIg: Gajdos 2005, (146); NHSE CCP (135). Eculizumab: Dhillon 2018, (147); European Medicines Agency 2019, (148). Rituximab: CADTH 2018, (149). Rixathon SmPC (150); Tandan 2017 (151).

B.1.3.2.3 Relevant NICE guidance, pathways or commissioning guides

There are currently no NICE technology appraisals or guidelines for gMG. NICE technology appraisals for zilucoplan (ID4008) and efgartigimod (ID4003) for gMG are currently in development. The appraisal for eculizumab (TA636) was terminated as no evidence submission was provided and the appraisal for ravulizumab (ID4019) has been terminated due to the evidence submission being withdrawn by the company.

B.1.3.2.4 Clinical guidelines

The 2015 Association of British Neurologist (ABN) management guidelines were designed to guide physicians and general neurologists in the management of MG (127). They attempt to steer a path between evidence-based practice and established best clinical practice (25, 127). The ABN guideline was published in 2015, and therefore does not include all the treatments currently used in MG. An update to the ABN guideline is expected in 2024 or 2025. European guidelines (Euro Myasthenia) are aimed at European clinicians with limited experience in MG (GPs and neurologists) (152). The German Neurological Society has recently updated their guideline for the management of myasthenic syndromes to discuss the currently available treatments for gMG. The guideline underlines how therapy decisions should consider age, antibody status, thymic pathology and disease activity (based on MG-specific scores) (134).

B.1.3.3 *Issues relating to current clinical practice*

B.1.3.3.1 Treatment burden

Currently, there are no medications licensed for the specific treatment of patients with MuSK-Ab+ in the UK (Section B.1.3.2.2) (25, 26, 49, 50, 122, 131). The use of unlicensed, non-targeted therapies that have not been assessed by NICE in patients with gMG presents a challenge in the evaluation of innovative targeted therapies for this disease and no such treatments have been reimbursed in the past 30 years. This difficulty is exacerbated by gMG being a rare disease with limited availability of clinical and economic data.

Treatments for gMG are associated with their own burden and patients must balance the benefits of controlling symptoms with severe and debilitating side effects. Current treatment options for MG rely on non-specific immunosuppression for symptom control (most of them used off-label and based on limited evidence (25, 26, 49, 50, 131), as there are no available therapies that specifically target the underlying pathophysiology of MG (25, 153). Long-term use of standard treatments is associated with side effects, for example, skin cancer with azathioprine (34). Corticosteroids are associated with severe side effects such as diabetes, osteoporosis, depression and infection, which can trigger a myasthenic exacerbation (3, 11, 31-33). Paradoxically, high dose CSs are associated with a temporary worsening of symptoms and an extended hospital stay (27, 154). Patients who are contraindicated to CSs need other treatment options (25, 26). Interviews with MG experts in the UK also highlighted the patient populations who, though not technically contraindicated to CS, should avoid their use and are in need of alternative therapeutic options, such as patients with comorbid diabetes or osteoporosis and high BMI (122).

Many patients with gMG are refractory to standard therapy and continue to experience poor symptom control (37, 38, 67). The only currently available treatments for patients who are refractory to standard therapies are IVIg and PLEX, both of which are used off-label as they are unlicensed for the chronic treatment of gMG in the UK (44, 155). In addition, IVIg and PLEX have limitations related to cost and patient and carer burden. Intravenous Ig supply is managed in the UK (36, 41, 67). A global shortage coinciding with increased usage of IVIg has resulted in strict national clinical guidelines for the use of IVIg (35, 36, 67). Administration of PLEX requires treatment at specialist centres over 4–5 consecutive days, which may involve patients having to travel long distances for treatment and even staying in hospital for repeat treatment (25, 26, 67). The IVIg infusion duration of 4–6 hours over 2–5 days is also burdensome for patients. IVIg and PLEX are associated with economic impacts for both patients and the NHS, related to high HCRU (from treatment and labour costs associated with treatment, see Section B.1.3.1.5), opportunity cost, productivity losses, and cost of travel for patients (19, 20, 43, 67). Both patients and the NHS incur opportunity costs; the NHS could direct the managed supply of IVIg and PLEX towards the treatment of patients with other indications without effective targeted treatments, whilst patients and their caregivers could experience lower economic and humanistic burdens.

B.1.3.3.2 Poor symptom control and delayed onset of treatment effect

Some patients with gMG continue to experience a severe disease burden and poor symptom control (37, 38). In patients with MuSK-Ab+ MG, the probability of achieving a complete stable remission is particularly low (99).

Delayed onset of treatment effect with NSISTs (usually 6–18 months, but it can take up to 2 years to achieve maximal clinical benefit) contributes to poor disease control, leaving patients with a high symptom burden and at risk of symptom exacerbation and crisis (30, 31, 156).

Patients may cycle through different ISTs until their symptoms are under control. About 15% of patients are refractory to available treatments and continue to experience active disease. Patients who are refractory to currently available treatments are at an increased risk of myasthenic exacerbation and crisis, a life-threatening complication of gMG, and are more likely to use healthcare resources, leading to a high economic burden (19-24, 31, 39, 40) (see Sections B.1.3.1.2 and B.1.3.1.5). The only available options for patients with refractory disease are IVIg and PLEX, but both are associated with limitations related to treatment burden and accessibility (see Section B.1.3.3.1). IVIg and PLEX were administered to 54.2% of patients subsequently treated with efgartigimod under EAMS in the UK between June 2022 and July 2023 (157). Based on expert opinion, nearly all patients requiring chronic IVIg or PLEX treatment will receive it in the UK (53).

B.1.3.3.3 Unmet need

Given the limitations of current treatment options for patients with refractory gMG, there is an urgent unmet need for new treatment options to control debilitating symptoms. A licensed, targeted treatment which controls symptoms will reduce the effects of debilitating symptoms on patients' lives and may decrease the need for CSs and the risk of myasthenic exacerbation (see section B.1.3.1.2) (158), as well as improving patient mental health and QoL in both patients and caregivers. Patients would also benefit from

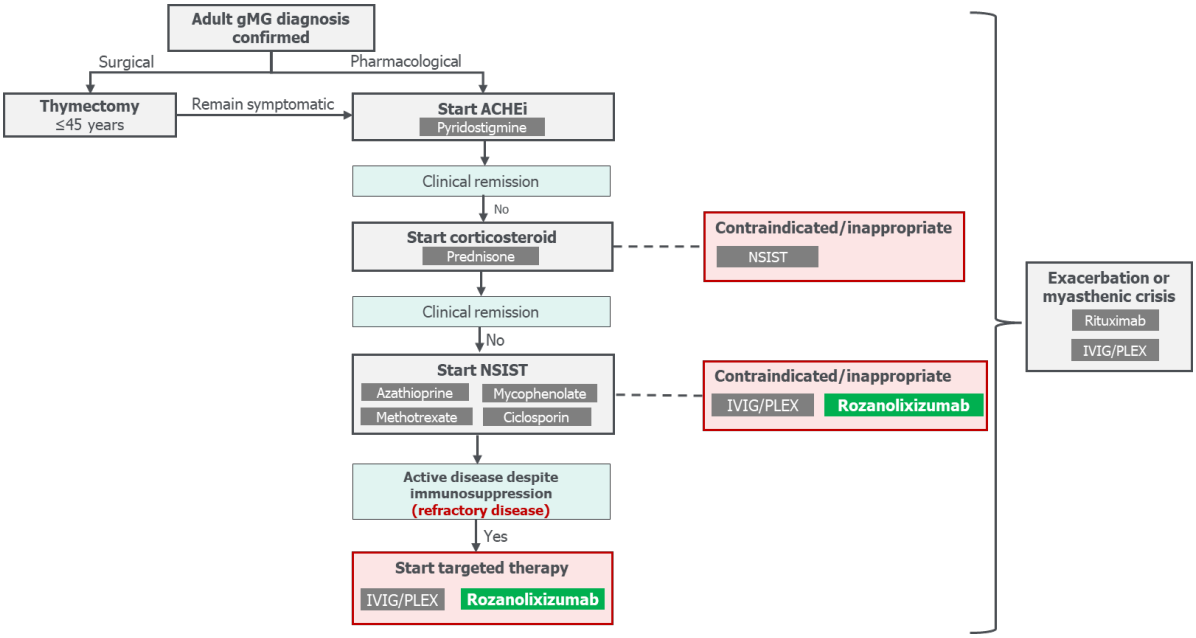
a treatment that has a short infusion time (up to 18 minutes) and can be administered in an outpatient setting, which will also reduce NHS resource use.

A consensus report by the Health Innovation Network (HIN), developed by clinicians and patients, highlighted requirements to elevate standards of care for people with MG in the UK, which included faster diagnosis, increased awareness of rare diseases among healthcare professionals, better co-ordination of care and improved access to specialist care, treatments and drugs (159). The need of a multi-disciplinary team to co-ordinate care was highlighted in the report, with patients with MG or their caregivers often responsible for maintaining communication between different specialist departments and/or their GPs. Neurologists will be responsible for managing most patients with refractory gMG, thus efficient co-ordination between primary and secondary care is needed in these patients (159).

B.1.3.4 *Rozanolixizumab place in therapy*

Rozanolixizumab is positioned as an add-on therapy to standard of care for adult patients with AChR-Ab+ gMG or MuSK-Ab+ gMG who are refractory[b] to current treatments, such that the disease is uncontrolled, as defined by inadequate response to ≥2 prior MG immunosuppressive therapies and an additional therapy such as IVIg or PLEX being considered or already utilised (Figure 4).

Figure 4: Proposed positioning of rozanolixizumab for gMG in the UK



Source: Adapted from the ABN management guidelines and validated by UK clinical expert opinion (127).
Abbreviations: ABN, Association of British Neurology Guidelines; gMG, generalised myasthenia gravis; IST,

[b] Refractory is defined as patients with gMG classified as MGFA class II–IVa with uncontrolled diseases (≥2 prior MG therapies such as prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids) and who are being treated with or considered for PLEX/IVIg.

immunosuppressant therapy; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant therapy; PLEX; plasma exchange; UK, United Kingdom.

Completed clinical trials (MycarinG and MG0007) have demonstrated the consistent efficacy of rozanolixizumab over five treatment cycles at the interim data cut-off (8 July 2022), with an acceptable safety profile in patients with gMG receiving concomitant standard of care treatment, as well as a fast onset of action (treatment effect of rozanolixizumab was observed as early as Day 8). Rozanolixizumab may also reduce the need for rescue therapy (with IVIg or PLEX), which may lead to reduced medical resource utilisation costs associated with managing exacerbations (122).

Rozanolixizumab is the first MG treatment to be licensed in both AChR Ab+ and MuSK Ab+ patients with gMG. Because of its targeted mechanism of action and fast onset of action it is estimated that rozanolixizumab will reduce the impact of uncontrolled disease on patients and improve QoL for patients and caregivers (45). As a once-weekly subcutaneous infusion administered for a 6-week treatment cycle that is repeated as needed, rozanolixizumab will avoid the need for frequent IV administration. No new infrastructure or capital investment would be required for its introduction to the NHS. Rozanolixizumab does not require hospital admission or the use of highly specialist equipment or complex training (unlike PLEX) and has a short infusion time (up to 18 minutes), facilitating access for all patients for whom rozanolixizumab therapy would be appropriate.

B.1.4 *Equality considerations*

There is geographic variability in treatment availability and access to specialist centres, which introduces inequality among patients with MG in terms of access to care. The introduction of a new, targeted, fast-acting therapy that can be subcutaneously administered by a healthcare professional in a suitable outpatient setting would help to mitigate this inequality and enable patients to live a much more flexible life in terms of family, work and social interactions.

There is health inequality between males and females in terms of the burden of MG. MG is more prevalent in female than male patients, with female patients accounting for approximately 60% of the MG population (78, 79). Studies of patients from Denmark, Finland and Sweden show increased mortality among younger (30–49 and 50–64 age groups) women compared with men with MG and the general population (102). In addition, females are younger than males at disease onset (mean age of disease onset is 35±18 vs 45±18 years, respectively [p<0.001]) (124) and onset of MG at age <50 years is three times more common in women than in men (160-162). Women with MG are therefore exposed to the negative impacts (economic, social, on QoL) earlier in life and for longer than men amounting to a greater total burden to their personal and working life.

B.2. Clinical effectiveness

Cyclic treatment with rozanolixizumab as an add-on therapy to SOC for patients with AChR Ab+ or MuSK Ab+ gMG leads to statistically significant and clinically meaningful improvements in the signs and symptoms of disease activity, as measured by MG-ADL, QMG, MG-C, and MGSPRO, with a fast onset of action (treatment effect of rozanolixizumab was observed as early as Day 8) and a consistent response over multiple treatment cycles (46, 47)

- **MycarinG**, a Phase III, randomised, placebo-controlled trial, provides pivotal clinical evidence for rozanolixizumab as an add-on therapy to SOC for patients with antibody positive gMG
- The open-label extension (OLE) study, **MG0007** (interim results; cut-off date 08 July 2022), demonstrates the consistent efficacy over multiple treatment cycles and the long-term safety of rozanolixizumab in this patient population
- In the MycarinG study, the primary efficacy point of change from baseline (CFB) to Day 43 in MG-ADL score was met
  - Treatment with rozanolixizumab resulted in significantly greater CFB to Day 43 in MG-ADL score compared with placebo (≈7 mg/kg: −3.370; ≈10 mg/kg: −3.403; placebo: −0.784). The LS mean difference vs placebo was statistically significant in both the rozanolixizumab ≈7 mg/kg (−2.586, p<0.001) and ≈10 mg/kg (−2.619; p<0.001) and was considered clinically meaningful
  - Rozanolixizumab demonstrated a rapid onset of action with treatment effect observed as early as Day 8
  - Both rozanolixizumab dosages were associated with consistently greater improvements from baseline to Day 43 in QMG, MG-C and MGSPRO scores (secondary endpoints) compared with placebo
- In the MG0007 study, following repeated cyclic treatment, rozanolixizumab (at the licensed dose of ≈7 mg/kg and also at ≈10 mg/kg) led to consistent and clinically meaningful improvements in MG-ADL, QMG and MG-C, and statistically significant improvements in MGSPRO scores
  - Responses for MG-ADL were seen as early as Day 8 of each treatment cycle, with a median time to MG-ADL response of [redacted] for the [redacted] of each of the first [redacted] 6-week treatment cycles
- **Pooled data** from MycarinG, MG0004 and MG0007 demonstrated that repeated cyclic treatment with rozanolixizumab led to [redacted] in each cycle in all efficacy endpoints and [redacted] across repeated cycles (Appendix M)
- Rozanolixizumab was generally well tolerated and displayed an acceptable safety profile in the MycarinG study, which was maintained over repeated cycles of treatment in MG0007
  - The most common TEAE in MycarinG was headache, occurring in 29 (45.3%) patients receiving rozanolixizumab ≈7 mg/kg

○ No new safety concerns were identified with repeated cycles in MG0007

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify all available clinical evidence in patients with MG.

The data sources used to identify the relevant studies included electronic databases and hand-searching of grey literature, including reference lists of included studies and other supplementary sources. Full details of the methodology used for the SLR including the search strategy, databases searched, and selection criteria are presented in Appendix D.

An updated search was carried out from 01 May 2023–24 January 2024, using the same methodology as the original search. The combined results of the May 2023 SLR and the January 2024 update are presented.

B.2.1.1 *Search strategy*

The methodology used for the SLR including the search strategy, databases searched, and selection criteria is presented in Appendix D. A summary of the inclusion and exclusion criteria is shown in Table 5.

Table 5: Eligibility criteria used in the search strategy (original SLR and 2024 update)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Adult patients (aged ≥18 years) with MG	
Intervention	**Pharmacological interventions** • Abatacept • Amifampridine (Firdapse®) • ARGX-113 (efgartigimod) • Azathioprine • Belimumab • Bortezomib • CFZ533 • Eculizumab • Immunoglobulin (IV/SC) • Leflunomide • Methotrexate • Mycophenolate mofetil • Prednisone • Pyridostigmine • Ravulizumab • Rituximab • Rozanolixizumab • Salbutamol • Tacrolimus • Zilucoplan (RA101495)	**Non-pharmacological interventions** • Behavioural methods • Rehabilitation programmes • Physical exercise programme using a rowing machine • Accelerometer measurements • Interval walking • Personalized discharge educational intervention **Surgical interventions/procedures** • Plasma exchange • Thymectomy • Plasmapheresis

Comparators	Interventions listed above	Placebo
Outcomes	**Efficacy outcomes** • Change from Baseline in MG-ADL score • Proportion of patients achieving MG-ADL response at study endpoint • Change from Baseline in QMG score • Change from Baseline in MG composite score • Test to evaluate muscle strength • Clinical absolute evaluation method • Number of episodes of Myasthenic Crisis • Number of exacerbations/ relapses • Response rate • Disease progression • Change from Baseline in MGSPRO 'fatigability' score • Change from Baseline in MGSPRO 'physical fatigue, limb and axial weakness' score • Change from Baseline in MGSPRO 'bulbar' score • Steroid/non-steroid dose • Rescue therapy	**Safety and tolerability outcomes** • Any adverse events • Any serious adverse events • Any adverse events leading to death • Infusion site-reactions • MG-specific adverse events • All withdrawals • Withdrawal due to adverse events • Withdrawals due to lack of efficacy
Study design	• RCTs • Non-RCTs • Single-arm studies	• Observational studies • Case-controlled studies • Cross-sectional studies
Language restrictions	English only	

Abbreviations: MG-ADL, myasthenia gravis activities of daily living; QMG, quantitative myasthenia gravis; MGSPRO, Myasthenia Gravis Symptoms patient-reported outcome; RCT, randomised controlled trial.

The PRISMA flow diagram of the numbers of records included and excluded at each stage of the selection process is shown in Figure 5 for the original search and in Figure 6 for the SLR update.

In the original SLR, searches of electronic databases yielded 13,425 references, of which 976 were identified as duplicates and were excluded. The remaining 12,449 references were initially screened based on title and abstract, and 11,406 references were excluded, leaving 1,043 references to be screened on the basis of the full publications. Full-text screening led to the exclusion of 836 references, resulting in 207 publications to be included in the SLR. In addition, 41 references were identified from registry searching, 43 from conference searching, nine from bibliography searching and two from clinical study report searching. Following linking of multiple publications of

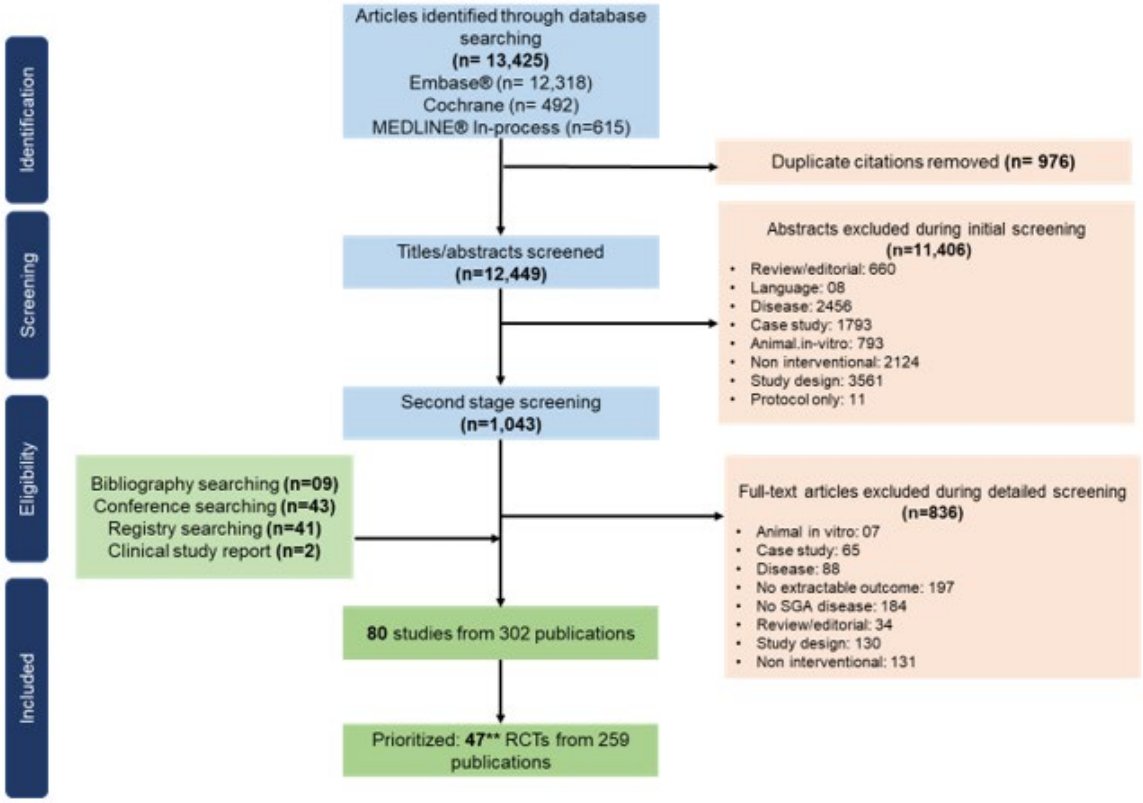
any single study, a total of 80 randomised controlled trials (RCTs) from 302 publications were included in the clinical review. Of the identified RCTs (n=80), only those where the definition of gMG aligned with that used in RAISE were considered for further data extractions and reporting (n=47).

In the 2024 SLR update, electronic database searched yielded 685 references. Due to the overlap of coverage between the databases, 103 references were found to be duplicates and were excluded and 517 references were further excluded at first pass leading to the inclusion of 65 references for full-text screening. Detailed screening of the references led to the exclusion of 11 references. Six references were identified from conference proceedings. Following linking of multiple publications of a study, a total of 60 references were included in the current clinical review. Finally, a total of eight RCTs from 19 publications were prioritized for reporting purposes. Compared with the original review, a single novel RCT was identified (163).

Based on these criteria, a total of 48 studies were included as relevant. Of these 48 studies, 14 included patients with mild to moderate, nine with mild to severe, 11 with moderate to severe, seven with severe, three with refractory and four with exacerbating MG.

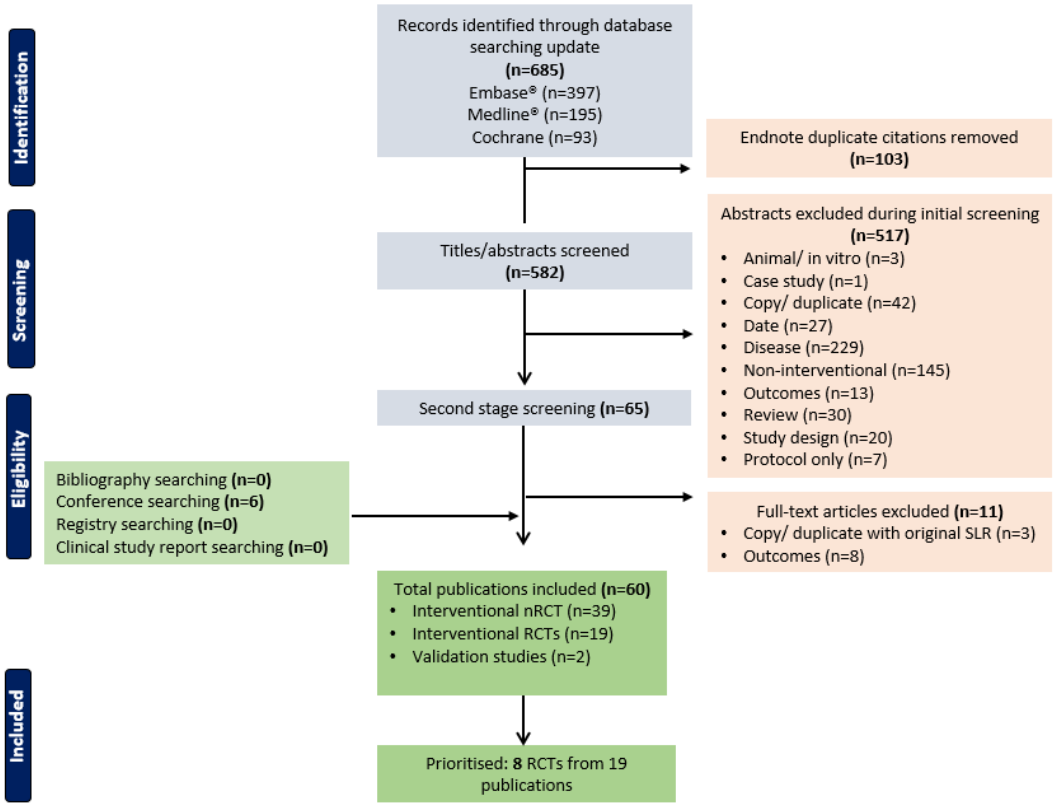
Details of the study selection process and a complete list of included studies are provided in Appendix D.

Figure 5: PRISMA flow diagram showing the study identification process (original SLR)



Abbreviations: MG, myasthenia gravis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SLR, systematic literature review.

Figure 6: PRISMA flow diagram showing the study identification process (SLR update)



Abbreviations: MG, myasthenia gravis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; SLR, systematic literature review.

B.2.2 *List of relevant clinical effectiveness evidence*

The systematic review of clinical evidence identified a single Phase III RCT of rozanolixizumab in the population of interest to this submission – MycarinG (MG0003) (Table 6). The open-label extension (OLE) phase of the MycarinG study, MG0007, is also included in this submission. Interim results from this study (data from cut-off point: 08 July 2022) are of relevance to this submission, as they provide evidence of the long-term efficacy and safety of rozanolixizumab in the patient population of interest and informed the economic model for rozanolixizumab. The study was completed on 25 January 2024 and the final results will be available later in 2024.

The SLR also identified:

- A Phase III trial (Study MG0004) evaluating rozanolixizumab as a treatment of gMG was also identified in the SLR. In response to feedback from clinicians and patients on the requirement for patients to attend weekly visits to the study centre for 52 weeks for treatment administration, it was decided to discontinue enrolment into the MG0004 study and instead evaluate the safety and efficacy of repeated 6-week dosing cycles in patients with worsening symptoms in study MG0007. Chronic weekly dosing is not reflected in the label or in the way the treatment is anticipated to be used in practise.
- A Phase IIa trial (Study MG0002), that demonstrated rozanolixizumab was well tolerated in patients with gMG.
- A Phase I trial (UP0018) in which the safety of rozanolixizumab was evaluated in healthy patients and which demonstrated that IgG concentration was reduced in a dose-dependent manner.

MG0004, MG0002, and UP0018 did not inform the economic model for rozanolixizumab (Table 6). As MG0004 provides additional evidence on the safety and tolerability of rozanolixizumab, the adverse events reported during this study are presented in Appendix G.

Table 6: List of relevant clinical evidence

Trial no. (acronym) and primary study ref(s)	Study design	Population	Intervention	Comparator	Supports application for marketing authorisation	Used in the economic model	Is study excluded from further discussion? If yes state rationale	Reported outcomes specified in the decision problem
MycarinG NCT03971422 (MG0003) Phase III RCT (46, 164) CSR	Randomised, double-blind, placebo-controlled study	Adult patients with gMG and a confirmed positive record of autoantibodies against AChR or MuSK and being considered for additional treatment such as IVIg or PLEX.	Six Q1W SC doses of rozanolixizumab: • ≈7 mg/kg (n=66) • ≈10 mg/kg (n=67)	Placebo (n=67)	Yes	Yes	No (pivotal Phase III trial)	See Table 1
NCT04650854 (MG0007) Phase III OLE (47) CSR	OLE study	Patients who had completed the observation period of MG0003 or required rescue therapy during the observation period of the lead-in study (MG0003) or completed at least six scheduled visits in MG0004 for rozanolixizumab treatment	Cycles of six Q1W SC doses of rozanolixizumab: • ≈7 mg/kg (n=88) • ≈10 mg/kg (n=77)	None	Yes	Yes	No (pivotal Phase III trial)	See Table 1

Trial no. (acronym) and primary study ref(s)	Study design	Population	Intervention	Comparator	Supports application for marketing authorisation	Used in the economic model	Is study excluded from further discussion? If yes state rationale	Reported outcomes specified in the decision problem
MG0004,† NCT04124965 Phase III OLE CSR	OLE study	Patients who had completed the observation period of MG0003 or required rescue therapy and rollover to OLE during the observation period of the lead-in study (MG0003)	Q1W SC doses of rozanolixizumab for 52 weeks: • ≈7 mg/kg • ≈10 mg/kg	None	No	No	Yes (only pivotal Phase III trials will be described in further detail. MG0004 was discontinued and replaced with MG0007; N.B. 60 patients from MG0004 rolled over to MG0007) Safety data from MG0004 are included in Appendix G	See Table 1
MG0002 NCT03971422 Phase II CSR	Randomised, double-blind, placebo-controlled study	gMG (Evidence of detectable AChR or MuSK and QMG score of ≥11 at Baseline and a serum total IgG concentration of >6 g/L at screening)	Period 1: Three Q1W SC infusions of rozanolixizumab ≈7 mg/kg Period 2: Three Q1W SC rozanolixizumab ≈7 mg/kg or ≈4 mg/kg	Period 1: Placebo Period 2: None	No	No	Yes (only pivotal Phase III trials will be described in further detail)	See Table 1

Trial no. (acronym) and primary study ref(s)	Study design	Population	Intervention	Comparator	Supports application for marketing authorisation	Used in the economic model	Is study excluded from further discussion? If yes state rationale	Reported outcomes specified in the decision problem
UP0018, NCT02220153 Phase I CSR	Randomised, double-blind, placebo-controlled, dose-escalating study	Healthy subjects	IV or SC doses of rozanolixizumab: • ≈1 mg/kg • ≈4 mg/kg • ≈7 mg/kg	Placebo	No	No	Yes (only pivotal Phase III trials will be described in further detail)	See Table 1

Abbreviations: AChR, acetylcholine receptor; CSR, clinical study report; gMG, generalised myasthenia gravis; IV, intravenous; MG, myasthenia gravis; MuSK, muscle-specific kinase; N/A, not applicable; OLE, open-label extension; Q1W; once-weekly; QMG, quantitative myasthenia gravis; SC, subcutaneous; TEAEs, treatment emergent adverse events.

† In response to feedback from clinicians and patients, it was decided to discontinue enrolment into the MG0004 study and instead evaluate the safety and efficacy of repeated 6-week dosing cycles in patients with worsening symptoms in study MG0007.

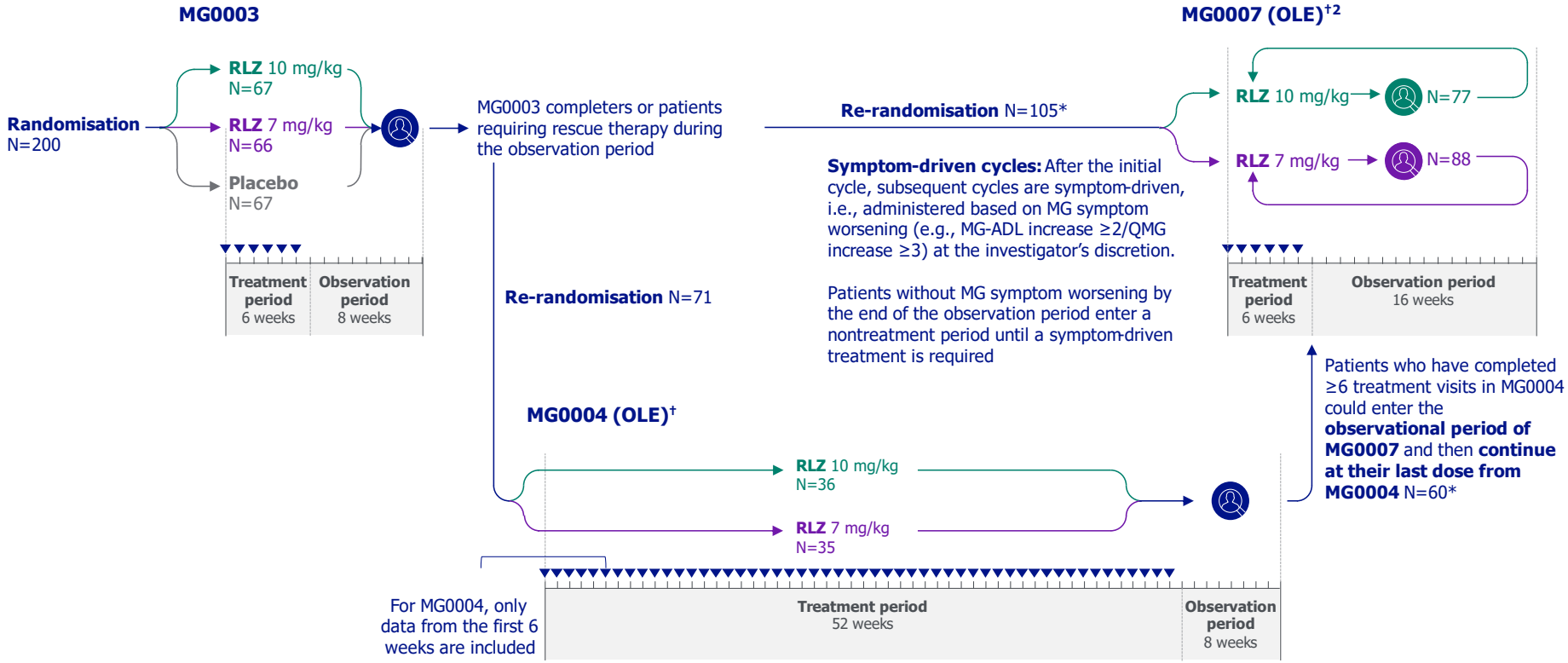
B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 *Comparative summary of RCT methodology*

MG0003 was a Phase III, multicentre, randomised, double-blind, placebo-controlled, three-arm study that evaluated the efficacy and safety of two dosages of rozanolixizumab (the licensed dose of ≈7 mg/kg and also ≈10 mg/kg) and matching placebo administered weekly in study participants with gMG, considered for additional therapy (such as IVIg or PLEX). This trial consisted of a 6-week treatment phase, followed by an 8-week observation period. If patients required rescue therapy, they were rolled into the OLE study MG0007 or MG0004.

MG0007 was an extension study of MG0003 and was open for study participants from MG0003 and MG0004 (MG0004 was discontinued). MG0007 was designed to evaluate 6-week treatment cycles of rozanolixizumab in study participants with gMG and was completed on 25 January 2024. Interim results (data cut-off July 2022) are included in this submission as the final results are not yet available The pivotal Phase III MG0003/MycarinG and open-label extension MG0007 trials are summarised in Figure 7 and Table 12.

Figure 7: MG0003, MG0004 and MG0007 study design overview



Permitted background therapy: Patients were permitted to receive concomitant conventional treatment for gMG (standard of care), such as CS and NSIST, as well as IVIg and PLEX in the event of myasthenic crisis

*Dose modifications from 10 mg/kg to 7 mg/kg and vice versa were permitted at the beginning of each treatment cycle at the investigator's discretion, provided the benefit-risk remains favourable for the patient. †Pooled data are reported across MycarinG, MG0004 (the first 6 weeks only) and MG0007 (interim analysis; data cut-off, 8 July 2022).

Abbreviations: CS, corticosteroids; IVIg, intravenous immunoglobulin; MG-ADL; myasthenia gravis activities of daily living; NSIST, non-steroid immunosuppressants; OLE, open-label extension; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous.

Source: 1. Bril et al 2023 (46, 164); 2. UCB DoF. 2022. MG0007 CSR (47); 3. UCB DoF. 2022. MG0004 CSR (164).

Table 7: Comparative summary of trial methodology

Trial number (acronym)	MG0003 NCT03971422	MG0007 NCT04650854
Location	Multiple sites across North America, Europe and East Asia	
Trial design	Randomised, double-blind, placebo-controlled Phase III study	OLE
Eligibility criteria for participants	**Key eligibility criteria** • ≥18 years of age at the time of signing ICF • Study participant had a documented diagnosis of gMG at Visit 1, based on the study participant's history and supported by previous evaluations • Confirmed positive record of autoantibodies against AChR or MuSK at screening. The presence of autoantibodies may have been confirmed with repeat testing at Visit 1 • MGFA Class II to IVa at Visit 1 • An MG-ADL score of at least 3 (with ≥3 points from non-ocular symptoms) and a QMG score of at least 11 at screening (Visit 1) and at Baseline (Visit 2) • In the opinion of the investigator, the patient was being considered for additional treatment, such as IVIg or PLEX **Exclusion criteria** • Study participant had a clinically relevant active infection (e.g. sepsis, pneumonia, or abscess) in the opinion of the Investigator, or had a serious infection (resulting in hospitalisation or requiring parenteral antibiotic treatment) within 6 weeks prior to the first dose of study medication • Study participants with a known TB infection, at high risk of acquiring TB infection, latent TB infection, or	• Participants who have entered or completed the observation period of MG0003 or • Required (but did not receive) rescue therapy (except IVIg or PLEX) during the observation period of MG0003 or • Completed at least six visits in MG0004

Trial number (acronym)	MG0003 NCT03971422	MG0007 NCT04650854
	current/history of non-TB mycobacterial infection were excluded • Severe (defined as Grade 3 on the MG-ADL scale) weakness affecting oropharyngeal or respiratory muscles, or who had myasthenic crisis or impending crisis at Visits 1 or 2.	
Settings and locations where the data were collected	Conducted at 81 centres located in 17 countries. (Belgium, Canada, Czech Republic, Denmark, France, Georgia, Germany, Hungary, Italy, Japan, Poland, Russian Federation, Serbia, Spain, Taiwan, United States)	Conducted at 69 centres located in 14 countries. (Canada, Czech Republic, Denmark, France, Georgia, Germany, Italy, Japan, Poland, Russian Federation, Serbia, Spain, Taiwan, United States)
Trial drugs	Six Q1W SC doses of rozanolixizumab: • ≈7 mg/kg (n=66) ○ < 50 kg = 280 mg ○ ≥50 kg to <70 kg = 420 mg ○ ≥70 kg to <100 kg = 560 mg ○ ≥100 kg = 840 mg • ≈10 mg/kg (n=67) ○ < 50 kg = 420 mg ○ ≥50 kg to <70 kg = 560 mg ○ ≥70 kg to <100 kg = 840 mg ○ ≥100 kg = 1120 mg • Placebo (n=67)	Cycles of six Q1W SC doses of rozanolixizumab repeated as needed based on evaluation of symptoms: • ≈7 mg/kg (n=88) • ≈10 mg/kg (n=77)
Permitted and disallowed concomitant medication	**Permitted** • Oral corticosteroids (e.g. prednisolone) • Methotrexate • Mycophenolate mofetil • Cyclosporine	

Trial number (acronym)	MG0003 NCT03971422	MG0007 NCT04650854
	• Azathioprine • Cholinesterase inhibitors • Tacrolimus **Disallowed** • All biologics, including rituximab • Cyclophosphamide • Pimecrolimus • IPP-201101 (Lupuzor™) • Immunoadsorption • Vinca alkaloids (vincristine, vinblastine)	
Primary outcomes (including scoring methods and timings of assessments)	Change from Baseline to Day 43 in MG-ADL score	Occurrence of TEAEs and TEAEs leading to withdrawal of rozanolixizumab
Other outcomes used in the economic model/specified in the scope	• Response rates for MG-ADL (used in economic model)	• Occurrence of serious TEAEs (specified in scope) • Occurrence of TEAEs of special monitoring (specified in scope)
Pre-planned subgroups	All subgroup analyses were descriptive; no statistical testing of treatment-by-subgroup interactions nor statistical testing of treatment effects within subgroups was carried out. No subgroup analysis was performed for safety variables. • Age (18 to <65 years, ≥65 years) • Age (18 to <65, 65 to <85, ≥85 years) • Sex (male, female) • Region (North America, Europe, and Asia [excluding Japan], Japan)	These evaluations are descriptive; no statistical testing of treatment-by-subgroup interactions nor statistical testing of treatment effects within subgroups will be carried out. • Age (18 to <65 years, ≥65 years) • Age (18 to <65, 65 to <85, ≥85 years) • Sex (male, female) • Region (North America, Europe, and Asia [excluding Japan], Japan)

Trial number (acronym)	MG0003 NCT03971422	MG0007 NCT04650854
	• Stratification factors: MG-specific autoantibodies, AChR(+/-) and MuSK(+/-)† • Duration of disease at Baseline (<median, ≥median) • MGFA disease class at Baseline • Thymectomy at Baseline (yes, no) • Baseline MG-ADL category (<5, ≥5) • Baseline Oral steroid (yes, no) • Baseline Immunosuppressants other than oral steroid (yes, no) • Baseline Cholinesterase inhibitor (yes, no)	• Stratification factor in MG0003: MG-specific autoantibody (AChR+ and MuSK+)‡ • Duration of disease at MG0003 Baseline (< median, ≥ median) • MGFA disease class at MG0003 Baseline • Thymectomy at MG0003 Baseline (yes, no) • MG0007 Baseline MG-ADL category (<5, ≥5).

Abbreviations: AChR, acetylcholine receptor; AChR +/-, acetylcholine receptor antibody positive/negative; gMG, generalised myasthenia gravis; ICF, informed consent form; IMP, investigational medicinal product; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; MG-C, myasthenia gravis composite; MG-QOL15r, myasthenia gravis quality of life 15-item scale; MGFA, Myasthenia Gravis Foundation of America; MGSPRO, Myasthenia Gravis symptoms Patient-reported outcome; MSE, minimum symptom expression; MuSK, muscle-specific tyrosine kinase; MuSK, muscle-specific tyrosine kinase antibody positive/negative; OLE, open-label extension; PLEX, plasma exchange; Q1W, once-weekly; QMG, quantitative myasthenia gravis; SC, subcutaneous; TB, tuberculosis; TEAE, treatment-emergent adverse events.
† The stratification factors AChR(+/-) and MuSK(+/-) in the subgroup analysis were based on the values from MG-specific autoantibody assessment taken at Baseline using the same algorithm for missing values as specified in statistical analysis protocol. Historical AChR(+/non+) and historical MuSK(+/non+) was also examined in the subgroup analysis; in this case, Baseline AChR(+/-) and Baseline MuSK(+/-) was replaced by historical AChR(+/non+) and historical MuSK(+/non+).
‡ Region as specified for MG0003 is used. The stratification factors AChR+ or AChR- and MuSK+ or MuSK- is based on the derived values from MG0003 subgroup analysis.

B.2.3.1.1 Patient disposition

MycarinG (MG0003)

In total, 200 patients were randomised to either placebo (n=67), rozanolixizumab ≈7 mg/kg (n=66), or rozanolixizumab ≈10 mg/kg (n=67); 128 completed the study (64%) and 72 (34%) discontinued permanently.

The incidence of discontinuations from the study was similar in the three treatment groups. The most common reasons for study discontinuation were mandatory withdrawal and rollover to MG0004 (n=21, 10.5%) or MG0007 (n=25, 12.5%). There were fewer discontinuations due to AEs in the rozanolixizumab ≈7 mg/kg (n=2, 3.0%) and placebo (n=2, 3.0%) groups compared with the rozanolixizumab ≈10 mg/kg group (n=5, 7.5%). Conversely, there were more discontinuations due to lack of efficacy in the placebo group (n=5, 7.5%) compared with the rozanolixizumab ≈7 mg/kg (n=1, 1.5%) and ≈10 mg/kg (n=1, 1.5%) groups.

The COVID-19 pandemic had no considerable impact on this study. Recruitment was paused due to the COVID-19 pandemic from 20 Mar 2020 to 03 Jun 2020, but already randomised study participants continued the study. A total of eight screen failures (out of 100) and one discontinuation (out of 72) were due to the COVID-19 pandemic.

Table 8: Disposition and discontinuation reasons (randomised set)

Category, n (%)	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67	All participants N=200
Started study	67 (100)	66 (100)	67 (100)	200 (100)
Completed study	42 (62.7)	43 (65.2)	43 (64.2)	128 (64.0)
Permanently discontinued study	25 (37.3)	23 (34.8)	24 (35.8)	72 (36.0)
Primary reason for discontinuation				
AE	2 (3.0)	2 (3.0)	5 (7.5)	9 (4.5)
Lack of efficacy	5 (7.5)	1 (1.5)	1 (1.5)	7 (3.5)
Lost to follow up	0 (0)	1 (1.5)	0 (0)	1 (0.5)
Other	18 (26.9)	19 (28.8)	18 (26.9)	55 (27.5)
Due to COVID pandemic	0 (0)	1 (1.5)	1 (1.5)	2 (1.0)
Mandatory withdrawal and rollover to MG0004	7 (10.4)	8 (12.1)	6 (9.0)	21 (10.5)
Mandatory withdrawal and rollover to MG0007	10 (14.9)	6 (9.1)	9 (13.4)	25 (12.5)

Abbreviations: ≈, equivalent dose; COVID-19, coronavirus disease 2019.
Note: Started study is defined as signing informed consent. Completed Study is defined as having completed the treatment and observation period.
Note: The COVID-19 period is based on the start, completed and discontinuation date relative to the

pandemic cut-off date (start date: 20 Mar 2020). This study extended from pre COVID-19 to during COVID-19 period. Post COVID-19 period does not apply.
Note: Mandatory withdrawal and rollover to MG0004 or MG0007 referring to participants requiring rescue therapy in the MG0003 observation period. Another 13 study participants rolled over to MG0004 (6 study participants) or MG0007 (7) after completion of the treatment period and during the observation period (data on file); the reasons provided for discontinuation for these study participants are “lack of efficacy” (6 study participants), “worsening of symptoms” (5), “adverse event” (1), and “other” (1).

MG0007

In total, [redacted] study participants rolled over from the MG0003 and MG0004 studies ([redacted] patients from the placebo treatment arm in MG0003 rolled over directly to MG0007). Of these, [redacted] were randomised to rozanolixizumab ≈7 mg/kg and [redacted] to rozanolixizumab ≈10 mg/kg. At the time of data cut-off (08 Jul 2022), [redacted] study participants had received rozanolixizumab in their first MG0007 cycle (safety set); no participants had completed the study, the majority (n=[redacted]) were still participating in the study, and [redacted] ([redacted]%) had discontinued the study. The most common reason for study discontinuation was TEAEs (n=[redacted], [redacted]%; n=[redacted] in the rozanolixizumab ≈7 mg/kg group and [redacted] in the rozanolixizumab ≈10 mg/kg group) (Table 9).

Study participant demographics were generally balanced between the treatment groups. In both treatment groups, there were more female than male study participants (n=[redacted], [redacted]% in the ≈7 mg/kg group and n=[redacted], [redacted]% in the ≈10 mg/kg group).

Table 9: Disposition and discontinuation reasons (safety set)

Category, n (%)	Rozanolixizumab ≈7 mg/kg N=[redacted]	Rozanolixizumab ≈10 mg/kg N=[redacted]	Rozanolixizumab total N=[redacted]
Started study	[redacted]	[redacted]	[redacted]
Completed study	[redacted]	[redacted]	[redacted]
Permanently discontinued study†	[redacted]	[redacted]	[redacted]
Primary reason for discontinuation			
AE	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Met withdrawal criteria due to being treated with prohibited treatment, plasmapheresis	[redacted]	[redacted]	[redacted]
Participant received rescue medication	[redacted]	[redacted]	[redacted]
Participant wanted to start a family	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; AE, adverse event; COVID-19, Coronavirus Disease 2019.
† All patients discontinued study during COVID-19.

Additional studies and pooled analyses

Patient disposition for study participants enrolled in MG0004 and included in the pooled safety and efficacy analyses are presented in Appendix D, as the data are not included in the economic model but provide additional evidence of the efficacy and safety of rozanolixizumab.

B.2.3.1.2 Patient demographics and baseline characteristics

MG0003

Study participant demographics were generally balanced across treatment groups and study periods (Table 10). The only notable differences were the higher proportion of female study participants in the placebo group (n=47, 70.1%) compared with the rozanolixizumab ≈7 mg/kg (n=39, 59.1%) and ≈10 mg/kg (n=35, 52.2%) groups, and the imbalance in the number of study participants in the <50 kg body weight category across treatment groups, with a lower proportion in the rozanolixizumab ≈10 mg/kg group (n=4, 6.0% in placebo; n=7, 10.6% in rozanolixizumab ≈7 mg/kg; n=1, 1.5% in rozanolixizumab ≈10 mg/kg).

Overall, treatment groups were generally well-balanced with regard to baseline characteristics. The only notable difference was the lower proportion of study participants who had undergone thymectomy in the rozanolixizumab ≈10 mg/kg group (20 [29.9%]) compared with the ≈7 mg/kg (32 [48.5%]) and placebo (31 [46.3%]) groups.

The study population was representative of the gMG patient population with moderate to severe disease at Baseline. At Baseline most study participants were Myasthenia Gravis Foundation of America (MGFA) disease class ≥III, the mean MG-ADL score was 8.3, the mean Quantitative Myasthenia Gravis (QMG) score was 15.6, and the mean (median) duration of disease was 8.6 (5.8) years (Table 11).

Table 10: Characteristics of participants in MG0003 across treatment groups

MG0003, NCT03971422 (n=200)	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67	All participants N=200
Patient demographics				
Age, years† Mean (SD)	50.4 (17.7)	53.2 (14.7)	51.9 (16.5)	51.8 (16.3)
Age categories, n (%)				
18 to <65 years	51 (76.1)	49 (74.2)	51 (76.1)	151 (75.5)
65 to <85 years	15 (22.4)	16 (24.2)	16 (23.9)	47 (23.5)
≥85 years	1 (1.5)	1 (1.5)	0 (0)	2 (1.0)
Sex, n (%)				
Male	20 (29.9)	27 (40.9)	32 (47.8)	79 (39.5)
Female	47 (70.1)	39 (59.1)	35 (52.2)	121 (60.5)

MG0003, NCT03971422 (n=200)	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67	All participants N=200
Weight, kg Mean (SD)	80.80 (22.57)	79.56 (25.52)	83.06 (23.73)	81.15 (23.88)
Height, cm Mean (SD)	168.98 (9.86)	169.00 (9.98)	171.07 (9.70)	169.69 (9.85)
BMI, kg/m^2 Mean (SD)	28.03 (6.19)	27.38 (6.86)	28.07 (6.28)	27.83 (6.42)
Body weight category, kg, n (%)				
<50	4 (6.0)	7 (10.6)	1 (1.5)	12 (6.0)
50 to <70	16 (23.9)	19 (28.8)	26 (38.8)	61 (30.5)
70 to <100	35 (52.2)	26 (39.4)	22 (32.8)	83 (41.5)
≥100	12 (17.9)	14 (21.2)	18 (26.9)	44 (22.0)
Race‡, n (%)				
Asian	5 (7.5)	9 (13.6)	7 (10.4)	21 (10.5)
Black	1 (1.5)	0 (0)	4 (6.0)	5 (2.5)
Native Hawaiian or other pacific islander	1 (1.5)	0 (0)	0 (0)	1 (0.5)
White	46 (68.7)	41 (62.1)	49 (73.1)	136 (68.0)
Missing	14 (20.9)	16 (24.2)	7 (10.4)	37 (18.5)
Ethnicity‡, n (%)				
Hispanic or Latino	5 (7.5)	5 (7.6)	3 (4.5)	13 (6.5)
Not Hispanic or Latino	48 (71.6)	47 (71.2)	58 (86.6)	153 (76.5)
Missing	14 (20.9)	14 (21.2)	6 (9.0)	34 (17.0)
Region, n (%)				
North America	21 (31.3)	21 (31.8)	18 (26.9)	60 (30.0)
Europe	41 (61.2)	36 (54.5)	43 (64.2)	120 (60.0)
Asia (excluding Japan)	1 (1.5)	4 (6.1)	2 (3.0)	7 (3.5)
Japan	4 (6.0)	5 (7.6)	4 (6.0)	13 (6.5)

Abbreviations: ≈, equivalent dose; BMI, body mass index; SD, standard deviation.

Note: Combined data are shown (i.e. from all study participants, including Stage 1 and Stage 2).

† Missing age was calculated as year of informed consent signed – year of birth.

Table 11: Baseline characteristics (randomised set)

MG0003, NCT03971422 (n=200)	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67	All participants N=200
MGFA Disease Class at Baseline, n (%)				
Class IIa	11 (16.4)	13 (19.7)	13 (19.4)	37 (18.5)
Class IIb	12 (17.9)	16 (24.2)	13 (19.4)	41 (20.5)
Class IIIa	28 (41.8)	21 (31.8)	26 (38.8)	75 (37.5)
Class IIIb	13 (19.4)	13 (19.7)	13 (19.4)	39 (19.5)
Class IVa	2 (3.0)	3 (4.5)	2 (3.0)	7 (3.5)
Class IVb	1 (1.5)	0 (0)	0 (0)	1 (0.5)
Undergone Thymectomy, n (%)	31 (46.3)	32 (48.5)	20 (29.9)	83 (41.5)
MG-ADL score, Mean (SD)	8.4 (3.4)	8.4 (3.8)	8.1 (2.9)	8.3 (3.4)
MG-ADL ≥5, n (%)	57 (85.1)	55 (83.3)	61 (91.0)	173 (86.5)
QMG score Mean (SD)	15.8 (3.5)	15.4 (3.7)	15.6 (3.7)	15.6 (3.6)
Myasthenic crisis in the past, n (%)				
Yes	23 (34.3)	19 (28.8)	17 (25.4)	59 (29.5)
No	44 (65.7)	46 (69.7)	49 (73.1)	139 (69.5)
Missing	0 (0)	1 (1.5)	1 (1.5)	2 (1.0)
Duration of disease, years Mean (SD)	9.418 (9.348)	6.877 (6.799)	9.561 (9.895)	8.627 (8.836)
Age at initial MG diagnosis, years Mean (SD)	41.4 (19.1)	46.6 (16.0)	42.6 (19.1)	43.5 (18.2)
Historical antibody status. n (%)				
AchR+	59 (88.1)	60 (90.9)	60 (89.6)	79 (89.5)
MuSK+	8 (11.9)	5 (7.6)	8 (11.9)	21 (10.5)
Baseline autoantibody status, n (%)				
AchR+	53 (79.1)	56 (84.8)	56 (83.6)	165 (82.5)
MuSK+	8 (11.9)	4 (6.1)	4 (6.0)	16 (8.0)
Total IgG,g/L, Mean (SD)	10.20 (2.61)	10.16 (3.18)	9.67 (2.61)	10.01 (2.81)

Abbreviations: ≈, equivalent dose; AchR, acetylcholine receptors; IgG, immunoglobulin G; MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific tyrosine kinase; QMG, quantitative myasthenia gravis.

Prior, baseline, and concomitant medications/therapies

Baseline medications used to treat gMG are summarised by pharmacological subgroup and preferred term (PT) in Table 12. The use of Baseline gMG medications was generally balanced across treatment groups.

Table 12: Baseline gMG medications (randomised set)

Pharmacological subgroup, PT	Placebo N=67 n (%)	Rozanolixizumab ≈7 mg/kg N=66 n (%)	Rozanolixizumab ≈10 mg/kg N=67 n (%)	All participants N=200 n (%)
At least 2 prior gMG specific therapies†				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroids for systemic use	38 (56.7)	43 (65.2)	48 (71.6)	129 (64.5)
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Methylprednisolone	[redacted]	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]	[redacted]
ISTs	33 (49.3)	32 (48.5)	38 (56.7)	103 (51.5)
Azathioprine	[redacted]	[redacted]	[redacted]	[redacted]
MMF	[redacted]	[redacted]	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]	[redacted]	[redacted]
Ciclosporin	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]
Mycophenolic acid	[redacted]	[redacted]	[redacted]	[redacted]
Leflunomide	[redacted]	[redacted]	[redacted]	[redacted]
AchEIs	60 (89.6)	55 (83.3)	57 (85.1)	172 (86.0)
Pyridostigmine bromide	[redacted]	[redacted]	[redacted]	[redacted]
Pyridostigmine	[redacted]	[redacted]	[redacted]	[redacted]
Ambenonium chloride	[redacted]	[redacted]	[redacted]	[redacted]
Ambenonium	[redacted]	[redacted]	[redacted]	[redacted]
Distigmine	[redacted]	[redacted]	[redacted]	[redacted]
Distigmine bromide	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; AChEIs, acetylcholinesterase inhibitors; gMG, generalised myasthenia gravis; IST, immunosuppressive therapies; MMF, mycophenolate mofetil; PT, preferred term.
†After AChEIs.
Note: Baseline medications include any medications that started prior to dosing and continued after (classified as prior and concomitant medications).

MG0007

Study participant demographics were generally balanced between the treatment groups. The only notable differences were the higher proportion of study participants from North America in the ≈7 mg/kg group (n=[redacted], [redacted]%) compared with the ≈10 mg/kg group (n=[redacted], [redacted]%) and the lower proportion of study participants from Europe in the ≈7 mg/kg group (n=[redacted], [redacted]%) compared with the ≈10 mg/kg group (n=[redacted], [redacted]%). This imbalance is not expected to influence the interpretation of the efficacy and safety results. Study participant demographic characteristics are summarised in Table 13.

In both treatment groups, there were more female than male study participants (n=[redacted], [redacted]% in the ≈7 mg/kg group and n=[redacted], [redacted]% in the ≈10 mg/kg group). The number of study participants in the <50 kg body weight category was low in both the rozanolixizumab ≈7 mg/kg group (n=[redacted], [redacted]%) and ≈10 mg/kg group (n=[redacted], [redacted]%).

Baseline characteristics were generally balanced between the treatment groups. The only notable differences were the lower proportion of study participants who had undergone thymectomy in the rozanolixizumab ≈7 mg/kg group (n=[redacted], [redacted]%) compared with the ≈10 mg/kg group (n=[redacted], [redacted]%) and the higher proportion of study participants who were MuSK-Ab+ at MG0003 Baseline in the rozanolixizumab ≈7 mg/kg group (n=[redacted], [redacted]%) compared with the ≈10 mg/kg group (n=[redacted], [redacted]%). Baseline characteristics are summarised for the safety set in Table 14.

Table 13: Characteristics of participants in MG0007 across treatment groups

MG0007, NCT04650854 (n=157)	**Rozanolixizumab ≈7 mg/kg N=79**	**Rozanolixizumab ≈10 mg/kg N=78**	**Rozanolixizumab total N=157**
Patient demographics			
Age, years† Mean (SD)	[redacted]	[redacted]	[redacted]
Age categories, n (%)‡			
18 to <65 years	[redacted]	[redacted]	[redacted]
65 to <85 years	[redacted]	[redacted]	[redacted]
≥85 years	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Weight, kg Mean (SD)	[redacted]	[redacted]	[redacted]
Height,§ cm Mean (SD)	[redacted]	[redacted]	[redacted]
BMI, kg/m^2 Mean (SD)	[redacted]	[redacted]	[redacted]
Body weight category, kg, n (%)			
<50	[redacted]	[redacted]	[redacted]

MG0007, NCT04650854 (n=157)	Rozanolixizumab ≈7 mg/kg N=79	Rozanolixizumab ≈10 mg/kg N=78	Rozanolixizumab total N=157
50 to <70	[redacted]	[redacted]	[redacted]
70 to <100	[redacted]	[redacted]	[redacted]
≥100	[redacted]	[redacted]	[redacted]
Race‡, n (%)			
Asian	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]
Native Hawaiian or other pacific islander	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Ethnicity. n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Region, n (%)			
North America	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]
Asia (excluding Japan)	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Worsening of disease, n (%)⁋			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Needed additional therapies in the observation period of MG0003 and entered MG0007, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; BMI, body mass index; gMG, generalised myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; QMG, Quantitative Myasthenia Gravis; SD, standard deviation.
† Age was at the time of Study MG0003 entry. Missing age was calculated as year of informed consent signed – year of birth.
‡ Clinicaltrials.gov age categories.
§ Height was captured at Screening Visit from MG0003 database and used in the BMI calculation.
⁋ Worsening of disease refers to the initial fixed cycle in MG0007. "Yes" reflects the Investigator indicating that the initial fixed cycle was driven by disease worsening. "No" reflects the Investigator indicating that the initial fixed cycle was not driven by disease worsening. Worsening of disease was defined as the worsening of gMG symptoms (e.g. an increase of 2 points on the MG-ADL or 3 points on the QMG scale) between 2 consecutive visits based on the Investigator's discretion.

Table 14: Baseline characteristics in MG0007 (safety set)

	Rozanolixizumab ≈7 mg/kg N=79	Rozanolixizumab ≈10 mg/kg N=78	Rozanolixizumab total N=157
Thymectomy at MG0007 Baseline, n (%)			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
MG-ADL score			
Mean (SD)	[redacted]	[redacted]	[redacted]
MG-ADL group, n (%)			
<5	[redacted]	[redacted]	[redacted]
≥5	[redacted]	[redacted]	[redacted]
MG-C score			
Mean (SD)	[redacted]	[redacted]	[redacted]
QMG score			
Mean (SD)	[redacted]	[redacted]	[redacted]
Duration of disease at MG0003 Baseline (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Age at initial MG diagnosis (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
MG-specific autoantibody at MG0007 Baseline, n (%)			
AchR+	[redacted]	[redacted]	[redacted]
MuSK+	[redacted]	[redacted]	[redacted]
Total IgG (g/L)			
Mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; AchR, acetylcholine receptor; IgG, immunoglobulin G; IMP, investigational medicinal product; MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; MG-C, myasthenia gravis composite; MuSK, muscle-specific kinase; QMG, quantitative myasthenia gravis; SD, standard deviation.
Note: Baseline was defined as the last available value prior to or on the same date of first administration of IMP in MG0007, unless otherwise specified.
Note: MG0003 MuSK and AchR antibody status are based on the derived values from MG0003 model analysis.

Prior, baseline, and concomitant medications/therapies

The use of AchEIs was similar in both treatment groups. The use of corticosteroids for systemic use (plain) was less common in the rozanolixizumab ≈7 mg/kg group (n=[redacted], [redacted]% study participants) compared with the ≈10 mg/kg group (n=[redacted], [redacted]%), as was the use of immunosuppressants (n=[redacted], [redacted]% in the ≈7 mg/kg group and n=[redacted], [redacted]% in the ≈10 mg/kg group). Prior medications used to treat gMG are summarised by pharmacological subgroup and PT in Table 15.

Table 15: Prior generalised myasthenia gravis medications (safety set)

Pharmacological subgroup, PT	Rozanolixizumab ≈7 mg/kg N=79 n (%)	Rozanolixizumab ≈10 mg/kg N=78 n (%)	Rozanolixizumab Total N=157 n (%)
Corticosteroids for systemic use, plain	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]
Methylprednisolone	[redacted]	[redacted]	[redacted]
Deflazacort	[redacted]	[redacted]	[redacted]
Betamethasone	[redacted]	[redacted]	[redacted]
ISTs	[redacted]	[redacted]	[redacted]
Azathioprine	[redacted]	[redacted]	[redacted]
MMF	[redacted]	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]	[redacted]
Ciclosporin	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Mycophenolic acid	[redacted]	[redacted]	[redacted]
Leflunomide	[redacted]	[redacted]	[redacted]
AchEIs	[redacted]	[redacted]	[redacted]
Pyridostigmine bromide	[redacted]	[redacted]	[redacted]
Pyridostigmine	[redacted]	[redacted]	[redacted]
Ambenonium chloride	[redacted]	[redacted]	[redacted]
Ambenonium	[redacted]	[redacted]	[redacted]
Distigmine	[redacted]	[redacted]	[redacted]
Distigmine bromide	[redacted]	[redacted]	[redacted]
Neostigmine metilsulfate	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; AchEIs, acetylcholinesterase inhibitors; IMP, investigational medicinal product; IST, immunosuppressive therapy; MMF, mycophenolate mofetil; PT, preferred term.
Note: Prior medications include any medications that started before the first administration of IMP in MG0007.

The concomitant use of AchEIs was similar in both treatment groups. The concomitant use of corticosteroids for systemic use (plain) was less common in the rozanolixizumab ≈7 mg/kg group (n=[redacted], [redacted]%) compared with the ≈10 mg/kg group (n=[redacted], [redacted]%), as was the use of immunosuppressants (n=[redacted], [redacted]% in the ≈7 mg/kg group and n=[redacted], [redacted]% in the ≈10 mg/kg group).

Additional studies and pooled analyses

Patient demographic and baseline characteristics for study participants enrolled in MG0004 and included in the pooled safety and efficacy analyses are presented in Appendices F and M, as the data are not included in the economic model.

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.4.1 *Analysis timepoints*

B.2.4.1.1 MycarinG (MG0003)

All data were analysed based on the scheduled visits across three study periods screening, treatment, and observation. The following definitions for starting and entering the study periods were applied.

Treatment period: Started with the first day of investigational medicinal product (IMP) and ended 7 days after the last IMP infusion (Day 43)/premature end of treatment visit assessments. All participants in the safety set (SS) were considered to have started the treatment period. A participant was considered to have completed the treatment period if the assessments at Baseline and at Day 43 of the treatment period were completed.

Observation period: Started on Day 43 period and ended after the final assessments on the last visit. Participants with an assessment on any observation period day were considered to have started the observation period. Participants who had a completed status in the study termination case report form (CRF) were considered to have completed the treatment and observation periods.

End of the study: Defined as the date of the last visit of the last participant in the study.

B.2.4.1.2 MG0007

All data were analysed based on the visits identified per the schedule of activities. The study cycle consists of the following periods:

- Treatment period: 6 weeks
- Observation period: 16 weeks
- Non-treatment period :Started one day after the end of the observation Period of each cycle and ends before the start of next cycle or the end of study assessment.

B.2.4.2 *Interim analysis*

B.2.4.2.1 MycarinG (MG0003)

:

The first periodic data review was performed when approximately 15 study participants had completed the 6-week treatment period. The second periodic data review was conducted after approximately 60 study participants had completed the 6-week treatment period (ad-hoc, as needed)

B.2.4.2.2 MG0007

The first data cut was performed for submission purposes, with a data cut-off date of 08 Jul 2022.

An overarching rozanolixizumab program IDMC oversees the safety of this study by reviewing safety data at periodic timepoints with other rozanolixizumab studies. The scope and role of the overarching program IDMC is described in an overarching IDMC charter and its study-specific attachment.

B.2.4.3 *Populations analysed*

MG0003

Patients were categorised into the following sets:

- The **randomised set** (RS) consisted of all study participants who were randomised, using the treatment assigned instead of the actual treatment received
- The **safety set** (SS) consisted of all randomised study participants who received at least one dose of IMP, analysed according to the actual treatment the participants received

All (n=200) randomised study participants received at least one dose of IMP and were included in the SS and full analysis set (FAS). All study participants randomised to the rozanolixizumab treatment groups (n=133, 66.5%) were included in the pharmacokinetic per-protocol set (PK-PPS) (Table 16). All study participants were analysed as randomised except for two study participants in the rozanolixizumab ≈7 mg/kg group, who had IPDs of incorrect treatment dose and received rozanolixizumab ≈10 mg/kg at the Baseline Visit. These two study participants were analysed as part of the rozanolixizumab ≈10 mg/kg group for the SS and PK-PPS.

Efficacy analyses were performed on the RS, unless otherwise specified. Safety and immunological analyses were performed on the SS. Pharmacokinetic analyses were performed on the PK-PPS and PD analyses were performed on the SS.

Table 16: Disposition of analysis sets in MG0003

Analysis set	Placebo N=67 n (%)	Rozanolixizumab ≈7 mg/kg N=66 n (%)	Rozanolixizumab ≈10 mg/kg N=67 n (%)	All participants N=200 n (%)
RS	67 (100)	66 (100)	67 (100)	200 (100)
SS	67 (100)	64 (97.0)	69 (103.0)	200 (100)
FAS	67 (100)	66 (100)	67 (100)	200 (100)
PK-PPS	0 (0)	64 (97.0)	69 (103.0)	133 (66.5)

Abbreviations: ≈, equivalent dose; FAS, full analysis set; PK-PPS, pharmacokinetic per-protocol set; RS, randomised set; SS, safety set.
Note: As per unblinded protocol deviation report, two study participants were randomised to rozanolixizumab ≈7 mg/kg, but were administrated rozanolixizumab ≈10 mg/kg at the Baseline Visit. These two study participants were analysed as part of the rozanolixizumab ≈7 mg/kg group in RS and FAS, but in rozanolixizumab ≈10 mg/kg group in SS and PK-PPS.

MG0007

Patients were categorised into the following sets:

- The FAS consists of all study participants who were randomised in MG0007 or in MG0004. Study participants enrolling from MG0004 used the last dosage received in MG0004 as their dose in MG0007
- The SS consists of all study participants in the FAS who receive at least one dose of IMP in MG0007

In total, 167 study participants were enrolled, two of which were considered screen failures. A total of 165 study participants were included in the FAS and 157 study participants (95.2%) received at least one dose of IMP and were included in the SS: 79 (89.8%) in the rozanolixizumab ≈7 mg/kg group and 78 (101.3%) in the rozanolixizumab ≈10 mg/kg group (Table 17).

Of the study participants scheduled to receive rozanolixizumab ≈7 mg/kg in Cycle 1, one discontinued before treatment (due to an AE), six participants were treated with ≈10 mg/kg, and three were yet to receive rozanolixizumab in MG0007. Of the study participants scheduled to receive rozanolixizumab ≈10 mg/kg in Cycle 1, three discontinued before treatment (one due to lack of efficacy and two due to withdrawal by the participant), one participant was treated with ≈7 mg/kg, and one was yet to receive rozanolixizumab in MG0007. All safety, efficacy, pharmacokinetic, pharmacodynamic, and immunological analyses were performed on the SS.

Table 17: Disposition of analysis sets in MG0007

Analysis set	Rozanolixizumab ≈7 mg/kg N=66 n (%)	Rozanolixizumab ≈10 mg/kg N=67 n (%)	All participants N=165 n (%)
ES	88 (100)	77 (100)	165 (100)
FAS	88 (100)	77 (100)	165 (100)
SS	79 (89.8)	78 (101.3)	157 (95.2)

Abbreviations: ≈, equivalent dose; ES, enrolled set; FAS, full analysis set; SS, safety set

B.2.4.4 *Statistical information*

Table 18: Summary of statistical analyses in RCTs

Trial no. (acronym)	MG0003	MG0007
Hypothesis objective	To demonstrate the clinical efficacy of rozanolixizumab in patients with gMG.	To assess the safety and tolerability of additional 6-week treatment cycles with rozanolixizumab in study participants with gMG.
Statistical analysis	The efficacy analyses were adjusted for the following covariates: • Baseline MG-ADL score • Region (North America, Europe, and Asia [excluding Japan], Japan) • Stratification factors: MG-specific autoantibodies, including AChR (+/-) and MuSK (+/-), both as binary variables	Statistical testing is not planned for this study, hence adjustment for covariates is not required.
Sample size, power calculation	Based on historical data, the mean difference in adjusted changes from Baseline of MG-ADL at Day 43, between rozanolixizumab and placebo, was assumed to be 1.5 to 2.0 and the standard deviation is assumed to be 3.5 to 4. A difference of >1.5 could be judged to be clinically meaningful. It was proposed that the interim analysis was to be conducted when approximately 90 eligible study participants had been treated and were evaluable for the primary endpoint, i.e. approximately 30 study participants per dose group in Stage 1. If the study was not stopped for futility after Stage 1, the sample size could be increased, subject to a maximum cap, to provide an overall conditional power target of 90% based on the observed effect size in Stage 1. For each dose that was not futile, the comparison-wise conditional power would be calculated which was the probability of, given the observed data, achieving a significant result for the completed study if only the considered treatment is selected. If 2 doses were selected, then the conditional power associated with the higher treatment effect was used to determine the Stage 2 sample size. Conditional power was calculated as described in formula 7.2 of Wassmer and Brannath (2016). Similarly, the Stage 2 sample size required to achieve a target conditional power of 90% was calculated using a formula derived from formula 7.4 of Wassmer and Brannath (2016) as follows.	No formal sample size calculation was performed. All eligible study participants from MG0003 and MG0004 were invited to participate in MG0007. Approximately 200 study participants are anticipated to be enrolled into MG0007.

Trial no. (acronym)	MG0003	MG0007
	Second stage sample size per arm $=2*SD^2*[\phi^{-1}(TP)+\phi^{-1}(1-CRP)]^2/Delta^2$ where, SD=pooled standard deviation from the Stage 1 statistical model using all dose groups TP=target conditional power=0.9 CRP=Conditional rejection probability at Stage 1 for the dose group being considered Delta=assumed true treatment effect for second stage data If two doses were considered for Stage 2 then the above formula would be applied with the conditional error divided by 2, to account for multiplicity. Depending upon the selection of one, or two, of the doses after Stage 1, a further 60, and to up to a maximum of 150 eligible study participants, would be randomised in Stage 2 of the study. Thus, the total sample size of the study could have ranged between 150 and 240 study participants if the study was not futile at Stage 1.	
Data management, patient withdrawals	Summaries of demographics and baseline characteristics are based on all participants in the analysis set and include a "Missing" category (corresponding to participants with missing data for the variable being summarised) as the last row in the list of categories being summarised. Summaries of safety variables (unless otherwise specified): are based only on those participants with observed data for the variable summarised. All summaries of PK variables are based on the observed values. No imputation was used.	The rules for handling missing data of individual items in the calculation of the scores are reported below. • MG-ADL and QMG: o If 1–2 items are not answered, the total score will be obtained by imputing the missing items with the average score across the remaining items o If >2 items are missing the total score will not be calculated • MG-C: if data are missing, the score will not be calculated • MGSPRO: If >30% of the responses are missing, the score will not be calculated • MG-QoL 15r: o If ≥70% of the items are answered, the total score will be generated after

Trial no. (acronym)	MG0003	MG0007
		imputing the missing responses by the average of available responses ○ If >30% of the items are missing, the total score will not be generated.

Abbreviations: AChR, acetylcholine receptor; gMG, generalised myasthenia gravis MG-ADL, myasthenia gravis activities of daily living; MG-C, myasthenia gravis composite; MG-QoL, myasthenia gravis quality of life; MGSPRO, Myasthenia Gravis symptoms Patient-reported outcome; MuSK, muscle-specific tyrosine kinase; QMG, quantitative myasthenia gravis; PK, pharmacokinetic; RCT, randomised controlled trial.

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

Quality assessment results for the RCTs are described in Table 19.

Table 19: Quality assessment results for parallel group RCTs

	MG0003	MG0007
Was randomisation carried out appropriately?	Yes, an IRT was used for assigning eligible study participants to a treatment regimen based on a predetermined production randomisation and/or packaging schedule provided by the Sponsor (or designee). The randomisation schedule was produced by the IRT vendor. The IRT generated individual assignments for kits of study medication, as appropriate, according to the visit schedule.	Yes, an IRT is used for assigning eligible study participants to a treatment regimen (as applicable) based on a predetermined production randomisation and/or packaging schedule provided by UCB (or designee). The randomisation schedule is produced by the IRT vendor. The IRT generates individual assignments for kits of study medication, as appropriate, according to the visit schedule. Study participants from MG0003 who completed the EOS Visit are re-randomised in MG0007. Randomisation in MG0007 is to a ratio of 1:1. Study participants from MG0004 are not re-randomised upon entering MG0007 but continue their last treatment regimen received in MG0004 for their first treatment cycle in MG0007. Study participants retain the same 5-digit number assigned at Screening in MG0003 that serves as the study participant identifier throughout the study.
Was the concealment of treatment allocation adequate?	Yes, all study participant treatment details, rozanolixizumab treatment group, planned dose, or placebo were allocated and maintained by the IRT system.	Yes, this is an OLE study and treatment details (i.e. dose arm) are not blinded. To maintain study integrity, IgG level remains blinded to the study sites and the UCB study team for the first four weeks of the study.

	MG0003	MG0007
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, study participant demographics were balanced across treatment groups. Apart from a higher proportion of female study participants in the placebo group (70.1%) compared with the rozanolixizumab ≈7 mg/kg (59.1%) and ≈10 mg/kg (52.2%) groups, and the number of study participants in the <50 kg body weight category, with a lower proportion in the rozanolixizumab ≈10 mg/kg group (1.5%) compared with placebo and rozanolixizumab ≈7 mg/kg (6.0% and 10.6%)	Yes, study participant demographics were generally balanced between the treatment groups apart from the higher proportion of study participants from North America in the ≈7 mg/kg group (32.9%) compared with the ≈10 mg/kg group (23.1%) and the lower proportion of study participants from Europe in the ≈7 mg/kg group (57.0%) compared with the ≈10 mg/kg group (67.9%).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, study participants and study staff remained blinded to treatment assignments until after the data had been cleaned, locked, and unblinded.	N/A. As MG0007 is an open-label study and all study participants received rozanolixizumab ≈7 mg/kg or ≈10 mg/kg.
Were there any unexpected imbalances in drop-outs between groups?	No. All groups were balanced and there were no un-expected imbalances in drop-outs.	No. All groups were balanced and there were no un-expected imbalances in drop-outs.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All outcomes were related to the clinical goals of gMG therapy, and safety.	No. All outcomes were related to the clinical goals of gMG therapy, and safety.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	All efficacy analyses were based on the randomized set and treatment assignment at randomization (i.e. intention to treat, not treatment received). Intention to treat and missing data and intercurrent events were handled appropriately.	All efficacy analyses were based on the randomized set and treatment assignment at randomization (i.e. intention to treat, not treatment received). Intention to treat and missing data and intercurrent events were handled appropriately.

Abbreviations: EOS, end of study; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; IRT, interactive response technology; OLE, open-label extension; RCT, randomised controlled trial.

B.2.6 *Clinical effectiveness results of the relevant studies*

B.2.6.1 *MycarinG (Study MG0003)*

B.2.6.1.1 Primary efficacy outcome

The primary endpoint of change from Baseline[c] (CFB) in MG-ADL score to Day 43 (Visit 10) was met, with patients in both rozanolixizumab treatment groups achieving a clinically relevant and statistically significant improvement (reduction of scores) (Table 20). The mean least square (LS) CFB was −3.370 for rozanolixizumab ≈7 mg/kg and −3.403 for rozanolixizumab ≈10 mg/kg compared with −0.784 for placebo. The differences in LS mean CFB in MG-ADL score between groups (rozanolixizumab minus placebo) were −2.586 (95% CI; −4.091, −1.249; p<0.001), in favour of rozanolixizumab ≈7 mg/kg over placebo, and −2.619 (95% CI; −3.994, −1.163; p<0.001), in favour of rozanolixizumab ≈10 mg/kg.

Approximately 70% of participants in the rozanolixizumab treatment groups reported a clinically meaningful improvement in MG-ADL.[d] A higher percentage of participants in the rozanolixizumab treatment groups reported an improvement compared with patients in the placebo group.

Table 20: MG-ADL CFB to Day 43 (Visit 10) (Hypothetical & Treatment Policy Strategy, randomised set)

Statistic	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
n	62	65	65
Mean (SE)	−0.65 (0.363)	−3.22 (0.480)	−3.20 (0.403)
LS Mean (SE)	−0.784 (0.488)	−3.370 (0.486)	−3.403 (0.494)
Difference vs placebo (95% CI) †	-	−2.586 (−4.091, −1.249)	−2.619 (−3.994, −1.163)
p-value	-	<0.001	<0.001

Abbreviations: ≈, equivalent dose; CFB, change from Baseline; CI, confidence interval; LS, least square; MAR, missing at random; MG-ADL, myasthenia gravis activities of daily living; MMRM, mixed model repeated measure; SE, standard error.
Note: Combined data are shown (i.e. from all study participants, including Stage 1 and Stage 2).

[c] Change from Baseline analyses are based on the Hypothetical & Treatment Policy Strategy, where study participants who experience ICEs regarding use of rescue therapy were treated as missing at and after the point of the ICE for the purpose of analysis. Data from study participants who discontinued treatment or the study due to TEAEs or COVID-19 infection or non-COVID-19 infection-related issues before Day 43 were used regardless of whether ICEs occurred. Any missing MG-ADL scores (including missing data after the ICEs) were handled based on maximum likelihood estimation under MAR assumption.
Baseline is defined as the last available value before or on the same date (and same time if time is collected for the individual assessment) of the first infusion of IMP in the treatment period, or if missing, the Screening value.

[d] Clinically meaningful is defined as a 2-point improvement in MG-ADL (165)

†All outputs are from the combined MMRM, except CIs and p-values, which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method.

B.2.6.1.2 Secondary efficacy outcomes

Overview

All secondary efficacy endpoints that were part of the sequential testing procedure showed statistically significant improvements from Baseline, for both rozanolixizumab treatment groups compared with placebo. The results of all secondary efficacy endpoints were supportive of and consistent with the primary analysis, and show the robust clinical efficacy of rozanolixizumab compared with placebo.

Change from Baseline to Day 43 (Visit 10) in the MG-C score

Results of the secondary endpoint MG-C score CFB to Day 43 (Visit 10) were supportive of the primary analysis with a statistically significant reduction (improvement) in LS mean MG-C total score for both rozanolixizumab treatment groups compared with placebo (p<0.001). A summary of the MG-C score CFB to Day 43 (Visit 10) is presented in Table 21.

Table 21: MG-C CFB to Day 43 (Visit 10) (Hypothetical & Treatment Policy Strategy, randomised set)

Statistic	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
n	62	65	62
Mean (SE)	−1.47 (0.722)	−5.23 (0.828)	−7.13 (0.857)
LS Mean (SE)	−2.029 (0.917)	−5.930 (0.916)	−7.554 (0.934)
Difference vs Placebo (95% CI)†	-	−3.901 (−6.634, −1.245)	−5.525 (−8.303, −2.968)
p-value	-	<0.001	<0.001

Abbreviations: ≈, equivalent dose; CFB, change from Baseline; CI, confidence interval; ; LS, least Square; MG-C, myasthenia gravis composite score; MMRM, mixed model repeated measure; SE, standard error.
†All outputs are from the combined MMRM, except CIs and p-values which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method.

Change from Baseline to Day 43 (Visit 10) in QMG score

Results of the secondary endpoint QMG score CFB to Day 43 (Visit 10) were supportive of the primary analysis with a statistically significant reduction (improvement) in LS mean QMG total score for both rozanolixizumab treatment groups compared with placebo (p<0.001). A summary of the QMG score CFB to Day 43 (Visit 10) is presented in Table 22.

Table 22: QMG CFB to Day 43 (Visit 10) (Hypothetical & Treatment Policy Strategy, randomised set)

Statistic	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
n	62	65	62
Mean (SE)	−0.89 (0.525)	−4.22 (0.574)	−5.62 (0.655)
LS Mean (SE)	−1.915 (0.682)	−5.398 (0.679)	−6.672 (0.692)
Difference vs Placebo (95% CI) †	-	−3.483 (−5.614, −1.584)	−4.756 (−6.821, −2.859)
p-value	-	<0.001	<0.001

Abbreviations: ≈, equivalent dose; CFB, change from Baseline: CI, confidence interval; LS, least square; MMRM, mixed model repeated measure; QMG, quantitative myasthenia gravis score; SE, standard error; TEAE, treatment-emergent adverse event.
†All outputs are from the combined MMRM, except CIs and p-values which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method.

Change from Baseline to Day 43 (Visit 10) in MGSPRO "Muscle Weakness Fatigability" score

Results of the secondary endpoint MGS PRO "Muscle Weakness Fatigability" score from Baseline to Day 43 (Visit 10) were supportive of the primary analysis with a statistically significant reduction (improvement) in LS mean Muscle Weakness Fatigability score for both rozanolixizumab treatment groups compared with placebo (p<0.001). A summary of the Muscle Weakness Fatigability score CFB to Day 43 (Visit 10) is presented in Table 23.

Table 23: MGSPRO "Muscle Weakness Fatigability" score CFB to Day 43 (Visit 10) (Hypothetical & Treatment Policy Strategy, randomised set)

Statistic	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
n	62	65	62
Mean (SE)	−6.14 (2.310)	−18.89 (3.197)	−20.92 (2.621)
LS Mean (SE)	−10.588 (3.034)	−23.029 (3.034)	−25.751 (3.095)
Difference vs placebo (95% CI)†	-	−12.441 (−21.804, −4.089)	−15.163 (−23.596, −6.450)
p-value	-	<0.001	<0.001

Abbreviations: ≈, equivalent dose; CFB, Change from Baseline; CI, confidence interval; LS, least square; MGSPRO, Myasthenia Gravis Symptoms Patient-reported outcome; MMRM, mixed model repeated measure; SE, standard error; TEAE, treatment-emergent adverse event.
†All outputs are from the combined MMRM, except CIs and p-values which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method.

Change from Baseline to Day 43 (Visit 10) in MGSPRO "Physical Fatigue" score

Results of the secondary endpoint MGSPRO "Physical Fatigue" score from Baseline to Day 43 (Visit 10) were supportive of the primary analysis with a statistically significant reduction (improvement) in LS mean Physical Fatigue score for both rozanolixizumab

treatment groups compared with placebo (p=0.012 for the ≈7 mg/kg group and p<0.001 for the ≈10 mg/kg group). A summary of the Physical Fatigue score CFB to Day 43 (Visit 10) is presented in Table 24.

Table 24: MGSPRO "Physical Fatigue" score CFB to Day 43 (Visit 10) (Hypothetical & Treatment Policy Strategy, randomised set)

Statistic	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
n	62	65	62
Mean (SE)	−7.53 (2.304)	−16.10 (2.817)	−21.88 (2.746)
LS Mean (SE)	−10.637 (3.051)	−19.287 (3.046)	−25.459 (3.107)
Difference vs Placebo (95% CI)†	-	−8.650 (−18.058, −0.134)	−14.822 (−23.759, −5.936)
p-value	-	0.012	<0.001

Abbreviations: ≈, equivalent dose; CFB, change from Baseline; CI, Confidence Interval; LS, least square; MMRM, mixed model repeated measure; MGSPRO, Myasthenia Gravis Symptoms Patient-reported outcome; SE, standard error; TEAE, treatment-emergent adverse event.
†All outputs are from the combined MMRM, except CIs and p-values which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method.

Change from Baseline to Day 43 (Visit 10) in MGSPRO "Bulbar Muscle Weakness" score

Results of the secondary endpoint MGSPRO "Bulbar Muscle Weakness" score CFB to Day 43 (Visit 10) were supportive of the primary analysis with a statistically significant reduction (improvement) in LS mean Bulbar Muscle Weakness score for both rozanolixizumab treatment groups compared with placebo (p<0.001). A summary of the Bulbar Muscle Weakness score CFB to Day 43 (Visit 10) is presented in Table 25.

Table 25: MGS PRO "Bulbar Muscle Weakness" score CFB to Day 43 (Visit 10) (Hypothetical & Treatment Policy Strategy, randomised set)

Statistic	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
n	62	65	62
Mean (SE)	−2.26 (2.124)	−13.69 (2.382)	−13.30 (2.062)
LS Mean (SE)	−3.519 (2.397)	−14.839 (2.406)	−14.224 (2.464)
Difference vs Placebo (95% CI)†	-	−11.320 (−18.958, −4.998)	−10.705 (−17.787, −3.998)
p-value	-	<0.001	<0.001

Abbreviations: ≈, equivalent dose; CFB, change from Baseline; CI, confidence interval; LS, least square; MMRM, mixed model repeated measure; MGSPRO, Myasthenia Gravis Symptoms Patient-reported outcome; SE, standard error; TEAE, treatment-emergent adverse event.
† All outputs are from the combined MMRM, except CIs and p-values which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method.

MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10)

At Day 43, the proportion of responders in both rozanolixizumab treatment groups (n=45, 68.2% in the ≈7 mg/kg group and n=41, 61.2% in the ≈10 mg/kg group) was more than double compared with the placebo group (n=19, 28.4%). A summary of MG-ADL responder status at Day 43 using the composite strategy (≥2.0 points improvement from Baseline) is presented in Table 26.

Table 26: MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10) (Composite Strategy, randomised set)

Statistic	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
n	67	66	67
Responder, n (%)	19 (28.4)	45 (68.2)	41 (61.2)
Odds Ratio vs Placebo† (95% CI)‡	-	5.765 (2.100, 14.882)	4.273 (1.653, 11.791)
p-value‡	-	<0.001	<0.001

Abbreviations: ≈, equivalent dose; AChR, acetylcholine receptor; CI, confidence interval; MG-ADL, myasthenia gravis activities of daily living; MuSK, muscle-specific kinase; TEAE, treatment-emergent adverse event.
Note: The analysis was based on the Composite Strategy, where study participants who received rescue therapy before Day 43 or discontinued from treatment or from the study due to TEAEs were treated as non-responders. Any missing data due to other reasons was imputed as non-responders.
Note: Percentages are based on the number of participants with data at Day 43 in the randomised Set.
† The odds ratios of the responder rates at Day 43 are estimated and tested between treatment groups (each rozanolixizumab dose vs placebo) using logistic regression model with factors of treatment group, Baseline MG-ADL score, and stratification factor (AChR+ or MuSK+). An odds ratio >1 indicates a greater likelihood of response on rozanolixizumab vs placebo.
‡ All outputs are from the combined model, except CIs and p-values which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method. The reported p-value is unadjusted for multiple testing.

B.2.6.1.3 Other efficacy endpoints

The results of all “other” efficacy endpoints were supportive of and consistent with the primary analysis, and showed the robust clinical efficacy of rozanolixizumab compared with placebo.

Rescue medication

No study participants required rescue therapy while receiving rozanolixizumab during the treatment period, compared with three (4.5%) study participants in the placebo group.

One (1.5%) of the three patients in the placebo group who received rescue therapy also received rescue treatment during the observation period (57 days after the last infusion). In the observation period, one (1.5%) study participant in the rozanolixizumab ≈7 mg/kg group and two (3.0%) study participants rozanolixizumab ≈10 mg/kg group received rescue treatment (37 days after the last infusion and 24 days after the last infusion for one study participant and 41 days for the other, respectively).

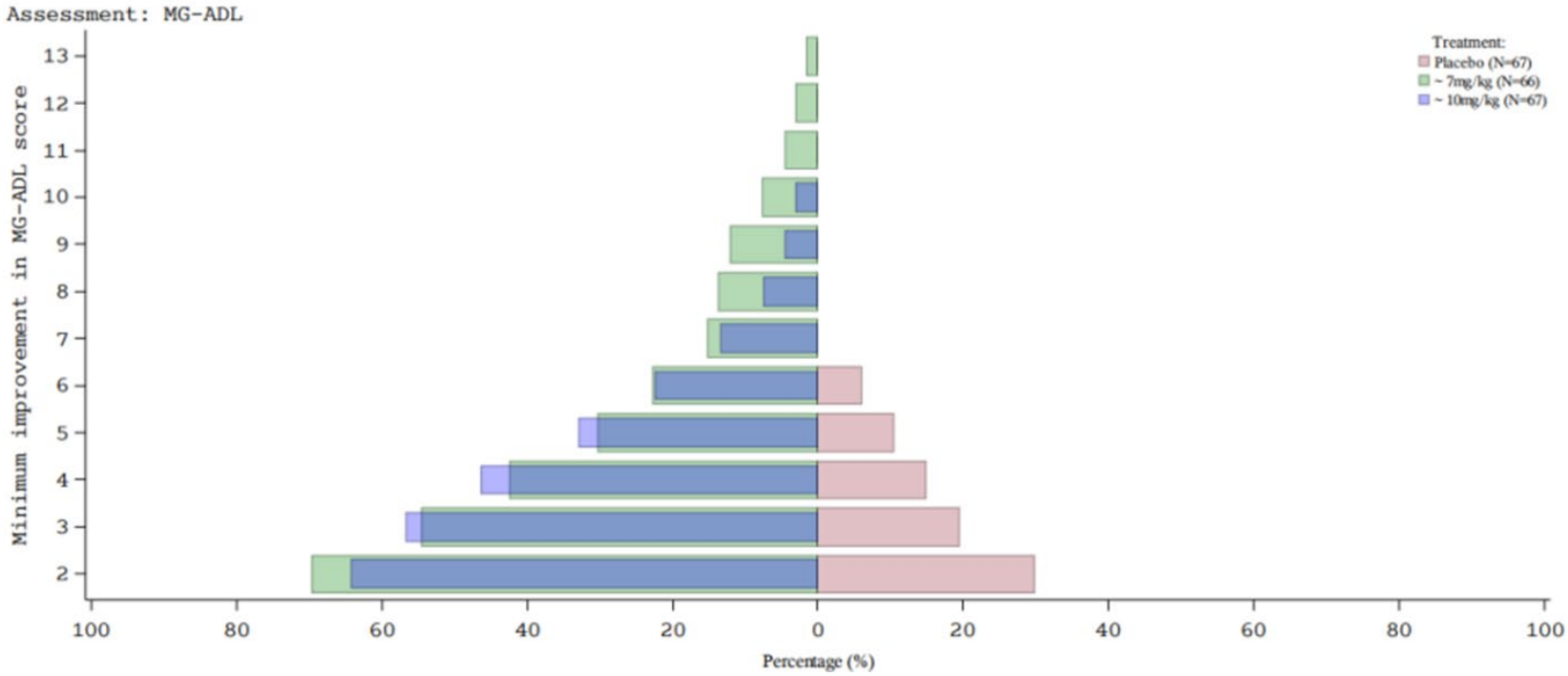
Fifty-nine (29.5%) study participants chose to rollover to the OLE studies MG0004 or MG0007 after completion of the treatment period and before the end of the observation

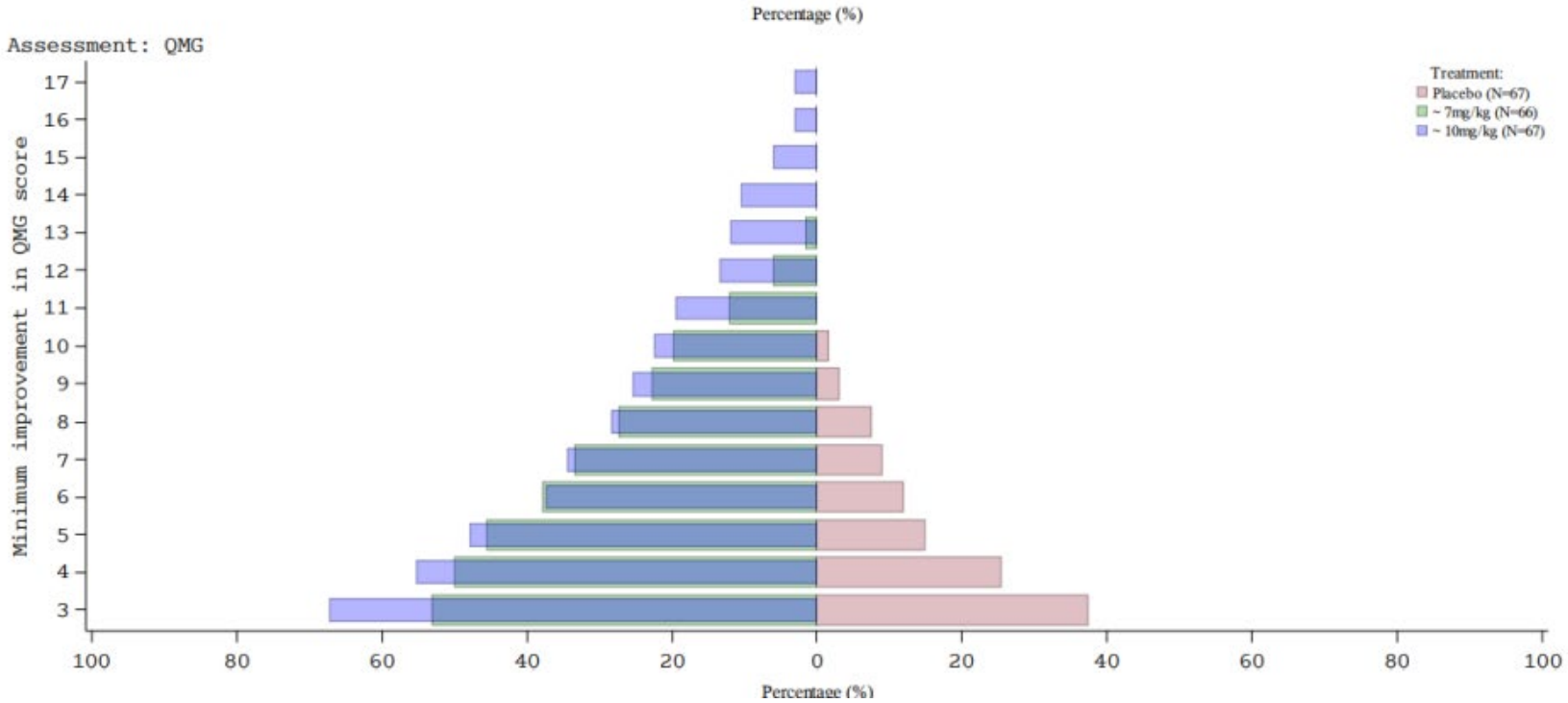
period and to receive rozanolixizumab instead of opting for permitted rescue therapy (IVIg or PLEX).

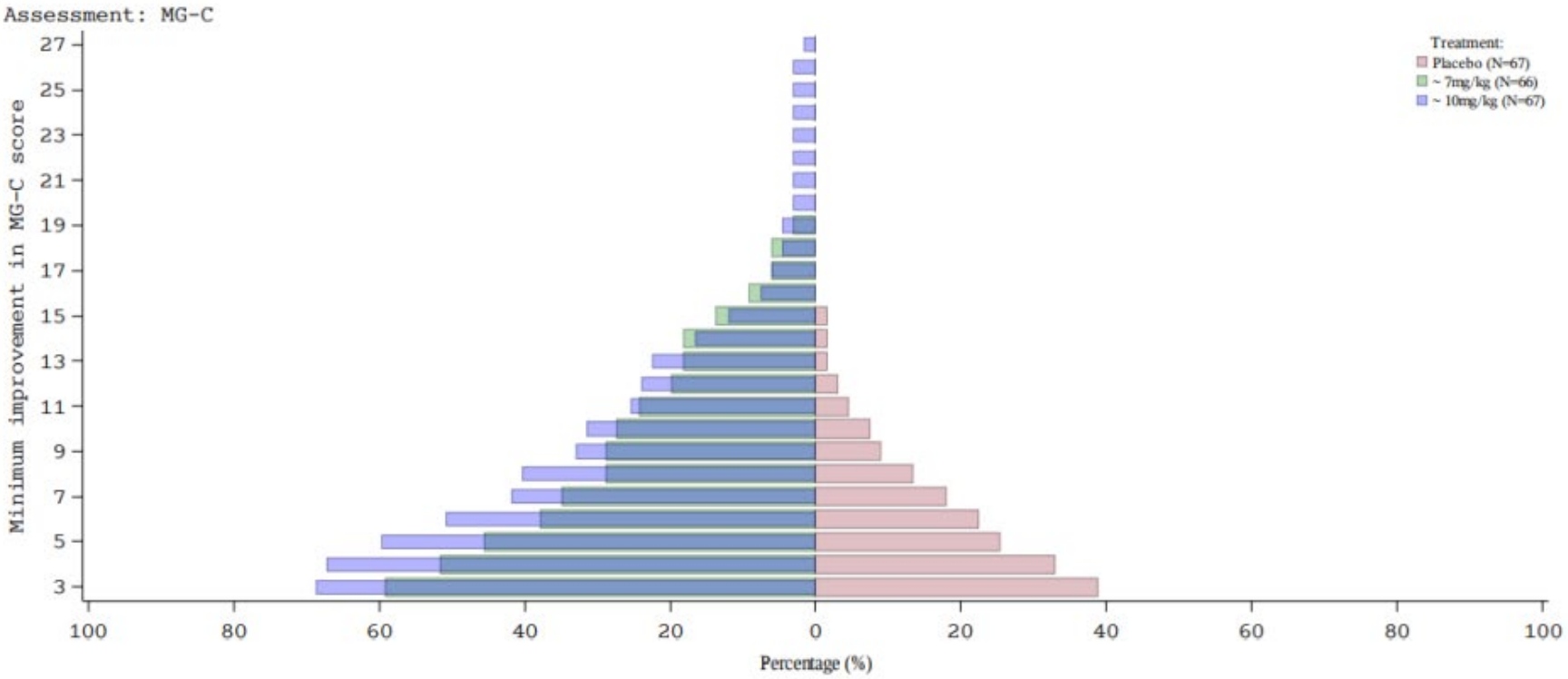
MG-ADL, MG-C and QMG responder

A greater proportion of study participants in the rozanolixizumab groups achieved higher minimum improvements in MG-ADL, MG-C, and QMG response at Day 43 compared with the placebo group. Divergent bar plots of improvement in MG-ADL, MG-C, and QMG responders at Day 43 are summarised by treatment group in Figure 8.

Figure 8: Divergent bar plots of improvement in MG-ADL, MG-C, and QMG responders at Day 43 by treatment (randomised set)




Assessment: QMG
Percentage (%)
Minimum improvement in QMG score
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
100
80
60
40
20
0
20
40
60
80
100
Percentage (%)
Treatment:
Placebo (N=67)
~ 7mg/kg (N=66)
~ 10mg/kg (N=67)



Abbreviations: ~, equivalent dose; MG-ADL, myasthenia gravis activities of daily living; MG-C, myasthenia gravis composite; QMG, quantitative myasthenia gravis.
Note: MG-ADL responder was defined as participants with ≥2.0 points improvement from Baseline; QMG responder was defined as participants with ≥3.0 points improvement from Baseline; MG-C responder was defined as study participants with ≥3.0 points improvement from Baseline.

MG-ADL responder rates and time to response

The proportion of study participants who achieved an MG-ADL response (≥2.0 points improvement from Baseline) was higher in both rozanolixizumab groups compared with the placebo group at the first post-Baseline measurement (Day 8). At Day 8, 34.8%, 37.9%, and 23.9% of study participants were MG-ADL responders in the rozanolixizumab ≈7 mg/kg, ≈10 mg/kg, and placebo groups, respectively. The highest responder rates observed were achieved at Day 43 (last measurement in the treatment period) for both rozanolixizumab treatment groups with 46 (71.9%) responders in the ≈7 mg/kg group and 43 (69.4%) in the ≈10 mg/kg group.

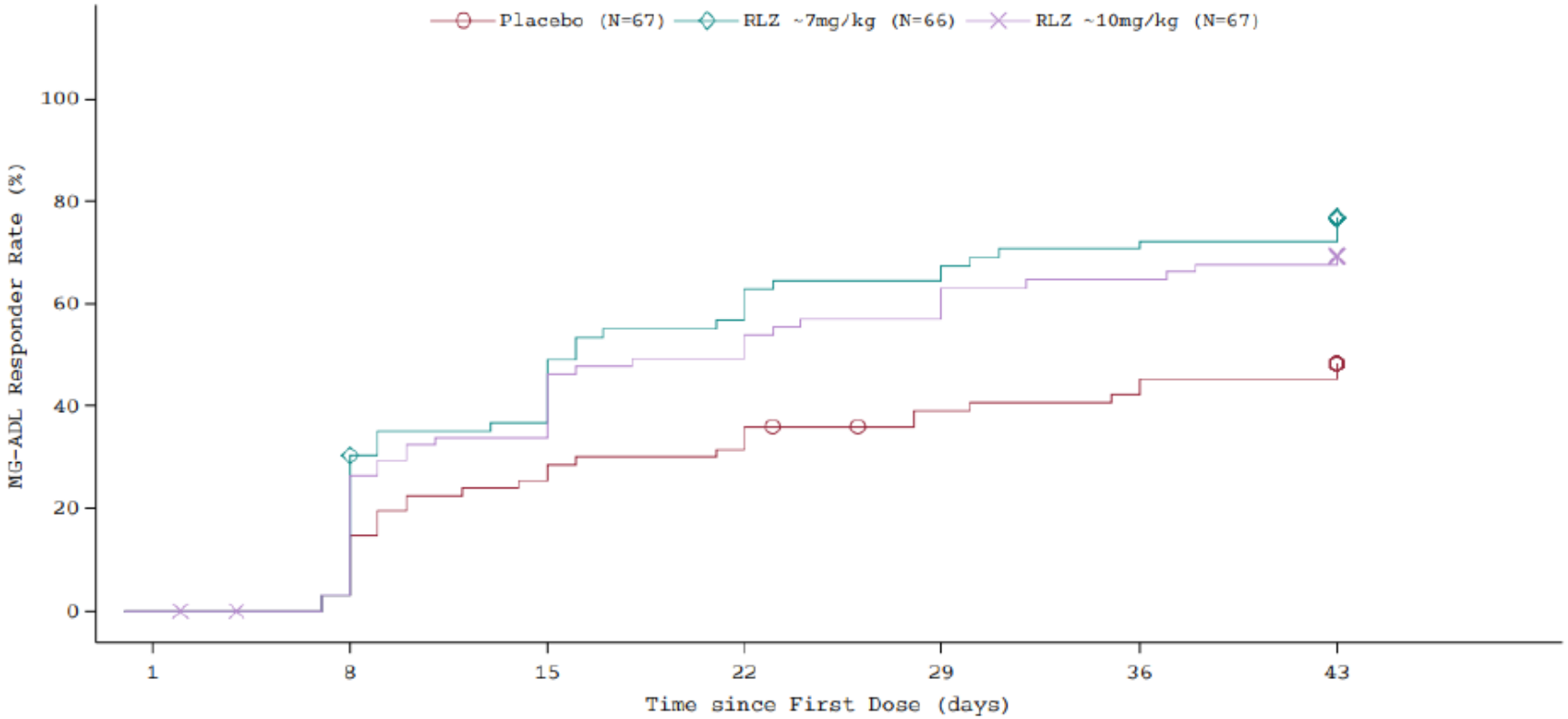
The median time to MG-ADL response was 16 days in the rozanolixizumab ≈7 mg/kg group, 22 days in the ≈10 mg/kg group, and was not determined for the placebo group, as the Kaplan-Meier plot did not cross at 50%. The hazard ratio for MG-ADL response was in favour of rozanolixizumab for both ≈7 mg/kg and ≈10 mg/kg groups. The time to MG-ADL response is summarised in Table 27 and presented graphically in Figure 9.

Table 27: Time to MG-ADL response (randomised set)

Statistic	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
Median (days)	NA	16	22
97.5% CI	22, NA	13, 23	15, 32
% Censored	52.24	24.24	32.84
Hazard ratio† (95% CI)‡	-	2.114 (1.181, 4.234)	1.772 (0.989, 3.558)
p-value	-	0.004	0.010

Abbreviations: ≈, equivalent dose; CI, confidence interval; MG-ADL, myasthenia gravis Activities of Daily Living; TEAE, treatment-emergent adverse event.
Note: Study participants who used rescue therapy before Day 43 or who were withdrawn from the treatment/study due to TEAEs before achieving first MG-ADL response, were censored at time of event. Study participants who never achieved a response by Day 43 were censored at the date of their last MG-ADL assessment.
† A hazard ratio >1 indicates that the time to MG-ADL response is improved for rozanolixizumab compared with placebo.
‡ All outputs are from the combined model, except CIs and p-values which are based on stagewise inverse normal combination using the Lehmacher and Wassmer method. The reported p-value is unadjusted for multiple testing.

Figure 9: Kaplan-Meier plot of time to MG-ADL response (randomised set)



Abbreviations: ~, equivalent dose; MG-ADL, myasthenia gravis activities of daily living; RLZ, rozanolixizumab; TEAE, treatment-emergent adverse event.
Note: MG-ADL response is defined as ≥2-point improvement (decrease) from Baseline.
Note: Study participants who used rescue therapy before Day 43 or who were withdrawn from the treatment/study due to TEAEs before achieving first MG-ADL response were censored at time of event. Study participants who never achieved a response by Day 43 were censored at the date of their last MG-ADL assessment.

MG-C responder rates

The proportion of study participants who achieved an MG-C response (defined as ≥3.0 points improvement from Baseline) was higher in both rozanolixizumab groups compared with the placebo group at the first post-Baseline measurement (Day 8). At Day 8, 43.9%, 53.0%, and 28.4% of study participants were MG-C responders in the rozanolixizumab ≈7 mg/kg, ≈10 mg/kg, and placebo groups, respectively. At the last measurement in the treatment period (Day 43), the responder rates were 60.9%, 74.2%, and 40.6% in the rozanolixizumab ≈7 mg/kg, ≈10 mg/kg, and placebo groups, respectively.

QMG responder rates

The proportion of study participants who achieved a QMG response (defined as ≥3.0 points improvement from Baseline) was higher in both rozanolixizumab groups compared with the placebo group at the first post-Baseline measurement (Day 8). At Day 8, 36.4%, 37.9%, and 17.9% of study participants were QMG responders in the rozanolixizumab ≈7 mg/kg, ≈10 mg/kg, and placebo groups, respectively. At the last measurement in the treatment period (Day 43), the responder rates were 54.7%, 72.6% and 39.1% in the rozanolixizumab ≈7 mg/kg, ≈10 mg/kg, and placebo groups, respectively.

Responder rates in historical MuSK-Ab+ study participants

Based on historical data, 21 study participants had MuSK-Ab+ status (n=5 [7.6%], n=8 [11.9%], and n=8 [11.9%] study participants in the rozanolixizumab ≈7 mg/kg, ≈10 mg/kg group, and placebo groups, respectively). Of these, 19 had available data at Day 43 (n=5 [7.6%], n=7 [10.4%], and n=7 [10.4%] study participants in the rozanolixizumab ≈7 mg/kg group, ≈10 mg/kg group, and placebo groups, respectively). One study participant in the ≈10 mg/kg group discontinued treatment after seven days of exposure due to AE but was identified as responder at the premature end of study Visit, and one study participant in the placebo group discontinued treatment after 22 days of exposure due to lack of efficacy.

The CFB to Day 43 in MG-ADL score was −6.265 (97.5% CI: −11.405, −1.126) and −4.169 (97.5% CI: −9.238, 0.900) in MuSK-Ab+ study participants who received rozanolixizumab at ≈7 mg/kg and ≈10 mg/kg, respectively (see Section B.2.7.4.1). At Day 43, all 12 MuSK-Ab+ study participants who received rozanolixizumab and had data available were MG-ADL and MG-C responders, and all but one were QMG responders, compared with one, zero, and two MG-ADL, MG-C, and QMG responders, respectively, of the seven MuSK-Ab+ study participants who received placebo and had data available.

Minimal symptom expression at any time during treatment and observation periods

A higher proportion of patients achieved minimal symptom expression (MSE) (defined as an MG-ADL total score of 0 or 1) at any time in both rozanolixizumab groups (n=17 [25.8%] study participants in the ≈7 mg/kg group and n=19 [28.4%] in the ≈10 mg/kg group) compared with the placebo group (n=2 [3.0%]) (Table 28).

Table 28: Minimal symptom expression at any time during treatment and observation periods (randomised set)

Statistic	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
n	67	66	67
Yes, n (%)	2 (3.0)	17 (25.8)	19 (28.4)

Abbreviations: ≈, equivalent dose; MG-ADL, myasthenia gravis activities of daily living.
Note: Percentages are based on the number of study participants with MG-ADL data in the randomised Set.

Change from Baseline in MG-QoL15r, EQ-5D-5L and MGII scores

Health-related quality of life was assessed in the MycarinG trial using two MG-specific instruments, MG-QoL15r and MGII), in addition to the EQ-5D-5L questionnaire.

A higher mean (SD) decrease (improvement) from Baseline in MG-QoL15r was observed at Day 43 for both rozanolixizumab groups (≈7mg/kg: −4.0 [6.1]; ≈10mg/kg: −5.3 [5.9]) compared with placebo (−1.3 [4.3]). Lower scores on this assessment reflect improved quality of life with reduced psychological and/or social impact of MG-specific impairments.

The mean scores for the EQ-5D-5L visual analogue score (VAS) at Baseline were 57.8, 56.8, and 54.4 for the rozanolixizumab ≈7mg/kg, ≈10mg/kg, and placebo groups, respectively. A higher mean (SD) increase (improvement) from Baseline in EQ-5D-5L VAS was observed at Day 43 for both rozanolixizumab groups (≈7mg/kg: 12.2 [19.9]; ≈10mg/kg: 11.4 [16.8]) compared with placebo (6.1 [18.2]).

A higher mean (SD) decrease (improvement) from Baseline in MGII was observed at Day 43 for both rozanolixizumab groups (≈7mg/kg: −12.4 [16.5]; ≈10mg/kg: −16.1 [12.1]) compared with placebo (−3.4 [10.4]). Results for CFB in MGII ocular and generalised domains scores were consistent with the overall score with greater improvements for rozanolixizumab compared with placebo. Upon request from a number of participating sites, during the study the completion of the MGII was revised from mandatory to optional to reduce study participant burden. Nonetheless, the MGII questionnaire was completed at Day 43 by most study participants who had data at Baseline: 49 of the 55 study participants in the rozanolixizumab ≈7mg/kg group, 49 of the 54 in the ≈10mg/kg group, and 48 of the 53 in the placebo group.

B.2.6.1.4 Conclusion

The clinical study MycarinG met its primary objective, demonstrating the clinical efficacy of rozanolixizumab at the licensed dose of ≈7 mg/kg and at the dose of ≈10 mg/kg

compared with placebo in patients with gMG. The results of all continuous secondary efficacy endpoints, MG-ADL responder, and “other” efficacy endpoints were consistent and supported the primary endpoint.

In addition, clinical efficacy was observed for AChR-Ab+ and MuSK-Ab+ study participants based on subgroup analyses, with improvements from Baseline in MG-ADL, MG-C, QMG, MGSPRO “Muscle Weakness Fatigability”, and “Physical Fatigue” scores that were consistent with the results observed in the overall population. Higher proportions of early responders were observed with both rozanolixizumab treatment groups compared with placebo (i.e. by the first post-Baseline measurement at Day 8), with clinically meaningful efficacy across multiple disease-specific endpoints, including PRO measures.

Rozanolixizumab is a once-weekly subcutaneous infusion (for a 6-week cycle), administered by a healthcare professional and requires no new infrastructure or capital investment for its incorporation in the NHS. In addition to the clinical benefits demonstrated in MycarinG, it is estimated that the availability of rozanolixizumab for patients with gMG is associated with both humanistic benefits for patients and reduced burden to the NHS (see Section B.3 for the cost-effectiveness of rozanolixizumab for patients with gMG). These results show that rozanolixizumab delivers improved clinical outcomes compared with the current standard of care in clinical trials and may improve outcomes in clinical practice.

Primary endpoint

- Treatment with rozanolixizumab resulted in a mean decrease in MG-ADL total score from Baseline to Day 43 of approximately 2.6 points compared with placebo for rozanolixizumab ≈7 mg/kg group and ≈10 mg/kg treatment groups ($p<0.001$). This difference was considered clinically meaningful.

Key secondary endpoints

- Clinically relevant and statistically significant improvements in MG-C and QMG were observed for both rozanolixizumab treatment groups compared with placebo ($p<0.001$)
- Statistically significant improvements in MGSPRO “Muscle Weakness Fatigability”, “Physical Fatigue” and “Bulbar Muscle Weakness” scores were observed for both rozanolixizumab treatment groups (all $p<0.001$ except for MGSPRO “Physical Fatigue” in the rozanolixizumab ≈7 mg/kg group [$p=0.012$])
- A higher proportion of MG-ADL responders was observed with rozanolixizumab (68.2% [≈7 mg/kg] and 61.2% [≈10 mg/kg]) compared with placebo (28.4%)

Other efficacy endpoints

- Rozanolixizumab showed improvements in all the “other” efficacy endpoints by Day 8 compared with placebo.
- No study participants required rescue therapy while receiving rozanolixizumab during the treatment period

- Starting on Day 8, the proportion of study participants who achieved an MG-ADL, MG-C, or QMG response was higher in both rozanolixizumab groups compared with the placebo group
- A higher proportion of study participants achieved MSE at any time during the study in both rozanolixizumab treatment groups (25.8% of study participants in the ≈7 mg/kg group and 28.4% in the ≈10 mg/kg group) compared with the placebo group (3%)
- The improvement in health-related QoL (based on MG-QoL15r) was higher for both rozanolixizumab treatment groups compared with placebo
- Improvements from Baseline in MGII overall score, ocular score, and generalised domain score were observed at Day 43 for both rozanolixizumab treatment groups compared with placebo
- Pre-specified subgroup analyses of the primary and secondary efficacy endpoints showed consistent results with the overall population for age, sex, weight, and region

B.2.6.2 *MG0007*

B.2.6.2.1 Primary outcome

There was no primary efficacy outcome in the open-label extension trial MG0007. The primary safety endpoints (the occurrence of TEAEs and TEAEs leading to withdrawal of rozanolixizumab) are described in Section B.2.10.1.2. All efficacy analyses are presented for the SS by study cycle and dose level received within the cycle and rozanolixizumab total. No statistical testing was performed.

Most participants in both treatment groups did not switch rozanolixizumab doses. Of the 61 study participants who received rozanolixizumab ≈7 mg/kg in Cycle 1 and had more than one treatment cycle, [redacted] ([redacted]%) continued to receive rozanolixizumab ≈7 mg/kg. Of the 60 study participants who received rozanolixizumab ≈10 mg/kg in Cycle 1 and had more than one treatment cycle, [redacted] ([redacted]%) continued to receive rozanolixizumab ≈10 mg/kg.

Results up to and including Cycle 5 are summarised below. For analyses in subsequent cycles where the number of participants was >10, results were consistent with the earlier cycles.

B.2.6.2.2 Secondary efficacy outcome

The secondary objective of MG0007 was to assess the efficacy of 6-week treatment cycles with rozanolixizumab in study participants with gMG through measurements of clinically relevant outcomes (CFBs in the MG-ADL, MG-C, and QMG total scores and the MGSPRO “Muscle Weakness Fatigability”, “Physical Fatigue” and “Bulbar Muscle Weakness” scores). Improvements in clinical and HRQoL outcomes were consistently observed for rozanolixizumab ≈7 mg/kg and rozanolixizumab ≈10 mg/kg with repeated cyclic treatment in MG patients. The MG-ADL responder rates were also supportive of the clinical benefit of rozanolixizumab with similar response rates observed over multiple cycles.

Median time to MG-ADL response was [redacted] for the majority of each of the first five 6-week treatment cycles. The median treatment-free interval between Cycles 1 and 2 was ~9 weeks, which was consistent between rozanolixizumab dose groups for the overall study population. For a subset of participants with a higher frequency of treatment cycles, shorter treatment-free intervals of ~5 weeks were observed across cycles.

Change from Baseline to Day 43 in MG-ADL score during each treatment cycle

Improvements (reductions from Baseline) in the MG-ADL score were observed from Day 8 and continued through to Day 43 in both rozanolixizumab treatment groups. A consistent and clinically meaningful reduction in MG-ADL was observed with repeated cyclic treatment. The mean CFB in MG-ADL score for both treatment groups is shown in Table 29.

Table 29: MG-ADL score CFB to Day 43 during each treatment cycle (safety set)

Treatment group	Statistic	Cycle [redacted]		Cycle [redacted]		Cycle [redacted]		Cycle [redacted]	
		Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline
Rozanolixizumab ≈7 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rozanolixizumab ≈10 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change from Baseline; IMP, investigational medicinal product; MG-ADL, myasthenia gravis activities of daily living; SD, standard deviation.

Note: Study participants were grouped according to the actual dose level received within the study cycle.

Note: Baseline values were defined as the last available value prior to or on the same date of first administration of IMP at each cycle (i.e. Baseline [Day 1]) value for that cycle.

Change from Baseline to Day 43 in MG-C total score during each treatment cycle

Improvements (reductions from Baseline) in the MG-C total score were observed at all timepoints up to Day 43 in both rozanolixizumab treatment groups. A consistent and clinically relevant reduction was observed with repeated cyclic treatment. The CFBs to Day 43 in the MG-C total score during the first four treatment cycles are summarised in Table 30.

Table 30: MG-C total score CFB to Day 43 during each treatment cycle (safety set)

Treatment group	Statistic	Cycle [redacted]		Cycle [redacted]		Cycle [redacted]		Cycle [redacted]	
		Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline
Rozanolixizumab ≈7 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rozanolixizumab ≈10 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change from Baseline; IMP, investigational medicinal product; MG-C, myasthenia gravis composite; SD, standard deviation.
Note: Study participants were grouped according to the actual dose level received within the study cycle.
Note: Baseline values were defined as the last available value prior to or on the same date of first administration of IMP at each cycle (i.e. Baseline [Day 1]) value for that cycle.
Note: MG-C scores range from 0 to 50, with a higher score indicating more severe disease.

Change from Baseline to Day 43 in QMG total score during each treatment cycle

Improvements (reductions from Baseline) in the QMG total score were observed at all timepoints up to Day 43 in both rozanolixizumab treatment groups. A consistent and clinically relevant reduction was observed with repeated cyclic treatment. The CFBs to Day 43 in the QMG total score during the first four treatment cycles are summarised in Table 31.

Table 31: QMG total score CFB to Day 43 during each treatment cycle (safety set)

Treatment group	Statistic	Cycle [redacted]		Cycle [redacted]		Cycle [redacted]		Cycle [redacted]	
		Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline
Rozanolixizumab ≈7 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rozanolixizumab ≈10 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change from Baseline; IMP, investigational medicinal product; QMG, quantitative myasthenia gravis; SD, standard deviation.
Note: Study participants were grouped according to the actual dose level received within the study cycle.
Note: Baseline values were defined as the last available value prior to or on the same date of first administration of IMP at each cycle (i.e. Baseline [Day 1]) value for that cycle.
Note: QMG scores range from 0 to 39 with a higher score indicating more severe disability.

Change from Baseline to Day 43 in MGSPRO "Muscle Weakness Fatigability" score during each treatment cycle

Improvements (reductions) in the mean MGSPRO "Muscle Weakness Fatigability" score from Baseline to Day 43 were observed in both rozanolixizumab treatment groups. A consistent response was observed with repeated cyclic treatment. The CFBs to Day 43 in the MGSPRO "Muscle Weakness Fatigability" score during the first four treatment cycles are summarised in Table 32.

Table 32: MGSPRO "Muscle Weakness Fatigability" score CFB to Day 43 during each treatment cycle (safety set)

Treatment group	Statistic	Cycle [redacted]		Cycle [redacted]		Cycle [redacted]		Cycle [redacted]	
		Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline
Rozanolixizumab ≈7 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rozanolixizumab ≈10 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change from baseline; IMP, investigational medicinal product; MGSPRO, Myasthenia Gravis Symptoms Patient-reported outcome; SD, standard deviation.

Note: Study participants were grouped according to the actual dose level received within the study cycle.

Note: Baseline values were defined as the last available value prior to or on the same date of first administration of IMP at each cycle (i.e. Baseline [Day 1]) value for that cycle.

Note: The muscle weakness fatigability scale score ranges from 0 to 100, with a higher result indicating more frequent and severe symptoms.

Change from Baseline to Day 43 in MGSPRO "Physical Fatigue" score during each treatment cycle

Improvements (reductions) in the mean MGSPRO "Physical Fatigue" score from Baseline to Day 43 were observed in both rozanolixizumab treatment groups. A consistent response was observed with repeated cyclic treatment. The maximum mean reduction from The CFBs to Day 43 in the MGSPRO "Physical Fatigue" score during the first four treatment cycles are summarised in Table 33.

Table 33: MGSPRO "Physical Fatigue" score CFB to Day 43 during each treatment cycle (safety set)

Treatment group	Statistic	Cycle [redacted]		Cycle [redacted]		Cycle [redacted]		Cycle [redacted]	
		Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline
Rozanolixizumab ≈7 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rozanolixizumab ≈10 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change from Baseline; IMP, investigational medicinal product; MGS PRO, Myasthenia Gravis Symptoms Patient-reported outcome; SD, standard deviation

Note: Study participants were grouped according to the actual dose level received within the study cycle.

Note: Baseline values were defined as the last available value prior to or on the same date of first administration of IMP at each cycle (i.e. Baseline [Day 1]) value for that cycle.

Note: The physical fatigue scale score ranges from 0 to 100, with a higher result indicating more frequent and severe symptoms

Change from Baseline to Day 43 in MGSPRO "Bulbar Muscle Weakness" score during each treatment cycle

Improvements (reductions) in the mean MGSPRO "Bulbar Muscle Weakness" score from Baseline to Day 43 were observed in both rozanolixizumab treatment groups. A consistent response was observed with repeated cyclic treatment. The maximum mean reduction from The CFBs to Day 43 in the MGSPRO "Bulbar Muscle Weakness" score during the first four treatment cycles are summarised in Table 34.

Table 34: MGSPRO "Bulbar Muscle Weakness" score CFB to Day 43 during each treatment cycle (safety set)

Treatment group	Statistic	Cycle [redacted]		Cycle [redacted]		Cycle [redacted]		Cycle [redacted]	
		Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline	Baseline observed result	Change from Baseline
Rozanolixizumab ≈7 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rozanolixizumab ≈10 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change from Baseline; IMP, investigational medicinal product; MGSPRO, Myasthenia Gravis Symptoms Patient-reported outcome; SD, standard deviation.

Note: Study participants were grouped according to the actual dose level received within the study cycle.

Note: Baseline values were defined as the last available value prior to or on the same date of first administration of IMP at each cycle (i.e. Baseline [Day 1]) value for that cycle.

Note: The bulbar muscle weakness scale score ranges from 0 to 100, with a higher result indicating more frequent and severe symptoms.

MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 during each treatment cycle

Consistent responder rates were observed with repeated cyclic treatment throughout the first five 6-week treatment cycles. High response rates were observed by Day 8 (first post-Baseline efficacy assessment) in all cycles. Responder rates continued to increase to Day 43. The observed MG-ADL responder rates at Day 43 during the first four treatment cycles are summarised in Table 35.

Table 35: Observed MG-ADL responder rates at Day 43 during each treatment cycle (safety set)

Treatment group	Cycle [redacted]		Cycle [redacted]		Cycle [redacted]		Cycle [redacted]	
	n	Responders n (%)	n	Responders n (%)	n	Responders n (%)	n	Responders n (%)
Rozanolixizumab ≈7 mg/kg (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rozanolixizumab ≈10 mg/kg (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rozanolixizumab total (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; MG-ADL, myasthenia gravis activities of daily living.
Note: Percentages were based on the number of study participants with non-missing data at each visit in the safety set.
Note: Study participants were grouped according to the actual dose level received within the study cycle.

Time to MG-ADL response (≥2.0-point improvement from Baseline) during each treatment cycle

Median time to MG-ADL response (≥2.0-point improvement from Baseline) was [redacted] for the majority of each of the first five 6-week treatment cycles. A difference in the time to response was observed in Cycle 1 between the two treatment groups ([redacted] for ≈7 mg/kg vs [redacted] for ≈10 mg/kg). The time to MG-ADL response during the first [redacted] treatment cycles is summarised in Table 36.

Table 36: Time to MG-ADL response during each treatment cycle (safety set)

Treatment	Statistic	Cycle [redacted]	Cycle [redacted]	Cycle [redacted]	Cycle [redacted]
Rozanolixizumab ≈7 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]
	Median (days)	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]	[redacted]
	% Censored	[redacted]	[redacted]	[redacted]	[redacted]
Rozanolixizumab ≈10 mg/kg (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]
	Median (days)	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]	[redacted]
	% Censored	[redacted]	[redacted]	[redacted]	[redacted]
Rozanolixizumab total (N=[redacted])	n	[redacted]	[redacted]	[redacted]	[redacted]
	Median (days)	[redacted]	[redacted]	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]	[redacted]	[redacted]
	% Censored	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CI, confidence interval; MG-ADL, myasthenia gravis activities of daily living.
Note: Study participants were grouped according to the actual dose level received within the study cycle.
Note: Time to MG-ADL response (in days) by study cycle was defined as Date of First MG-ADL Response within study cycle - Date of MG-ADL Baseline within study cycle + 1.
Note: Study participants who used rescue therapy within study cycle or who were withdrawn from the treatment/study due to TEAEs before achieving first MG-ADL response within study cycle were censored at time of event. Study participants who never achieved a response within study cycle were censored at the date of their last MG-ADL assessment.
Note: Survival estimate was calculated from Kaplan-Meier analysis.

B.2.6.2.3 Other efficacy endpoints

The MG-C and QMG responder rates and minimal symptom expression results were supportive of the consistent clinical benefit of rozanolixizumab with repeated cyclic treatment. Patient-reported outcomes including EQ-5D-5L and MG-QOL15r further supported the consistent benefit of rozanolixizumab in MG patients.

MG-C responder rates for each treatment cycle

For the first [redacted] 6-week treatment cycles, all MG-C responder rates (responder defined as ≥3.0 points improvement from Baseline) at Day 43 were [redacted]% and ranged from [redacted]% (Cycle [redacted]) to [redacted]% (Cycle [redacted]).

QMG responder rates for each treatment cycle

For the first [redacted] 6-week treatment cycles, all QMG responder rates (responder defined as ≥3.0 points improvement from Baseline) at Day 43 were [redacted]% and ranged from [redacted]% (Cycle [redacted]) to [redacted]% (Cycle [redacted]).

Minimal symptom expression (at any time during treatment and observation periods)

Minimal symptom expression[e] was consistently achieved across cycles ranging from [redacted]% to [redacted]% in the rozanolixizumab ≈7 mg/kg group at any time in the first [redacted] 6-week treatment cycles and from [redacted]% to [redacted]% in the ≈10 mg/kg group. For participants who required more frequent treatment cycles (i.e. those participants included in Cycle [redacted]), a high proportion of participants still achieved minimal symptom expression ([redacted]% and [redacted]% in the ≈7 mg/kg group and ≈10 mg/kg groups, respectively).

Change from Baseline to Day 43 in EQ-5D-5L

The mean scores for the EuroQol visual analogue scale at Baseline (Cycle [redacted]) were [redacted] and [redacted] for the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg groups, respectively. The mean increase (improvement) from Baseline in EuroQol visual analogue scale at any visit during the treatment periods of the first five treatment cycles was generally consistent across cycles ranging from [redacted] to [redacted] in the rozanolixizumab ≈7 mg/kg group and from [redacted] to [redacted] in the ≈10 mg/kg group.

Change from Baseline to Day 43 in MG-QOL15r

The mean MG-QOL15r scores at Cycle [redacted] Baseline were [redacted] and [redacted] for the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg groups, respectively. Improvements from Baseline to Day 43 were observed for both rozanolixizumab treatment groups with a consistent response observed with repeated cyclic treatment. The mean reduction (improvement) from Baseline at any visit during the treatment periods of the first five treatment cycles ranged from [redacted] to [redacted] in the rozanolixizumab ≈7 mg/kg group and from [redacted] to [redacted] in the ≈10 mg/kg group.

Use of rescue therapy (IVIg or PLEX)

The proportion of study participants requiring rescue therapy during MG0007 by study cycle was similar between the two doses. Overall, in the first five treatment cycles, [redacted]% of the study participants needed rescue therapy. In total, [redacted] study participants in the rozanolixizumab ≈7 mg/kg group and [redacted] in the ≈10 mg/kg group received rescue therapy; the majority during Cycle [redacted] ([redacted] [[redacted]%] and [redacted] [[redacted]%] study participants in the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg group, respectively).

At the data cut-off date, there were 9/157 cases of rescue therapy use.

[e] Minimal symptom expression is designed to assess how many study participants become free or virtually free of MG symptoms as measured by achieving an MG-ADL score of 0 or 1 on therapy

B.2.6.2.4 Medical resource utilisation and health economics

In total, [redacted] ([redacted]%) and [redacted] ([redacted]%) study participants in the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg groups, respectively, had at least one hospitalisation/emergency room visit each. The most frequent reasons for hospitalisation/emergency room visit were AEs (n=[redacted] [[redacted]%] and n=[redacted] [[redacted]%] in the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg groups, respectively) and the study disease (n=[redacted] [[redacted]%] and n=[redacted] [[redacted]%], respectively). There was no hospitalisation/emergency room visit due to lack of efficacy.

B.2.6.2.5 Conclusion

Primary endpoint

Please see section B.2.10.1.2 for the primary endpoint of safety.

Secondary endpoints

MG0007 data show that, following repeated cyclic treatment, rozanolixizumab (at the licensed doses of ≈7 mg/kg and also at ≈10 mg/kg) leads to consistent improvements in all efficacy endpoints tested in the study; onset and depth of response were similar to those seen in MG0003.

- Clinically relevant improvements from Baseline in the secondary efficacy endpoints MG-ADL, MG-C, QMG, and the main MGSPRO scales mean total scores were observed for both rozanolixizumab treatment groups. Responses were consistent with repeated cyclic treatment
- Responses for MG-ADL were seen as early as Day 8 of each treatment cycle, with a median time to MG-ADL response of [redacted] for the majority of each of the first five 6-week treatment cycles
- In study participants who were AChR-Ab+, improvements from Baseline to Day 43 in MGADL, MG-C, and QMG total score were consistent with the results of the overall population
- In study participants who were MuSK-Ab+, improvements from Baseline to Day 43 in MGADL, MG-C, and QMG total score were numerically greater in the initial cycles compared with the results of the overall population

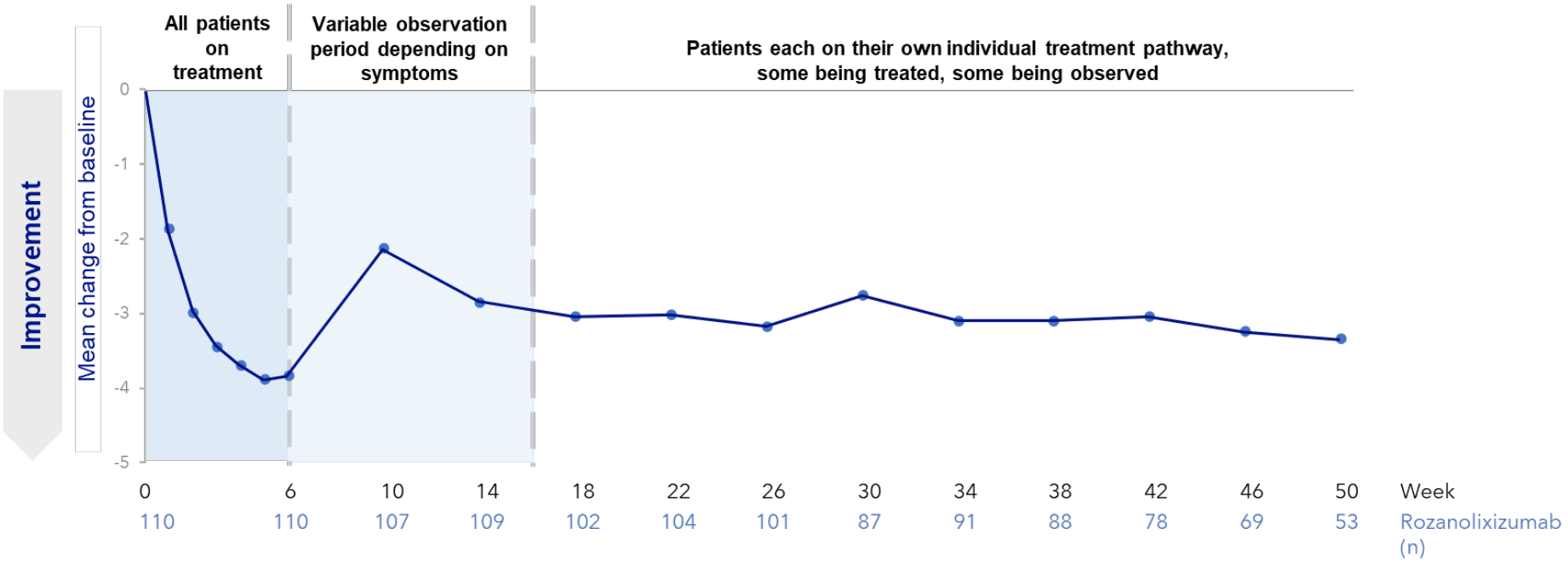
B.2.6.3 *Pooled efficacy analysis*

The pooled efficacy analysis included [redacted] patients (enrolled in either MycarinG, MG0007 or the first 6 weeks of MG0004) with at least two treatment cycles based on gMG symptoms worsening (symptom-driven treatment cycle) as assessed by the investigator considering an increase of ≥2.0 points on the MG-ADL scale or ≥3.0 points on the QMG scale (see Appendix D). The objective of the pooled efficacy analysis was to assess participants response after each symptom-driven cycle of treatment with rozanolixizumab ≈7 mg/kg or ≈10 mg/kg (166).

The results are presented in Appendix M. The pooled efficacy analysis supported [redacted] from Baseline to Day 43 of each symptom-driven cycle in MG-ADL, QMG, MG-G total scores, and in MGSPRO scores for “Muscle Weakness Fatigability”, “Physical Fatigue” and “Bulbar Muscle Weakness” in each treatment cycle. [redacted] in efficacy endpoints were [redacted] across repeated cycles; the CFB in

MG-ADL score stabilised around a 3-point improvement compared with Baseline (Figure 10).

Figure 10: Mean MG-ADL reduction from baseline (relative week, pooled analysis†)



† Pooled efficacy data for patients receiving ≥2 rozanolixizumab treatment cycles based on gMG symptom worsening.

B.2.7 *Subgroup analysis*

Subgroup analyses performed in MycarinG and MG0007 are listed below. Subgroup analyses were performed to evaluate the efficacy of rozanolixizumab in patients stratified to specific disease characteristics.

B.2.7.1 *Methodology*

The primary and continuous secondary efficacy endpoints in MycarinG were evaluated for subgroups of interest including:

- Age (18 to <65 years, ≥65 years)
- Age (18 to <65, 65 to <85, ≥85 years)
- Sex (male, female)
- Region (North America, Europe, and Asia [excluding Japan], Japan)
- Stratification factors: MG-specific autoantibodies, AChR Ab+ and MuSK Ab+[f]

The MG-ADL scores and CFB were summarised in the five subgroups listed above and additional subgroups as follows:

- Duration of disease at Baseline (<median, ≥median)
- MGFA disease class at Baseline
- Thymectomy at Baseline (yes, no)
- Baseline MG-ADL category (<5, ≥5)

The following subgroups of MG Baseline medications were derived in the analysis datasets and used for ad-hoc reporting purposes. Refer to Section B.2.3.1.2 (Table 12) for the definition of MG Baseline medications.

- Baseline oral steroid (yes, no)
- Baseline ISTs other than oral steroids (yes, no)
- Baseline AChEI (yes, no)

To support the goal of a fixed dosing strategy for rozanolixizumab, additional subgroup analyses were performed by administered dose group for each weight subgroup below:

- Weight (<50 kg, 50–<70 kg, 70–<100 kg, ≥100 kg, total)
- Administered dose (placebo, rozanolixizumab 280 mg, rozanolixizumab 420 mg, rozanolixizumab 560 mg, rozanolixizumab 840 mg, rozanolixizumab 1120 mg, rozanolixizumab total)

A post-hoc analysis was performed to assess the efficacy and safety of rozanolixizumab in patients who have ≥2 prior MG-specific medications (after AChEIs) (see Section B.2.7.4.2).

[f] The stratification factors AChR Ab+ and MuSK Ab+ in the subgroup analysis were based on the values from MG-specific autoantibody assessment taken at Baseline using the same algorithm for missing values. Historical AChR Ab+ and historical MuSK Ab+ was also examined in the subgroup analysis; in this case, Baseline AChR Ab+ and Baseline MuSK Ab+ was replaced by historical AChR Ab+ and historical MuSK Ab+.

B.2.7.2 *Participant characteristics*

The subgroups specified in the NICE Decision problem include patient stratification by MG-specific antibodies and adults with severe MG needing IVIg or PLEX. Efficacy outcomes for study participants stratified by AChR and MuSK antibody status are presented in Section B.2.7.4.1 for MycarinG (MG0003) and Section B.2.7.4.2 for MG0007. A post-hoc analysis for patients with ≥2 prior MG therapies (i.e. prednisone, azathioprine, MMF, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, or other corticosteroids or ISTs) is presented in Section B.2.7.4.2. These patients are considered to have uncontrolled, refractory disease and are eligible for IVIg/PLEX (36, 167).

Patient demographic and baseline characteristics for study participants with historical MuSK or AChR Ab+ status, ≥2 prior MG medications and stratified by disease severity (based on MG-ADL Baseline score) are provided in Appendix E.1.

B.2.7.3 *Statistical information*

All subgroup analyses were descriptive; no statistical testing of treatment-by-subgroup interactions nor statistical testing of treatment effects within subgroups was carried out. No subgroup analysis was performed for safety variables.

B.2.7.4 *Results*

B.2.7.4.1 MycarinG (Study MG0003)

Primary endpoint

Changes from Baseline in MG-ADL total score to Day 43 were [redacted] with the results in the overall study population for all subgroups (Table 37).

Table 37: Change from Baseline to Day 43 (Visit 10) in MG-ADL score by subgroups (randomised set)

Subgroup	Placebo N=67		Rozanolixizumab ≈7 mg/kg N=66		Rozanolixizumab ≈10 mg/kg N=67	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Historical AChR Ab+						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Historical MuSK Ab+						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease severity by Baseline MG-ADL score						
<5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; AChR, acetylcholine receptor; MG-ADL, Myasthenia Gravis Activities of Daily Living; MuSK, muscle-specific kinase; N/A, not available; SD, standard deviation.

Secondary endpoints

Changes in MG-C total score and QMG score from Baseline to Day 43 were [redacted] with the results in the overall study population for all subgroups considered

(Table 38 and Table 39, respectively), similar to the subgroup analyses of the primary endpoint. An exception was the observed trend towards a [redacted] from Baseline to Day 43 in both QMG and MG-C scores in the historical MuSK-Ab+ study participants receiving ≈7 mg/kg compared with the other subgroups.

Table 38: Change from Baseline to Day 43 (Visit 10) in MG-C score by subgroups (randomised set)

Subgroup	Placebo N=67		Rozanolixizumab ≈7 mg/kg N=66		Rozanolixizumab ≈10 mg/kg N=67	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Historical AChR Ab+						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Historical MuSK Ab+						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; AChR, acetylcholine receptor; MG-C, Myasthenia Gravis Composite; MuSK, muscle-specific kinase; SD, standard deviation.

Table 39: Change from Baseline to Day 43 (Visit 10) in QMG score by subgroups (randomised set)

Subgroup	Placebo N=67		Rozanolixizumab ≈7 mg/kg N=66		Rozanolixizumab ≈10 mg/kg N=67	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Historical AChR Ab+						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Historical MuSK Ab+						
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; AChR, acetylcholine receptor; MuSK, muscle-specific kinase; QMG, Quantitative Myasthenia Gravis; SD, standard deviation.

Subgroup analyses indicated a trend towards [redacted] responder rates in historical MuSK Ab+ compared with historical AChR Ab+ study participants. [redacted] with historical MuSK Ab+ status who received rozanolixizumab ≈7 mg/kg (n=[redacted]) were responders for MG-ADL, MG-C and QMG at Day 43. Amongst historical AChR Ab+ participants receiving rozanolixizumab ≈7 mg/kg (n=[redacted]), responder rates at Day 43 were [redacted]% for MG-ADL, [redacted]% for QMG and [redacted]% for MG-C.

B.2.7.4.2 Post hoc analysis

Primary endpoint

Amongst study participants who have a history of ≥2 MG specific therapies the CFB in MG-ADL total score to Day 43 was [redacted] with the CFB observed in the overall study population (Table 40).

Table 40: Change from Baseline to Day 43 (Visit 10) in MG-ADL score by post hoc subgroups

Subgroup	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
Overall			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
≥2 MG specific therapies			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean difference (97.5% CI)		[redacted]	[redacted]
p value		[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; SD, standard deviation.

Secondary endpoints

Changes from Baseline to Day 43 in MG-C total score and QMG score were [redacted] with the results in the overall study population for participants who have a history of ≥2 MG specific therapies (Table 41 and Table 42, respectively), similar to the post hoc analysis of the primary endpoint. One exception was the LS mean difference in MG-C score between rozanolixizumab ≈7 mg/kg and placebo, which had a p value of [redacted] in the patients with a history of ≥2 MG specific therapies.

Table 41: Change from Baseline to Day 43 (Visit 10) in MG-C score by post hoc subgroups

Subgroup	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
Overall			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
≥2 MG specific therapies			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean difference (97.5% CI)		[redacted]	[redacted]
p value		[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; MG, myasthenia gravis; MG-C, Myasthenia Gravis Composite; SD, standard deviation.

Table 42: Change from Baseline to Day 43 (Visit 10) in QMG score by post hoc subgroups

Subgroup	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
Overall			
n	64	64	62
Mean (SD)	[redacted]	[redacted]	[redacted]
≥2 MG specific therapies			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean difference (97.5% CI)		[redacted]	[redacted]
p value		[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; MG, myasthenia gravis; QMG, Quantitative Myasthenia Gravis; SD, standard deviation.

Responder rates at Day 43 for MG-ADL (Table 43), MG-C (Table 44) and QMG (Table 45) scores in participants with a history of ≥2 MG specific therapies were also consistent with the results of the overall population.

Table 43: MG-ADL responder rates (Observed) by post hoc subgroups

Subgroup	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
	n (%)	n (%)	n (%)
Overall			
Responder	20 (31.3)	46 (71.9)	43 (69.4)
Non-responder	44 (68.8)	18 (28.1)	19 (30.6)
≥2 MG specific therapies			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]
OR vs placebo (97.5% CI)		[redacted]	[redacted]
p value		[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CI< confidence interval; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; OR, odds ratio.

Table 44: MG-C responder rates (Observed) by post hoc subgroups

Subgroup	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
	n (%)	n (%)	n (%)
Overall			
Responder	26 (40.6)	39 (60.9)	46 (74.2)

Non-responder	38 (59.4)	25 (39.1)	16 (25.8)
≥2 MG specific therapies			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; MG, myasthenia gravis; MG-C, Myasthenia Gravis Composite.

Table 45 QMC responder rates (Observed) by post hoc subgroups

Subgroup	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
	n (%)	n (%)	n (%)
Overall			
Responder	25 (39.1)	35 (54.7)	45 (72.6)
Non-responder	39 (60.9)	29 (45.3)	17 (27.4)
≥2 MG specific therapies			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; MG, myasthenia gravis; QMG, Quantitative Myasthenia Gravis.

Extent of exposure

Based on an integrated pooled analysis (see Section B.2.10.3 and Appendix F), the annualised number of infusions and cycles were comparable between the overall population (see Section B.2.10) and participants who received ≥2 prior MG-specific therapies. In the subgroup of patients with ≥2 prior MG-specific therapies the mean (SD) annualised number of infusion was [redacted] and a mean (SD) annualised number of treatment cycles was [redacted].

B.2.7.4.3 MG0007

Change from Baseline to Day 43 in MG-ADL score during each treatment cycle by subgroups

The subgroups explored were age, sex, region, weight, MG-specific autoantibodies, duration of disease at Baseline, MGFA disease class at Baseline, thymectomy at Baseline, and Baseline MG-ADL category. Improvements (mean reductions from Baseline) in MG-ADL score over time for the different subgroups were generally consistent with the results in the overall study population.

An exception was the observed trend towards a larger improvement from Baseline in MuSK-Ab+ study participants than in the overall population at Day 43 for Cycle [redacted] vs [redacted]) and Cycle [redacted] vs [redacted]). The response was similar for Cycle [redacted] vs [redacted]) and Cycle [redacted] vs [redacted]), although conclusions should be drawn with caution due to the low number of participants in this subgroup.

Change from Baseline to Day 43 in the MG-C total score during each treatment cycle by subgroups

The subgroup of AChR-Ab+ (n≤[redacted] study participants per treatment group and timepoint) showed a trend in MG-C total score change from Baseline to Day 43 similar to the overall population. A trend towards a better response in MuSK-Ab+ study participants than in the overall population at Day 43 was observed for Cycle [redacted] vs [redacted]) and Cycle [redacted] vs [redacted]). The response was generally similar for Cycle [redacted] vs [redacted]) and Cycle [redacted] vs [redacted]).

Change from Baseline to Day 43 in QMG total score during each treatment cycle by subgroups

The subgroup AChR-Ab+ (n≤[redacted] study participants per treatment group and timepoint) showed a trend in QMG total score change from Baseline to Day 43 similar to the overall population. A trend towards a better response in MuSK-Ab+ study participants than in the overall population was observed.

Change from Baseline to Day 43 in MGSPRO "Muscle Weakness Fatigability" score during each treatment cycle by subgroups

The subgroup of AChR-Ab+ (n≤[redacted] study participants per treatment group and timepoint) study participants showed a trend in the "Muscle Weakness Fatigability" score change from Baseline to Day 43 similar to the overall population. A trend towards a better response in MuSK-Ab+ study participants than in the overall population was observed, although conclusions should be drawn with caution due to the low number of participants in this subgroup.

Change from Baseline to Day 43 in MGSPRO "Physical Fatigue" score during each treatment cycle by subgroups

The subgroup of AChR-Ab+(n≤[redacted] study participants per treatment group and timepoint) study participants showed a trend in "Physical Fatigue" score change from Baseline to Day 43 similar to the overall population. A trend towards a better response in MuSK-Ab+ study participants than in the overall population was observed, although conclusions should be drawn with caution due to the low number of participants in this subgroup (n≤8 per treatment group and cycle).

Change from Baseline to Day 43 in MGSPRO "Bulbar Muscle Weakness" score during each treatment cycle by subgroups

The subgroup of AChR-Ab+ (n≤[redacted] study participants per treatment group and timepoint) study participants showed a trend in "Bulbar Muscle Weakness" score change from Baseline to Day 43 similar to the overall population. A trend towards a better response in MuSK-Ab+ study participants than in the overall population was observed, although conclusions should be drawn with caution due to the low number of participants in this subgroup (n≤8 per treatment group and cycle).

B.2.8 *Meta-analysis*

A network meta-analysis (NMA) was conducted to estimate the comparative efficacy between rozanolixizumab, zilucoplan, efgartigimod, ravulizumab, eculizumab, IVIg, and placebo. The relevant comparators for this submission are efgartigimod, zilucoplan, IVIg, and PLEX (however, IVIg and PLEX were not included in the NMA due to the lack of a connecting study with Phase III data), thus only the results for these comparators are presented.

An NMA was preferred to a pairwise meta-analysis, as it allowed all available and relevant evidence to be included and more precise treatment effects to be calculated. The results from the NMA will inform the economic model to provide cost-effectiveness estimates of rozanolixizumab against relevant comparators.

A recently published meta-analysis of randomised and placebo-controlled trials of innovative therapies in MG (efgartigimod, ravulizumab, rozanolixizumab, zilucoplan, eculizumab, and rituximab) (168), reports results that are consistent with the analyses presented here.

B.2.9 *Indirect and mixed treatment comparisons*

In order to identify evidence on the efficacy of comparator treatments of relevance to the decision problem, an SLR was performed. Please see Section B.2.1 for details of the methodology.

B.2.9.1.1 Trials used to inform the analysis

In total, 47 studies (all RCTs) qualified for inclusion from the clinical SLR. Of these, 35 were excluded due to interventions not being of interest, resulting in the inclusion of 12 studies in the analysis (Table 46). One study (Howard 2013) compared eculizumab with placebo and presented crossover data at 32 weeks; data before the crossover period at Week 16 are also available, and these were used in the NMA.

Table 46: Studies included in the network meta-analysis

Trial	Primary publication – author (year)	Trial phase	Intervention	Comparator
ADAPT	Howard et al, 2021 (169)	Phase III	Efgartigimod	Placebo
CHAMPION MG	Vu et al, 2021 (170)	Phase III	Ravulizumab	Placebo
MycarinG	Bril et al, 2023 (46)	Phase III	Rozanolixizumab (7 or 10 mg/kg)	Placebo
RAISE	Howard et al, 2023 (171)	Phase III	Zilucoplan (0.3 mg/kg)	Placebo
REGAIN	Howard et al, 2017 (172)	Phase III	Eculizumab	Placebo
RINOMAX	Piehl et al, 2022 (133)	Phase III	Rituximab	Placebo
BeatMG	Nowak et al, 2021 (132)	Phase II	Rituximab	Placebo

Trial	Primary publication – author (year)	Trial phase	Intervention	Comparator
Howard 2013	Howard et al, 2013 (173)	Phase II	Eculizumab	Placebo
Bril 2021	Bril et al, 2021 (174)	Phase II	Rozanolixizumab	Placebo
Howard 2019	Howard et al, 2019 (175)	Phase II	Efgartigimod	Placebo
Howard 2020	Howard et al, 2020 (176)	Phase II	Zilucoplan (0.3 mg/kg)†	Placebo
Wolfe 2002	Wolfe et al, 2002 (177)	Phase II	IVIg	Placebo

Abbreviations: IVIg, intravenous immunoglobulin.
† Zilucoplan 0.1 mg/kg dosage data were not used for analysis

B.2.9.1.2 Studies excluded from the analysis

Of the 35 studies excluded from the feasibility assessment, 13 studies did not have any outcomes of interest, 18 studies did not have any interventions of interest, two studies were not connected to the network, one study had study cross-over study design and one study was Phase IV with outcomes reported at Week 2 (Appendix D.3).

B.2.9.1 *Methods and outcomes of included studies*

B.2.9.1.1 Rationale for choice of outcome measure and scale

An overview of the outcomes considered of relevance, analysed, and included in the NMA are described in Appendix D.2.

Table 47: Description of network meta-analyses conducted

Subject	Trial Phase included	Endpoint	Justification
MG-ADL Responders	Phase III	≥2 point improvement in MG-ADL response at study endpoint	≥2 point improvement in MG-ADL was the primary endpoint in MycarinG
CFB in MG-ADL	Phase III	CFB to primary study endpoint in MG-ADL	Piehl 2022 (16 weeks) and MycarinG (6 and 14 weeks) were utilised

Abbreviations: CFB, change from Baseline; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living.

B.2.9.1.2 Participants included

The NMA included patients with gMG, which is aligned with the decision problem.

B.2.9.2 *Methods of analysis and presentation of results*

B.2.9.2.1 Methodology

Analysis was performed in a Bayesian framework and involved a model with parameters, data, and a likelihood distribution and prior distributions. Where results of the RCTs

formed part of one evidence network and were deemed sufficiently similar for each population of interest, they were synthesised by means of NMAs by outcome of interest.

Under the assumption of consistency, the NMA model relates the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of each intervention. Based on these basic parameters, the relative treatment effects between each of the contrasts in the network were obtained.

Model Selection

The deviance information criterion (DIC) was used to compare the goodness-of-fit of competing models. DIC provides a measure of model fit that penalises model complexity, described in Equation 1.

Equation 1: Deviance information criterion

$$DIC = \overline{D} + pD, pD = \overline{D} - \widehat{D}$$

$\overline{D}$ ("Dbar") is the posterior mean residual deviance, pD is the effective number of parameters and $\widehat{D}$ is the deviance evaluated at the posterior mean of the model parameters. In general, a more complex model resulted in a better fit to the data, demonstrating a smaller residual deviance. The model with the better trade-off between fit and parsimony had a lower DIC. A difference in DIC of about 5 points can be considered meaningful.

Evaluation of inconsistency

Prior to the actual NMA, the consistency between direct and indirect comparisons was evaluated for networks that include closed loops. In each of the networks, no closed loops of more than one trial connecting different interventions existed; therefore, inconsistency was not assessed.

Fixed and random-effects models

Both fixed-effect and random-effects models were considered for the NMA. Given that the networks generally consisted of only one trial per direct comparison, the fixed-effect model was preferred, as heterogeneity could not be estimated.

Binary outcomes

For binary outcomes (e.g. MG-ADL responders), the NMA was performed based on the proportion of patients experiencing the event of interest using a regression model with a binomial likelihood and logit link or RD with normal likelihood and natural scale link. In these NMAs, each included trial reports the proportion of patients reaching an endpoint. The standard model for dichotomous outcomes uses a logit link function and a binomial likelihood. The modelled parameter is the proportion of success from the binomial, which is assumed to be constant.

Additional outcome data reported in study figures were digitised (Digitizeit; http://www.digitizeit.de/). Relative treatment effects were expressed as ORs.

Continuous outcomes

For continuous outcomes (e.g., change from Baseline in MG-ADL scores), the NMA was performed based on the mean change from Baseline in the outcome and the corresponding standard errors, using a regression model with a normal likelihood and identify link. Additional outcome data reported in study figures were digitised (Digitizeit; http://www.digitizeit.de/). Relative treatment effects were expressed as mean differences (MD) in change from Baseline (CFB) for the outcomes assessed.

Prior distributions

In order not to influence the observed results by the prior distribution, non-informative prior distributions were used for the model parameter(s).

Software

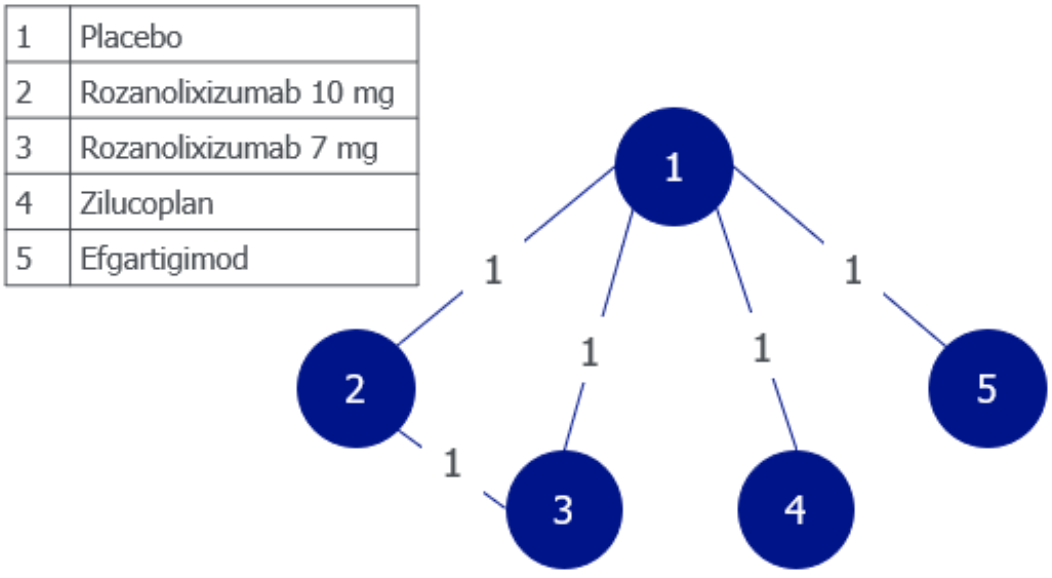
The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in OpenBUGS. All analyses were performed using R version 4.2.2 (http://www.r-project.org/) and OpenBugs version 3.2.3 (OpenBUGS Project Management Group); the code will be included in the submission.

B.2.9.3 *Results*

MG-ADL responders

In the analysis, five Phase III trials that reported on MG-ADL ≥2 point improvement were included (Figure 11). The modelled probability of response is presented in Table 48.

Figure 11: NMA evidence network



Abbreviation: NMA, network meta-analysis.

Table 48: MG-ADL probability of response

Intervention	Mean	SE
Placebo	[redacted]	[redacted]
Zilucoplan	[redacted]	[redacted]

Efgartigimod	[redacted]	[redacted]
Rozanolixizumab 7 mg	[redacted]	[redacted]
Rozanolixizumab 10 mg	[redacted]	[redacted]

Abbreviations: MG-ADL, myasthenia gravis activities of daily living; SE, standard error.

Change from Baseline in MG-ADL score

The modelled treatment outcomes for mean change as derived from the NMA included efficacy from Phase III trials at the time of primary endpoint assessment (Figure 11). The modelled treatment outcomes for mean change as derived from the NMA are provided in Table 49.

Results from the analysis showed all interventions exhibited a statistically significant improvement in MG-ADL score (based on change from baseline) when compared to placebo.

Table 49: Modelled treatment outcomes for mean change from baseline in MG-ADL score

Intervention	Mean	SE
Placebo	[redacted]	[redacted]
Zilucoplan	[redacted]	[redacted]
Rozanolixizumab 7 mg	[redacted]	[redacted]
Rozanolixizumab 10 mg	[redacted]	[redacted]
Efgartigimod	[redacted]	[redacted]

B.2.9.3.1 Choice of model

Please see Section B.2.9.2.1.

B.2.9.3.2 Heterogeneity and inconsistency

The studies included in the NMA present with heterogeneity, which must be considered when interpreting the results of the NMA. As the evidence base for the comparators is so limited, heterogeneity could not be avoided by removing a trial from the analysis, as with only a single trial available for most comparators (at Phase 2 and 3), this would exclude that comparator entirely.

Heterogeneity is present in the baseline characteristics, such as the Baseline MG-ADL scores, suggesting there might be differences in the severity of disease between trial populations. Baseline characteristics for the comparator trials are provided in Appendix D.3.

Trial design is also heterogenous with cyclic dosing of rozanolixizumab and efgartigimod (and IVIg, although not included in the NMA) vs daily administration of zilucoplan. This means the timepoint of the analysis is influential on the results for a cyclical treatment. There is also heterogeneity in the response assessment timepoint between the trials. Analysis using a refractory subgroup population was not performed because there was no pre-specified subgroup in the rozanolixizumab trial program so it would introduce more uncertainty, the refractory and overall population had similar results and therefore

the overall population could be assumed to be representative of refractory patients, and there were no refractory data available for efgartigimod since refractory and non-refractory populations were not defined in ADAPT.

B.2.10 *Adverse reactions*

Rozanolixizumab as an add-on therapy to standard treatment was associated with an acceptable safety profile and was generally well tolerated by patients with gMG (46, 47).

In **MycarinG**:

- A total of 52 (81.3%) study participants in the rozanolixizumab ≈7 mg/kg group, 48 (69.6%) in the ≈10 mg/kg group, and 56 (83.6%) in the placebo group received all six infusions.
- The incidence of TEAEs was comparable between the two rozanolixizumab treatment groups and higher compared with placebo.
    - The most frequently reported TEAEs were headache, gastrointestinal disturbances (nausea, diarrhoea, and vomiting), pyrexia, and arthralgia.
- The majority of TEAEs categorised as mild or moderate in severity.
- The incidence of severe TEAEs and TEAEs leading to study- or IMP discontinuation was similar in the rozanolixizumab ≈7 mg/kg and placebo groups; the incidence of these events was higher in the rozanolixizumab ≈10 mg/kg group.
- There were no deaths reported in the study.

In **MG0007**, repeated cyclic treatment with rozanolixizumab was generally well tolerated with an acceptable safety profile. No increase in the incidence of TEAEs, including severe or serious TEAEs was observed with repeated cycles of treatment. No new safety signals were identified.

Based on an integrated **pooled safety analysis**, the mean annualised number of treatment cycles and infusions was [redacted] and [redacted], respectively. The results from the pooled analysis supported the acceptable safety profile and tolerability of repeated cyclic treatment with rozanolixizumab.

B.2.10.1 *Studies reported in section 2.2*

Safety evidence for rozanolixizumab in the population of interest for this submission is provided by the MycarinG (MG0003) study and the OLE phase, MG0007 (interim results cut-off date: 08 July 2022). Key safety outcomes for both studies are presented in Sections B.2.10.1.1 and B.2.10.1.2, respectively.

B.2.10.1.1 MG0003

Extent of exposure

The median duration of treatment with the study medication was 36.0 days for all treatment groups (including mock infusions) and all study participants received at least one infusion (excluding mock infusions). A total of 52 (81.3%) study participants in the

rozanolixizumab ≈7 mg/kg group, 48 (69.6%) in the ≈10 mg/kg group, and 56 (83.6%) in the placebo group received all six infusions (excluding mock infusions).

Mock infusions using placebo were given to reduce unblinding potential when IgG levels dropped below 1 g/L. No study participants in the placebo group needed mock infusions, whereas mock infusions were administered in both rozanolixizumab groups: three total infusions in two study participants in the ≈7 mg/kg group and four total infusions in two study participants (two infusions each) in the ≈10 mg/kg group.

Adverse events

Overall, the number of study participants who experienced TEAEs was comparable in the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg groups (52 [81.3%] and 57 [82.6%], respectively) and lower in the placebo group (45 [67.2%]). A similar pattern was observed for TEAEs considered by the Investigator to be related to the IMP: the number of study participants was comparable in the rozanolixizumab ≈7 mg/kg (n=32 [50.0%]) and ≈10 mg/kg (n=39 [56.5%]) groups, and lower in the placebo group (n=22 [32.8%]). An overview of TEAEs in MycarinG (MG0003) is summarised in Table 50.

No deaths were reported during the study. The number of study participants who experienced serious TEAEs was comparable across all groups: Five (7.8%) in the rozanolixizumab ≈7 mg/kg group, seven (10.1%) in the ≈10 mg/kg group, and six (9.0%) in the placebo group. The number of study participants who experienced TEAEs leading to discontinuation from the study was two (3.1%) in the rozanolixizumab ≈7 mg/kg group, five (7.2%) in the ≈10 mg/kg group, and two (3.0%) in the placebo group. The number of study participants who experienced TEAEs leading to temporary discontinuation of IMP was higher in the rozanolixizumab ≈7 mg/kg (n=3 [4.7%]) and ≈10 mg/kg (n=6 [8.7%]) groups compared with the placebo group (n=1 [1.5%]).

The number of study participants who experienced severe TEAEs was three (4.7%) in the rozanolixizumab ≈7 mg/kg group, 13 (18.8%) in the ≈10 mg/kg group, and three (4.5%) in the placebo group.

Table 50: Overview of TEAEs (safety set)

Adverse events	Placebo N (%) [n] N=67	Rozanolixizumab ≈7 mg/kg N (%) [n] N=64	Rozanolixizumab ≈10 mg/kg N (%) [n] N=69
Any TEAE	45 (67.2) [191]	52 (81.3) [208]	57 (82.6) [266]
Serious SAE	6 (9.0) [6]	5 (7.8) [7]	7 (10.1) [8]
TEAEs resulting in permanent withdrawal from rozanolixizumab	2 (3.0) [2]	2 (3.1) [2]	4 (5.8) [7]
Treatment-related TEAEs†	22 (32.8) [94]	32 (50.0) [90]	39 (56.5) [139]
Severe TEAEs‡	3 (4.5) [3]	3 (4.7) [4]	13 (18.8) [16]
All deaths (number of study participants with AEs leading to death)	0	0	0
Deaths (TEAEs leading to death)	0	0	0

Abbreviations: ≈, equivalent dose; [n], number of events; AE, adverse event; CTCAE, common terminology criteria for adverse events; IMP, investigational medicinal product; N, number of study participants in group; SAE, serious adverse event; TEAE, treatment-emergent adverse events.
Note: "All deaths" is based on all study participants screened and refers to all deaths occurring on study.
† Based on Investigator assessment.
‡ Severe TEAEs are those with CTCAE Grade 3 or above, or those with "severe" intensity as assessed by the Investigator.

Most common TEAEs

In all treatment groups, the system organ class (SOC) with the most frequently reported TEAEs was nervous system disorders (reported in 37 [57.8%], 33 [47.8%], and 21 [31.3%] study participants in rozanolixizumab ≈7 mg/kg, ≈10 mg/kg, and placebo groups, respectively) followed by gastrointestinal disorders (reported in 21 [32.8%], 21 [30.4%], and 16 [23.9%]), general disorders and administration site conditions (reported in 16 [25.0%], 27 [39.1%], and 13 [19.4%]), infections and infestations (reported in 10 [15.6%], 21 [30.4%], and 13 [19.4%]), and musculoskeletal and connective tissues disorders (reported in 15 [23.4%], 13 [18.8%], and nine [13.4%]) SOCs. Overall, the most common TEAEs by PT were headache, diarrhoea, pyrexia, nausea, and arthralgia (Table 51).

In addition, from the TEAEs reported in >2 study participants in any treatment group, the following were reported only with rozanolixizumab: rash, chest pain, oral herpes, and renal impairment.

Table 51: Incidence of TEAEs by PT in >2 study participants in any treatment group (safety set)

MedDRA (v24.0) SOC, PT	Placebo N=67 N (%) [n]	Rozanolixizumab ≈7 mg/kg N=64 N (%) [n]	Rozanolixizumab ≈10 mg/kg N=69 N (%) [n]
Any TEAE	**45 (67.2) [191]**	**52 (81.3) [208]**	**57 (82.6) [266]**

MedDRA (v24.0) SOC, PT	Placebo N=67 N (%) [n]	Rozanolixizumab ≈7 mg/kg N=64 N (%) [n]	Rozanolixizumab ≈10 mg/kg N=69 N (%) [n]
Gastrointestinal disorders	**16 (23.9) [39]**	**21 (32.8) [40]**	**21 (30.4) [39]**
Diarrhoea	9 (13.4) [14]	16 (25.0) [18]	11 (15.9) [18]
Nausea	5 (7.5) [12]	5 (7.8) [7]	8 (11.6) [8]
Vomiting	1 (1.5) [4]	2 (3.1) [4]	4 (5.8) [4]
Abdominal pain upper	2 (3.0) [4]	3 (4.7) [3]	2 (2.9) [2]
General disorders and administration site conditions	**13 (19.4) [24]**	**16 (25.0) [24]**	**27 (39.1) [52]**
Pyrexia	1 (1.5) [1]	8 (12.5) [10]	14 (20.3) [25]
Chest pain	0	2 (3.1) [2]	3 (4.3) [4]
Infections and infestations	**13 (19.4) [16]**	**10 (15.6) [10]**	**21 (30.4) [24]**
Nasopharyngitis	3 (4.5) [4]	1 (1.6) [1]	5 (7.2) [5]
Oral herpes	0	0	3 (4.3) [3]
Urinary tract infection	4 (6.0) [4]	2 (3.1) [2]	2 (2.9) [2]
Injury, poisoning and procedural complications	**5 (7.5) [10]**	**5 (7.8) [5]**	**4 (5.8) [6]**
Fall	3 (4.5) [3]	0	2 (2.9) [4]
Musculoskeletal and connective tissue disorders	**9 (13.4) [13]**	**15 (23.4) [30]**	**13 (18.8) [19]**
Arthralgia	2 (3.0) [2]	4 (6.3) [6]	5 (7.2) [5]
Myalgia	1 (1.5) [1]	2 (3.1) [9]	4 (5.8) [4]
Muscle spasms	1 (1.5) [1]	3 (4.7) [4]	0
Nervous system disorders	**21 (31.3) [52]**	**37 (57.8) [70]**	**33 (47.8) [65]**
Headache	13 (19.4) [31]	29 (45.3) [54]	26 (37.7) [52]
Myasthenia gravis	3 (4.5) [3]	3 (4.7) [3]	3 (4.3) [3]
Somnolence	3 (4.5) [8]	1 (1.6) [1]	0
Renal and urinary disorders	**2 (3.0) [2]**	**1 (1.6) [2]**	**4 (5.8) [6]**
Renal impairment	0	0	3 (4.3) [3]
Respiratory, thoracic and mediastinal disorders	**4 (6.0) [6]**	**4 (6.3) [6]**	**7 (10.1) [7]**
Oropharyngeal pain	1 (1.5) [1]	0	3 (4.3) [3]
Skin and subcutaneous tissue disorders	**4 (6.0) [4]**	**6 (9.4) [6]**	**11 (15.9) [12]**
Rash	0	3 (4.7) [3]	3 (4.3) [3]
Vascular disorders	**1 (1.5) [1]**	**7 (10.9) [7]**	**6 (8.7) [8]**
Hypertension	0	5 (7.8) [5]	0

Abbreviations: ≈, equivalent dose; [n], number of events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of study participants in group; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Serious TEAEs

Serious TEAEs reported by study participants were comparable between the rozanolixizumab ≈7 mg/kg (five [7.8%]), rozanolixizumab ≈10 mg/kg (seven [10.1%]), and placebo (six [9.0%]) groups (Table 52). The only serious TEAEs reported in >1 study participant per treatment group were:

- Myasthenia gravis: one (1.6%) study participant in the rozanolixizumab ≈7 mg/kg group, two (2.9%) in the ≈10 mg/kg group, and one (1.5%) in the placebo group
- Myasthenic crisis: Zero study participants in the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg groups and two (3.0%) study participants in the placebo group

One study participant had a serious TEAE of headache in the rozanolixizumab ≈10 mg/kg group (Table 52).Serious TEAEs considered by the Investigator to be related to the IMP were reported in a comparable number of study participants in the rozanolixizumab ≈7 mg/kg (three [4.7%]), ≈10 mg/kg (two [2.9%]), and placebo (one [1.5%]) groups. Descriptions of the serious TEAEs considered related to rozanolixizumab by the Investigator are provided below.

Table 52: Incidence of serious TEAEs (safety set)

MedDRA (v24.0) SOC PT	**Placebo N=67 N (%) [n]**	**Rozanolixizumab ≈7 mg/kg N=64 N (%) [n]**	**Rozanolixizumab ≈10 mg/kg N=69 N (%) [n]**
Any serious TEAE	**6 (9.0) [6]**	**5 (7.8) [7]**	**7 (10.1) [8]**
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Thoracic vertebral fracture	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]	[redacted]

MedDRA (v24.0) SOC PT	Placebo N=67 N (%) [n]	Rozanolixizumab ≈7 mg/kg N=64 N (%) [n]	Rozanolixizumab ≈10 mg/kg N=69 N (%) [n]
Metastatic squamous cell carcinoma	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Myasthenia gravis	[redacted]	[redacted]	[redacted]
Myasthenic crisis	[redacted]	[redacted]	[redacted]
Seizure	[redacted]	[redacted]	[redacted]
Product issues	[redacted]	[redacted]	[redacted]
Device dislocation	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorder disorders	[redacted]	[redacted]	[redacted]
Cervical dysplasia	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose, [n], number of events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of study participants in each group; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

TEAEs leading to discontinuation

Treatment-emergent AEs leading to discontinuation from the study were reported in two (3.1%) study participants in the rozanolixizumab ≈7 mg/kg group, five (7.2%) in the ≈10 mg/kg group, and two (3.0%) in the placebo group.

In the rozanolixizumab ≈7 mg/kg group, TEAEs of arthralgia and headache that led to discontinuation from the study were reported for one study participant each. In the rozanolixizumab ≈10 mg/kg group, TEAEs of diarrhoea, abdominal pain, vomiting, metastatic squamous cell carcinoma, device dislocation, and pruritus that led to discontinuation from the study were reported for one study participant each. In the placebo group, TEAEs of myasthenia gravis and myasthenia gravis crisis that led to discontinuation from the study were reported for one study participant each. No study participants in the rozanolixizumab ≈7 mg/kg or ≈10 mg/kg groups discontinued from the study due to TEAEs of myasthenia gravis or myasthenia gravis crisis.

Adverse events of special interest

No cases of potential Hy's Law were reported and no study participants met potential drug-induced liver injury (PDILI) criteria.

All study participants had at least one post-Baseline liver laboratory assessment and there were no notable differences by treatment group in elevated LFTs. Three study participants had elevated LFTs; additionally, two participants had elevated LFTs outside the “treatment-emergent” window (i.e. 8 weeks after the last IMP dose) (Table 53).

Table 53: Elevated LFT events

Elevated LFT	Treatment group	AEs	Medical history
Treatment-emergent			
AST >3x ULN ALP >1.5x ULN	≈7 mg/kg	Non-serious TEAEs of hepatic fibrosis non-alcoholic fatty liver disease Investigator assessment: not related to IMP	Increased hepatic enzymes
TBL >1.5x ULN	≈10 mg/kg	No associated TEAE	
TBL >2x ULN	≈10 mg/kg	Non-serious TEAE of blood bilirubin increased Investigator assessment: IMP related	
Not treatment-emergent†			
TBL >2x ULN.	≈7 mg/kg	No associated AE	Gilbert’s syndrome
AST >10x ULN ALT >10xULN	≈10 mg/kg	AE of increased LFT was reported in MG0007	

Abbreviations: AE, adverse event; ALT, alanine transamidase; AST, aspartate transamidase; IMP, investigational medicinal product; LFT, liver function test; TBL, total bilirubin; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.
†At least 8 weeks after the last IMP dose.

Immunological results

ADA

Up to end of study [EOS] Visit, [redacted] ([redacted] %) study participants across both rozanolixizumab treatment groups had developed treatment-induced (TI) anti-drug antibody (ADA) to rozanolixizumab. A summary of individual and combined ADA participant classification by rozanolixizumab treatment group is provided in Table 54.

Approximately half of the TI-ADA positive study participants ([redacted] [[redacted] %] of the rozanolixizumab-treated study participants) were neutral antibody (NAb) positive. and no study participants had pre-existing NAb. At Day 43 (end of treatment period) [redacted] of the [redacted] treatment-emergent ADA positive (TE-ADA) study participants were ADA positive for the first time.

The TE-ADA or neutralising ADA did not appear to have a clinically meaningful impact on the PK, PD, or efficacy of rozanolixizumab. The rozanolixizumab plasma concentrations, IgG, and MG-ADL profiles were generally similar between study participants with TE-ADA (including neutralising ADA) and those without.

Table 54: ADA classification up to Day 99 (safety set)

ADA classification	Rozanolixizumab ≈7 mg/kg N=[redacted] n/Nsub (%)	Rozanolixizumab ≈10 mg/kg N=[redacted] n/Nsub (%)	Rozanolixizumab total N=[redacted] n/Nsub (%)
Individual study participant category			
ADA-NEG†	[redacted]	[redacted]	[redacted]
TI-POS‡	[redacted]	[redacted]	[redacted]
TB-POS§	[redacted]	[redacted]	[redacted]
Combined study participant category			
TE-POS¶	[redacted]	[redacted]	[redacted]
TE-POS, NAb-POS††	[redacted]	[redacted]	[redacted]
TE-POS, NAb-NEG‡‡	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; ADA, antidrug (rozanolixizumab) antibody; Nab, neutralising antibody; NEG, negative; Nsub, number of study participants with a non-missing measurement for ≥1 post-Baseline visit; POS, positive; TB, treatment-boosted; TE, treatment-emergent; TI, treatment-induced.
Note: Percentages are calculated based on Nsub. Post-Baseline timepoints where no ADA sample was collected were ignored in the categorisation.
† Study participants who had an ADA NEG sample at Baseline and at all points post-Baseline.
‡ Study participants who had an ADA NEG sample at Baseline and had ≥1 ADA POS sample at any point post-Baseline
§Study participants who had an ADA POS sample at Baseline and ≥1 ADA POS sample at any point post-Baseline, with increased titre values vs Baseline.
¶ Includes study participants who were TI-ADA POS (category 3) or TB-ADA POS (category 4).
†† Includes study participants who were TE-ADA POS (category 7) and had ≥1 NAb POS sample.
‡‡ Includes study participants who were TE-ADA POS (category 7) and had no NAb POS samples.

Safety by ADA

No trends were observed in the safety profile of rozanolixizumab in TE-ADA positive study participants compared with those who did not develop ADA.

Incidences of TEAEs were comparable in TE-ADA positive and ADA negative study participants: no notable trends were observed in the different TEAE categories or in the most commonly reported TEAEs, compared with ADA negative study participants. None of the TE-ADA positive study participants discontinued the study or the IMP permanently. Consistent with the overall safety findings, the incidence of TEAEs coded under the standardised MedDRA queries hypersensitivity was similar in the TE-ADA positive category (5 [10.4%] study participants) compared with the ADA negative category (6 [7.5%] study participants).

Change from Baseline in serum immunoglobulin concentrations, plasma complement concentrations, serum cytokines, tetanus antibodies

There was no treatment effect on serum IgA, IgE, and IgM levels over time in the rozanolixizumab treatment groups. There were no apparent changes in serum and plasma complement concentrations over time.

No clinically meaningful trends were observed for change from Baseline in serum cytokines.

The magnitude of reduction in anti-tetanus toxoid serum titres was generally consistent with the reduction in total IgG levels. Anti-tetanus toxoid serum titres recovered to near Baseline values at the end of the observation period.

Safety conclusions from MG0003

Overall, the data indicate that rozanolixizumab has an acceptable safety profile and is generally well tolerated. The incidence of TEAEs and TEAEs considered by the investigator to be related to rozanolixizumab was comparable between the two rozanolixizumab treatment groups and higher compared with placebo.

The incidence of severe TEAEs and TEAEs leading to study- or IMP discontinuation was similar in the rozanolixizumab ≈7 mg/kg and placebo groups; the incidence of these events was higher in the rozanolixizumab ≈10 mg/kg group. The incidence of SAEs was comparable among the three treatment groups. There were no deaths reported in the study. The most frequently reported TEAEs were headache, gastrointestinal disturbances (nausea, diarrhoea, and vomiting), pyrexia, and arthralgia.

Overall, infusions were well tolerated with a low incidence of local injection site reactions. No TEAEs suggestive of anaphylactic or serious hypersensitivity reactions were reported.

B.2.10.1.2 Post hoc analysis

Adverse events

The TEAEs experienced by participants who had a history of ≥2 prior MG therapies are reported in Appendix F. The incidences of TEAEs, treatment-related TEAEs and serious TEAEs were consistent with those observed in the overall population.

B.2.10.1.3 MG0007

Extent of exposure

Of the [redacted] study participants who received rozanolixizumab in MG0007, [redacted] ([redacted] %) rolled over directly from MG0003 and [redacted] ([redacted] %) rolled over from MG0004. Of the study participants rolling over directly from MG0003, 35 had received placebo in that study and were first exposed to rozanolixizumab in MG0007. The median (range) number of treatment cycles was [redacted] to [redacted], with comparable median total number of treatment cycles and number of treatment cycles per participant year between the treatment groups. Of the [redacted] study participants, [redacted]%) did not switch their dose of rozanolixizumab during study participation.

For Cycle [redacted] to Cycle [redacted], the median number of infusions was [redacted] per cycle. [redacted] study participants, enrolled from MG0004, and were yet to receive rozanolixizumab at the interim data cut-off and were not included in the SS.

Adverse events

Overall, [redacted] TEAEs were reported in [redacted]%) study participants. There was a lower number of events in the rozanolixizumab ≈7 mg/kg group compared with the ≈10 mg/kg group for: any TEAEs, serious TEAEs, treatment-related TEAEs (per Investigator

assessment), severe TEAEs, TEAEs leading to discontinuation from the study, and TEAEs leading to permanent discontinuation of rozanolixizumab. [redacted] %) deaths were reported during the study, all considered by the Investigator to be unrelated to rozanolixizumab. An overview of TEAEs summarised in Table 50.

There was no increase in the incidence of TEAEs in any of the categories reported from cycle to cycle. The incidence of SAEs and TEAEs leading to study or study treatment discontinuation remained low (<9%) with repeated cyclic treatment. Within each treatment cycle the numbers of any TEAEs were lower in the rozanolixizumab ≈7 mg/kg group compared with the ≈10 mg/kg group. The numbers of study participants in Cycle [redacted] were too low to draw any conclusions.

Table 55: Overview of TEAEs by most recent dose for the entire study (safety set)

Adverse events	Rozanolixizumab ≈7 mg/kg N=[redacted] N (%) [n]	Rozanolixizumab ≈10 mg/kg N=[redacted] N (%) [n]	Rozanolixizumab total N=[redacted] N (%) [n]
Any TEAE	[redacted]	[redacted]	[redacted]
Serious SAE	[redacted]	[redacted]	[redacted]
Study participant discontinuation from study due to TEAEs	[redacted]	[redacted]	[redacted]
TEAEs resulting in permanent withdrawal from rozanolixizumab	[redacted]	[redacted]	[redacted]
Temporary discontinuation of IMP due to TEAEs	[redacted]	[redacted]	[redacted]
TEAEs requiring dose change	[redacted]	[redacted]	[redacted]
Treatment-related TEAEs†	[redacted]	[redacted]	[redacted]
Severe TEAEs‡	[redacted]	[redacted]	[redacted]
All deaths (number of study participants with AEs leading to death)	[redacted]	[redacted]	[redacted]
Deaths (TEAEs leading to death)	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; [n], number of events; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; IMP, investigational medicinal product; N, number of study participants reporting at least 1 TEAE in that category; SAE, serious adverse event; TEAE, treatment-emergent adverse events.
Note: "All Deaths" were based on all study participants screened and refers to all deaths occurring on study.
Note: Study participants who switched doses may be counted in both rozanolixizumab doses.
† Based on Investigator assessment
‡ Severe TEAEs were those with CTCAE Grade 3 or above, or those with intensity classified as "severe" by the Investigator.

TEAEs

The SOC with the most frequently reported TEAEs was nervous system disorders, followed by infections and infestations, gastrointestinal disorders, general disorders and administration site conditions, investigations, and musculoskeletal and connective tissue

disorders. At the SOC level, there was a >10% point difference in the incidence of TEAEs in the rozanolixizumab ≈10 mg/kg group compared with the ≈7 mg/kg group for gastrointestinal disorders, investigations, nervous system disorders, and vascular disorders (Table 56).

Headache was the most frequently reported TEAE in both treatment groups: [redacted] %) study participants in the rozanolixizumab ≈7 mg/kg group and [redacted] %) in the ≈10 mg/kg group. The following TEAEs were also reported in >10% of study participants in at least one of the treatment groups: diarrhoea, COVID-19, blood IgG decreased, nausea, and pyrexia (Table 56).

Table 56: Incidence of TEAEs in ≥5% of study participants (any treatment group) by most recent dose (safety set)

MedDRA (v24.0) SOC PT	Rozanolixizumab ≈7 mg/kg N=[redacted] N (%) [n]	Rozanolixizumab ≈10 mg/kg N=[redacted] N (%) [n]	Rozanolixizumab total N=[redacted] N (%) [n]
Any TEAE	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Blood immunoglobulin G decreased	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]

MedDRA (v24.0) SOC PT	Rozanolixizumab ≈7 mg/kg N=[redacted] N (%) [n]	Rozanolixizumab ≈10 mg/kg N=[redacted] N (%) [n]	Rozanolixizumab total N=[redacted] N (%) [n]
Arthralgia	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Myasthenia gravis	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; [n], number of individual occurrences of the TEAE; MedDRA=Medical Dictionary for Regulatory Activities; N, number of study participants reporting at least 1 TEAE within SOC/PT; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event
Note: Study participants who switched doses may be counted in both rozanolixizumab doses.

Deaths

Fatal TEAEs were reported in [redacted] %) study participant in the rozanolixizumab ≈7 mg/kg group (pneumonia) and [redacted] %) study participants in the rozanolixizumab ≈10 mg/kg group (COVID-19 and COVID-19 pneumonia). All deaths were considered by the Investigator to be unrelated to the study drug.

Other serious adverse events by most recent dose

Serious TEAEs were reported in [redacted] %) study participants in the rozanolixizumab ≈7 mg/kg group and [redacted] %) in the ≈10 mg/kg group. Overall, the SOCs with serious TEAEs reported in >1 study participant were nervous system disorders ([redacted] %] study participants), infections and infestations ([redacted] %]), gastrointestinal disorders ([redacted] %]), and neoplasms benign, malignant and unspecified (including cysts and polyps) ([redacted] %]).

Serious TEAEs with PT myasthenia gravis were reported in [redacted] %) study participants in the rozanolixizumab ≈7 mg/kg group and [redacted] %) in the ≈10 mg/kg group. Other serious TEAEs reported in >1 study participant were myasthenia gravis crisis ([redacted] %] in the ≈10 mg/kg group) and COVID-19 (reported in [redacted] %] study participant in the rozanolixizumab ≈7 mg/kg group and [redacted] %] in the ≈10 mg/kg group). [redacted] serious TEAEs were considered by the Investigator to be related to the IMP: [redacted] %) study participant in the rozanolixizumab ≈7 mg/kg group and [redacted] %) in the ≈10 mg/kg group.

Adverse events of special interest

No cases of potential Hy's Law were reported. [redacted] study participants had elevated LFTs:

- [redacted] in the rozanolixizumab ≈7 mg/kg group (previously treated with placebo in MG0003) experienced increased TBL (>1.5x ULN and >2x ULN) in Cycle [redacted] had a history of increased TBL during MG0003 and of cholelithiasis/cholecystectomy, and suspected Gilbert's syndrome. The bilirubin values during MG0007 are in line with the suspected Gilbert's syndrome
- [redacted] in the rozanolixizumab ≈7 mg/kg group (previously treated with placebo in MG0003 and rozanolixizumab ≈10 mg/kg in MG0004) experienced increased TBL (>1.5x ULN) during Cycle [redacted]. [redacted] had a history of increased TBL at Screening and during MG0003
- [redacted] receiving rozanolixizumab ≈10 mg/kg (previously treated with rozanolixizumab ≈7 mg/kg in MG0003) experienced increased TBL (>1.5x ULN and >2x ULN) during Cycle [redacted], Cycle [redacted], and Cycle [redacted]. [redacted] had a history of increased TBL at Baseline in MG0003, and of Gilbert's syndrome. The bilirubin values are in line with what would be expected in a patient with Gilbert's syndrome
- [redacted] in the rozanolixizumab ≈10 mg/kg group (previously treated with rozanolixizumab ≈7 mg/kg in MG0003) experienced increased ALP (>1.5x ULN) in Cycle [redacted] and Cycle [redacted]. [redacted] had a history of increased AST and ALP during MG0003
- [redacted] (previously treated with placebo in MG0003 and rozanolixizumab ≈10 mg/kg in MG0004) experienced increased ALP (>1.5x ULN) on Cycle 2 Day 43 while receiving treatment with rozanolixizumab ≈10 mg/kg

Immunological results

Data are discussed up to Cycle [redacted] as there were not enough study participants in later cycles for a meaningful assessment of the ADA results.

As of the latest data cut, [redacted] %) study participants across both rozanolixizumab treatment groups had developed treatment-emergent ADA to rozanolixizumab (all cases were TI-ADA except [redacted], who was TB-ADA positive), and [redacted] %) study participants were NAb positive.

The proportion of study participants who became TE-ADA positive up to Day 43 of each treatment cycle increased with additional cycles ([redacted] %, [redacted] %, [redacted] %, [redacted] %, and [redacted] % of study participants for Cycles [redacted] to [redacted]). The proportion of study participants who developed NAb also increased with additional treatment cycles, with [redacted] %, [redacted] %, [redacted] %, [redacted] %, and [redacted] % of study participants up to Day 43 in Cycles [redacted] to [redacted].

No impact on the safety profile of rozanolixizumab was observed in study participants who tested positive for ADA. The incidences of TEAEs were lower or comparable in TE-ADA positive vs TE-ADA negative study participants. The incidence of TEAEs related to injection site reactions was also comparable between TE-ADA positive and negative study participants, while the incidence of TEAEs related to hypersensitivity was lower for TE-ADA positive vs negative study participants.

Safety conclusions from MG0007

MG0007 data indicate that following repeated cyclic treatment, rozanolixizumab was generally well tolerated with an acceptable safety profile for both ≈7 mg/kg and ≈10 mg/kg.

Primary endpoint

- Overall, [redacted] ([redacted] %) study participants experienced TEAEs that led to discontinuation from the study: [redacted] ([redacted] %) in the rozanolixizumab ≈7 mg/kg group and [redacted] ([redacted] %) in the ≈10 mg/kg group. The most common reason for discontinuation was associated with MG worsening ([redacted] [redacted] %] participants, leading to protocol-mandated withdrawal due to receiving rescue therapy). The incidence of other TEAEs leading to discontinuation was low ([redacted] [redacted] %])

Secondary endpoints

- Upon repeated cyclic treatment, discontinuations due to TEAEs across cycles were consistently low, ranging from [redacted] % to [redacted] %.
- The safety profile was consistent with repeated cyclic treatment and no increase in the incidence of TEAEs, including severe TEAEs, or serious TEAEs was observed
- For most TEAE categories, there was a lower number of events following administration of ≈7 mg/kg than following ≈10 mg/kg. At the SOC level, there was a >10% point difference in the incidence of TEAEs in the rozanolixizumab ≈10 mg/kg group compared with the ≈7 mg/kg group for gastrointestinal disorders, investigations, nervous system disorders, and vascular disorders
- There were three fatal TEAEs during the study; all were assessed as not related by the Investigator
- Overall, subcutaneous injections were well-tolerated with a low incidence of injection site reactions with repeated cyclic treatment

B.2.10.2 *MG0004*

The clinical systematic review, detailed in Section B.2.1, also included adverse events, and identified the Phase 3 study MG0004.

Patient disposition and definitions of study group are presented in Appendix D. The adverse events reported in the study, together with patient demographics and baseline characteristics, are described in Appendix F.

Data from MG0004 indicate that rozanolixizumab has an acceptable safety profile and is generally well tolerated. Headache was the most frequently reported TEAE, followed by diarrhoea, blood immunoglobulin G decreased, nausea, pyrexia and urinary tract infection. Treatment-emergent AEs were mostly mild or moderate in intensity. No TEAEs suggestive of anaphylactic or serious hypersensitivity reactions were reported. Overall, infusions were well tolerated with low incidence of local injection site reactions reported. Treatment-emergent AEs led to discontinuation from study in [redacted] ([redacted] %) participants in the rozanolixizumab ≈7 mg/kg group and zero in the ≈10 mg/kg group. No death was reported during the study. No new safety signal was identified.

B.2.10.3 *Pooled safety analysis*

A pooled safety analysis was performed to assess the long-term safety of repeated cyclic treatment with rozanolixizumab. Patient disposition and definitions of study group are presented in Appendix D. The adverse events reported in the study, together with patient demographics and baseline characteristics, are described in Appendix F (166).

Based on the pooled safety analysis, the mean annualised number of treatment cycles per patient was [redacted] and the mean annualised number of infusions was [redacted]. The results from the pooled safety analysis support the acceptable safety profile and tolerability of repeated cyclic treatment with rozanolixizumab at both the licensed dose of ≈7 mg/kg and the higher dose of ≈10 mg/kg. No increase in the incidence of TEAEs, severe TEAEs, AEs of special interest or hypersensitivity reactions were observed with repeated cycles of treatment.

B.2.10.4 *Safety overview*

Rozanolixizumab as an add-on to SOC was associated an acceptable safety profile and is generally well-tolerated. In MycarinG the incidence of TEAEs was similar in the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg groups (n=52 [81.3%] and n=57 [82.6%]) and lower in the placebo group (n=45 [67.2%]). The incidence of SAEs in MycarinG was comparable among the three treatment groups and there were no deaths reported in the study. The number of study participants who experienced TEAEs leading to temporary discontinuation of IMP was higher in the rozanolixizumab ≈7 mg/kg (n=3 [4.7%]) and ≈10 mg/kg (n=6 [8.7%]) groups compared with the placebo group (n=1 [1.5%]). Infusions were well-tolerated with a low incidence of local injection-site reactions reported.

The safety profile of rozanolixizumab in the OLE MG0007 was consistent with findings in the MycarinG Phase III study, with no new safety signals observed, demonstrating long-term safety and tolerability up to [redacted] treatment cycles with rozanolixizumab.

B.2.11 *Ongoing studies*

All studies have been completed. MG0007 was completed on 25 January 2024 and the final results are expected later in 2024.

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

B.2.12.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

Summary of efficacy evidence

Mycarin G

Patients who received treatment with rozanolixizumab in the MycarinG study achieved a clinically meaningful and statistically significant reduction (improvement) in MG-ADL scale scores compared with the placebo group, therefore meeting the primary endpoint. The mean decrease from Baseline in MG-ADL total score to Day 43 was approximately 2.6 points compared with placebo for both rozanolixizumab treatment groups ($p<0.001$).

Rozanolixizumab showed a statistically significant improvement compared with placebo in all secondary endpoints included in the sequential testing procedure, supporting the primary efficacy endpoint. Clinically relevant and statistically significant improvements in MG-C and QMG were observed for both rozanolixizumab treatment groups compared with placebo ($p<0.001$). Statistically significant improvements in MGSPRO “Muscle Weakness Fatigability”, “Physical Fatigue”, and “Bulbar Muscle Weakness” scores were observed for both rozanolixizumab treatment groups (all $p<0.001$ except for MGSPRO “Physical Fatigue” in the rozanolixizumab ≈7 mg/kg group [$p=0.012$]). In addition, a higher proportion of MG-ADL responders (≥2.0 point improvement at Day 43) was observed with rozanolixizumab (68.2% [≈7 mg/kg] and 61.2% [≈10 mg/kg]) compared with placebo (28.4%).

Rozanolixizumab showed an improvement compared with placebo in all secondary efficacy endpoints as early as Day 8. Clinical efficacy was observed for AChR-Ab+ and MuSK-Ab+ study participants based on subgroup analyses, with improvements from Baseline in MG-ADL, MG-C, QMG, MGSPRO “Muscle Weakness Fatigability”, and MGSPRO “Physical Fatigue” scores that were consistent with the results observed in the overall population. Reducing the need for rescue therapy may lead to reduced medical resource utilisation costs associated with managing exacerbations.

Results from the MycarinG study indicate that rozanolixizumab offers clinically meaningful benefits for patients with gMG who need a treatment that controls symptoms with a fast onset of action, reduces treatment burden, and improves QoL.

MG0007

Following repeated cyclic treatment, rozanolixizumab (both ≈7 mg/kg and ≈10 mg/kg) showed consistent improvements for all efficacy endpoints tested in the study; onset and depth of response were similar to those seen in MG0003.

Summary of safety

Mycarin G

Rozanolixizumab was associated with an acceptable safety profile and was generally well-tolerated by patients with gMG, with the majority of TEAEs categorised as mild or moderate in severity. The incidence of TEAEs was similar in the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg groups (n=52 [81.3%] and n=57 [82.6%]) and lower in the placebo group (n=45 [67.2%]). The incidence of SAEs in MycarinG was comparable among the three treatment groups and there were no deaths reported in the study.

MG0007

The safety profile of rozanolixizumab in MG0007 was consistent with findings in the MycarinG study, with no new safety signals observed demonstrating the safety and tolerability over repeat treatment cycles.

Conclusions

There is an urgent unmet need for treatments that reduce the symptom burden and improve QoL for patients with gMG, especially those who are refractory to current treatments. These patients experience severe symptoms that negatively impact all aspects of their lives and put them at risk of life-threatening exacerbation and myasthenic crisis (4, 21-24).

Rozanolixizumab as a treatment for patients with gMG is associated with significant improvements in the symptoms of disease activity and QoL, as measured by MG-ADL, QMG, MGC, and MG-QoL15r, with a fast onset of action, and sustained clinical benefit over repeat treatment cycles.

B.2.12.2 *Strengths and limitations of the clinical evidence base for the technology*

Strengths of the evidence base

The efficacy and safety of rozanolixizumab has been extensively studied through the MycarinG clinical trial programme. MycarinG is a robustly designed, global, double-blind, randomised, placebo-controlled trial including a population that closely reflects the real-world patient population eligible for treatment with rozanolixizumab.

- The programme included 200 patients with gMG which is a robust number of patients given the rare disease
- The study population at enrolment represented a broad range of patients and was well-balanced between the three treatment groups, with respect to the key demographic and disease-specific variables
- Efficacy data for the primary and secondary endpoints are supported by sensitivity- and subgroup analyses. When the primary and secondary efficacy endpoints were analysed using additional analysis sets, alternative missing data assumptions, and an additional analysis method, results were consistent with the main primary and secondary efficacy analyses
- The use of PROs (MG-ADL and MGSPRO), together with a clinician-reported outcome (QMG) and a composite score (MG-C), is important to show how

treatment translates into clinically meaningful benefits, with outcomes that accurately reflect the impact of gMG on QoL (for example fatigue) captured by the clinical evaluation of rozanolixizumab

Long-term effectiveness and safety of rozanolixizumab are demonstrated in the ongoing extension study (MG0007).

- The clinical and safety profile of rozanolixizumab was maintained over repeat treatment cycles

Potential limitations of the evidence base

This submission is for patients with antibody positive gMG who are refractory to standard therapies. However, the evidence base for rozanolixizumab (the MycarinG clinical study) includes patients with non-refractory gMG at baseline (as defined here by patient who did not have a history of ≥2 prior MG-specific therapies). Subgroup analyses were conducted on the populations of interest to the submission (AChR Ab+ and MuSK Ab+ participants), with similar outcomes to the broad population, and enabled robust -cost-effectiveness analyses. A post hoc analysis was performed on patients with a history of ≥2 prior MG specific therapies (after AChEIs), and also showed similar outcomes to the overall population. No UK sites were included in the clinical trial program.

B.3. Cost effectiveness

Summary

- A state transition Markov model was developed to evaluate the cost-effectiveness of rozanolixizumab as a treatment for adult patients with refractory gMG and autoantibodies against AChR or MuSK, from the perspective of the UK NHS/PSS. This model structure effectively captures the chronic nature of gMG.
- The base case compared rozanolixizumab with zilucoplan, efgartigimod, IVIg/SCIg, and PLEX in adult patients, utilising the MycarinG trial as the source of baseline demographic and disease characteristics for rozanolixizumab.
- Base case deterministic incremental cost-effectiveness ratios (ICERs) for rozanolixizumab compared with zilucoplan, efgartigimod, IVIg/SCIg, and PLEX are [redacted], respectively.
- The model predicts discounted QALY gains of +0.0913 vs zilucoplan, +0.0175 vs efgartigimod, +0.1588 vs IVIg/SCIg and +0.1018 vs PLEX.

B.3.1 *Published cost-effectiveness studies*

B.3.1.1 *Identification of studies*

A SLR was conducted to identify relevant economic evidence of medicines for patients with gMG relevant to the decision problem.

Electronic databases were searched on 01 May 2023 via the OVID platform using pre-determined search strategies, and included MEDLINE®, MEDLINE® In-Process, Embase, EconLit, and NHS-EED. Supplementary searches of public registries and databases, reference lists, previous Health Technology Assessments (HTAs) appraisals, and conference proceedings were performed to identify data not captured in the database search. An update search of the SLR was conducted on 01 February 2024. Full details of the searches and results for economic evaluation studies identified are reported in Appendix G.

The review identified twelve economic evaluations, of which two were HTA appraisals. However, none of these economic evaluations was considered relevant for the economic analysis. The majority of the studies were published as conference abstracts (n=9) and the remaining three as journal articles. Furthermore, three studies assessed myasthenic crisis, two studies each assessed refractory MG and MG with exacerbations, while the remaining five studies did not provide much information on disease type. Identification of resource use and cost data from the published literature relevant to the decision problem is described in Section B.3.5.1.

B.3.2 *Economic analysis*

At present, there are no completed NICE technology appraisals providing guidance for medicines indicated for gMG. As the SLR did not identify any previous economic

evaluation that compared rozanolixizumab to standard therapies in a UK setting, a *de novo* economic model was built in Microsoft® Excel to address the decision problem. The main features of the economic analysis are outlined in Table 58.

B.3.2.1 *Patient population*

The *de novo* cost-effectiveness analysis evaluates rozanolixizumab as an add-on to standard therapy for the treatment of adult patients with refractory antibody-positive gMG.

A post hoc analysis of participants in MycarinG who received ≥2 prior MG specific therapies (after AChEIs), which can be viewed as a proxy for refractory patients, was performed. The outcomes in this subgroup of refractory patients (n=[redacted]% of full cohort) were comparable with those observed in the overall trial population (Section B.2.7.4.2). Baseline characteristics for these participants (Appendix E.1.2) were also comparable with the overall MycarinG population (Section B.2.3.1.2). Consequently, clinical data from the full trial population in MycarinG was used in the model as it was pre-specified and powered for the primary endpoint in the trial (change from baseline in MG-ADL score, which is used as a key input in the model), and the results for the full trial population are representative of the results for patients with refractory disease. In addition, there are a lack of data in refractory patients for the comparators.

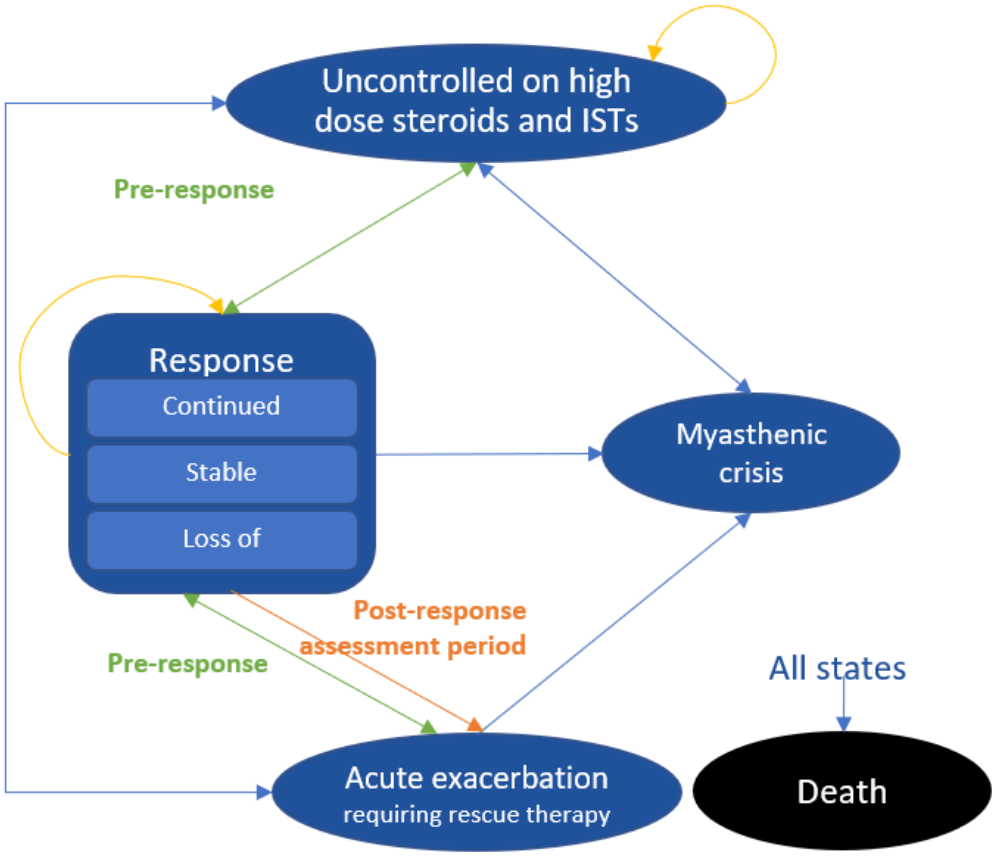
B.3.2.2 *Model structure*

Recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision-Making task force were followed to ensure the proposed model structure (178):

- Was a realistic representation of the natural history and clinical pathway of refractory gMG
- Can demonstrate the impact of the intervention on the natural history and clinical pathway of refractory gMG
- Adequately addresses the decision problem

A Markov model was selected to illustrate the progression through seven different health states, evaluating patients on high-dose steroids and ISTs, and modelling their response to treatment and associated rates of exacerbation and myasthenic crisis. It captures the chronic nature of gMG. The cycle length is 2 weeks, providing a compromise between capturing the rapid transition of patients between key health states and the lack of long-term efficacy data, also meaning that a half-cycle correction is not required. The model structure also allows for simplifying assumptions to be made about the long-term effects of treatments. The model structure is presented in Figure 12.

Figure 12: Model structure



MG-ADL data collected in MycarinG are used to model treatment response. All patients enter the model in the 'Uncontrolled on high dose steroids and ISTs' health state, with a baseline MG-ADL score equal to the average baseline score reported in MycarinG (8.3). Patients who meet the treatment response criteria (a decrease of ≥2 points in MG-ADL score) transition to the 'response' health state at the response assessment timepoint (which differed by treatment and is shown in Figure 12). At this point, patients separate into one of the three response sub-groups (continued, loss or stable response) defined in Table 57. In the pre-response assessment period, the model assumes that all responders report the same MG-ADL score equivalent to stable response until the response assessment time-point.

Within each health state (except death), patients are at risk of 'exacerbation', 'crisis' or 'death'. The model considers the impact of acute exacerbations and crises that require hospitalisations on costs and HRQoL, and the impact of the chronic use of corticosteroids on costs. A Markov model was considered a simple but effective model to describe such a progression.

B.3.2.3 *Health states*

The model is structured around seven mutually exclusive health states, described in Table 57.

Table 57: Health states in the model

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 score 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 the following: • 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 neurologist to use PLEX or IVIg as a rescue therapy
Myasthenic crisis	Exacerbation requiring intubation
Death	Death health state

Abbreviations: IVIg, intravenous immunoglobulin; ISTs, immunosuppressant therapies; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living score; PLEX, plasma exchange

B.3.2.4 *Perspective*

Analyses were conducted from the perspective of the NHS and of the Personal Social Services (PSS) in England, as per NICE reference case (179).

B.3.2.5 *Time horizon and model cycle length*

The NICE reference case states that model time horizons should be long enough to capture all benefits of the treatment (179); therefore, a lifetime time horizon was applied to the model due to the chronic nature of the condition, including the ongoing medical management required to address the symptoms of the disease. The lifetime time horizon captures all relevant costs and health outcomes associated with gMG and the respective treatments and reflects the relatively early age of diagnosis for patients with MG (average age of diagnosis in the MycarinG trial was 51.8 years).

The model applies a 2-week cycle length, which was considered by clinicians to be sufficient to account for the time patients may spend recovering from a worsening of symptoms, e.g. exacerbation or myasthenic crisis (180). Half-cycle correction was not

implemented in the model, because a 2-week cycle length is short enough to capture the rapid transition of patients between key health states while accounting for the lack of long-term efficacy data.

B.3.2.6 *Discounting*

The model applies an annual discount rate of 3.5% for costs and benefits in the base case, as per the NICE reference case.

B.3.2.7 *Model features*

The features of the cost-effectiveness model are presented in Table 58.

Table 58: Features of the economic analysis

Factor	Chosen values	Justification
Model type	Markov	Effectively captures the chronic nature of gMG
Perspective	NHS and PSS	As per NICE reference case
Time horizon	Lifetime	As per NICE reference case (179) and appropriate to capture all costs and benefits for a lifelong condition
Model cycle length	2 weeks	Considered short enough to capture changes in health and tolerability
Discounting	3.5% for costs and QALYs	As per NICE reference case
Type of economic analysis	Cost-utility analysis	As per NICE reference case
Source of efficacy	1. Change in MG-ADL score was the primary endpoint in the MycarinG trial and predictor of HRQoL. Change in MG-ADL and rate of responders for rozanolixizumab and comparators are informed by a NMA. 2. The efficacy results for rozanolixizumab and the baseline demographics and characteristics included in the model are for the overall population from MycarinG.	1. There are no head-to-head data for any of the comparators, so a NMA was performed. 2. The efficacy outcomes and baseline characteristics in the subgroup of refractory patients (n=[redacted]% of full cohort) were comparable with those observed in the overall trial population (Section B.3.2.1). Consequently, clinical data from the full population in MycarinG was used in the model as it was pre-specified and powered for the primary endpoint in the trial (change from baseline in MG-ADL score, which is used as a key input in the model). In addition, there are a lack of data in refractory patients for the comparators.
Source of utilities	Utility values were derived from a repeated measures regression model of UK crosswalk utilities from MycarinG (181). For this model, treatment arms were pooled.	As per NICE reference case, EQ-5D utilities were collected from the relevant population in the MycarinG study. Literature values were used for 'crisis' utility and scenarios where data from the study population are not available

Factor	Chosen values	Justification
Source of costs	Pack costs were obtained from the BNF (182-192) or published list price for efgartigimod (135), and confidential net price for zilucoplan. Administration costs were sourced from the NHS Schedule of Reference Costs 2020/2021 (193) or PSS Research Unit Costs (194).	As per NICE reference case

Abbreviations: BNF, British National Formulary; EQ-5D, EuroQoL five dimensions; HRQoL, health-related quality of life; gMG, generalised myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; QALY, quality-adjusted life year; PSS, Personal Social Service.

B.3.2.8 *Intervention technology and comparators*

The intervention examined is:

- Rozanolixizumab, a once-weekly subcutaneous infusion for a 6-week treatment cycle in addition to standard of care therapies. The model uses the annualised number of cycles from the rozanolixizumab clinical trial program of [redacted].

The comparative treatments included in the analysis were identified through desk research and validated by UK clinical experts:

- Efgartigimod (subject to ongoing NICE technology appraisal)
- Zilucoplan (subject to ongoing NICE technology appraisal)
- Chronic IVIg/SCIg
- Chronic PLEX

B.3.3 *Clinical parameters and variables*

The MycarinG trial (Section B.2.6.1) and NMA (Section B.2.9) were the key data sources used to inform the clinical model inputs. Data from MycarinG provide evidence to demonstrate the efficacy of rozanolixizumab in addition to SoC in the management of gMG. The MG0007 open-label extension provides evidence for repeated treatment cycles with rozanolixizumab, including patients who switched from the placebo arm of the MycarinG trial.

The base-case population considered in the model – adult patients with AChR-Ab+ or MuSK Ab+ refractory gMG – is an optimised population within the licensed indication in the European SmPC and within the MHRA-licensed population for rozanolixizumab.

B.3.3.1 *Rate of response*

There were no head-to-head trials to compare rozanolixizumab with any of the comparators. Therefore, as recommended in the NICE process and methods guide, a network meta-analysis (NMA) was performed to evaluate the rate of response of each treatment relative to placebo, as described in Section B.2.9 (195). Treatment response rates were calculated based on the odds ratio output from the NMA, applied to a referent response rate (SoC).

Firstly, ORs were converted to relative risks using the following formula due to difficulties associated with the interpretation of ORs (196):

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

Where *t* is the comparator treatment with known OR versus the referent treatment.

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

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

The referent response rate was calculated as the simple average response rate across the studies used in the NMA. Odds ratios and calculated response rates used in the model are summarised in Table 59.

Response probabilities were applied up until the "Response assessment timepoint" (Table 59). This time point represented the period in which physicians may wait to see if a patient responds to treatment, the assumption being that if they have not responded at this point then treatment should be discontinued. This is a conservative assumption as some patients respond to later cycles but not to the first cycle. Base case response timepoints were populated based on the trial endpoint associated with each of the comparators, due to limited information regarding the use of treatments in clinical practice.

After the response assessment time point, the model assumed patients who have not responded will not respond to treatment and subsequently discontinue treatment. Therefore, the probability of patients transitioning from the 'Uncontrolled on high dose steroids' health state to the 'Response' health states after this time point was assumed to be zero.

Table 59: Response rates and timepoints

Treatment	Odds ratio	Response rate	Source	Response timepoint used in the model (weeks)	Source
Rozanolixizumab	[redacted]	[redacted]	Data on file (NMA) (195)	6	Data on file (MycarinG)
Zilucoplan	[redacted]	[redacted]	Data on file (NMA) (195)	12	Howard et al 2023 (RAISE) (171)
Efgartigimod	[redacted]	[redacted]	Data on file (NMA) (195)	10	Howard et al 2021 (ADAPT) (169)
Chronic IVIg/SCIg†	1.87	51.00%	Barth et al 2011 (197)	6	Assumption
Plasma exchange†	2.38	57.00%	Barth et al 2011 (197)	6	Assumption

Abbreviations: ITC, indirect treatment comparison; IVIg, intravenous immunoglobulin; NMA, network meta-analysis; OR, odds ratio; SCIg, subcutaneous immunoglobulin; SoC, standard of care.
† OR was not derived from ITC, it has been estimated to ensure the same calculated response rate from the literature. The ORs for IVIg/SCIg and PLEX were based on QMG score rather than MG-ADL score.

B.3.3.2 *Time on treatment*

Myasthenia gravis is a chronic, debilitating disease with unpredictable symptom burden; therefore, patients are expected to receive treatment for the rest of their lifetime. Rozanolixizumab demonstrated a rapid onset of action, resulting in a reduction in symptom expression as early as Day 8 in some patients. Rozanolixizumab was well tolerated and demonstrated a good safety profile in MycarinG and MG0007. Rozanolixizumab's rapid onset of action will support making decisions on patients who are responding or likely to respond to rozanolixizumab and should continue treatment. Post response assessment period, patients who do not respond, or those who lose their initial response, are not assumed to continue to receive treatment due to lack of efficacy. Discontinuation of rozanolixizumab would be considered where patients have not responded to therapy or have lost response and/or for safety and tolerability issues. These assumptions were made for modelling purposes and to be consistent with non-cyclical treatments. A consistent cohort response was seen in the rozanolixizumab trial program, as shown in Figure 10.

B.3.3.3 *Transition probabilities*

The probabilities of entering a specific health state during each cycle of the Markov model for rozanolixizumab are based on the number of patients who, in the MycarinG study, moved between health states during the pre-specified periods. The number of patients in each health state at the start and end of a period is used to estimate the transition probability matrices that are then applied over the time horizon of the analysis in the rozanolixizumab arm of the model. The transition matrices calculated and applied in the model are presented in Appendix N.1.

B.3.3.4 *Efficacy (MG-ADL reduction)*

At the outset, patients in the MycarinG trial presented with a baseline average MG-ADL score of 8.3, indicating a severe level of disease, posing significant treatment challenges.

To determine the long-term health implications by treatment, specifically the speed and magnitude of symptom improvements and the sustained response level, expected MG-ADL scores were tracked over time depending on the following four key factors:

- Proportion of patients showing an initial response (Table 57, above)
- Proportion of patients showing signs of continued response (i.e. MG-ADL scores continue to fall over time)
- Proportion of patients who lose their initial treatment response (i.e. patients whose MG-ADL score initially improves, but over time their MG-ADL score starts to increase as their disease worsens)
- Proportion of patients who have a stable response (i.e. patients who experience an initial improvement in MG-ADL score, but after the response assessment their MG-ADL score remains stable)

Due to a lack of available data, the model assumed that all responders would have the same treatment-specific MG-ADL score within each treatment arm, assuming equivalence to stable responders, up until the response assessment time-point, at which point patients are assumed to separate into one of the three response sub-groups (continued, loss, or stable) and experience the associated MG-ADL score.

Patients transition to one of the above three response health states (continued, stable, loss of response) based on a reduction ≥2 in the MG-ADL score using the odds ratios and response rates described in Section B.3.3.1.2. It was assumed for all treatments that, of those patients in the response health states, [redacted] had loss of response, [redacted] had continued response, and [redacted] had stable response. The change from baseline for each health state differed.

The data on stable responders for rozanolixizumab, zilucoplan and efgartigimod were extracted from the NMA. There was a lack of Phase 3 trial data for IVIg and PLEX; therefore, the response rates for these comparators were taken from a publication by Barth et al (197). This paper reported change in QMG score and not MG-ADL. Therefore, the change from baseline in QMG score was converted to MG-ADL score on the basis that the QMG scale is 62.5% larger than the MG-ADL scale. The continued response assumes approximately [redacted] improvement vs stable response based on the difference between the largest CFB MG-ADL score in MG0007 [redacted]; cycle 4) and the CFB MG-ADL score reported for the primary endpoint of MycarinG (–3.22).

The model assumed that [redacted] of responders will not maintain their response after the 'Time of response assessment'. The intention of this functionality is to account for those patients who may initially show signs of symptom improvement, but for reasons outside of a clinician’s control they stop observing symptom improvements and instead deteriorate.

The model accounts for a slow return to baseline MG-ADL score (i.e. the same as a patient who did not respond) over a period of time. In the base case, the model assumes patients return to baseline disease severity within [redacted] of response assessment, based on the time taken for patients to return to a QMG score similar to their baseline after switching treatments in the Phase 2 eculizumab clinical trial (173), due to immature discontinuation data from MycarinG and MG0007. In absence of evidence, the worsening of MG-ADL was assumed to follow a linear trend back to the baseline MG-ADL score.

The average change in MG-ADL score from baseline with different treatments is shown in Table 60. In the uncontrolled response state, the average MG-ADL score did not change from baseline.

Table 60: Average MG-ADL score change from baseline

Treatments	Loss of response	Stable response	Continued response
Rozanolixizumab	0.00	[redacted]	[redacted]
Zilucoplan	0.00	[redacted]	[redacted]
Efgartigimod	0.00	[redacted]	[redacted]

Treatments	Loss of response	Stable response	Continued response
IVIg/SCIg	0.00	[redacted]	[redacted]
Plasma exchange	0.00	[redacted]	[redacted]

Abbreviations: IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; SCIg, subcutaneous immunoglobulin.

The treatment effect is modelled as change in MG-ADL score. Reduced MG-ADL score is modelled as being associated with a lower probability of exacerbation and myasthenic crisis (i.e. the probability of having a crisis is higher in health states with greater disease activity). Thus, changes in MG-ADL score also impact the probability of transitioning to the crisis health state.

B.3.3.5 *Clinical events*

Patients in any response health state had an annual rate of experiencing an exacerbation of 0.244 based on the incidence of 'any exacerbation' (mild, moderate, or severe) from Abuzinadah et al 2021 (95). The annual rate of myasthenic crisis was based on the incidence of exacerbations requiring intubation and was estimated as 0.0231 (95). For those patients in the uncontrolled health state, a relative risk of 2.67 was applied, based on the increased risk associated with patients with moderate to severe onset MG (95).

A summary of the annual event rates used in the base case of the model is presented in Table 61.

Table 61: Clinical event rates

Clinical events	Exacerbation	Myasthenic crisis	Source
Uncontrolled	0.651	0.062	Abuzinadah et al 2021 (95)
Response	0.244	0.023	

To account for patients who experience an exacerbation that deteriorates into a myasthenic crisis, the model includes a 2-week event rate that is applied to all patients in the exacerbation health state. In the model base case, this value is 0.184, as identified from the incidence of patients receiving IVIg who required mechanical ventilatory assistance after 15 days (146). The incidence was converted to a two-weekly probability using the following formula:

$$2 - week\ event\ rate = 1 - e^{\frac{\ln(1-0.1954)}{(15/14)}}$$

General population background mortality was implemented for patients using the most recent National Life Tables for England (198). Patients in the myasthenic crisis health state had an increased risk of death, with 4.47% of patients in the myasthenic crisis health state dying within 2 weeks (161).

The transition probabilities used in the model are presented in Appendix N.1.

B.3.3.6 *Clinical expert assessment of applicability of clinical parameters*

Clinical expert opinion was used to validate the approach taken in the CEM. Interviews with key opinion leaders (KOLs) from the UK were conducted to understand the extent to which the analyses reflect clinical understanding of gMG for the average patient, including:

- The appropriateness of the current model framework including the patient pathway and key assumptions made
- Input data used within the analyses

Discussions focused on the following and their application in the model:

- Chronic treatments for patients with gMG
- Positioning of rozanolixizumab in the model
- SoC treatments and shares of use
- Treatment response times
- Time to treatment of exacerbations and myasthenic crisis
- Model structure, health states and health state definitions
- Predictors of clinical events (acute exacerbations and myasthenic crisis)
- MG-ADL improvements on treatment
- Chronic IVIg dosage in the UK
- Resource use for controlled and uncontrolled patients
- Scenarios for discontinuation of treatment in the model

These themes were further tested in additional clinician interviews and an advisory board conducted in the UK, with a focus on the refractory patient population.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 *Health-related quality-of-life data from clinical trials*

EQ-5D-5L data were collected in the MycarinG trial.

B.3.4.2 *Mapping*

The EQ-5D-5L data collected in MycarinG were mapped onto the 3L scale using the algorithm developed by Hernandez-Alava et al (2017), in line with the NICE reference case. The UK tariff was used for mapping the EQ-5D-5L to the value sets.

B.3.4.3 *Health-related quality-of-life studies*

A systematic review was conducted to identify HRQoL studies from the published literature relevant to the decision problem. In particular, disease-specific questionnaires (e.g. MG QoL-15 and MG QoL-15r) and generic QoL measures (e.g. SF-36 and EQ-5D, in line with NICE reference case) were sought for patients with gMG.

Electronic databases were searched on 01 May 2023 via the OVID platform using pre-determined search strategies, and included MEDLINE®, MEDLINE® In-Process, Embase, EconLit, and NHS-EED. Supplementary searches of public registries and databases, reference lists, previous HTA appraisals, and conference proceedings were performed to

identify data not captured in the database search. Full details of the searches and results for HRQoL studies identified are reported in Appendix H.

In total, 95 studies reported data pertaining to humanistic burden of MG across various geographies (see Appendix H). Of these, 13 studies were conducted in the USA, eight each in Germany and China, seven in Japan, six in Brazil, four each in Canada, India, and Serbia, three each in Italy and Turkey, two each in Australia, Denmark, Thailand, Spain, Saudi Arabia, France, and Russia. One study each in Austria, Netherlands, Norway, Sweden, Malaysia, Poland, South Africa, and South Korea. Three studies were conducted in two countries: UK and US, Norway and Netherlands, Sweden and Estonia, and two studies were conducted in multiple countries. In the remaining eight studies, the country was not reported. The majority of studies were cross-sectional (n=48), 32 were observational, eight were surveys, five were registry-based studies, and two were case control- studies. The majority (n=47) were conducted with single centre, 31 studies did not provide this information, and 17 were multicentre studies.

Four studies reported utility values among patients with MG, assessed using EQ-5D index and SF-6D (see Appendix H). Utilities were higher among patients in remission (0.92 [EQ-5D], 0.86 [SF-6D]) and with minimal manifestations; (0.94 [EQ-5D] and 0.83 [SF-6D]) (199). Increasing disease severity, as assessed by MGFA class, was associated with decreasing utility values (107, 199). The utility value for overall MG population when assessed using EQ-5D index ranged from 0.68 (107) to 0.8 (5, 200, 201).

In the economic model, utility values were not taken from published literature but were derived from the regression model from the clinical trial data, in line with the NICE reference case.

B.3.4.4 *Key differences*

In the model, the utility values are calculated based on the regression model described in Section B.3.4.6. Table 62 describes the utility values from published literature.

Table 62: Utility values from published literature

Study name	Group	n	EQ-5D Mean (SD)	SF-6D Mean (SD)
Barnett 2018	MG: with minimal manifestation	7	0.92 (0.04)	0.86 (0.14)
	MG: with pharmacologic remission	13	0.94 (0.03)	0.83 (0.07)
	MGFA class: I	52	0.89 (0.06)	0.81 (0.14)
	MGFA class: IIa	69	0.77 (0.15)	0.67 (0.13)
	MGFA class: IIb	44	0.79 (0.19)	0.68 (0.13)
	MGFA class: IIIa	25	0.58 (0.25)	0.54 (0.13)
	MGFA class: IIIb	35	0.59 (0.26)	0.56 (0.11)
	MGFA class: IVa	2	0.20 (0.17)	0.98 (0.06)

Study name	Group	n	EQ-5D Mean (SD)	SF-6D Mean (SD)
	MGFA class: IVb	7	0.60 (0.23)	0.53 (0.09)
Dewilde 2022	MG: Overall (real world sample)	610	0.689 (0.22)	
	MGFA class: I (real world sample)	83	0.817 (0.17)	
	MGFA class: II (real world sample)	162	0.766 (0.15)	
	MGFA class: III (real world sample)	226	0.648 (0.20)	
	MGFA class: IV (real world sample)	85	0.53 (0.27)	
	MGFA class: V (real world sample)	6	0.36 (0.50)	
Andersen 2022	MG overall (MG patients with no further details to patient disease characteristics)	100	0.8 (0.2)	
Mendoza 2020	MG overall (MG patients with no further details to patient disease characteristics)	124	0.8 (0.19)	

Abbreviations: EQ-5D, European quality of life-5 dimensions; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; SD, standard deviation; SF-6D, short-form-6 dimensions.

B.3.4.5 *Adverse reactions*

Adverse event reactions were not included in the model, since no AEs were considered to meet the inclusion criteria of serious AEs with an incidence ≥5% in the MycarinG trial.

B.3.4.6 *Health-related quality-of-life data used in cost-effectiveness analysis*

As the time horizon of the model is lifetime, it was important to consider the impact of age- and sex-related disutility. The regression algorithm from Ara and Brazier (2010) was used to generate utility multipliers to decrease baseline utility as patients age within the model (200). The regression algorithm used is detailed below:

$$EQ\text{-}5D = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

Utility values were derived from a repeated measures regression model of UK crosswalk utilities from MycarinG (181). For this model, treatment arms were pooled.

$$Utility\ Change = \beta_0 + \beta_1 \times EQ\text{-}5D_{baseline} + \beta_2 \times MG - ADL_{CFB}$$

The change in utility depended on the patient's baseline EuroQOL-5 Dimension (EQ-5D) score, and MG-ADL score, which are described in Table 63.

Table 63: Utility equation and parameter estimates

Parameter	Estimate	SE	p value
Baseline EQ-5D	0.6327		
Intercept [β0]	0.2024	0.02819	<0.0001
Coefficient of baseline EQ-5D (β1)	–0.2794	0.04162	<0.0001
Coefficient of MG-ADL score (β2)	–0.0221	0.002664	<0.0001

Abbreviations: EQ-5D, EuroQoL-5 dimensions; MG-ADL, myasthenia gravis activities of daily living.

B.3.4.6.1 Clinical event disutilities

Exacerbations were associated with disutilities in the model, derived from patient-level data in the REGAIN trial, and reported in eculizumab's CADTH model (201), where an exacerbation was associated with a weighted average disutility of 0.20. This disutility was applied for 11.8 days, the expected duration of an exacerbation. A patient was then assumed to incur the average utility across the response and uncontrolled health states, weighted by the proportion of patients in each health state for the remaining 2.2 days of a cycle. Following an exacerbation in the weeks prior to response assessment, patients return to one of the three response sub-groups to continue treatment and accrue costs and health outcomes associated with these patient groups accordingly. However, after the response assessment timepoint, patients who experience an exacerbation are assumed to discontinue treatment and transition to the uncontrolled health state where they accrue the costs and health outcomes associated with uncontrolled patients.

The disutility experienced from myasthenic crisis was 0.39, based on the disutility associated with emergency mechanical ventilation (202). This was considered by the CADTH economic review group to be more reliable than the analysis conducted from the REGAIN trial due to the small sample size (N=1) of those who experienced a myasthenic crisis during the trial. This disutility was applied for the full model cycle in which a patient transitioned into the myasthenic crisis health state based on the assumption that the treatment of a myasthenic crisis would last 14 days. Following a successfully treated myasthenic crisis, patients transition to the Uncontrolled health state and accrue 2-weekly costs and health outcomes associated with uncontrolled patients.

B.3.4.6.2 Clinical expert assessment of applicability of health state utility values

An advisory board was conducted in September 2023 with UK MG clinicians and UK health economists to elicit their expert opinion on the inputs and assumptions in the model, which validated and informed the inputs and assumptions used.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

B.3.5.1 *Resource identification, measurement and valuation studies*

A systematic review was conducted to identify resource use and cost data from the published literature relevant to the decision problem.

Electronic databases were searched on 01 May 2023 via the OVID platform using pre-determined search strategies, and included MEDLINE®, MEDLINE® In-Process, Embase, EconLit, and NHS-EED. Supplementary searches of public registries and databases, reference lists, previous HTA appraisals, and conference proceedings were performed to identify data not captured in the database search. The search strategy used has been described previously as part of the cost-effectiveness systematic review (see appendices document, Appendix G). An update search was performed on 01 February 2024. A summary of included studies are provided in Appendix I.

A total of 63 studies were identified in the original search that reported information pertaining to cost and resource use in MG. Of the identified studies, 34 were conducted in the US, three studies each was conducted in China and Germany, two studies each were conducted in England, Sweden, India and Japan and one each in Belgium, UK, Finland, Greece, Bulgaria, Germany, Taiwan, and Egypt. Two studies were conducted in multiple countries. Information pertaining to country was not reported in the remaining five studies.

The 2024 review update identified a total of 22 studies describing cost and resource use. Of the 22 studies, nine were conducted in the USA, two studies each were conducted in Japan and Sweden, and one each in Taiwan, Italy, Greece, Czech Republic, Spain, Norway. Three studies were conducted in multiple countries.

To identify relevant resource use and cost estimates for patients with gMG in a UK setting, UK clinicians with experience of treating patients with gMG were surveyed. NHS Reference Costs, the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care, the Monthly Index of Medical Specialities (MIMS), and the drugs and pharmaceutical electronic market information tool (eMIT) were used to inform unit costs in the model. The following cost categories are incorporated into the economic model and described in this section:

- Drug acquisition costs
- Drug administration costs
- Vaccination costs
- Routine care costs
- Clinical event management costs

Table 64: Studies reporting resource data

Study, Year, Country	Cost year	Applicability to clinical practice in England	Resource type	Technology costs (£)
BNF 2020 (202)	2023	Completely applicable as derived from England database	IVIg (per unit cost)	6,480
NHS 2021-22 (203)	2023	Completely applicable as derived from England database	Plasma exchange (per unit cost)	11,722

Jones 2021(204)	2021	Completely applicable as derived from England database	GP visits	33
Jones 2021 (204)	2021	Completely applicable as derived from England database	Visit to other healthcare professionals	52
NHS 2021-22 (205)	2023	Completely applicable as derived from England database	Outpatient hospital visits	486
NHS 2021-22 (206)	2023	Completely applicable as derived from England database	Presenting at emergency room	278
NHS 2021-22	2023	Completely applicable as derived from England database	Hospital stay (with ICU, cost per critical care period)	11,738
NHS 2021-22 and 2017-18 (207) †	2023	Completely applicable as derived from England database	Hospital stay (no ICU, cost per day)	595

Abbreviations: BNF, British National Formulary; GP, general practice; ICU, intensive care unit; IVIg, intravenous immunoglobulin; NHS, National Health Service.
†The total non-elective long stay costs from 2021/22 were divided by the average length of stay in days from 2017/18 to find the unit cost per day for each HRG code (AA26C-H: Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury), then a weighted average of the unit cost by activity for each HRG code was taken).

B.3.5.1.1 Appropriateness of NHS Ref costs/PbR tariffs

Unit costs were applied to resource use estimates, based on the latest values reported in the NHS reference costs and the PSSRU in the UK.

B.3.5.1.2 Clinical expert assessment of applicability of cost and healthcare resource use values

Expert opinion, as described in Section B.3.3.6, was sought to assess applicability of cost and healthcare resource use values. The KOLs confirmed that the drugs modelled within the economic analysis are representative of UK clinical practice and provided insight into the respective usage of each treatment. Resource use for controlled and uncontrolled patients as applied in the model was validated by the KOLs.

B.3.5.2 *Intervention and comparators' costs and resource use*

B.3.5.2.1 Treatment costs

Rozanolixizumab is a subcutaneous short infusion (up to 18 minutes) delivered via a syringe pump. Total drug acquisition costs are calculated for all patients remaining alive in each arm of the model, based on net price. Rozanolixizumab costs are applied to all patients remaining on treatment in the rozanolixizumab arm. Patients receiving rozanolixizumab are assumed to receive SoC therapies as background treatment. Costs

for these treatments are therefore applied to all surviving patients in both model arms throughout the modelled time horizon. The weighted list price per mg used in the model, based on the assumption that all treatment vial sizes were used equally; the sources for costs and posology are shown below in Table 65.

Table 65: Unit costs associated with the technology in the economic model

Treatment	Weighted list price per mg (£)	Cost source	Posology	Posology source
Rozanolixizumab	[redacted]	Assumption	• <50 kg = 280 mg • ≥50 kg to < 70 kg = 420 mg • ≥70 kg to < 100 kg = 560 mg • ≥100 kg = 840 mg Weekly administration for 6 weeks	Assumption: Assumed launch posology
Zilucoplan	[redacted]	Assumption	• <56 kg: 16.6 mg • ≥56 kg <77 kg: 23.0 mg • ≥77 kg: 32.4 mg Daily administration	Assumption Assumed launch posology
Efgartigimod	16.42	Product information	10 mg/kg weekly administrations	Product information
IVIg/SCIg	0.07	BNF	1,000 mg/kg, Q3W	NCT02473952
PLEX	2,587.45	BNF	Administered over 5 days Q4W	Expert opinion

Abbreviations: BNF, British National Formulary; IVIg, intravenous immunoglobulin; PLEX< plasma exchange; Q4W, every 4 weeks; SCIg, subcutaneous immunoglobulin.
† The price shown is net price.

Due to the anticipated increased use of SCIg, the model weights the immunoglobulin cost based on the respective use of IVIg and SCIg at 50% for each. This input only impacts the acquisition and administration costs associated with immunoglobulin. The efficacy and safety profile of both modes of administration were assumed to be equivalent.

B.3.5.2.2 Administration costs

Administration costs are shown in Table 66. Administration costs for rozanolixizumab were assumed to cover 60 minutes of nurse time on treatment initiation, but this was reduced to 30 minutes in subsequent model cycles.

Table 66: Administration costs as implemented in the model

Administration route	Unit cost per treatment cycle (£)	Reference
Rozanolixizumab	Initial cycle: £41.00; subsequent cycles: £20.50¶	Nurse time: 60 minutes, Band 5 hospital-based nurse (194)
Zilucoplan†	41.00	Nurse time: 60 minutes, Band 5 hospital-based nurse (194)
Efgartigimod	195.74	NHS collection of costs WF01B (193)
IVIg/SCIg	195.74	NHS collection of costs WF01B (193)
PLEX	303	NHS reference cost SA44A – single plasma exchange (205)

Abbreviations: IVIg, intravenous immunoglobulin; NHS, National Health Service; SCIg, subcutaneous immunoglobulin; SOC, standard of care.
†Costs were applied as one-off costs associated with the cost of training patients to self-inject the treatment in future model cycles. The healthcare system was assumed not to incur any costs for self-injections in subsequent cycles. ¶ Administration costs for rozanolixizumab were assumed to cover 60 minutes of nurse time on treatment initiation, but this was reduced to 30 minutes in subsequent model cycles.

B.3.5.3 *Health-state costs and resource use*

Annual resource use associated with patients with gMG in the 'Uncontrolled on high dose ISTs' and 'Response' health states were sourced from the literature (Table 67) and validated with UK clinical experts. Additionally, clinical event costs show the one-off costs patients incur as they transition through the 'Exacerbation' and 'Myasthenic crisis' health states (208). Unit costs were sourced from the PSS Research Unit (194), national schedule of NHS costs (193), and BNF (182).

Table 67: Health state resource use and unit costs

Resource	Costs		Health state			
			Frequency of resource use (19, 161) and length of stay (209)			
	Unit costs	Cost source	Uncontrolled	Response	Exacerbation	Myasthenic crisis
Health state resource use (all treatments except PLEX)						
GP visits (194)	£33	Per surgery consultation lasting 9.22 minutes (210).	13.62	9.53	0.82	0.06
Visit to other Healthcare Professionals (194)	£52	Hospital based scientific and professional staff. Band 6 - physiotherapists/OTs. Cost per working hour (210).	11.47	6.89	0.58	0.32
Outpatient hospital visits (193)	£486	Outpatient care. Consultant led. Neurology Service. WF02A - Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up. (211)	7.10	4.77	0.75	0.50
Presenting at ER (193)	£278	Weighted average of Total codes VB01Z to VB09Z - Emergency Medicine, Any Investigation with Category 1-5 Treatment. (211)	0.44	0.33	0.38	1.00
Hospital stay (with ICU, cost per critical care period) (193)	£11,738	Weighted average of total costs for HRG codes XC01Z-ZC07Z: adult critical care, 1-6 organs supported. (211)	0.13	0.07	0.03	1.00

Resource	Costs		Health state			
			Frequency of resource use (19, 161) and length of stay (209)			
	Unit costs	Cost source	Uncontrolled	Response	Exacerbation	Myasthenic crisis
Hospital stay (no ICU, cost per day) (193)	£595	National Schedule of NHS Costs Year 2021-2022, 2017-18- Divided the total non-elective long stay costs from 2021/22 by the average length of stay (days) from 2017/18 to find the unit cost per day for each HRG code (AA26C-H: Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury), then took a weighted average of the unit cost by activity for each HRG code.	1.40, length of stay: 1.19 days	0.75, length of stay: 1.19 days	0.33, length of stay: 7.50 days	1, length of stay: 15 days
Corticosteroid usage cost (212)			£7,743.00	£2,949.50		
Total costs			**£14,896.09**	**£7,390.33**	**£10,280.19**	**£32,662.41**
Health state resource use (PLEX)						
Hospital stay (no ICU, cost per day) (193)	£595	National Schedule of NHS Costs Year 2021-2022, 2017-18- Divided the total non-elective long stay costs from 2021/22 by the average length of stay (days) from 2017/18 to find the unit cost per day for each HRG code (AA26C-H: Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury), then took a weighted average of the unit cost by activity for each HRG code.	1.40, length of stay: 1.19 days	0.75, length of stay: 1.19 days	0.33, length of stay: 7.50 days	0.33, length of stay: 15 days
Total cost (PLEX)			**£14,896.09**	**£7,390.33**	**£14,081.96**	**£32,931.31**

Abbreviations: ER, emergency department; GP, general practice; ICU, intensive care unit; IVIg, intravenous immunoglobulin; PLEX, plasma exchange.

B.3.5.4 *Adverse reaction unit costs and resource use*

Adverse event costs were not included in the model, since no AEs were considered to meet the inclusion criteria of serious AEs with an incidence ≥5% in MycarinG trial.

B.3.6 *Severity*

It is not anticipated that severity weighting will be applicable for this appraisal.

B.3.7 *Uncertainty*

As gMG is a rare disease with limited innovative licensed medicines over the last two decades, there is a paucity of clinical data, particularly long-term efficacy data for the current comparator treatments. Clinical data on treatment response that uses a homogenous definition of response across all comparators is also lacking. Although the impact of this absence is lessened by the incorporation of NMA outputs, it still limits the robustness of the results. A further limitation of the model is the comparison of cyclically and chronically administered treatments.

There is some uncertainty and assumptions made surrounding the inputs to the model, again due to the paucity of available data in gMG. Probabilistic and deterministic sensitivity analyses have been performed to address this uncertainty, as well as a number of scenario analyses.

B.3.8 *Summary of base-case analysis inputs and assumptions*

B.3.8.1 *Summary of base-case analysis inputs*

A summary of the base case inputs and variables is provided in Appendix N.

B.3.8.2 *Assumptions*

A list of the additional assumptions made within the model and not discussed in the previous sections can be found in Table 68.

Table 68: Additional model assumptions

Variable	Assumption	Rationale
Treatment response	Treatment response rate, informed by the NMA, is applied in each model cycle up until the time of response assessment. After this point it is assumed that patients in the 'Uncontrolled on high dose steroids and ISTs' will not respond and therefore discontinue treatment	This represents the time at which response was assumed to be assessed, representing the time in clinical practice when a healthcare professional assesses whether to continue/discontinue treatment depending on response
Disease worsening	Transition from exacerbation to crisis is independent of treatment received in the model	There is no evidence to suggest that once a patient's disease has worsened that further deterioration to a

Variable	Assumption	Rationale
		myasthenic crisis is a result of the initial treatment received
	Patients in the 'Uncontrolled on high dose steroids and ISTs' health state do not experience disease worsening over time (as defined by an increase in MG-ADL score)	Patients who require a change in treatment due to lack of control on high dose steroids and ISTs do not worsen, but will maintain their current state of health, unless they specifically worsen to an exacerbation or into a myasthenic crisis. A similar assumption was suggested by clinical experts during the eculizumab CADTH submission (208)
Mortality rate	Patients experience the same risk of mortality as the general public, unless patients experience a myasthenic crisis	Based on existing literature (213)
Time on treatment	Only patients in the 'Continued response' and 'Stable response' health states receive active treatment	Patients who do not respond, or those who lose their initial response, will not continue to receive treatment due to lack of efficacy
End of life costs	End of life costs are included as a one-off cost that is borne by the healthcare provider	This represents the additional costs associated with increased resource use of terminal patients

Abbreviations: AE, adverse event; CADTH, Canadian Agency for Drugs and Technologies in Health; IST, immunosuppressive therapy; MG-ADL, myasthenia gravis-activities of daily living.

B.3.9 *Base-case results*

Table 69 presents the base case results for rozanolixizumab versus efgartigimod (subject to NICE appraisal), zilucoplan (subject to NICE appraisal), IVIg/SCIg and PLEX. In patients with gMG, treatment with rozanolixizumab results in incremental QALYs of 0.1075, 0.0913, 0.1588 and 0.1018 when compared with efgartigimod, zilucoplan, IVIg/SCIg and PLEX, respectively. This results in ICERs of [redacted] in comparison with efgartigimod, zilucoplan, IVIg/SCIg and PLEX, respectively. The base case economic results are reported with the current PAS discount of [redacted] applied to the list price of rozanolixizumab.

At willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, the incremental net monetary benefit shows that the introduction of rozanolixizumab would be [redacted] compared with [redacted] and [redacted].

B.3.9.1 *Base-case incremental cost effectiveness analysis results*

Table 69: Base-case results

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Rozanolixizumab	[redacted]	18.3627	8.1967				
IVIg/SCIg	[redacted]	18.3605	8.0379	[redacted]	0.0022	0.1588	[redacted]
Efgartigimod	[redacted]	18.3621	8.1792	[redacted]	0.0006	0.0175	[redacted]
PLEX	[redacted]	18.3611	8.0950	[redacted]	0.0016	0.1018	[redacted]
Zilucoplan	[redacted]	18.3604	8.1054	[redacted]	0.0023	0.0913	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; LYG, life years gained; PLEX, plasma exchange; QALY, quality-adjusted life year; SCIg, subcutaneous immunoglobulin.

Table 70: Net monetary benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	INMB at £20,000	INMB at £30,000
Rozanolixizumab	[redacted]	8.1967				
IVIg/SCIg	[redacted]	8.0379	[redacted]	0.1588	[redacted]	[redacted]
Efgartigimod	[redacted]	8.1792	[redacted]	0.0175	[redacted]	[redacted]
PLEX	[redacted]	8.0950	[redacted]	0.1018	[redacted]	[redacted]
Zilucoplan	[redacted]	8.1054	[redacted]	0.0913	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; IVIg, intravenous immunoglobulin; LYG, life years gained; PLEX, plasma exchange; QALYs, quality-adjusted life years; SCIg, subcutaneous immunoglobulin.

The disaggregated model results are presented in Appendix J.1.2.

B.3.9.2 *Clinical outcomes from the model*

The clinical outcomes assessed are the event rates in various heath states of the model, presented in Table 71.

Table 71: Summary of clinical outcomes: Time (years) spent in health states

	Rozanolixizumab	IVIg/SCIg	Efgartigimod	PLEX	Zilucoplan
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myasthenic crisis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

B.3.10 *Exploring uncertainty*

B.3.10.1 *Probabilistic sensitivity analysis*

A probabilistic sensitivity analysis (PSA) was performed using a second-order Monte Carlo simulation with 1,000 iterations. In each iteration, input parameters were randomly sampled from the parameter distribution to reflect the uncertainty around their estimates. For the odds ratios used to calculate response rates, samples from the NMA's Convergence Diagnostic and Output Analysis were used instead of using a calculated distribution. This approach had the advantage that correlation between the odds ratio parameters was preserved. The model then calculated the average per patient outcomes across all results.

B.3.10.1.1 Inputs

The input parameters considered in the PSA are detailed in Appendix O.1.

B.3.10.1.2 Results

The base-case ICER and the PSA mean ICER are shown in Table 72.

Table 72: PSA results

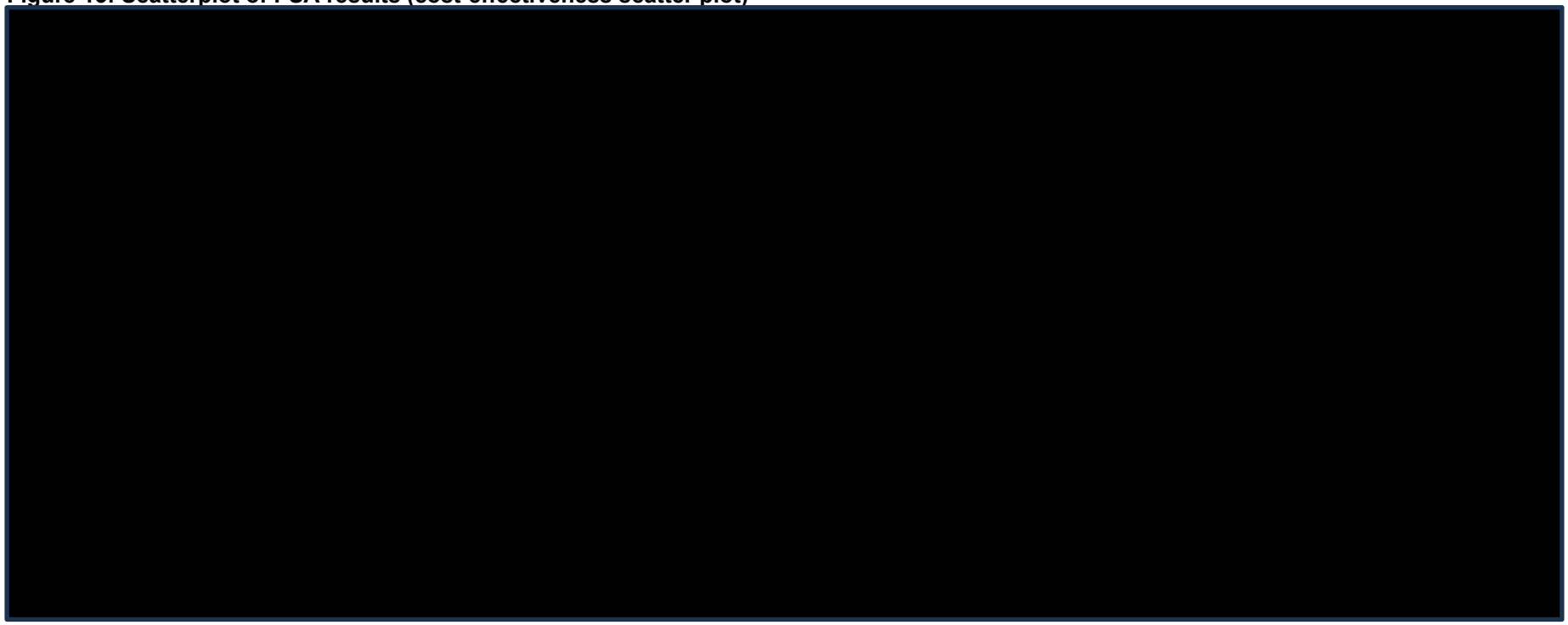
Treatment	Total		Incremental		Pairwise ICER per QALY gained
	Costs	QALYs	Costs	QALYs	
Rozanolixizumab	[redacted]	8.1233			
IVIg/SCIg	[redacted]	7.9949	[redacted]	0.1284	[redacted]
Efgartigimod	[redacted]	8.1338	[redacted]	-0.0105	[redacted]
PLEX	[redacted]	8.0509	[redacted]	0.0724	[redacted]
Zilucoplan	[redacted]	8.0605	[redacted]	0.0628	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; PSA, probabilistic senstivity analysis; SCIg, subcutaneous immunoglobulin.

[redacted]

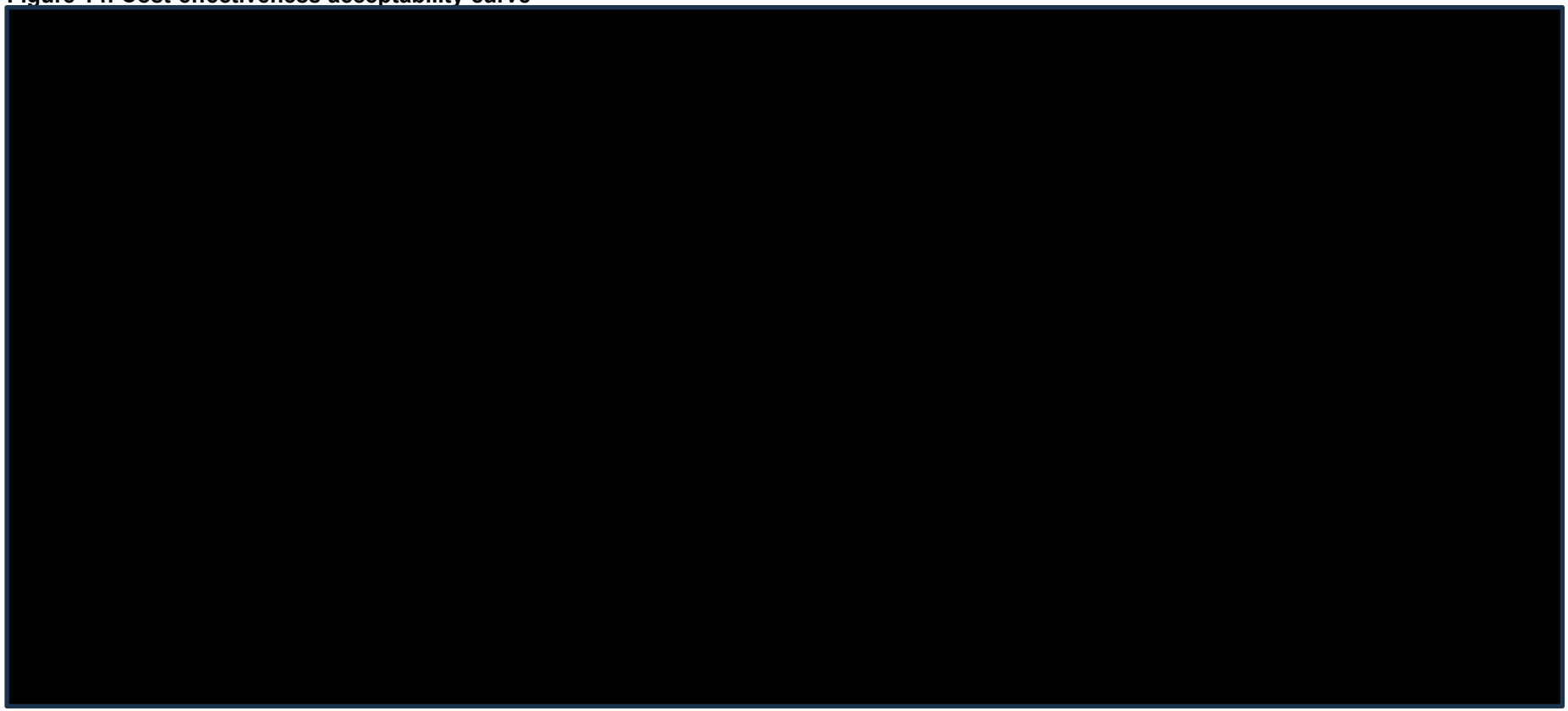
A cost-effectiveness scatterplot is shown in Figure 13. Points plotted in the north-west quadrant represent simulations in which the intervention was dominated by the comparator, i.e., the intervention incurred increased costs and generated fewer QALYs in contrast to the comparator. Points plotted in the south-east quadrant represent simulations in which the intervention was the dominant treatment, i.e., the intervention provided more benefit at a reduced cost relative to the comparator. Points plotted in the north-east and south-west quadrants reflect scenarios where the cost-effectiveness is conditional upon the willingness-to-pay threshold. The cost-effectiveness acceptability curve for all treatments is shown in Figure 14, showing the probability that each treatment is cost effective at different willingness-to-pay thresholds.

Figure 13: Scatterplot of PSA results (cost-effectiveness scatter plot)



Abbreviations: IVIg, intravenous immunoglobulin; QALY, quality-adjusted life year; PSA, probabilstic sensitivity analysis; QALY, quality-adjusted life year; SCIg, subcutaneous immunoglobulin.

Figure 14: Cost-effectiveness acceptability curve



Abbreviations: IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.

B.3.10.1.3 Discussion of variation between base case and PSA results

Table 73 presents the variation between the base case results PSA results. The PSA results are aligned with the base case results

Table 73: Variation between base case and PSA results

	Total Costs (%)	Total QALYs (%)
Rozanolixizumab	4.62%	0.90%
IVIg/SCIg	1.04%	0.54%
Efgartigimod	1.11%	0.56%
PLEX	1.04%	0.55%
Zilucoplan	6.92%	0.56%

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; PSA, probabilistic sensitivity analysis; SCIg, subcutaneous immunoglobulin.

B.3.10.2 *Deterministic sensitivity analysis*

For the DSA, model inputs were varied based on published standard errors for the respective model inputs. However, when these data were not available, a ±20% variation of the base case value was assumed conservatively. The most impactful inputs were summarised in a tornado diagram. The primary outcome considered in the DSA was the net monetary benefit (NMB) due to its stability where use of the incremental cost-effectiveness ratio (ICER) may produce extreme values and be difficult to interpret when the results fall in different quadrants of the cost-effectiveness plane.

B.3.10.2.1 Inputs

The input parameters considered in the DSA are detailed in Appendix O.2.

B.3.10.2.2 Results

Tornado diagrams showing the main drivers of the model are shown in Figure 15, Figure 16, Figure 17 and Figure 18 for the comparison vs efgartigimod, zilucoplan, IVIg/SCIg, and PLEX, respectively. These results are also shown in tabular form in Table 74, Table 75, Table 76 and Table 77, respectively.

Figure 15: Tornado diagram for rozanolixizumab versus efgartigimod

Table 74: Tabular results of DSA for rozanolixizumab versus efgartigimod based on NMB

Rank	Parameter	NMB (£) with low value	NMB (£) with high value	Difference (£)
1	Exacerbation annual event rate - responders (0.19 to 0.31)	[redacted]	[redacted]	[redacted]
2	% showing stable response - Efgartigimod ([redacted] to [redacted])	[redacted]	[redacted]	[redacted]
3	Odds ratio (ITC) - Efgartigimod ([redacted] to [redacted])	[redacted]	[redacted]	[redacted]
4	% showing stable response - Rozanolixizumab ([redacted] to [redacted])	[redacted]	[redacted]	[redacted]
5	Myasthenic crisis annual event rate - responders (0.01 to 0.05)	[redacted]	[redacted]	[redacted]
6	Odds ratio (ITC) - Rozanolixizumab ([redacted] to [redacted])	[redacted]	[redacted]	[redacted]
7	Avg. age of population (41.44 to 62.16)	[redacted]	[redacted]	[redacted]
8	Exacerbation annual event rate - uncontrolled (0.52 to 0.78)	[redacted]	[redacted]	[redacted]

9	% showing continued response - Efgartigimod (to)			
10	% showing loss of response - Efgartigimod (to)			

Figure 16: Tornado diagram for rozanolixizumab versus zilucoplan

Table 75: Tabular results of DSA for rozanolixizumab versus zilucoplan based on NMB

Rank	Parameter	NMB (£) with low value	NMB (£) with high value	Difference (£)
1	Average patient weight (kg) (64.92 to 97.38)			
2	% showing stable response - Zilucoplan (to)			
3	Exacerbation annual event rate - responders (0.19 to 0.31)			
4	Odds ratio (ITC) - Zilucoplan (to)			
5	% showing stable response - Rozanolixizumab (0.72 to 1.00)			

6	Myasthenic crisis annual event rate - responders (0.01 to 0.05)	[redacted]	[redacted]	[redacted]
7	Odds ratio (ITC) - Rozanolixizumab ([redacted] to [redacted])	[redacted]	[redacted]	[redacted]
8	Avg. age of population (41.44 to 62.16)	[redacted]	[redacted]	[redacted]
9	Exacerbation annual event rate - uncontrolled (0.52 to 0.78)	[redacted]	[redacted]	[redacted]
10	% showing continued response - Zilucoplan ([redacted] to [redacted])	[redacted]	[redacted]	[redacted]

Figure 17: Tornado diagram for rozanolixizumab versus IVIg/SCIg

Table 76: Tabular results of DSA for rozanolixizumab versus IVIg/SCIg based on NMB

Rank	Parameter	NMB (£) with low value	NMB (£) with high value	Difference (£)
1	Average patient weight (kg) (64.92 to 97.38)	[redacted]	[redacted]	[redacted]
2	% showing stable response - Rozanolixizumab ([redacted] to [redacted])	[redacted]	[redacted]	[redacted]

3	% showing stable response - IVIg/SCIg ([redacted] to [redacted])	[redacted]	[redacted]	[redacted]
4	Odds ratio - IVIg/SCIg (1.49 to 2.24)	[redacted]	[redacted]	[redacted]
5	Odds ratio (ITC) - Rozanolixizumab ([redacted] to [redacted])	[redacted]	[redacted]	[redacted]
6	Exacerbation annual event rate - responders (0.19 to 0.31)	[redacted]	[redacted]	[redacted]
7	% of pts treated with IVIg (0.40 to 0.60)	[redacted]	[redacted]	[redacted]
8	Myasthenic crisis annual event rate - responders (0.01 to 0.05)	[redacted]	[redacted]	[redacted]
9	Exacerbation annual event rate - uncontrolled (0.52 to 0.78)	[redacted]	[redacted]	[redacted]
10	% showing continued response - Rozanolixizumab ([redacted] to [redacted])	[redacted]	[redacted]	[redacted]

Figure 18: Tornado diagram for rozanolixizumab versus PLEX

Table 77: Tabular results of DSA for rozanolixizumab versus PLEX based on NMB

Rank	Parameter	NMB (£) with low value	NMB (£) with high value	Difference (£)
1	% showing stable response - Plasma exchange (to)			
2	Odds ratio (ITC) - Plasma exchange (1.90 to 2.85)			
3	% showing stable response - Rozanolixizumab (to)			
4	Odds ratio (ITC) - Rozanolixizumab (to)			
5	IVIg resource use - exacerbation (0.58 to 0.87)			
6	Exacerbation annual event rate - uncontrolled (0.52 to 0.78)			
7	Avg. age of population (41.44 to 62.16)			
8	PLEX resource use - exacerbation (other costs) (0.22 to 0.33)			

9	Hospital stay (with ICU, cost per critical care period) resource use - myasthenic crisis (0.80 to 1.20)	[redacted]	[redacted]	[redacted]
10	PLEX resource use - myasthenic crisis (other costs) (0.76 to 1.14)	[redacted]	[redacted]	[redacted]

B.3.10.3 *Scenario analysis*

Scenario analyses were performed to investigate uncertainty around the structural assumptions of the model.

B.3.10.3.1 Patient weight

In this scenario, the mean Baseline weight of the refractory cohort (patients who had received ≥2 prior MG-specific therapies [after AChEIs]) from the MycarinG trial was utilised, i.e. [redacted] kg.

Technologies	Total			Incremental vs. rozanolixizumab			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Rozanolixizumab	[redacted]	18.3627	8.1967				
IVIg/SCIg	[redacted]	18.3605	8.0379	[redacted]	0.0022	0.1588	[redacted]
Efgartigimod	[redacted]	18.3621	8.1792	[redacted]	0.0006	0.0175	[redacted]
PLEX	[redacted]	18.3611	8.0950	[redacted]	0.0016	0.1018	[redacted]
Zilucoplan	[redacted]	18.3604	8.1054	[redacted]	0.0023	0.0913	[redacted]

B.3.10.3.2 Response assessment timepoint

In this scenario, the same response assessment time-point was used across all the treatments, i.e. 6-weeks from MycarinG trial.

Technologies	Total			Incremental vs. rozanolixizumab			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Rozanolixizumab	[redacted]	18.3627	8.1967				
IVIg/SCIg	[redacted]	18.3605	8.0379	[redacted]	0.0022	0.1588	[redacted]
Efgartigimod	[redacted]	18.3622	8.1838	[redacted]	0.0005	0.0129	[redacted]
PLEX	[redacted]	18.3611	8.0950	[redacted]	0.0016	0.1018	[redacted]
Zilucoplan	[redacted]	18.3605	8.1101	[redacted]	0.0022	0.0866	[redacted]

B.3.10.3.3 Proportion of responders for IVIg and PLEX

In this scenario, a responder rate of [redacted] was applied for IVIg and PLEX, based on clinical expert opinion (53).

Technologies	Total			Incremental vs. rozanolixizumab			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Rozanolixizumab	[redacted]	18.3627	8.1967				
IVIg/SCIg	[redacted]	18.3623	8.0615	[redacted]	0.0004	0.1352	[redacted]

Technologies	Total			Incremental vs. rozanolixizumab			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Efgartigimod	[redacted]	18.3621	8.1792	[redacted]	0.0006	0.0175	[redacted]
PLEX	[redacted]	18.3623	8.1224	[redacted]	0.0004	0.0743	[redacted]
Zilucoplan	[redacted]	18.3604	8.1054	[redacted]	0.0023	0.0913	[redacted]

B.3.11 *Subgroup analysis*

No subgroup analysis was performed.

B.3.12 *Benefits not captured in the QALY calculation*

The economic evaluation has attempted to encompass all conceivable benefits of rozanolixizumab in the QALY estimation. However, there are notable benefits of rozanolixizumab therapy for gMG that remain outside the scope of this evaluation. In particular, patient HRQoL was assessed using the EQ-5D instrument, which is non-disease-specific and therefore may be insensitive to the most common symptoms of MG, such as fatigue, vision impairment, and hand weakness (119-121). The Office of Health Economics (OHE) suggests that generic measures of HRQoL may fail to reflect what matters to patients by not capturing symptoms such as fatigue (119). In addition, the EQ-5D may miss changes in QoL when patients' symptoms and functioning are unpredictable and fluctuate over time. It is likely that the widespread use of non-disease-specific instruments may lead to underrepresentation of the impact of MG on patients' HRQoL (121, 214).

Additionally, the rarity of gMG presents inherent difficulties in gathering substantial QoL data and patient-reported outcomes.

Furthermore, the impact of a subcutaneous administration option on patient burden/patient preference and carer quality of life, as well as health-related quality of life, is unlikely to be captured in the QALY estimation. Administration of PLEX requires treatment at specialist centres over 4–5 consecutive days, which may involve patients having to travel long distances for treatment and even staying in hospital for repeat treatment (25, 26). The IVIg infusion duration of 4–6 hours over 2–5 days is also burdensome for patients. Both patients and the NHS incur opportunity costs; the NHS could direct the managed supply of IVIg and PLEX towards the treatment of patients with other indications without effective targeted treatments, whilst patients and their caregivers could experience lower economic and humanistic burdens.

Finally, the economic model has not captured the full impact of gMG on carer disutility or on societal impact (productivity losses due to absenteeism). A survey of expert physicians across France, Germany, Italy, Spain, the UK, and the US reported that 38% of patients with gMG required a caregiver (14, 17, 18). In total, 25% of caregivers changed their work status or retired as a result of needing to provide care (18), which will affect both costs and QoL for the carer. Unemployment rates are higher for patients with MG than the general population or matched control groups, and higher compared with

other chronic conditions (13-16). This, along with sickness absence and the resulting reduced income, will affect both cost and QoL of patients for much of their working lives, since MG is diagnosed at an early working age (124).

B.3.13 *Validation*

B.3.13.1 *Validation of de novo cost-effectiveness analysis*

A rigorous and comprehensive quality check of the model was conducted to ensure the completed model contained no errors and worked as intended. A series of tests and checks were also conducted on the model engine. Among other reviews, the validator:

- Confirmed that all model inputs were correctly linked to the model engine
- Checked all cells with "IF logic" in detail, confirming that the statements provided the correct value for each condition
- Traced all links between the calculation sheets and results sheet to make sure that the proper outputs were displayed in the correct location
- Thoroughly reviewed and debugged all Visual Basic for Applications code
- Searched for common Microsoft Excel® errors (e.g.,!#REF errors, unused named ranges, broken links, links to external workbooks, copy/paste errors) and resolved them as needed
- Checked all text and formatting to ensure that there were no typographical errors or formatting irregularities

Finally, an extreme value sensitivity analysis was conducted on all applicable model inputs. While conducting the analysis, the validator noted the direction and magnitude of change for each extreme value tested and confirmed that this aligned with the expected result (e.g., if all drug cost inputs are set to 0, the model should output total drug costs of 0 as well). The model validation process uncovered minimal discrepancies and no impactful model calculation errors. Feedback from the validation was addressed in the model, and the refined post-validation model was used to generate the final results.

B.3.14 *Interpretation and conclusions of economic evidence*

This analysis assessed the cost-effectiveness of rozanolixizumab vs efgartigimod and zilucoplan as the main comparator and IVIg/SCIg and PLEX as alternative comparators, from an NHS and PSS perspective in England. A *de novo* model was developed with seven mutually exclusive health states (i.e. Stable response, Continued response, Loss of response, Uncontrolled on high dose steroids and ISTs, Exacerbation, Myasthenic crisis, Death) to evaluate the cost-effectiveness of rozanolixizumab as a treatment for adult patients with gMG. The economic evaluation of rozanolixizumab was conducted according to UK HTA guidelines.

Costs and outcomes were estimated based on the most relevant sources available in the UK including BNF and PSSRU. The results of the base case analysis indicate that the ICER for rozanolixizumab is [redacted] in comparison with efgartigimod with incremental costs of [redacted] and incremental QALYs of 0.0175. In comparison with zilucoplan, the ICER is [redacted] with incremental costs of [redacted] and incremental QALYs of 0.0913. In comparison with IVIg/SCIg, the ICER is [redacted] with incremental costs of [redacted] and incremental QALYs of 0.1588. For the

comparison versus PLEX, the ICER is [redacted], with incremental costs of [redacted] and incremental QALYs of 0.1018.

The model parameters with the most significant impact on the ICER, as identified from the DSA performed, included clinical parameters at the top followed by costs parameters.

The model estimates the costs and health outcomes associated with the adoption of rozanolixizumab compared with current and upcoming therapeutics in the treatment of patients with gMG who are currently uncontrolled on high dose steroids and ISTs. The model is flexible to allow the user to edit inputs and vary assumptions, which is important to manage uncertainty in the available data.

The strength of the economic evaluation is its flexibility and scope for future expansion and enhancement; the model can accommodate a wide variety of inputs, and the key parameters of the model are user-modifiable. In this analysis, the healthcare resource use and cost parameters in the model were derived from recent sources, the majority from the UK databases. Furthermore, the mortality data were adjusted using UK life table data.

The limitations of this analysis are largely centred around the availability, or lack thereof, of long-term efficacy data for any of the comparators. Therefore, the assumptions that most responders maintain their response is uncertain past the current data cut of MycarinG, with scenario analyses indicating that this assumption can substantially impact the health outcomes in the model.

In addition, the analysis is limited by the availability of response data that uses a homogenous definition of response across all comparators. Future iterations of the analysis would benefit from accounting for the heterogeneity between trial patients and definitions, most significantly by attempting to correct for the discrepancy in definitions of response used across the different comparators for which data were available.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Rozanolixizumab for antibody-positive generalised myasthenia gravis

Summary of Information for Patients (SIP)

12th March 2024

File name	Version	Contains confidential information	Date
SIP	1.0	Yes	12th March 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: rozanolixizumab Brand name: Rystiggo®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with generalised myasthenia gravis (gMG) who are positive for anti-acetylcholine receptor (AChR) or anti muscle-specific kinase (MuSK) antibodies and who are refractory (i.e. experience symptoms despite receiving standard treatment) and therefore require an additional treatment on top of their standard prescribed therapies to help control their disease.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

European Medicines Agency Positive opinion was granted on 9th November 2023 from the Committee for Medicinal Products for Human Use (CHMP): https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-rystiggo_en.pdf Marketing authorisation was granted on 5th January 2024 as add-on to standard therapy for the treatment of gMG in adult patients who are anti-AChR or anti-MuSK antibody positive: https://www.ema.europa.eu/en/medicines/human/EPAR/rystiggo#ema-inpage-item-authorisation-details UK regulatory approval Medicines and Healthcare products Regulatory Agency (MHRA) approval was granted on 7th March 2024.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

MyAware are members of the MG community (patient advocacy groups [PAGs] from across Europe). A representative from MyAware is joining a UCB-sponsored MG patient reported

outcomes discussion group and the PAG will be compensated for its participation. There are no other collaborations or financial support being provided.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is myasthenia gravis?

Myasthenia gravis (MG) is a rare, chronic disease in which the body's immune system is overactive and attacks healthy tissue (an 'autoimmune disease'). In myasthenia gravis, antibodies damage the site of communication between nerves and muscles, leading to muscle weakness (1, 2). The majority of patients who present with MG symptoms (initially confined to the outer eye muscles in most cases) develop generalised MG (gMG) within two years (3-5), which is associated with weakness in the muscles of the head, neck, arms, hands, legs and torso (6).

What is the impact of MG on people living with the condition?

Patients experience debilitating fatigue and weakness in muscles, including those responsible for vital functions, e.g. breathing, swallowing and mobility. Persistent fatigue is one of the most common symptoms of MG and negatively impacts daily activities – such as walking, self-care and going to work – to such an extent that employment and working hours are impacted and caregiver support is often needed (7-11). The symptoms of gMG are unpredictable and fluctuate in intensity. Patients can experience sudden worsening of their symptoms that requires urgent intervention to prevent life-threatening deterioration of muscle weakness and respiratory failure (known as a myasthenic crisis) (12, 13), which requires treatment and mechanical ventilation in an intensive care unit (14, 15).

Myasthenia gravis has a profound impact on the quality of life of affected people. The severe, chronic symptoms of gMG can negatively impact patients' mental health and can lead to depression, fear and anxiety (16-18), particularly in those with active disease despite receiving standard therapy (9, 19-21). Patients feel that living with gMG impacts their decision to have a family and raises concerns about the effects of gMG on their ability to cope as a parent (18). Younger patients in particular may feel a sense of loss due to restrictions in activity and limitations in life choices (18).

How many people develop MG?

It is estimated that there are currently 19,053 people living with MG in England (22).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

There is no formal pathway for diagnosis recommended by NICE. Myasthenia gravis is a rare disease and therefore unfamiliar to many doctors, and an overlap in symptoms with other neurological diseases can result in an MG diagnosis being missed or delayed (4, 23).

The Association of British Neurology (ABN) management guidelines and others recommend that MG is diagnosed through a combination of patient medical history, clinical symptoms, physical and neurological exams, auto-antibody serum testing, and electrophysiological tests (24-26).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

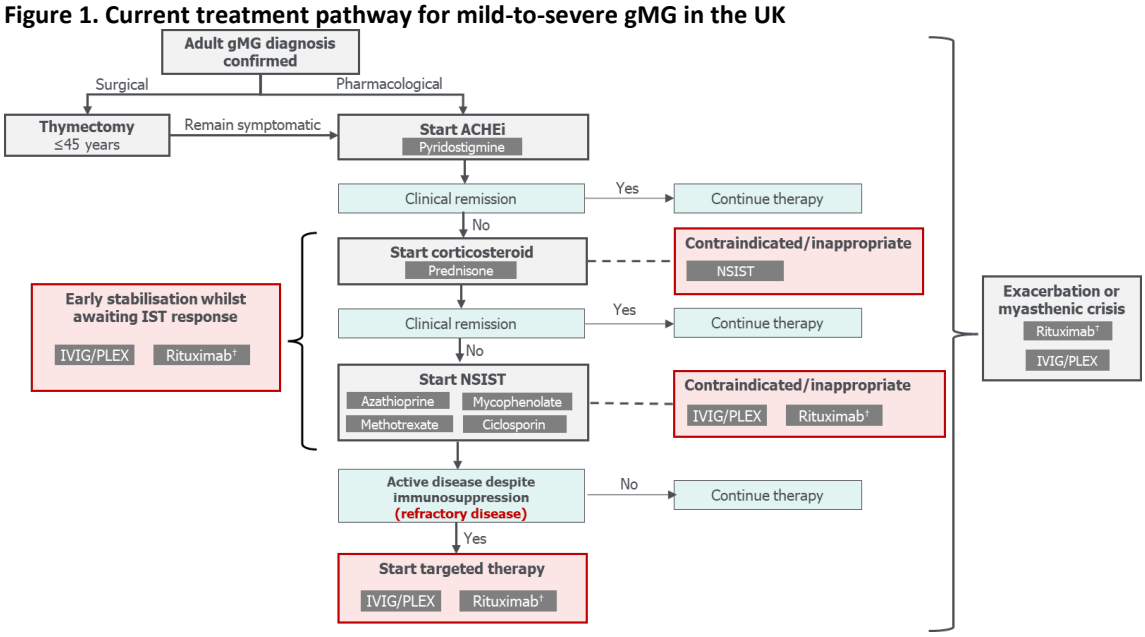
- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatments are currently available?

There are no treatments addressing the root cause of MG, therefore current options for patients are based on non-specific suppression of the immune system (26, 27). Many of these medicines are currently not licensed for MG in the UK (including azathioprine, mycophenolate mofetil , methotrexate, ciclosporin and rituximab) (26, 28). There are no completed NICE technology appraisals for gMG therapies or guidance for the management of patients.

Standard of care starts with acetylcholinesterase inhibitors (AChEIs), such as pyridostigmine (Figure 1) (26, 28). If treatment with AChEIs is not effective, corticosteroids such as prednisolone may be added (26, 28). Non-steroidal immunosuppressive therapies (NSISTs) may be offered in addition to steroids as current standard of care, with the aim of reducing the corticosteroid dose over time. Patients may cycle through different immunosuppressive therapies, some of which take up to 6–18 months to show a therapeutic effect, until their symptoms are under control. For patients who continue to experience active disease despite maximal immunosuppressive therapy, intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) can be used, although both are associated with limitations related to treatment burden (long infusion duration for which some patients have to travel long distances); they are also costly to the healthcare system and are supported by limited evidence. Furthermore, supply of IVIg is managed in the UK and PLEX is available in few specialised centres (26, 28, 29).

Figure 1. Current treatment pathway for mild-to-severe gMG in the UK



† In the UK, IVIg or PLEX are the first choice to stabilise patients with exacerbation or myasthenic crisis, while rituximab is used for maintenance after stabilisation. As opposed to its use for refractory patients (shown here), expert opinion sought by the All Wales

Therapeutic and Toxicology Centre (AWTTC) suggested rituximab could be used, together with corticosteroids, as a first therapy for patients with newly diagnosed gMG and antibodies against AChR or MuSK (30).
Abbreviations: ABN, Association of British Neurology; AChEi, acetylcholinesterase inhibitors; AChR, acetylcholine receptor; gMG, generalised myasthenia gravis; IST, immunosuppressive therapy; IVIg, intravenous immunoglobulin; MuSK, muscle-specific kinase; NSIST, non-steroidal IST; PLEX, plasma exchange.
Source: Adapted from the ABN management guidelines and validated by UK clinical expert opinion (26, 31).

Why is there a need for new treatments?

Patients with active disease despite receiving standard therapy experience ongoing, burdensome symptoms, poor quality of life, and are at risk of myasthenic exacerbation and crisis (14, 19-21, 32-35). Given the limitations of current treatment options (e.g. side effects such as diabetes and osteoporosis, and prolonged time to onset of treatment effect), there is an urgent need for novel, licensed, more targeted treatments. A targeted treatment with a fast onset of action that minimises both symptom burden and the burden of therapy, and reduces the risk of myasthenic exacerbations and crises, would reduce the clinical impact and improve the quality of life of adult patients with gMG. Patients would also benefit from a treatment that offers more convenience and fit better into their everyday lives than some existing therapies, which can require long infusion times.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patients with gMG experience debilitating symptoms that severely impact all aspects of their lives (18), leading to poor quality of life (36-38). Factors associated with worse quality of life include refractory gMG (compared with non-refractory disease), severe disease (compared with less severe disease), antibodies against MuSK (compared with antibodies against AChR), female gender, and age <40 years (compared with age >65 years) (9, 19, 37, 38).

In addition to the burden of living with symptoms of gMG, quality of life is impacted by the serious side effects from long-term use of corticosteroids (such as increased infection risk, depression, osteoporosis and diabetes) and NSISTs (including liver and kidney dysfunction and increased risk of infection and skin cancer), as well as other common side effects affecting quality of life (such as mood swings and weight gain) (26, 39, 40).

Of patients with gMG participating in a survey, 50% reported that their disease impacted their ability to lead a full life. Of patients with moderate to severe disease, 48% felt their ability to perform daily routines was considerably impaired by their disease (41).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Rozanolixizumab is a monoclonal antibody that reduces levels of immunoglobulin G (IgG) antibodies, including IgG auto-antibodies against AChR or MuSK, thereby helping to improve symptoms of MG.

The Phase III MycarinG clinical trial met its primary and all its secondary efficacy and safety endpoints. Patients who received rozanolixizumab, in addition to standard treatment, experienced statistically significant and clinically meaningful improvements in symptoms of gMG at Day 43, with improvements observed as early as 8 days after starting treatment in some patients. Rozanolixizumab was generally well tolerated in patients with gMG (42).

It is anticipated that rozanolixizumab will be offered as an add-on to current standard of care for patients with refractory gMG, as these patients have an urgent need for a treatment with a fast onset of action that can control symptoms and reduce the risk of myasthenic exacerbation/crisis.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

It is anticipated that rozanolixizumab will be offered as an add-on to current standard of care for patients with refractory gMG. No interaction studies have been performed.

Based on its mechanism of action, rozanolixizumab is expected to decrease the blood serum concentration of IgG-based treatments (e.g. rituximab and IVIg) and Fc-peptide fusion proteins; therefore, it is recommended to initiate these treatments 2 weeks after administration of rozanolixizumab. If administered at the same time as rozanolixizumab, it is recommended to monitor for decreased efficacy of IgG-based treatments (43).

Because of the temporary reduction in IgG levels with rozanolixizumab treatment, the use of live or live-attenuated vaccines is not recommended as the immune system might be impaired in its ability to respond to these vaccine formulations. All live and live-attenuated vaccines should be administered according to immunisation guidelines and at least 4 weeks before initiation of treatment with rozanolixizumab. All other vaccinations should take place at least 2 weeks after the last infusion of a treatment cycle and 4 weeks before initiating the next cycle.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Rozanolixizumab is administered as a short (up to 18 minutes), once-weekly, subcutaneous infusion, followed by 15 minutes monitoring post-administration, for 6 weeks (one treatment cycle). Patients receive subsequent treatment cycles depending on their symptoms and according to clinical evaluation. Approximately 90% of patients in the clinical trials had intervals of 4–

13 weeks between cycles, while 10% of patients had a treatment-free interval of less than 4 weeks. Rozanolixizumab should be administered by a healthcare professional in an outpatient setting (e.g. infusion centre, hospital) and does not require highly specialised equipment or training (43). Home administration, performed by a qualified healthcare professional, may be considered by the physician for patients who have tolerated administration of rozanolixizumab well in the clinic.

The recommended weekly dose during a 6-week cycle is based on patient weight (Table 1) and should be administered once weekly for each 6-week treatment cycle. Subsequent treatment cycles should be administered according to clinical evaluation.

Table 1. Total weekly dose by body weight range

Body weight	Dose	Number of vials†
≥35–<50 kg	280 mg/2 mL	1
≥50–<70 kg	420 mg/3 mL	2
≥70–<100 kg	560 mg/4 mL	2
≥100 kg	840 mg/6 mL	3

†Each vial contains excess volume for priming the syringe driver.
Source: SmPC for rozanolixizumab (43).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Phase II trial: MG0002 (Number of participants = 43)

Locations: Belgium, Canada, Czechia, Denmark, Germany, Spain and the US

Population: Patients aged ≥18 years with gMG and auto-antibodies against AChR or MuSK

Key inclusion criteria:

- Quantitative Myasthenia Gravis (QMG) score >11
- Patient would be considered for treatment with IVIg and/or PLEX

Key exclusion criteria:

- A total serum IgG level ≤6 g/L or an absolute neutrophil count <1,500 cells/mm^3
- Patient received a live vaccine within 8 weeks prior to Baseline, or intended to receive a live vaccine during the study or within 7 weeks following the final dose of rozanolixizumab

Comparators: In dosing period 1, patients were randomised to receive either placebo or rozanolixizumab (≈7 mg/kg) + standard of care. In dosing period 2, each group from dosing period 1 was randomised to receive rozanolixizumab at either ≈7 mg/kg or ≈4 mg/kg + standard of care.

Start/completion: May 2017 to May 2018

Study publication: https://pubmed.ncbi.nlm.nih.gov/33219142/

National Clinical Trials link: https://clinicaltrials.gov/study/NCT03052751

Phase III trial: MycarinG, MG0003 (Number of participants = 200)

Locations: Belgium, Canada, Czechia, Denmark, France, Georgia, Germany, Hungary, Italy, Japan, Poland, Russia, Serbia, Spain, Taiwan and the US

Population: Patients aged ≥18 years with gMG and auto-antibodies against AChR or MuSK

Key inclusion criteria:

- Myasthenia Gravis Foundation of America [MGFA] Class II to IVa

- Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥3, with ≥3 points from non-ocular symptoms, and QMG score ≥11 at Screening and Baseline
- Stable MG treatment prior to Baseline and during the study (except for AChEIs)
- Patient was being considered for additional treatment such as IVIg and/or PLEX

Key exclusion criteria:

- A total serum IgG level ≤5.5 g/L or an absolute neutrophil count <1,500 cells/mm^3
- Clinically relevant active infection or serious infections, i.e. mycobacterial infections, hepatitis B or C, or HIV infection
- Treatment with PLEX or IVIg one month and/or monoclonal antibodies 3–6 months before receiving rozanolixizumab

Comparators: Patients were randomised to receive either 6-week cycles of rozanolixizumab at either ≈7 mg/kg or ≈10 mg/kg weekly or a placebo in addition to their standard gMG medications

Start/completion: June 2019 to June 2021

Study publication: https://pubmed.ncbi.nlm.nih.gov/37059507/

National Clinical Trials link: https://classic.clinicaltrials.gov/ct2/show/NCT03971422

Phase III extension trial: MG0004 (Number of participants = 71)

Locations: Canada, Czechia, Denmark, France, Germany, Italy, Japan, Poland, Russia, Spain, Taiwan and the US

Population: Patients aged ≥18 years with gMG and auto-antibodies against AChR or MuSK

Key inclusion criteria:

- Patients who had completed the observation period of MG0003 or required rescue therapy during the observation period of MG0003

Key exclusion criteria:

- Evidence of active or latent tuberculosis (TB) infection
- Patient met any mandatory withdrawal or study discontinuation criteria in MG0003 or permanently discontinued rozanolixizumab in this study
- Patient received a live vaccine within 8 weeks prior to Baseline or intended to receive a live vaccine during the study or within 8 weeks following the final dose of rozanolixizumab
- Severe (defined as Grade 3 on the MG-ADL scale) weakness affecting oropharyngeal or respiratory muscles, or experiencing myasthenic crisis or impending crisis
- Patients with a lifetime history of suicide attempt or who experienced suicidal ideation since the last visit in MG0003

Comparators: None. All participants received weekly infusions of rozanolixizumab at either ≈7 mg/kg or ≈10 mg/kg + standard of care (open-label study with no control treatment)

Start/completion: October 2019 to September 2021 (MG0004 was discontinued[1] and replaced with MG0007; 60 participants from MG0004 enrolled in MG0007)

Study publication: No publication is currently available for this study

National Clinical Trials link: https://clinicaltrials.gov/study/NCT04124965

[1] The trial was discontinued in response to feedback from clinicians and patients on the requirement for patients to visit the study centre weekly for a year (52 weeks) for treatment administration. Chronic weekly dosing of rozanolixizumab is not expected in clinical practice.

<u>Phase III extension trial:</u> MG0007 (Number of participants = 165)

Locations: Canada, Czechia, Denmark, France, Georgia, Germany, Italy, Japan, Poland, Russia, Serbia, Spain, Taiwan, and the US

Population: Patients aged ≥18 years with gMG and auto-antibodies against AChR or MuSK

Key inclusion criteria:

- Patients who entered or completed the observation period of MG0003 or required rescue therapy during the observation period of MG0003 or completed at least six scheduled visits in MG0004 for rozanolixizumab treatment

Key exclusion criteria:

- Evidence of active or latent TB infection, high risk of acquiring TB infection, or current/history of nontuberculous mycobacterial infection
- Patient met any mandatory withdrawal or study discontinuation criteria in MG0003 or MG0004, or permanently discontinued rozanolixizumab in either study
- Patient intends to receive a live vaccination during the course of the study or within 8 weeks following the final dose of rozanolixizumab
- Patient with severe (defined as Grade 3 on the MG-ADL scale) weakness affecting oropharyngeal or respiratory muscles, or who has a myasthenic crisis or impending crisis

Comparators: None. All participants received 6-week cycles of rozanolixizumab at a weekly dose of ≈7 mg/kg or ≈10 mg/kg + standard of care (open-label with no control treatment)

Start/completion: February 2021 to January 2024

Study publication: Interim study results have been presented at medical conferences (44-47)

National Clinical Trials link: https://clinicaltrials.gov/study/NCT04650854

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Rozanolixizumab, in addition to standard treatments for gMG, provides significant improvements in the signs and symptoms of gMG disease activity and quality of life, with a fast onset of action, and consistent efficacy across key physician and patient-reported outcomes.

<u>MycarinG (pivotal Phase III study)</u>

Rozanolixizumab reduces disease activity and symptom burden in patients with gMG

Section B.2.6.1.1 of the company submission

In the MycarinG study, the primary efficacy endpoint (change in MG-ADL score, which measures the symptoms of MG related to activities of daily living, from the start of the study) was met. Patients who received rozanolixizumab, at either ≈7 mg/kg or ≈10 mg/kg, + standard therapy had a greater change from Baseline to Day 43 in MG-ADL score compared with patients treated with standard treatment + placebo (≈7 mg/kg: −3.370; ≈10 mg/kg: −3.403; placebo: −0.784, where a reduction in score means an improvement in symptoms). In both rozanolixizumab dosage groups, the significant difference in change in MG-ADL score vs placebo was also considered clinically meaningful (least squares [LS] mean difference −2.62 and −2.59 in the ≈7 mg/kg and ≈10 mg/kg groups, respectively; $p<0.001$ for both analyses).

Rozanolixizumab also improved QMG, Myasthenia Gravis Composite (MG-C), and MG symptoms patient-reported outcome (MGSPRO) scores. Patients who received rozanolixizumab at either

dosage + standard therapy reported a statistically significant reduction (improvement) in LS mean score from Baseline to Day 43 in QMG ($p<0.001$) and MG-C ($p<0.001$) total scores and MGSPRO for "Physical Fatigue" ($p=0.012$), "Muscle Weakness Fatigability" ($p<0.001$) and "Bulbar Muscle Weakness" (weakness in the muscle of the neck and jaw that can cause difficulties in chewing, swallowing and speaking; $p<0.001$) compared with patients who received placebo + standard therapy.

MG0007 (open-label extension study)

Section B.2.6.2 of the company submission

In MG0007, repeated cyclic treatment with rozanolixizumab (at both ≈7 mg/kg and ≈10 mg/kg dosages) in addition to standard treatment leads to consistent improvements with each cycle in symptoms of disease activity, based on multiple physician and patient-reported outcomes including MG-ADL, QMG, MG-C and MGSPRO.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the clinical trial program, rozanolixizumab + standard treatment provided improvements to quality of life compared with placebo + standard treatment.

Patient quality of life was assessed in the MycarinG trial using:

- the MG-specific self-administered patient-reported outcome survey Myasthenia Gravis quality of life survey (MGQoL15r)
- the EuroQoL-5D-5L survey (a standardised and widely used survey for measuring health status, assessing five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

Patients who received rozanolixizumab, at either dosage, + standard therapy reported greater improvements from Baseline in both quality-of-life scores compared with patients who received placebo + standard treatment. Furthermore, MycarinG demonstrated a greater reduction from baseline in MG-ADL score in patients who received rozanolixizumab + standard treatment vs placebo + standard treatment (primary efficacy endpoint), indicating that rozanolixizumab reduces the burden that MG symptoms have on patient daily lives.

In the extension study (MG0007), repeated cycles of rozanolixizumab treatment provided improvement in quality of life based on the scores from MGQoL15R and EQ-5D-5L surveys.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The most frequent side effects experienced by patients treated with rozanolixizumab were general disorders and gastrointestinal disorders. Headache, diarrhoea, and fever were classified as

very common (may affect more than 1 in 10 people). Reported common side effects (may affect up to 1 in 10 people) were joint pain, rapid swelling under the skin in face, throat, arms and legs, skin rash, and injection skin reaction (including redness, inflammation and pain).

During the double-blind MycarinG study, rozanolixizumab was generally well tolerated and had an acceptable safety profile in patients with gMG. The number of patients reporting adverse events was higher with the study drug vs placebo. Most side effects following treatment were categorised as mild or moderate in severity. Rozanolixizumab continued to be well tolerated in the Phase III extension study (MG0007), with no new safety signals observed.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There are no treatments recommended by NICE that specifically target the abnormal immunological processes in gMG to control disease activity and symptoms in patients with active disease despite maximal immunosuppressive therapy. Treatments such as IVIg and PLEX are available for these patients, although both are associated with treatment burden and are costly to the healthcare system (26, 29, 48). Additionally, patients with gMG and antibodies against MuSK are less responsive to AChEIs and tend to remain dependent on high-dose corticosteroids despite receiving NSISTs at the same time (49). For those patients with MuSK antibodies who are refractory to these treatments, remaining therapeutic options are limited to rituximab, which can take up to 12 months to have an effect on patient symptoms, and PLEX, as IVIg is usually less effective (49). Rituximab is not licensed in the UK, but is available based on a commissioning policy from NHS England (50). Thus, there is a clear need for a treatment with a more targeted mechanism of action (see Section 3k) to control symptoms and reduce the burden of gMG on patients and their families.

The clinical benefits of rozanolixizumab as add-on to standard therapy, demonstrated in the MycarinG study and the open-label extension (MG0007), help address these unmet needs for patients with gMG who continue to experience disease activity despite maximal immunosuppressive treatment. These patients experience chronic, ongoing symptoms that interfere with daily living and reduce their quality of life (29, 51-53). In addition, patients with ongoing symptoms have a high treatment burden related to cycling through different therapies with little or no relief from their symptoms. Patients whose symptoms are not controlled live with the risk of myasthenic exacerbation and crisis (14, 32, 34, 35). Rozanolixizumab has been shown to have a fast onset of action and is the first MG treatment to be licensed as a targeted treatment in adult patients with gMG and auto-antibodies against AChR or MuSK (54).

The primary outcome in the MycarinG study (change in MG symptoms [measured by MG-ADL score]) and other key outcomes assessed in this trial and the extension study (MG0007) are expected to translate into clinical benefits to patients in real-world practice, including:

- Improvements in signs and symptoms of gMG, and how they interfere with activities of daily living
- Reduced disease severity
- Improvements in quality of life
- Consistent efficacy and tolerability with repeated cycles of treatment.

As a short (up to 18 minutes), once-weekly subcutaneous infusion, rozanolixizumab is anticipated to avoid the need for frequent IV administration, thus minimising the treatment burden to patients. Rozanolixizumab does not require hospital admission (unlike IVIg and PLEX) or the use of

highly specialist equipment or complex training (unlike PLEX), facilitating access for all patients eligible for treatment. Patients will initially need to attend an outpatient clinic to receive rozanolixizumab to ensure the infusion is tolerated well. Home administration by a healthcare professional will be considered based on clinician evaluation.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The most frequent adverse events experienced by patients are described in Section 3g.

The following warning and precautions have been identified:

- Clinicians may not prescribe rozanolixizumab if a patient is currently having or is likely to have a myasthenic crisis;
- Aseptic meningitis, an inflammation of the membranes that surround the brain and spinal cord, has been observed in association with the ≈10 mg/kg dose of rozanolixizumab, a dose which is not expected to be used in clinical practice. Patients developing severe headaches, fever, neck stiffness, nausea, vomiting and/or intolerance to bright lights should seek immediate medical attention;
- As rozanolixizumab causes a temporary reduction in IgG levels, the risk of infections may increase. Treatment with rozanolixizumab should not be initiated in patients with a clinically important active infection until the infection is adequately treated. During treatment, signs and symptoms of infection (e.g. fever, cough, sore throat) should be monitored. If a clinically important active infection occurs, withholding rozanolixizumab until the infection has resolved should be considered;
- The rozanolixizumab solution contains a protein that can cause allergic reactions (such as rash, swelling and itching) in some people. Patients should be monitored for 15 minutes after treatment administration;
- See Section 3b for precautions related to vaccination

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

- What is the structure of the model? Explain how the model reflects the experience of having the condition over time.

The MycarinG clinical trial used MG-ADL score, which assesses patients' speech, swallowing, breathing and ability to perform tasks such as brushing hair or teeth and standing up from a chair. The MG-ADL scores collected in the MycarinG clinical study were used to reflect the experience of patients with refractory gMG in the health economic model.

The model estimated the impact of rozanolixizumab compared with two new targeted treatments, efgartigimod and zilucoplan (both subject to NICE evaluation), as well as current standard therapies for refractory patients (IVIg and PLEX) on patients' clinical outcomes and quality of life. This evaluation used a measure called the quality-adjusted life year (QALY), which combines both changes in life expectancy and in patient quality of life. The use of NHS resources was also included in the model.

- Describe briefly which trial outcomes feed into the economic model. If trial data used for a certain length of time followed by extrapolation, please note how long the trial data was used for and briefly how the data has been extrapolated.

The clinical effectiveness of rozanolixizumab was modelled using MG-ADL data reported from the MycarinG study.

Primary clinical inputs used in the health economic model (Chapter in Company Submission)
Improvement in MG-ADL score compared with baseline (the start of the trial) (B.3.3)
The percentage of patients who responded to treatment (B3.3)
Annual rate of experiencing an exacerbation or crisis (B.3.3)

Modelling how much a treatment improves quality of life

- How is the treatment modelled to change a person's quality of life compared with the treatments already in use? This should include after stopping treatment if relevant. For example, say if the treatment improves quality of life because of improving symptoms or decreases quality of life because of side effects.

The impact of the treatment on symptoms and quality of life of patients with gMG in the MycarinG study, compared with standard treatments, is the primary measure of treatment impact in the health economic model. Treatment is assumed to stop if symptoms start to deteriorate, and all patients are assumed to be 'uncontrolled' when they stop treatment. Rozanolixizumab was found to improve patient quality of life more than efgartigimod, IVIg, PLEX and zilucoplan.

- Which quality of life measure(s) did you use to estimate a person's quality of life over time and on treatments? Are there any aspects of the condition or its treatments affecting quality of life which may not have been fully captured by the methods used to estimate quality of life?

A quality-of-life questionnaire called the EuroQoL-5D (EQ-5D) was used to measure the effect of treatment on patient quality of life.

As gMG is a relapsing and remitting rare disease, collecting robust quality-of-life data can be challenging. Furthermore, EQ-5D is a general measure of health-related quality-of-life (rather than being specific to gMG), and so may not fully capture all relevant aspects of gMG that impact quality of life, such as fatigue, vision impairment, and hand weakness. A QALY calculation based on EQ-5D data may not capture all the health-related benefits of rozanolixizumab treatment specific to patients and carers. The impact of a short infusion time and of the possibility of home administration on patient burden/patient preference and carer quality of life is also unlikely to be captured in the QALY calculation.

Modelling how the costs of treatment differ with the new treatment

- Does the medicine lead to any cost implications (positive or negative) for the health service (e.g., drug costs, number of days in hospital)?

Based on the company's economic analysis, rozanolixizumab as a treatment for patients with gMG is considered to offer good value for money, representing a cost-effective use of NHS resources.

Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g., where it is given or the monitoring that is needed)?

Rozanolixizumab is a subcutaneous infusion with a short infusion duration (up to 18 minutes) that has the potential for home administration. This may minimise the treatment burden and effect on patients' lives compared with other treatments administered intravenously (efgartigimod, IVIg and PLEX), which can only be given in hospital and often require a hospital stay. This will also be beneficial to the health service in terms of cost and clinician/nurse time and will free up space on infusion suites.

Uncertainty

- Are there any key assumptions you have made in your model about the medicine's benefits or costs because of lack of data?

As gMG is a rare disease, there is a lack of clinical data available, particularly long-term efficacy data. Therefore, assumptions are applied in the health economic model, including:

- Uncontrolled patients do not experience disease worsening over time (as defined by an increase in MG-ADL score)
- The likelihood of an exacerbation worsening and becoming a crisis is not related to the specific treatment a patient is receiving
- Unless in crisis, gMG patients have the same overall risk of death as the general population
- Patients who do not respond, or lose their initial response, do not continue to receive treatment
- Adverse events are not included because there were no side effects during the clinical trial that were judged to be serious that were experienced by 5% of patients or more.

- Did you test using alternative assumptions or data in your model? Which had the largest effect on your cost effectiveness estimates?

The parameter with the largest effect on the results of the comparison with efgartigimod was the annual rate of exacerbations in patients who had responded to treatment. The parameter affecting the comparisons vs IVIg and zilucoplan the most was average patient weight, and the parameter affecting the comparison vs PLEX the most was the percentage of patients showing a stable response with PLEX. Three scenarios were tested: using the average patient weight of the refractory gMG cohort from MycarinG rather than the whole cohort; a 6-week response assessment time point for all treatments; and a higher response rate for IVIg and PLEX based on clinical opinion. These scenarios did not change the cost-effectiveness conclusions.

- What is the modelled benefit in overall survival, quality adjusted life years and the incremental cost effectiveness ratio?

Based on the model, rozanolixizumab provides more QALYs (a measure of improved patient health) compared with efgartigimod, IVIg, PLEX and zilucoplan.

- Are there any benefits or disadvantages of the treatment not captured in the modelling?

The impact of a subcutaneous infusion with short administration time, that has the potential to be administered at home, on patient and carer quality of life is unlikely to be captured (e.g. impact on employment for patient and caregivers, cost of travel to hospital for treatment). The

model also does not include the burden on caregivers or the impact of gMG on a patient's or caregiver's ability to work.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Rozanolixizumab is the first MG treatment to be licensed in adult patients with gMG and auto-antibodies against MuSK or AChR (54). Unlike current standard treatments, which are based on non-specific suppression of the immune system instead of targeting the root cause of MG (26, 27), rozanolixizumab reduces the levels of IgG antibodies in circulation, including the auto-antibodies produced in patients with gMG that impair communication between nerves and muscles. Rozanolixizumab has also demonstrated a fast onset of action (as early as 8 days after administration in some patients), in contrast to existing chronic non-targeted treatments for gMG, which can take up to 6–18 months to show an effect (54, 55).

It is estimated that rozanolixizumab will reduce the devastating impact of uncontrolled disease on patients and the healthcare system, improving outcomes (including quality of life) for patients with high unmet needs. Rozanolixizumab has been shown to reduce symptom burden for patients with gMG and antibodies against AChR or MuSK who have active disease despite standard therapy.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

There is geographic variability in treatment availability and access to specialist centres, which introduces potential inequality among patients with MG in access to care. The introduction of a new, targeted, fast-acting therapy that can be administered in multiple outpatient settings and does not require highly specialised equipment or specific training would help mitigate this inequality, and enable patients to live a much more flexible daily life.

Myasthenia gravis is more common in females (60% of patients) than males (40% of patients) (56), and females are younger than males at disease onset (mean age of disease onset is 35 ±18 years in females vs 45 ±18 years in males [p<0.001]) (57). Women are therefore exposed to the economic, social, and quality-of-life impact earlier in life and for longer than men and over more of their working lives, amounting to a greater total burden.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's project information and documents, Rozanolixizumab for treating antibody-positive generalised myasthenia gravis [ID5092]: https://www.nice.org.uk/guidance/indevelopment/gid-ta10994
- EUPATI guidance on patient involvement in HTA: https://toolbox.eupati.eu/resources/patient-toolbox/guidance-for-patient-involvement-in-hta/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative: https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: https://eurohealthobservatory.who.int/publications/i/health-technology-assessment-an-introduction-to-objectives-role-of-evidence-and-structure-in-europe-study NHS page for myasthenia gravis: https://www.nhs.uk/conditions/myasthenia-gravis/
- Myaware, a UK charity solely dedicated to the support, care and advocacy of people affected by myasthenias: https://www.myaware.org/
- Muscular Dystrophy UK, the leading charity for over 60 muscle wasting and weakening conditions, including myasthenia gravis: https://www.musculardystrophyuk.org/conditions/myasthenia-gravis
- UCB's clinical studies index for rozanolixizumab: https://www.ucb.com/clinical-studies/Clinical-studies-index/Rozanolixizumab-UCB7665

4b) Glossary of terms

Adverse event/side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe.

B

Crisis: See myasthenic crisis.

Clinical trial: A type of research study that tests new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study (58).

D

Exacerbation: See myasthenic exacerbation.

EMA (European Medicines Agency): The regulatory body that evaluates, approves, and supervises medicines throughout the European Union.

F

G

HRQoL (health-related quality of life): An individual's perception of the impact of health status on their quality of life (59).

HTA (Health Technology Assessment) organisations: Organisations that make recommendations on the reimbursement of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones.

I

J

K

L

Myasthenic crisis: A life-threatening deterioration of muscle weakness and respiratory failure requiring treatment in an intensive care unit with mechanical ventilation and hospitalisation.

Myasthenic exacerbation: A sudden worsening of symptoms that requires urgent intervention to prevent a myasthenic crisis.

N

O

P

QALY (quality-adjusted life-year): A way of measuring how well medical treatments lengthen and/or improve patients' lives (60).

Quality of life: The overall enjoyment of life. Many clinical trials assess it to measure aspects of an individual's sense of wellbeing and ability to carry out activities of daily living (58).

Refractory: When gMG has not responded to other systemic treatments and an additional therapy such as IVIg or PLEX is being considered.

Subcutaneous: Under the skin.

Symptom: A physical or mental problem that a person experiences that may indicate a disease or condition. Some examples of symptoms are fatigue, nausea, and pain.

T

U

V

W

X

Y

Z

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

April 2024

File name	Version	Contains confidential information	Date
	1.0	**Yes**	**19th April 2024**

Section A: Clarification on effectiveness data

Company trials

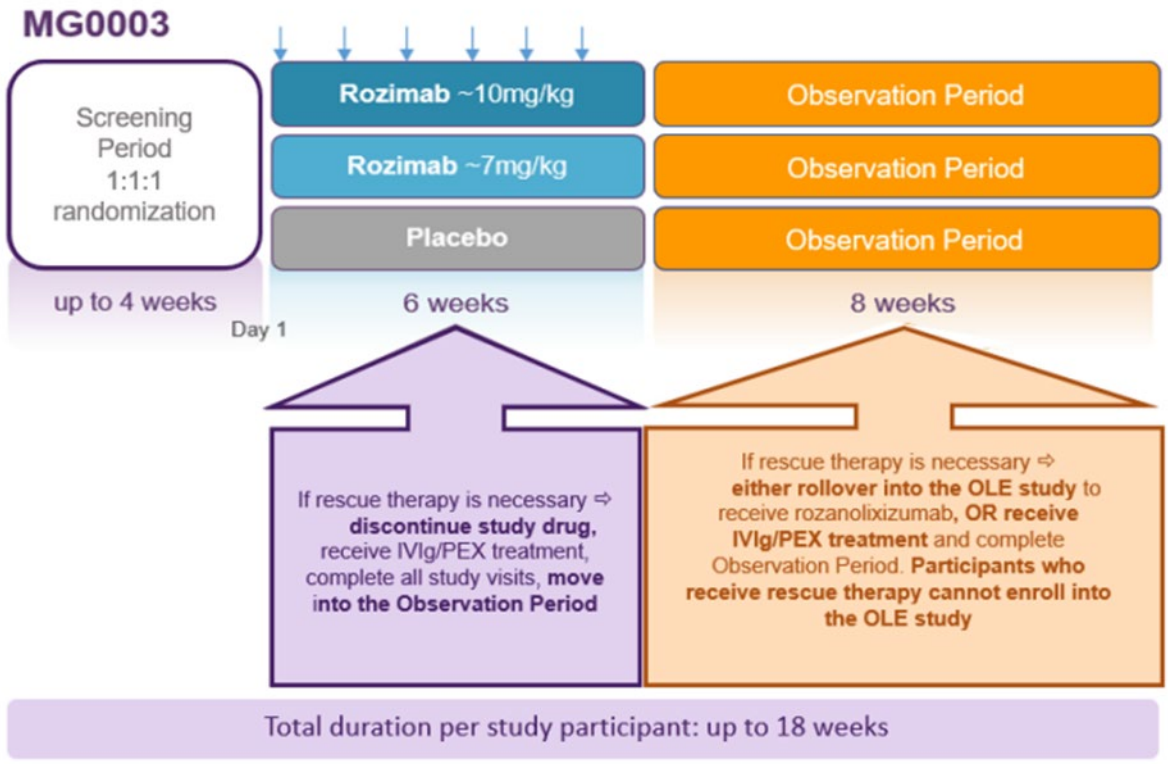
A1. Company submission section B.2.3.1 and company submission Figure 7 state that patients requiring rescue therapy during the observation period of MG0003 were rolled into the OLE studies. However, the trial publication, Bril et al. 2023, states that patients rolled over into the OLE trials if their disease severity worsened in the observation period and that patients requiring rescue therapy during the observation period discontinued the trial and were not eligible for the OLE studies. Please clarify which document is correct.

The information reported in the company submission is correct. As per the MycarinG (MG0003) protocol (1), study participants who completed the Treatment Period of the trial and required initiation of rescue therapy after they started the 8-week Observation Period, could either opt to receive intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) or complete the End of Study visit and immediately roll over into an open-label extension (OLE) study where they received rozanolixizumab. Study participants who opted to receive IVIg/PLEX completed any remaining visits in the Observation Period and were not invited to join an OLE study (1). Please see Figure 1 for a schematic representation of the MG0003 study design.

The Methods section in Bril et al. 2023 (2) states that patients who received IVIg/PLEX were not eligible to join an OLE, in accordance to the MG0003 protocol detailed above, but it does not make clear that patients requiring IVIg/PLEX had the choice between rolling over to an OLE or receiving rescue therapy:
'The treatment period was 6 weeks' duration, followed by 8 weeks of observation. Patients who had disease worsening could be considered for rescue therapy (intravenous immunoglobulin or plasma exchange) at the investigator's discretion. Patients who received rescue therapy during the treatment period completed their remaining weekly visits in the treatment period (without receiving further study drug) before moving to the observation period. Patients who completed the observation period or whose disease severity worsened (investigator judgment) during the observation period could roll over from this trial to one of two open-label extension (OLE) trials (the MG0004 trial [completed; NCT04124965; EudraCT 2019-000969-

21] or the MG0007 trial [ongoing; NCT04650854; EudraCT 2020-003230-20]). Patients who received rescue therapy meaning IVIg or PLEX during the observation period discontinued the trial and were not eligible for the OLE trials.'

Figure 1: MycarinG (MG0003) study design



Abbreviations: ≈, equivalent dose; IVIg, intravenous immunoglobulin; OLE, open-label extension; PEX, plasma exchange; rozimab, rozanolixizumab.

A2. Company submission Figure 7 states "Permitted background therapy: Patients were permitted to receive concomitant conventional treatment for gMG (standard of care), such as CS and NSIST, as well as IVIg and PLEX in the event of myasthenic crisis". Please clarify which treatments refer to conventional therapy and which treatments refer to rescue therapy.

Conventional treatment for generalised myasthenia gravis (gMG) (standard of care, SoC) included permitted concomitant medications, i.e. cholinesterase inhibitors (stable dose before Baseline not required), oral corticosteroids (stable dose for 4 weeks before Baseline), azathioprine, ciclosporin, methotrexate, mycophenolate mofetil, and tacrolimus (all administered for 6 months before study initiation and on stable dose for 2 months prior to Baseline).

Rescue medication referred to IVIg and PLEX. Study participants who experienced disease worsening (i.e. a 2-point increase in Myasthenia Gravis Activities of Daily Living [MG-ADL] score or a 3-point increase on the Quantitative Myasthenia Gravis [QMG] scale between two consecutive visits) were considered for rescue therapy at the discretion of the Investigator.

A3. Please provide precise quantitative data to support the statement in company submission section B.2.6.2.1 that "Most participants in both treatment groups did not switch rozanolixizumab doses."

Dose switches from ≈10 mg/kg to ≈7 mg/kg equivalent and vice versa were permitted at the beginning of each treatment cycle in MG0007 at the Investigator's discretion, and if the benefit-risk remained favourable for the study participant.

A total of [redacted] study participants received rozanolixizumab in MG0007. Of these, [redacted] did not switch their dose of rozanolixizumab during study participation.

A total of [redacted] study participants received rozanolixizumab ≈7 mg/kg in Cycle 1. Of these, [redacted] had only one treatment cycle and [redacted] continued to receive rozanolixizumab ≈7 mg/kg in subsequent cycles. [redacted] study participants switched to rozanolixizumab ≈10mg/kg in subsequent cycles.

A total of [redacted] study participants received rozanolixizumab ≈10 mg/kg in Cycle 1. Of these, [redacted] had only one treatment cycle and [redacted] continued to receive rozanolixizumab ≈10 mg/kg in subsequent cycles. [redacted] study participants switched to rozanolixizumab ≈7mg/kg in subsequent cycles.

a) **How many participants switched doses in each treatment group in MycarinG?**

   While the first part of Question A3 refers to section B2.6.2.1, which reports on the OLE MG0007, the specific questions a–c are about MycarinG (MG0003). UCB have thus based the following responses on MG0003. Based on the clinical trial protocol (Section 6.6), dose changes were not permitted in MG0003 (1).

b) **Does the statement in company submission section B.2.6.2.1 include the two participants, referenced in company submission Table 16, who were**

randomised to ~7 mg/kg but who were administered ~10 mg/kg at their baseline visit?

Section B.2.6.2.1 refers to the OLE MG0007 and not to MG0003, thus the two patients referenced in Table 16 of Document B are not included in this statement.

Patients who rolled over to the OLE were re-randomised and could change dose, as the MG0007 protocol permitted dose switches at the start of a new cycle according to the Investigator's discretion (3).

c) Did the participants who received the erroneous dose at baseline (question A3b above) revert to the ~7 mg/kg dose for all subsequent study visits?

In MG0003, two patients who were randomised to receive the ≈7 mg/kg dose erroneously received the ≈10 mg/kg dose at the Baseline Visit. The two patients remained on the ≈10 mg/kg dose for the duration of the treatment cycle and were analysed as part of the rozanolixizumab ≈10 mg/kg group in the safety set (SS) and as part of the ≈7 mg/kg group in the randomised set (RS) and the full-analysis set (FAS) (Table 16, Document B) (1).

A4. Please explain the rationale for focusing on three of the five MGS-PRO scales for reporting as secondary outcomes; why are the results for ocular weakness and respiratory weakness ('other' outcomes in MycarinG) not reported?

The secondary efficacy endpoints in the MycarinG study were:

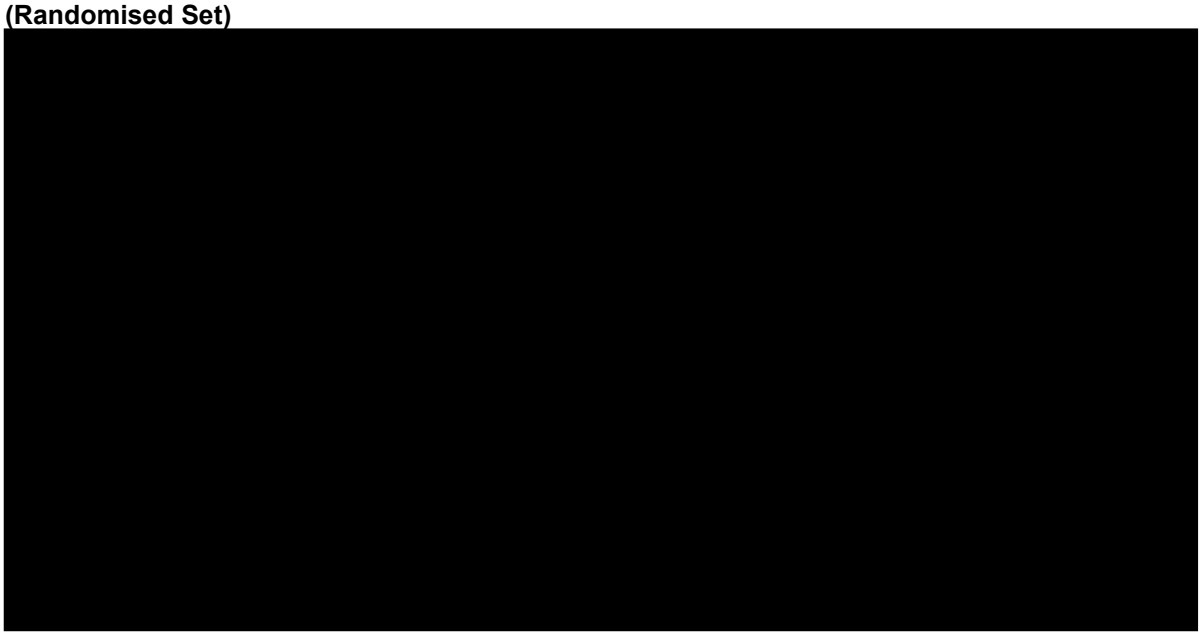
- MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10)
- Change from Baseline (CFB) to Day 43 (Visit 10) in the Myasthenia Gravis Composite (MG-C) score
- CFB to Day 43 (Visit 10) in QMG score
- CFB to Day 43 (Visit 10) in the Myasthenia Gravis Symptoms Patient-reported Outcomes (MGSPRO) 'Muscle Weakness Fatigability' score
- CFB to Day 43 (Visit 10) in the MGSPRO 'Physical Fatigue' score
- CFB to Day 43 (Visit 10) in the MGSPRO 'Bulbar Symptoms' score

The CFB to Day 43 (Visit 10) in the MGSPRO ‘Muscle Weakness Fatigability’, ‘Physical Fatigue’ and ‘Bulbar Muscle Weakness’ scores were included as secondary endpoints in the hierarchical testing procedure (1) because they are reflective of the symptoms that are more common and relevant to the target population of the MG0003 study.

Conversely, CFB in the MGSPRO ‘Respiratory Muscle Weakness’ and ‘Ocular Muscle Weakness’ scores, reported at each scheduled assessment during Treatment and Observation Periods, were included as ‘Other’ efficacy endpoints in the hierarchical testing procedure (1).

For completeness, observed results for CFB in MGSPRO “Respiratory Muscle Weakness” and “Ocular Muscle Weakness” are shown in Figure 2 and Figure 3, respectively. The change from baseline in MGSPRO “Respiratory Muscle Weakness” and “Ocular Muscle Weakness” scores by visit showed [redacted] in both rozanolixizumab groups compared with placebo. [redacted] in the MGSPRO “Respiratory Muscle Weakness” and “Ocular Muscle Weakness” were observed starting from Day [redacted] and Day [redacted], respectively.

Figure 2: Mean CFB in MGSPRO “Respiratory Muscle Weakness” score by treatment (Randomised Set)



Abbreviations: ≈, equivalent dose; CFB, change from Baseline; MGSPRO, Myasthenia Gravis Symptoms Patient-reported Outcome.

Figure 3: Mean CFB in MGSPRO "Ocular Muscle Weakness" score by treatment (Randomised Set)

Abbreviations: ≈, equivalent dose; CFB, change from Baseline; MGSPRO, Myasthenia Gravis Symptoms Patient-reported Outcome.

A5. The company submission only reports a summary of the EQ-5D VAS results. As the EQ-5D data informs the model, please provide full EQ-5D VAS and index scale results for the whole population and refractory population in MycarinG and MG0007.

The EQ-5D crosswalk utility data and visual analogue scale (VAS) scores for the whole MycarinG population are reported in Table 1 and Table 2, respectively.

Table 1: EQ-5D UK crosswalk utility data – MycarinG (MG0003) Randomised Set

	N	Mean (SD)	Median (min, max)
Randomised set (N=200)			
Baseline	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change for baseline; EQ-5D, EuroQoL 5-dimensions questionnaire; SD, standard deviation.

Table 2: EQ-5D VAS scores by treatment group – MycarinG (MG0003) Randomised Set

	N	Mean (SD)	Median (min, max)
Placebo (N=67)			
Baseline	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]

	N	Mean (SD)	Median (min, max)
Rozanolixizumab ≈7 mg/kg (N=66)			
Baseline	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]
Rozanolixizumab ≈10 mg/kg (N=67)			
Baseline	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]
Rozanolixizumab total (N=133)			
Baseline	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change for baseline; EQ-5D, EuroQoL 5-dimensions questionnaire; SD, standard deviation; VAS, visual analogue scale.

The EQ-5D crosswalk utility data and VAS scores for the MycarinG refractory subgroup (≥2 prior MG specific therapies) are reported in Table 3 and Table 4, respectively.

Table 3: EQ-5D UK crosswalk utility data – MycarinG (MG0003) patients with ≥2 prior MG specific therapies

	N	Mean (SD)	Median (min, max)
≥2 MG specific therapies (N=[redacted])			
Baseline	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change for baseline; EQ-5D, EuroQoL 5-dimensions questionnaire; MG, myasthenia gravis: SD, standard deviation.

Table 4: EQ-5D VAS scores by treatment group – MycarinG (MG0003) patients with ≥2 prior MG specific therapies

	N	Mean (SD)	Median (min, max)
Placebo (N=[redacted])			
Baseline	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]
Rozanolixizumab ≈7 mg/kg (N=[redacted])			
Baseline	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]

	N	Mean (SD)	Median (min, max)
Rozanolixizumab ≈10 mg/kg (N=[redacted])			
Baseline	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]
Rozanolixizumab total (N=[redacted])			
Baseline	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change for baseline; EQ-5D, EuroQoL 5-dimensions questionnaire; MG, myasthenia gravis; SD, standard deviation; VAS, visual analogue scale.

As MG0007 was completed in January 2024, the data are still being processed and will not be available until completion of the CSR, which is expected in July 2024. Currently only the EQ-5D VAS scores for the whole population are available. The EQ-5D VAS scores by treatment group for Cycles [redacted] are reported in Table 5.

Table 5: EQ-5D VAS scores by treatment group –MG0007 Safety Set

	Rozanolixizumab ≈7 mg/kg			Rozanolixizumab ≈10 mg/kg			Rozanolixizumab total		
	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)
Cycle [redacted]									
N	[redacted]			[redacted]			[redacted]		
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle [redacted]									
N	[redacted]			[redacted]			[redacted]		
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle [redacted]									
N	[redacted]			[redacted]			[redacted]		
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle [redacted]									
N	[redacted]			[redacted]			[redacted]		
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CFB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change for baseline; EQ-5D, EuroQoL 5-dimensions questionnaire; SD, standard deviation; VAS, visual analogue scale.

A6. Company submission Appendices F.1.3 and M.1 to M.4 report data for MycarinG and MG0007 (and for MG0004 for safety results) described as a "pooled" analysis. However, these studies include the same patients followed through the cycles of their treatment pathway. They are not parallel sets of participants. Please explain the rationale for reporting the "pooled" analysis.

To assess long-term efficacy and safety of repeated cyclic treatment with rozanolixizumab, data were pooled across the Phase 3 studies (i.e. MycarinG, MG0007 and MG0004).

The purpose of the pooled analyses was to assess

- the response after each treatment cycle, where the need for each treatment cycle is based on worsening of gMG symptoms (referred to as a symptom-driven treatment cycle), and
- the time to symptom worsening (i.e. the need for a new treatment cycle) or treatment-free interval
- the first cycle of patients who received placebo in MG0003 and went on to receive rozanolixizumab in MG0004 or MG0007 combined with the first cycle of patients who received rozanolixizumab in MG0003 (and so on with second cycle onwards).

To assess the long-term efficacy of repeated cyclic treatment, efficacy data were pooled from the completed MycarinG and MG0004 studies, and from all completed visits in MG0007 as of the 08 Jul 2022 cut-off date. MG0002 was not pooled with the Phase 3 studies due to its different study design (i.e. duration of placebo-controlled period of 4 vs 14 weeks), different dose regimen (i.e. 3 vs 6 subcutaneous [SC] infusions in the double-blind period) and dosing (i.e. weight-based dosing vs weight tier-based dosing). Additionally, as MG0002 is a short-term trial without an extension study, it cannot be used to assess the impact of repeated cycles of treatment.

A7. Company submission section B.2.7.4.3 reports subgroup results for each outcome per cycle as [redacted] for AChR+ patients. Please provide the sample size for each cycle, for both the AChR+ and MuSK+ patient groups.

The sample sizes for each cycle for both acetylcholine receptor antibody-positive (AChR Ab+) and muscle-specific kinase antibody-positive (MuSK Ab+) patient subgroups for the outcome CFB in MG-ADL score are reported in the tables below.

Table 6: AChR Ab+ patients sample size in each cycle

Cycles	Rozanolixizumab ≈7 mg/kg, N	Rozanolixizumab ≈10 mg/kg, N	Rozanolixizumab total, N
Cycle [redacted]	[redacted]	[redacted]	[redacted]
Cycle [redacted]	[redacted]	[redacted]	[redacted]
Cycle [redacted]	[redacted]	[redacted]	[redacted]
Cycle [redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Ab+, antibody-positive; AChR, acetylcholine receptor.
Source: Tables, Listing and Figures MG0007 CSR 08 Jul 2022 data cut-off.

Table 7: MuSK Ab+ patients sample size in each cycle

Cycles	Rozanolixizumab ≈7 mg/kg, N	Rozanolixizumab ≈10 mg/kg, N	Rozanolixizumab total, N
Cycle [redacted]	[redacted]	[redacted]	[redacted]
Cycle [redacted]	[redacted]	[redacted]	[redacted]
Cycle [redacted]	[redacted]	[redacted]	[redacted]
Cycle [redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Ab+, antibody-positive; MuSK, muscle-specific kinase.
Source: Tables, Listing and Figures MG0007 CSR 08 Jul 2022 data cut-off.

A8. Mock infusions, company submission section B.2.10.1.1.

a) What are mock infusions? Would they be administered for a whole cycle or for a single dose?

Mock infusions contained only placebo irrespective of investigational medicinal product (IMP) designation. Mock infusions were administered for as long as IgG levels remained below the protocol-defined threshold, as described below in the response to part **b.**

b) How do they reduce the risk of unblinding when IgG dropped below 1 g/L? Did the investigators remain unblinded, or only the patients?

If immunoglobulin G (IgG) levels either dropped below 1 g/L or were 1–2 g/L and the study participant was experiencing a non-serious infection which was persisting or recurrent, rozanolixizumab treatment may be temporarily discontinued. Temporary treatment discontinuation due to low IgG levels may informally unblind the treatment assignment to the participant and site personnel. Therefore, infusions were continued but given as mock infusions (only placebo irrespective of IMP designation). Allocation of mock kit numbers were handled via the interactive responsive technology (IRT). An unblinded Medical Monitor informed the Investigator of the initiation of mock infusions and brought attention to any potential infection risk. The Medical Monitor continued to review available safety data for these study participants, while IgG levels were at the protocol-defined low threshold values, and directly contacted the Investigator if the review identified additional information that may be important in participant care. When the IgG levels had returned to the protocol-defined levels to re-initiate IMP, the unblinded Medical Monitor informed the Investigator. Based on the clinical situation, the Investigator had the option of holding the dose until deemed appropriate.

c) Please explain whether the mock infusions are relevant to how rozanolixizumab would be used in clinical practice.

Mock infusions were included as part of MycarinG protocol if study participants IgGs levels dropped below the values, as indicated in the answer above, with the aim of monitoring patients closely for any potential infection risk and in the context of a clinical trial.

The use of mock infusions is not expected in clinical practice, however administration of rozanolixizumab may be temporarily discontinued in the presence of clinically important infection, as described in the warning and precaution section of Rystiggo’s Prescribing Information:

Treatment with rozanolixizumab should not be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated. During treatment with rozanolixizumab, clinical signs and symptoms of infections

should be monitored. If a clinically important active infection occurs, withholding rozanolixizumab until the infection has resolved should be considered.

NMAs

A9. PRIORITY QUESTION. Please provide the statistical code and input data for the NMAs.

The OpenBUGS code for the 2-point change network meta-analysis (NMA) has been provided with this response.

A10. PRIORITY QUESTION. Exclusion of trials from NMAs according to their study phase is not appropriate since the phase II / III designation of a trial may have no bearing on the trial's reliability. A phase II trial could, depending on its characteristics such as sample size, potentially be as informative as a phase III trial and might increase statistical power if included in the analysis. Please conduct an NMA scenario analysis that includes both phase II and phase III trials where feasible.

The Phase II studies were excluded from the NMA as they are either unlikely to be powered for efficacy outcomes or have a different disease score as primary endpoint (or both) (4, 5). All Phase II trials identified in the systematic literature review (SLR) enrolled a small number of patients with MG, with ≤27 patients included in each treatment arm (4-9). Thus, the small number of patients enrolled limits the utility of these analyses. UCB acknowledges that uncertainty remains in the NMA when including only Phase III studies and does not wish to violate the plausibility of the assumption of transitivity by including Phase II studies of products where a high-quality Phase III study is available. Thus, including Phase II studies will not further mitigate any existing uncertainty.

In addition, during the submission to NICE for zilucoplan, a scenario was conducted in the NMA to compare zilucoplan with IVIg using Phase II trials. The results actually showed a worsening of disease (as measured by MG-ADL score) with IVIg, which led to the use of placebo data from the NMA as a proxy for CFB for stable response with IVIg. Indeed, the Phase II trial itself (which enrolled 15 patients) showed numerically better results with placebo than with IVIg (5). Therefore, it was concluded that the inclusion of Phase II trials would undermine the NMA results.

A11. PRIORITY QUESTION. The company's Decision Problem focuses on refractory patients. The whole trial population (i.e. randomised set) in MycarinG includes some non-relevant patients, i.e. non-refractory patients, and also those with MuSK antibodies who would be expected to differ in prognosis and treatment response. Please conduct an NMA comparison of rozanolixizumab against zilucoplan as follows:

a) **Restrict the analysis to all refractory patients (AChR+ and MuSK+) in MycarinG to match the Decision Problem.**

b) **Restrict the analysis to refractory patients who are AChR+ (i.e. [redacted] patients) in MycarinG to better match to the zilucoplan refractory population that only consisted of AChR+ patients.**

The NMA could not be conducted in the subgroup of patients with refractory gMG since there are no or insufficient data on refractory patients for the comparators in order to inform the network. In addition, introducing heterogeneity in the sample sizes will serve to increase uncertainty rather than achieve the objective of reducing it. Data are available for MG-ADL 2-point responder rate for refractory patients for efgartigimod, but not for change from baseline in MG-ADL score, and there are no data on refractory patients available for IVIg or PLEX. In addition, the timelines of the zilucoplan appraisal have been updated and are now only 2 months apart from those of rozanolixizumab, and, therefore, UCB do not anticipate zilucoplan being in established clinical practice by the time of the rozanolixizumab decision making and therefore do not view it as a relevant comparator.UCB would also like to clarify that even though the total refractory subgroup in MycarinG included [redacted] patients, only [redacted] patients are relevant in this appraisal, as the other [redacted] patients received rozanolixizumab at the ≈10 mg/kg dose, which is not licensed in the UK.

A12. Baseline characteristics of the trials included in the NMAs are reported in company submission Appendix D Tables 13 to 24. However, no discussion of these data is provided. Please clarify what the treatment effect modifiers are for refractory generalised MG and whether these are homogenous across the trials included in the NMAs. If the treatment effect modifiers are not

homogenous, please explain how this affects interpretation of the NMA results.

Overall, patient demographic and baseline characteristics were comparable between the MycarinG overall population (Tables 10 and 11, Section B.2.3.1.2) and the refractory population, defined as patients who received ≥2 prior MG specific therapies (Tables 29 and 30, Appendix E.1.3). The only observed differences were a higher proportion in the refractory subgroup of patients who identified as Asian ([redacted] vs 10.5%) and had undergone thymectomy ([redacted] vs 41.5%) vs the whole study population. Based on CFB in MG-ADL score (primary endpoint), prior thymectomy did not impact treatment outcomes in the MycarinG study (Table 8). Data on treatment outcomes were not available for the Asian subgroup.

Table 8: CFB in MG-ADL score in patients who had undergone thymectomy at Baseline

Subgroup	Placebo N=67	Rozanolixizumab ≈7 mg/kg N=66	Rozanolixizumab ≈10 mg/kg N=67
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; MG-ADL, Myasthenia Gravis Activities of Daily Living; SD, standard deviation.

Across the trials included in the NMAs, heterogeneity was identified in the disease-specific scores and the duration of disease. Patient (MG-ADL) and clinician (QMG) reported disease scores were homogenous across MycarinG, ADAPT and REGAIN (1, 10, 11), while patients enrolled in RAISE and CHAMPION MG had scores associated with slightly more severe disease (12, 13). Conversely, patients enrolled in RINOMAX not only had scores associated with milder disease, they also had a very short disease duration (a few months) compared with patients enrolled in all other included studies (average of ~8–9 years) (1, 10-14). Finally, demographic and baseline characteristics in refractory and non-refractory study participants enrolled in RAISE were comparable (12).

While some heterogeneity is present in the patient baseline characteristics, due to lack of data, it is not possible to quantitatively establish effect modifiers for refractory gMG. Furthermore, with the exception of RAISE (zilucoplan), no data on refractory patients are available from the comparator trials.

A13. PRIORITY QUESTION. Please investigate the feasibility of using a matched-adjusted indirect comparison (MAIC) or other suitable statistical approach to account for heterogeneity of treatment effect modifiers and other trial characteristics between the trials included in the indirect comparisons. Such an analysis could help to clarify whether the NMA results are sensitive to clinical heterogeneity and potentially reduce this uncertainty.

a) **If possible, please include both phase II and phase III trials to increase the sample size for the analysis.**

b) **If possible, please apply the analysis to the subgroups referred to in question A10 above, i.e. limited to refractory (AChR+ and MuSK+) and also to refractory AChR+ only.**

c) **For all matching analyses conducted please provide an indication of the matching achieved (i.e. model fit and the distribution of weights).**

Matched adjusted indirect comparisons were conducted for rozanolixizumab vs efgartigimod and IVIg. It was not possible to apply the analysis to refractory patients or refractory AChR-Ab+ patients only, since there are no or insufficient data on the refractory cohort for the comparators to inform the analysis. There are data for MG-ADL 2-point responder rate for refractory patients for efgartigimod but no description of the baseline characteristics of this subgroup to match to, nor data on the change from baseline in MG-ADL score. Furthermore, there are no data available on refractory patients for IVIg or PLEX. Finally, as mentioned in question A11, since the zilucoplan timelines have been updated and are now only 2 months apart from the rozanolixizumab timelines, UCB do not anticipate zilucoplan being in established clinical practice by the time of the rozanolixizumab decision making and therefore do not view it as a relevant comparator.

For the MAIC vs efgartigimod, matching was performed between MycarinG (2) and ADAPT (10). A comparison of patient demographic and baseline characteristics is provided in Table 9.

Table 9: Comparison of patient demographic and baseline characteristics – rozanolixizumab vs efgartigimod

Characteristics	ADAPT (10) (N=129)	MycarinG† (2) (N=164)	SMD	CI	p-value	Matched for analysis
Age, years, mean (SD)	46.9 (15.4)	51.8 (16.7)	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	86 (67%)	94 (60%)	[redacted]	[redacted]	[redacted]	[redacted]
Race – White, n (%)	110 (85%)	109 (70%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior thymectomy, n (%)	75 (58%)	71 (40%)	[redacted]	[redacted]	[redacted]	[redacted]
Time since gMG diagnosis, year, mean (SD)	9.3 (8.2)	8.4 (8.9)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline QMG score, mean (SD)	15.6 (4.8)	15.6 (3.6)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline MG-ADL score, mean (SD)	8.8 (2.3)	8.2 (3.3)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline MGC score, mean (SD)	18.35 (5.7)	16 (6.4)	[redacted]	[redacted]	[redacted]	[redacted]
Any steroid at baseline	97 (75%)	102 (62%)	[redacted]	[redacted]	[redacted]	[redacted]
Any NSIST at baseline	77 (60%)	84 (50%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; gMG, generalised myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-C, Myasthenia Gravis Composite; MGQoL-15r, Myasthenia Gravis Quality of Life 15-item; NSIST, non-steroidal immunosuppressive treatment; SD, standard deviation; SMD, standardised mean difference.
† MycarinG sample only includes patients who are MuSK negative after sub-setting.

A comparison of the baseline characteristics before and after matching is presented in Table 10, and the distribution of rescaled weights was between [redacted], as shown in Figure 4.

Table 10: Comparison of baseline characteristics before and after matching – rozanolixizumab vs efgartigimod

Parameter	ADAPT	MycarinG – Before matching	MycarinG – After matching
QMG score at baseline	15.60	15.64	[redacted]
MG-ADL score at baseline	8.80	8.22	[redacted]
MG duration, years	9.30	8.43	[redacted]
NSISTs at baseline, %	60%	51%	[redacted]
CS at baseline, %	75%	62%	[redacted]
Prior thymectomy, %	58%	43%	[redacted]

Parameter	ADAPT	MycarinG – Before matching	MycarinG – After matching
MG-C score at baseline	18.35	15.99	[redacted]
Age, years	46.93	51.78	[redacted]
Sex (Female), %	67%	57%	[redacted]
Race (White), %	85%	66%	[redacted]

Abbreviations: CS, corticosteroids; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-C, Myasthenia Gravis Composite; NSIST, non-steroidal immunosuppressive treatment; QMG, Quantitative Myasthenia Gravis.

Figure 4: Distribution of rescaled weights – rozanolixizumab vs efgartigimod

[redacted]

Results for the comparison between rozanolixizumab 7 mg/kg and efgartigimod at 4 weeks are shown in Table 11.

Table 11: Results through anchored MAIC at 4 weeks – rozanolixizumab vs efgartigimod

Comparison	Rozanolixizumab ≈7 mg/kg vs efgartigimod	Lower 95% CI	Upper 95% CI
CFB in MG-ADL (treatment difference)	[redacted]	[redacted]	[redacted]
Rate of responders with ≥2-point improvement (odds ratio)	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change from baseline; CI, confidence interval; MAIC, matched adjusted indirect comparison; MG-ADL, Myasthenia Gravis Activities of Daily Living.

A scenario was also conducted comparing rozanolixizumab at 6 weeks' timepoint and efgartigimod at 4 weeks' timepoint. Results are shown in Table 12.

Table 12: Results through anchored MAIC at 4/6 weeks – rozanolixizumab vs efgartigimod

Comparison	Rozanolixizumab ≈7 mg/kg vs efgartigimod	Lower 95% CI	Upper 95% CI
CFB in MG-ADL (treatment difference)	[redacted]	[redacted]	[redacted]
Rate of responders with ≥2-point improvement (odds ratio)	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change from baseline; CI, confidence interval; MAIC, matched adjusted indirect comparison; MG-ADL, Myasthenia Gravis Activities of Daily Living.

For the MAIC vs IVIg, matching was performed between MycarinG (2) and Barth 2011 (15). A comparison of patient demographic and baseline characteristics is provided in Table 12.

Table 13: Comparison of patient demographic and baseline characteristics – rozanolixizumab vs IVIg

Characteristics	Barth 2011 (15) – IVIg (N=41)	MycarinG (2) – RLZ ≈7 mg/kg (N=66)	SMD	CI	p-value	Matched for analysis
Age, years, mean (SD)	57 (18)	53.2 (14.7)	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	24 (58%)	39 (59%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment with IVIg, n (%)	9 (21%)	12 (18%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment with PLEX, n (%)	4 (10%)	0 (0%)	[redacted]	[redacted]	[redacted]	[redacted]
CS treatment at baseline, n (%)	14 (34%)	42 (64%)	[redacted]	[redacted]	[redacted]	[redacted]
Azathioprine at baseline, n (%)	6 (14%)	17 (26%)	[redacted]	[redacted]	[redacted]	[redacted]
Mycophenolate mofetil at baseline, n (%)	2 (5%)	8 (12%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior thymectomy, n (%)	13 (31%)	32 (48%)	[redacted]	[redacted]	[redacted]	[redacted]
Time since gMG diagnosis, years, mean (SD)	5.92 (7.5)	6.9 (6.8)	[redacted]	[redacted]	[redacted]	[redacted]
AChR-Ab+, n (%)	28 (68%)	56 (85%)	[redacted]	[redacted]	[redacted]	[redacted]
MuSK-Ab+, n (%)	2 (5%)	4 (6%)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline QMG score, mean (SD)	14.26 (4)	15.4 (3.7)	[redacted]	[redacted]	[redacted]	[redacted]

MGFA class ≤3, n (%)	39 (94%)	37 (57%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; Ab, antibody; AChR, acetylcholine receptor; CI, confidence interval; CS, corticosteroid; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressive treatment; QMG, Quantitative Myasthenia Gravis; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; PLEX, plasma exchange; RLZ, rozanolixizumab; SD, standard deviation; SMD, standardised mean difference.

A comparison of the baseline characteristics before and after matching is presented in Table 13 and the distribution of rescaled weights, between [redacted] is shown in Figure 5.

Table 14: Comparison of baseline characteristics before and after matching – rozanolixizumab vs IVIg

Parameters	**IVIg (Barth 2011)**	**Rozanolixizumab ≈7 mg/kg (MycarinG) – Before matching**	**Rozanolixizumab ≈7 mg/kg (MycarinG) – After matching**
QMG score at baseline	14.26	15.44	[redacted]
MG duration, years	5.92	6.88	[redacted]
Prior thymectomy, %	32%	48%	[redacted]
CS at Baseline, %	34%	64%	[redacted]
AChR-Ab+, %	68%	85%	[redacted]
Prior IVIg, %	22%	18%	[redacted]
Azathioprine at Baseline, %	15%	26%	[redacted]
Mycophenolate at Baseline, %	5%	12%	[redacted]
MUSK-Ab+, %	5%	6%	[redacted]
Age, years	57.00	53.20	[redacted]
Sex (Female), %	59%	59%	[redacted]

Abbreviations: ≈, equivalent dose; Ab, antibody; AChR, acetylcholine receptor; CS, corticosteroids; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MuSK, muscle-specific kinase; QMG, Quantitative Myasthenia Gravis.

Figure 5: Distribution of rescaled weights – rozanolixizumab vs IVIg

Abbreviation: IVIg, intravenous immunoglobulin.

Results for the comparison between rozanolixizumab ≈7 mg/kg and efgartigimod at 4 weeks are shown in Table 14.

Table 15: Results through unanchored MAIC – rozanolixizumab vs IVIg

Comparison	Rozanolixizumab ≈7 mg/kg vs IVIg	Lower 95% CI	Upper 95% CI
CFB in QMG at 4 weeks (treatment difference)	[redacted]	[redacted]	[redacted]
Rate of responders at 2 weeks (odds ratio)	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; CFB, change from baseline; CI, confidence interval; IVIg, intravenous immunoglobulin; MAIC, matched adjusted indirect comparison; QMG, Quantitative Myasthenia Gravis.

A14. PRIORITY QUESTION. Please comment on the risks of bias of the trials included in the NMAs. If appropriate, please conduct scenario analyses to investigate the impact of risk of bias on the NMA results.

An analysis of the risks of bias of the trials included in the NMA is provided in Section 4.3 of the clinical SLR report (10798_SLR in MG_Clinical update_29FEB2024.docx) provided in the reference pack accompanying the submission.

Following the NICE checklist, clinical trials were assessed for the following items: randomisation approach, baseline characteristics comparability across cohorts,

blinding, imbalance in study withdrawals, outcomes selection and reporting, and statistical analyses. As summarised in Table 7 of the SLR report, all trials included in the NMA were associated with a low risk of biases across all items. The only exception was RINOMAX, the phase 3 trial for rituximab (14), where the risks of randomisation and allocation concealment and imbalance in the withdrawals were not clear. Since it was not possible to establish the risk of bias in this study, the data are not available to conduct a scenario analysis to investigate the impact of the biases in randomisation and allocation concealment and imbalance in the withdrawals on the NMA results.

A15. Please explain how the NMA results should be interpreted given that the placebo response varied between the included trials. If possible, please use a baseline risk model or other approach to investigate and account for the differences in placebo responses.

We acknowledge that there was heterogeneity in the placebo response observed across the trials included in the NMA, which may impact the results of the meta-analysis.

It is possible that the placebo effect was more pronounced for the zilucoplan and ravulizumab trials because of their chronic dosing, which led to more frequent administrations during the trials vs cyclical dosing with rozanolixizumab and efgartigimod. In addition, differences in SoC treatments across the trials could have contributed to the variation in the placebo responses observed.

Despite these differences in the placebo response, all new targeted therapies evaluated in the NMA are significantly more efficacious than SoC (corticosteroids and/or non-steroidal immunosuppressive therapies [NSISTs]) and/or placebo. These results are supported by the independent published NMA of innovative treatments in MG by Sacca et al, 2023, which showed that all targeted treatments were associated with a significantly greater improvement in MG-ADL and QMG vs placebo (SoC) (16).

Due to the limited number of studies and datapoints, the Bayesian NMA methodology was preferred as the most robust approach over alternative methodologies such as a baseline risk model or meta-regression.

A16. Company submission section B.2.9.2 states some outcome data were obtained by digitising study figures. Please clarify which data this refers to.

The following data points were digitised to calculate the change from baseline in MG-ADL score:

- ADAPT study, Week 10, placebo and efgartigimod
- CHAMPION MG study, Week 12, placebo and ravulizumab
- MycarinG study, Week 10, placebo and rozanolixizumab ≈7 mg/kg and ≈10 mg/kg
- REGAIN, Week 12, placebo and eculizumab.

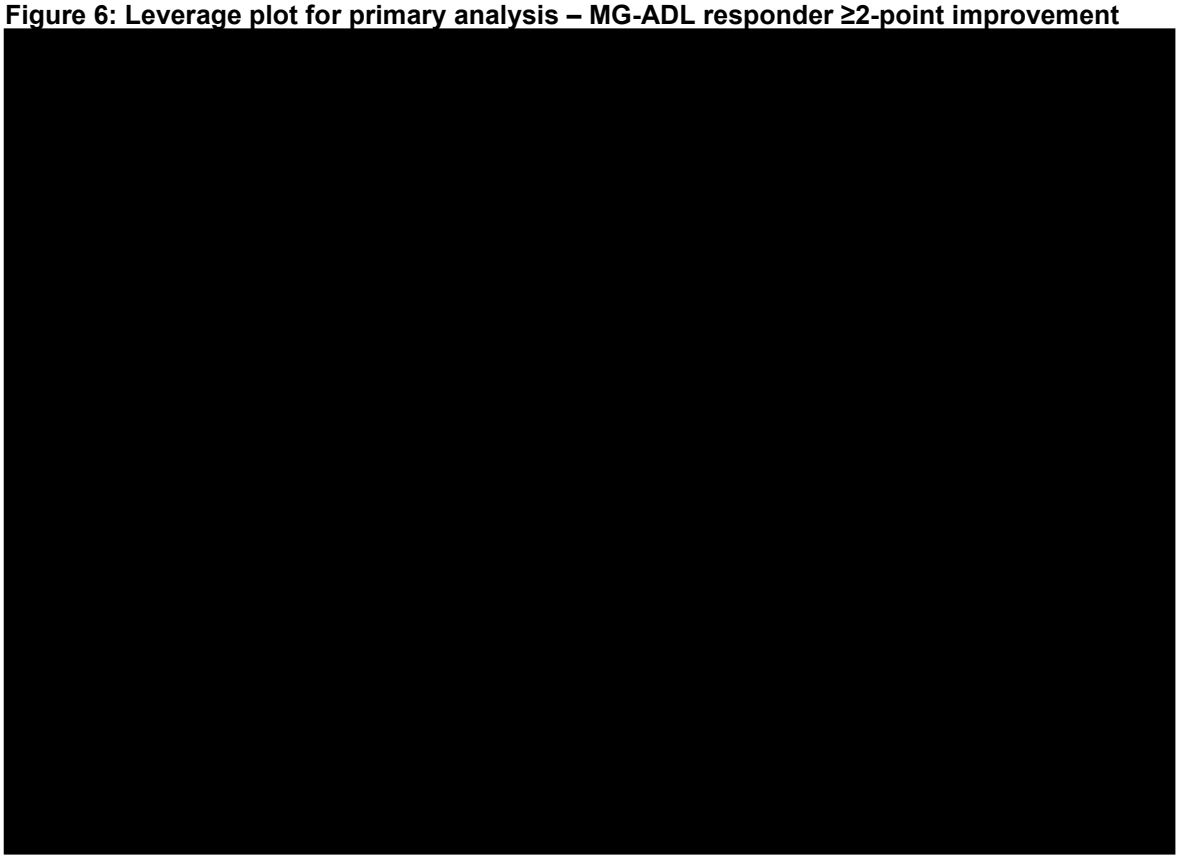
The information can also be found in the submitted NMA report (Table 7: Change from baseline in MG-ADL score) (17).

A17. Please present model fit for all the analyses referred to above in terms of DIC.

The leverage plots for the primary analysis (Figure 6) and the two scenario analyses (Figure 7Figure 8) presented in the NMA are show below.

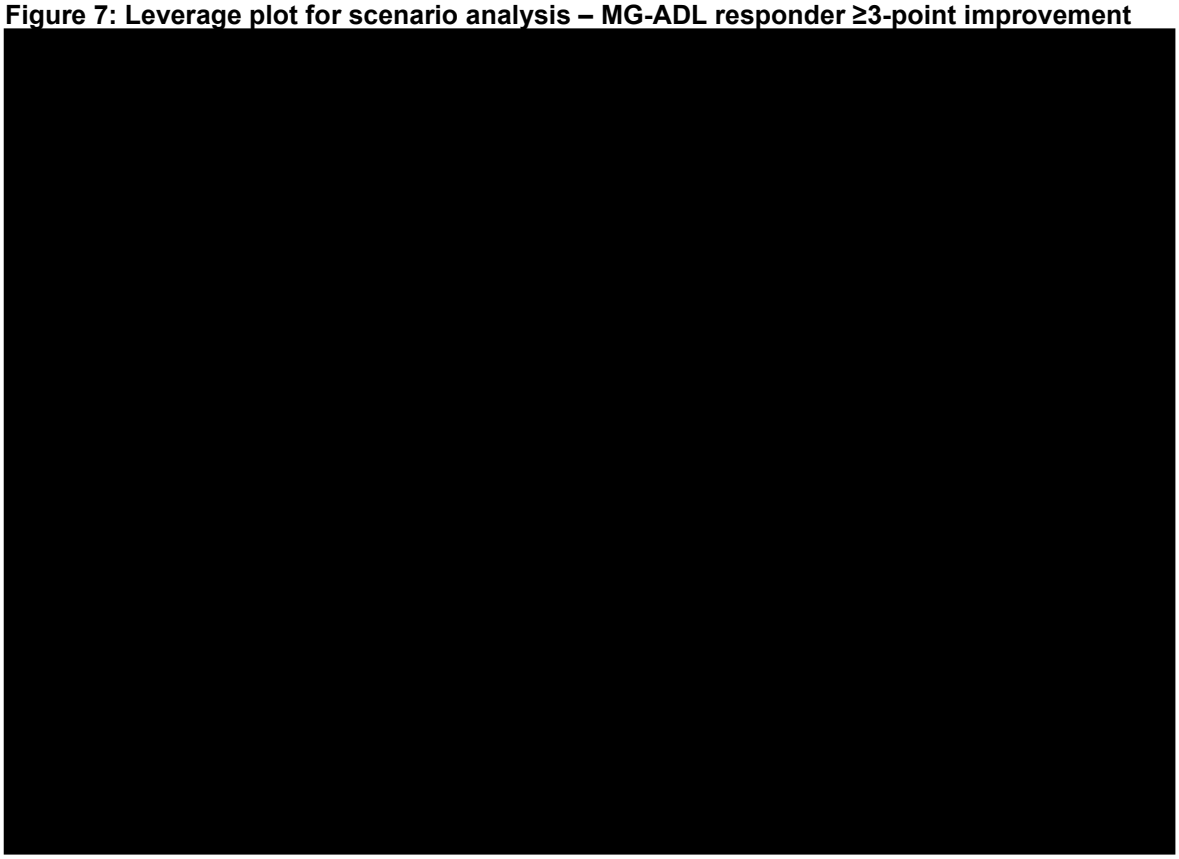
The deviance information criterion (DIC) was [redacted] in the primary analysis, [redacted] in the ≥3-point improvement scenario analysis and [redacted] in the CFB in MG-ADL score scenario analysis.

Figure 6: Leverage plot for primary analysis – MG-ADL responder ≥2-point improvement



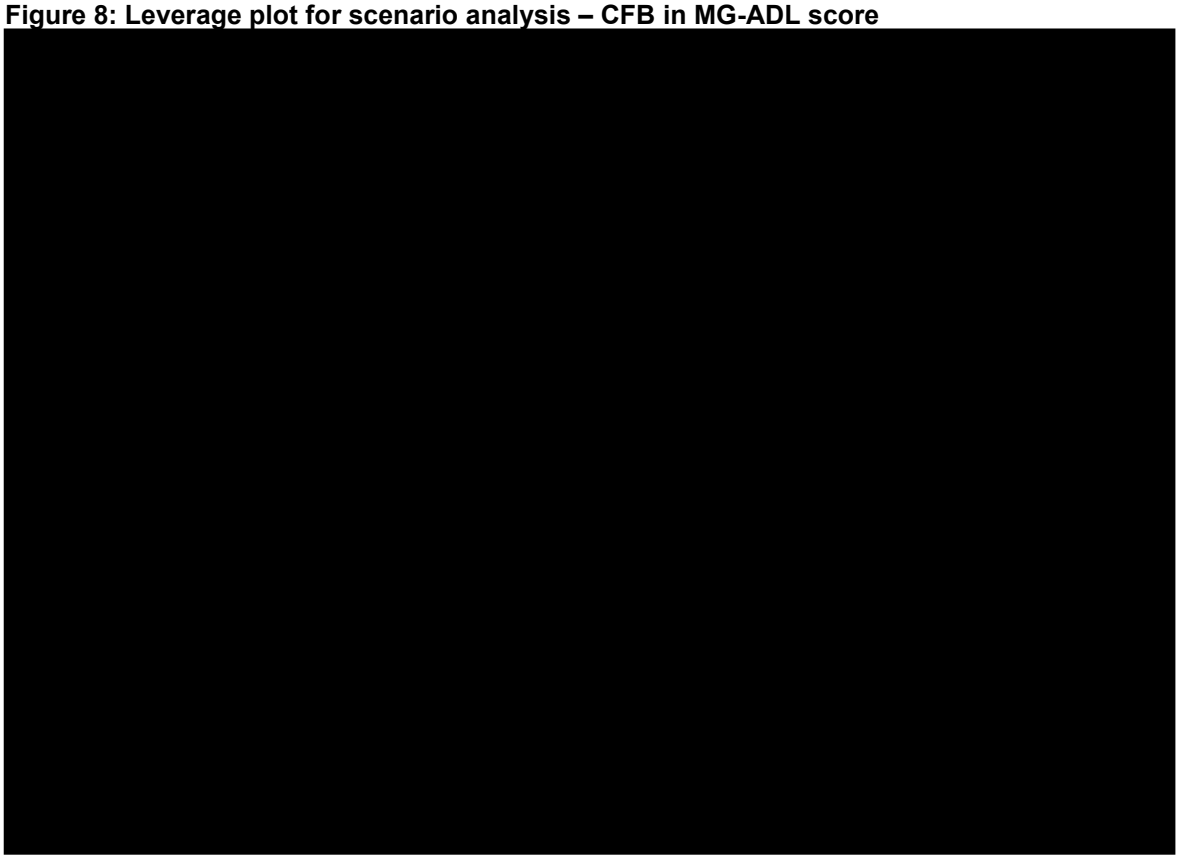
Abbreviations: DIC, deviance information criterion; Dres, overall residual deviance; MG-ADL, Myasthenia Gravis Activity of Daily Living; pD, leverage.

Figure 7: Leverage plot for scenario analysis – MG-ADL responder ≥3-point improvement



Abbreviations: DIC, deviance information criterion; Dres, overall residual deviance; MG-ADL, Myasthenia Gravis Activity of Daily Living; pD, leverage.

Figure 8: Leverage plot for scenario analysis – CFB in MG-ADL score



Abbreviations: CFB, change from baseline; DIC, deviance information criterion; Dres, overall residual deviance; MG-ADL, Myasthenia Gravis Activity of Daily Living; pD, leverage.

Section B: Clarification on cost-effectiveness data

B1. The NICE scope specifies that subgroup analyses may be considered for AChR+ and MuSK+ patients. The company's model includes patients with refractory antibody positive generalised MG, the parameters of which are informed by those of the overall trial population in MycarinG. Given that MuSK+ patients have poorer prognosis than AChR+ patients, please provide analyses for the refractory patients in both the AChR+ and MuSK+ subgroups separately.

As previously discussed, an analysis using the refractory population is not possible, since there are no or insufficient data on refractory patients for the comparators in order to inform the network. There are data for MG-ADL 2-point responder rate for refractory patients for efgartigimod, but not for change from baseline in MG-ADL score, and there are no data on refractory patients available for IVIg or PLEX. In addition, the timelines for the appraisal for zilucoplan have been updated and are now only 2 months apart from those of rozanolixizumab. Therefore, UCB do not believe that zilucoplan will be a relevant comparator in time for the rozanolixizumab decision, since it will not have time to become part of established clinical practice. An analysis in MuSK-Ab+ patients is not possible since there are no data for this subgroup for any of the comparators.

However, the clinical results for rozanolixizumab in the refractory population are similar to the overall population, and therefore it can be assumed that the cost-effectiveness results will also be similar. In addition, since the vast majority (91.7%) of refractory patients are AChR-Ab+, it also follows that the results in these patients will be similar. While it was not possible to compare rozanolixizumab with efgartigimod in the refractory population, the MAIC compares the AChR-Ab+ populations for each treatment, since there are no MuSK-Ab+ in the ADAPT trial and MuSK Ab+ patients were excluded from the rozanolixizumab dataset.

Results from cost-effectiveness analyses using the results from the MAICs (Table 15) show that the incremental cost-effectiveness ratios (ICERs) versus efgartigimod [redacted] and the ICER vs IVIg [redacted].

Table 16: Cost-effectiveness results from MAICs

	Total costs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Rozanolixizumab	[redacted]			
Efgartigimod at 4 weeks for both treatments	[redacted]	[redacted]	0.0929	[redacted]
Efgartigimod at 4 weeks/ roxanolixizumab at 6 weeks	[redacted]	[redacted]	0.0595	[redacted]
IVIg	[redacted]	[redacted]	0.1073	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MAIC, matched adjusted indirect comparison; QALY, quality-adjusted life year.

B2. PRIORITY QUESTION The NICE scope specifies that standard of care (SoC) with or without intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) is a relevant comparator. Therefore, please provide a version of the economic model that includes SoC as a comparator. Please add the facility to include proportions of patients who receive IVIg/SCIg and PLEX within this SoC comparator arm.

UCB considers pairwise comparison against IVIg and PLEX as the most appropriate comparison against rozanolixizumab. In line with MycarinG inclusion criteria, rozanolixizumab is anticipated to be used for refractory patients who are being treated or considered for IVIg/PLEX therapy. Secondly, rozanolixizumab positioning is such that it will be considered as an option for patients with active disease despite SoC (excluding IVIg and PLEX). According to the commissioning criteria policy for the use of immunoglobulins, IVIg and PLEX may be considered for patients who have failed standard treatments, including steroids and immunosuppression. The use of IVIg and PLEX in this population segment is also supported by UK clinical expert opinion. Additionally, three clinical experts consulted by the EAG as part of the zilucoplan NICE appraisal advised that both IVIg and PLEX are used as chronic therapies for refractory patients and that practically all patients who are eligible for treatment with chronic IVIg or PLEX would receive it. Therefore, given rozanolixizumab is intended to mainly displace IVIg and PLEX in clinical practice, UCB considers these treatments as the most relevant SoC comparators in this appraisal.

B3. The company submission reports in several sections that the company received clinical advice from experts and the company provided reports of

expert engagement. The information concerning a UCB advisory board included in the submission was for the zilucoplan advisory board. Consequently, the number of experts who provided information for rozanolixizumab, their geographic locations, type of institution (e.g. general or specialist care centre), and any potential conflicts is unclear. Please provide this information for all instances in the company submission where expert opinion is reported.

The details of the experts and confidentiality states are available and have been provided together with this response.

B4. PRIORITY QUESTION. The company's revised economic model (submitted with the erratum) uses a referent response rate of [redacted], obtained from the SoC arm. Please provide clarification on how this estimate was calculated.

The referent response rate in the revised economic model (submitted with the erratum) was obtained by running a baseline random effects model using all the placebo response rates reported in data network. This includes the placebo response rates reported in four studies (ADAPT, CHAMPION-MG, MycarinG and RAISE). The associated WINBUGS code for is reported here below.

MGADL Responder (Placebo_absolute)

```
# Binomial likelihood, logit link
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){          # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])          # Likelihood
   logit(p[i]) <- mu[i]                  # Log-odds of response
   mu[i] ~ dnorm(m,tau.m)     # Random effects model
  }
mu.new ~ dnorm(m,tau.m)       # predictive dist. (log-odds)
m ~ dnorm(0,.0001)            # vague prior for mean
var.m <- 1/tau.m              # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)             # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m                 # posterior probability of response
logit(R.new) <- mu.new        # predictive probability of response
}
```

###
#########
####################### **<u>MG-ADL response PA</u>**
##########################

Data

list(ns=4) # ns=number of studies

n[]	r[]	# Study
64	31	# ADAPT
89	47	# CHAMPION MG
64	20	# MycarinG trial
88	59	# RAISE trial

END

B5. PRIORITY QUESTION In the original company submission, the model used an odds ratio of 1.87 and 2.38 for IVIg and PLEX respectively. However, in the revised company submission (submitted with the erratum), the values used are 1.04 for IVIg and 1.33 for PLEX respectively. Please clarify why the odds ratios of these two treatments arms have changed in the revised model, given that these were estimated from a published study by Barth et al. and not from the company's revised NMA.

The change in the odd ratios (ORs) reported in the erratum is due to the new referent response rate, which changed from 35% in the original submission to 50% in the erratum. The ORs were back calculated using the new referent rate of 50% using the goal-seek functionality in Excel. Please note that the response rates for both IVIg and PLEX, which are used in the calculations downstream, remain unchanged.

B6. PRIORITY QUESTION. Company submission Section B.3.3.5 reports that the model includes a 2-week event rate of 0.184 applied to all patients in the exacerbation health state who may worsen to myasthenic crisis. In the following equation reported in the company submission, what is the source of the estimate 0.1954?

$$2 - week\ event\ rate = 1 - e^{\frac{-\ln(1-0.1954)}{(15/14)}}$$

The Gajdos et al. 2005 study outlines a trial conducted in patients with gMG who experienced acute exacerbations (18). There was a cumulative incidence of patients who required mechanical ventilation (assumed proxy for myasthenic crisis) of 19.54 after 15 days. Therefore, this value was taken as the probability of a patient in exacerbation worsening to a myasthenic crisis within 15 days. As this was reported within a 15-day period (18), a minor adjustment was made in the calculations to ensure the probability aligned with the 14-day cycles in the model, therefore 0.184 is the correct value to be used in the model.

B7. PRIORITY QUESTION. The economic model gives the zilucoplan response rate, derived from data from trial publications, as 40%. Howard et al. (2023) (RAISE RCT) report that 73% of patients in the zilucoplan arm responded by week 12 i.e. ≥3 point reduction in MG-ADL score by week 12. Please explain this discrepancy and which is the correct response rate?

UCB acknowledge that the response rate provided in the model for zilucoplan was incorrect. The correct value is 73.1% as reported in Howard et al (12). There was also an error in the response rate for rozanolixizumab, which should be 68.2% (see Table 26, Document B). However, the incorrect values provided in the submitted model does not impact the results as this setting (data from trial publications) was not used either in the base case analysis or in any of the scenario analyses presented in the submission; data from the NMA were used instead.

B8. PRIORITY QUESTION. In the company submission erratum Figure 13 (scatter plot of PSA results), please explain the bimodal distribution of the results for rozanolixizumab vs zilucoplan, why is this distribution different to the shape of the scatterplots for the other three treatments?

The bimodal distribution of the results for rozanolixizumab vs zilucoplan is due to the patient mean weight input in the model. Patient weight is included in the probabilistic sensitivity analysis (PSA), and values are sampled from the log-normal distribution based on the mean weight, i.e. 81.15 kg (SE=8.28). For some of the iterations, the probabilistic average weight is less than 77 kg, which results in a shift in the loading dose of zilucoplan from 32.4 mg to 23 mg. Because of this shift, the drug cost of zilucoplan changes significantly, leading to the observed bimodal distribution.

We have performed a scenario analysis to include and exclude patient weight in the PSA and presented the results below. The bimodal distribution is observed when patient weight is included in the PSA (Figure 9) and not when it is excluded (Figure 10).

Figure 9: PSA – Patient weight included

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 10: PSA – Patient weight excluded

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Section C: Textual clarification and additional points

C1. Please explain why in company submission Table 9 (p 55) the rozanolixizumab total column has a higher N-value than the sum of the two rozanolixizumab cohorts.

The N for the two rozanolixizumab cohorts were wrongly reported in column headings of Table 9. The rozanolixizumab ≈7 mg/kg and ≈10 mg/kg cohorts included [redacted] and [redacted] patients, respectively, leading to a total of [redacted] patients. A corrected version of Table 9 is reported below.

Table 17 (Table 9 in Document B):Disposition and discontinuation reasons (safety set)

Category, n (%)	Rozanolixizumab ≈7 mg/kg N=[redacted]	Rozanolixizumab ≈10 mg/kg N=[redacted]	Rozanolixizumab total N=[redacted]
Started study	[redacted]	[redacted]	[redacted]
Completed study	[redacted]	[redacted]	[redacted]
Permanently discontinued study†	[redacted]	[redacted]	[redacted]
Primary reason for discontinuation			
AE	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Met withdrawal criteria due to being treated with prohibited treatment, plasmapheresis	[redacted]	[redacted]	[redacted]
Participant received rescue medication	[redacted]	[redacted]	[redacted]
Participant wanted to start a family	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; AE, adverse event; COVID-19, Coronavirus Disease 2019.
† All patients discontinued study during COVID-19.

C2. In company submission Table 17 the numbers in the three analysis sets are higher than the N-values in the column headings. Please explain this.

The N for the two rozanolixizumab cohorts were wrongly reported in column headings of Table 17. The patients enrolled in the rozanolixizumab ≈7 mg/kg and

≈10 mg/kg cohorts in the OLE study MG0007 were 88 and 77 patients, respectively, leading to a total of 165 patients. A corrected version of Table 17 is reported below.

Table 18 (Table 17 in Document B): Disposition of analysis sets in MG0007

Analysis set	Rozanolixizumab ≈7 mg/kg N=88 n (%)	Rozanolixizumab ≈10 mg/kg N=77 n (%)	All participants N=165 n (%)
ES	88 (100)	77 (100)	165 (100)
FAS	88 (100)	77 (100)	165 (100)
SS	79 (89.8)	78 (101.3)	157 (95.2)

Abbreviations: ≈, equivalent dose; ES, enrolled set; FAS, full analysis set; SS, safety set.

C3. There are discrepancies in reporting the MG-ADL response rate at day 43 in MycarinG, between company submission Table 6 (rozanolixizumab 7mg/kg 68.2%; rozanolixizumab 10mg/kg 61.2%) and the text at the top of company submission page 82 (rozanolixizumab 7mg/kg 71.9%; rozanolixizumab 10mg/kg 69.4%). Please explain this.

The discrepancy in the MG-ADL responder rates reported in Table 26 and on page 82 is due to the different strategy used to calculate the responder rates in the two endpoints.

Table 26 reports the MG-ADL response rates at Day 43 as per the pre-defined secondary efficacy endpoint. In this analysis, participants were classified as responders if they reported at least a 2-point improvement (decrease) from Baseline to Visit 10 (Day 43) in MG-ADL score with intercurrent events handled using a Composite Strategy, i.e. participants who receive rescue therapy prior to Day 43 or discontinue treatment or the study due to treatment-emergent adverse events (TEAEs) were treated as non-responders. Any missing data due to other reasons were imputed as non-responders. This resulted in MG-ADL responder rates of 68.2% in the rozanolixizumab ≈7 mg/kg cohort and 61.2% in the rozanolixizumab ≈10 mg/kg cohort.

The analysis of MG-ADL responder rates reported on page 82 is part of the “other" efficacy endpoints and assessed the observed number and percentage of responders by treatment group and visit. As this analysis did not use the Composite Strategy, patients were not excluded if they received rescue therapy or discontinued

either treatment or study due to TEAEs, resulting in slightly higher responder rates: 71.9% and 69.4% for rozanolixizumab ≈7 mg/kg and rozanolixizumab ≈10 mg/kg, respectively.

C4. The CON markup is not consistent for the sample sizes reported in company submission Tables 40 to 42. Please clarify which markup is correct.

The markup provided in Table 40, which includes the sample sizes in the markup, is correct.

Addendum

UCB would like to correct a mistake in the reporting of the distribution of AChR Ab+ patients in age categories (Table 27, Appendix E.1.2). The correct age categories are presented below in Table 18.

Table 19: Age distribution of AChR-Ab+ patients enrolled in MycarinG

	Placebo N=59	Rozanolixizumab ≈7 mg/kg N=60	Rozanolixizumab ≈10 mg/kg N=60
Age categories, n (%)[†]			
≤18 years	[redacted]	[redacted]	[redacted]
19 to <65 years	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; AChR Ab+, acetylcholine receptor antibody positive.
† Clinicaltrials.gov age categories.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Myaware and Muscular Dystrophy UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Myaware is the only charity in the UK dedicated solely to the care and support of people affected by myasthenia gravis. Founded in 1968, we are working hard to raise awareness of myasthenia gravis, provide support for people with myasthenia gravis and their families, whilst offering advice and tips for living with the condition. There are currently around 3000 active members of myaware, all of whom have full access to a wide range of support services and events including our specialist benefits advisor and telephone or Skype counsellor. Myaware has a long history of working with patients with myasthenia. Before covid this entailed regular face to face meetings, and since Covid regular quarterly zoom meetings. Myaware also host three closed Facebook pages in which living with MG is discussed daily. We also fund the research that brings us closer to finding a cure as well as funding specialists nurses and advisors. We campaign for better medical services for people with myasthenia gravis and work to inform medical professionals. Muscular Dystrophy UK (MDUK) is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 110,000 children and adults in the UK. We fund research, provide vital information, advice, resources and support for people with these conditions, their families and the professionals who work with them. Collaboration lies at the heart of our work and as such this submission has been collated together jointly between MDUK and Myaware.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Myaware has received funding from UCB totalling £334.78 to cover the cost of accommodation associated with attendance of the MG: Connects meeting in Manchester. Not ongoing. Muscular Dystrophy UK have received the following funding from comparator treatment company Roche. • £720.00 from Roche on 17 April 2023 for participation in its SMA Adult Activation Advisory Board. Not ongoing. • £1,710.83 in June 2023 towards pass, accommodation and travel costs associated with MDUK attendance of the European Paediatric Neurology Society congress. Not ongoing. • MDUK received grant funding of £25,000 on 24 August 2023 and £25,000 on 31 October 2023. This is funding for the work of the UK SMA Newborn Screening Alliance and is not being retained by MDUK. Not ongoing. • £900.00 fee for participation by Director of Care, Campaigns and Support in the Roche Neuromuscular Summit: Advocacy Panel on 5 September 2023. Not ongoing. Not ongoing. • £417.50 reimbursement for Conservative Party Conference Not-for-Profit ticket fee to participate in a Health and Care Forum fringe event on 2 October 2023. Not ongoing. • £190.00 covering of accommodation costs associated with participation in Health and Care Forum fringe event at Conservative Party Conference on 2 October 2023. Not ongoing. • £2,750.00 on 1 November 2023 for sponsorship of SMA patient information virtual seminar. Not ongoing. • £600.00 fee for participation by Director of Care, Campaigns and Support alongside SMA UK in co-creation exercise on health inequity on 2 November 2023. Not ongoing. • MDUK will receive a donation for a member of staff to attend the Muscular Dystrophy Association Conference 2023, covering the cost of registration, accommodation and travel. Amount to be confirmed. Not ongoing. Muscular Dystrophy UK is due to receive from comparator company Argenx £2,610 (plus VAT) fee for support provided in May 2023 for the gathering of carer insight into the carer disutility caused by generalised myasthenia gravis. Not ongoing. Muscular Dystrophy UK received grant funding of £45,000 on 21 December 2023 from comparator company Novartis. This is funding for the work of the UK SMA Newborn Screening Alliance and is not being retained by MDUK. Not ongoing.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	We do not have any direct or indirect links, nor funding from the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gathered information through the following avenues: - A patient survey on the impact of living with Myasthenia Gravis where we had 551 respondents. - A focus group to gather feedback on living with the condition and current treatments which was attended by 21 people living with Myasthenia Gravis. The focus group was aimed particularly at understanding what it is like to live with the condition and insight into current treatments. - Published evidence on disease burden and media case studies/published reports. - one-to-one in-depth telephone interviews with 21 carers of people living with Myasthenia Gravis, conducted by the Research Institute for Disabled Consumers.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Myasthenia Gravis (MG) is an autoimmune condition that can affect anyone, old or young and of any gender. People with MG have characteristically fatigable muscles and the harder they try, the weaker they get. They are often strongest in the mornings and get weaker throughout the day. The course of the disease is extremely variable, between individuals and individual people with myasthenia can vary considerably from day to day. Some days are better than others; for no "apparent" reason. Life threatening "myasthenic crisis" can happen suddenly, requiring hospitalisation, and necessitating lifesaving treatment. Our survey revealed MG has a physical, emotional, and financial impact on individuals and their families: **Physical Impact** The first signs of MG often are: droopy eyelids and possibly double vision, tiredness and weakness in the neck arms and legs. It is common that people find their faces are affected, this means smiling, making facial expressions, or chewing may become difficult. The symptoms often evolve into difficulty swallowing and breathing. In addition, some peoples' speech can be difficult, especially if they have been talking for a long time, they may realise their speech has started to sound different, possibly slurred. As the day goes on, some people find they are getting weaker, and they may need a rest. Pushing yourself to do things, like walk and talk, may make this even worse. From our survey, one respondent told us: "*I am unable to do the majority of the things I used to do due to my extreme weakness, breathlessness and fatigue. I have had to reduce my working hours. I can't do much around the house or garden fatigued most of time and really weak physically*." Another told us: "*Constant double vision, poor balance, cannot drive, some bad days, poor bladder control, need to know nearest toilets. I have been refused service as restaurant owners think I am drunk and have commented on my eyes, been asked to leave*." Further, 40% of respondents were admitted to hospital within the first year of their diagnosis, of which 15% landed in intensive care, mainly for close monitoring. **Emotional impact**

	Almost seven in ten (68%) respondents said having MG has had a negative impact on their social life and increased feelings of anxiety, with one respondent telling us: *"I've had myasthenia for 60 years and I thought I could manage it very well. What I have found is I have become very suspicious of people. I didn't go out beforehand. So many letters from the NHS made me feel extremely vulnerable and now when I go shopping I look at which is the shortest queue and I'm quite suspicious of people. And that is so unlike me. But now I want to withdraw from people."* Another respondent told us: "*Due to fatigue and embarrassment with my slurry speech, I don't feel comfortable going out too much. I also can't walk for long durations and am unable to walk long distances which has changed me as a person with regards to feeling comfortable going out with friends and even leaving the house unless necessary*." These feelings are only further exacerbated due to the unpredictability of their symptoms which can be difficult to explain to others, with 27% of respondents finding it difficult to talk about their condition with their community. One example is: "*Because I appear well and bubbly, it feels like I'm creating a problem where none is apparent. It is difficult to explain to people how you can be all right one minute and then extremely fatigued the next. People look at me and see a "normal" person and are quite surprised when I reveal I have a disability and have never heard of or understand MG*". This emotionally impacts not only the individual, but also their families, with 50% of respondents stating that their condition has negatively impacted their family's mental health. For example, respondents told us the following: "*Being diagnosed at a young age this has been stressful for my family, especially my parents seeing me unwell and admitted to hospital numerous times and in intensive care. Caused them worry and stress which continues any time I am unwell*." "*Having your mother in hospital when doing A level exams and starting University without support is difficult*."

	"*…hit my partner very hard as she saw me at the most life-threatening stages through which I passed completely unaware*." Further, the impact of living with MG on mental health has been exacerbated by the pandemic. Members who have been shielding for a significant amount of time, due to the medications used to treat/manage MG, have suffered from extreme isolation. There has also been a knock-on effect in terms of consultation and face-to-face interaction with specialists. There has been an increased feeling of vulnerability in the community. For example, one attendee in our focus group told us: "*I was diagnosed 5-6 years before COVID. What I found was things take longer to compute and I had to think about things a lot more, which has an invisible effect on your mental health. It makes you more tired. With COVID you are reminded all the times of the dangers out there, which had an impact. The impact of MG on my mental health is the constant awareness of it and it is grinding you down and you have to think about the things that you do and say, and I find it tiring*." Another told us about the sense of visibility the pandemic has put on their condition: "*Shielding has led to the exposure of medical history due to work-from-home schemes. First time people found out you had a medical condition, making you stand out and encourage feelings of resentment. Having the vaccine improved my mental health by allowing more freedom from isolation and shielding. However, I was made to feel vulnerable by wearing masks at the office*." **Financial Impact** Over a third (37%) of respondents have had to stop working or change roles due to their condition. This was mainly due to fatigue, breathing challenges, vision problems, voice becoming slurred, inability to focus, unable to drive to and from work (when remote working not possible). Similarly, 37% also stated their condition had negatively impacted them financially, with many needing to change to part time working. However, some respondents told us that the hardest part was the limbo before receiving their diagnosis, where they had to take time off work due to illness resulting in loss of salary and found themselves unable to explain to employers what additional support they may need or to arrange a working pattern that suits them better.

	One respondent told us: "*Having a job paying £30,000 then having to go on benefits which only pays a pittance meant I had to cash in my private pensions and now being in a low paid job due to having to find work that fits around my MG*" For those in employment, there was a consensus in our focus group that employers are relatively understanding and generous with time and resources for employees with MG. However, MG has been seen by members as holding back their careers. For example, attendees have been wary of changing their careers or looking for better opportunities in their profession, which has limited their career progression. This is because they don't know if their new employer will be as supportive as their previous one. For example, one attendee told us: "*One of the worst things I found when I was working was (that) some days I'm good and some days I'm bad. And people will say to you 'well you don't look ill'. If you have a broken leg, it's broken until it heals. MG isn't like that*." Another attendee told us: "*I had a very encouraging employer and they helped me a lot. They supported me, I had regular reviews. They did know about MG. Even within the health service though they didn't have an in-depth understanding of it. I had regular reviews and eventually with their support I realised I had to take early retirement. Which is where my problems started as I was initially refused the ill-health pension. I went to my doctor, and he told me this was the system, people get refused and [they] don't `fight back. [But] He wrote a great report with the support of my employer and managed to get me accepted for the ill-health pension*." However, despite reports of support from employers being common amongst attendees, there was also evidence of a lack of awareness and response from occupational health representatives. "*My employer (university) is incredibly generous. Occupational health not so much. They have to assess me every year even though myasthenia is not going to go away. It really has affected my career choices. I have a supportive employer, so I don't dare change jobs in case I end up somewhere where my employer doesn't understand. I was headhunted while I was being diagnosed but had to turn down a lucrative and exciting prospect. It's accepting the fact that I won't be looking for a change of employer of job for a long time. Career progression has slowed down massively, so myasthenia will affect my finances at some point.""*

	A lot of work is still required to create policies and pathways for managing myasthenia in the workplace, and these have yet to come to fruition in the occupational health sector. Another attendee commented: "*Occupational health – the first assessment I had they basically said to me that I should meet my employer halfway and go part-time. It felt like they just dismissed me. There is a lot of identity tied to work and it is really shaken up when there is a diagnosis and extra hoops to jump through*." A lack of understanding in terms of capability or the ever-evolving nature of myasthenia has left patients feeling unsupported and misunderstood, which in turn has affected career prospects and the desire to advance for fear of not receiving support universally. This has had a knock-on effect on their families, with 30% stating their condition has negatively impacted their family financially who rely on both salaries to pay for mortgage and costs of living. Additionally, having MG has led to additional costs for adaptations. For example, one respondent told us they had to purchase various electrical appliances to maintain the individual's independence such as purchasing a specific kettle as they can't lift their current kettle because they are too weak. **Impact on carers** As well as the references above to the impact on carers, to look into this issue further MDUK supported research conducted by the Research Institute for Disabled Consumers (RIDC) that recruited 21 carers of people with a diagnosis of gMG. In line with NICE's definition of a carer, participants confirmed that they supported a family member, partner or friend with needs that resulted from living with gMG. The research was conducted between 13 June 2023 and 21 June 2023 through one-to-one in-depth telephone interviews. Participants were asked to what extent their responsibilities around caring for someone with generalised myasthenia gravis effects their quality of life on a scale of 1-5, where 1 is not at all affected and 5 is extremely significantly affected. The average score given was 3.4 and no one gave a score of 1 (three people gave a score of 2; nine people gave a score of 3; six people gave a score of 4; three people gave a score of 5). Participants were asked in which aspect of daily living (if any) they experienced any impact due to caring for someone with generalised myasthenia gravis. Participants could select more than one option. None said that it had no impact.

	• 19 people (90%) said it impacted their ability to undertake their usual activities such as personal shopping/ hobbies • 16 people (76%) said it impacted their mobility/ ability to move around • 14 people (67%) said it caused anxiety/depression • 11 people (52%) said it impacted their personal care e.g. washing/dressing • 5 people (24%) said it caused them pain/discomfort Asked about the impact that caring for someone with generalised myasthenia gravis has on specific activities (participants could select more than one option); • 21 people (100%) said their social life • 19 people (90%) said working/studying • 18 people (86%) said sleeping • 8 people (38%) said eating Comments relating to the impact on social life included; *"You can't do anything social or working. I like music and the cinema and you cannot go to music or jazz clubs. You can't socialise."* *"My social life is affected, and I cannot hang out as much as I want to. I can't be free and be outdoors as much as I would like to."* *"Social life and dating are impossible. No sports or any other things like you could do before. You try to do them, but you get a call and then you have to go home."* *"It becomes very difficult as I have no time for leisure anymore. My personal life is tough as my caring takes a whole lot of time and I do not have much sleep."*

	"Getting to leisure and recreational activities. I love sport but I have to limit the time I spend outside as the person I am caring for may need me at any time. [It alters] the way I would live otherwise." *"I was able to crochet more before care giving. My hobby was too time consuming so I am unable to continue doing what I like. I have had to stop."* In terms of the impact of caring for someone with generalised myasthenia gravis on employment, only two participants (10%) in the research were not employed; eight (38%) were employed part-time; seven (33%) were employed full-time; three (14%) were self-employed; and one (5%) was employed but on long-term medical leave. Nine participants (43%) said they worked less hours as a result of their responsibilities as a care giver. *"My part-time job is online as you cannot be taken away physically from the person you are taking care of. Some days he cannot move his body."* *"I can't commute because my dad is more important."* *"Mostly at work I get called home. It is really stressful. I have no peace of mind. I can get called at any time."* In terms of the impact of caring for someone with generalised myasthenia gravis on studying, comments from participants included; *"I would love to further my education but I can only do a little online study. Taking care of your relation takes up your time and is paramount."* *"Academics are online but there is no social element for you to do some interaction. You can get the qualifications online but it is not the same experience."* Five participants (24%) in the research stated that being a carer for someone with generalised myasthenia gravis caused them pain or discomfort, with comments including;

	"The stress sometimes and always being active it gets very stressful and heavy on my lower back." *"Lifting her with my legs. Helping her stand and communicating with her for a long time is tiring. Standing for a long time to communicate and support her."* *"In terms of pain I am constantly having to be up all of the time and being on my feet and moving around has caused mild pain and feeling lightheaded due to a lack of sleep."* 14 participants (67%) said that they experienced anxiety and/or depression as a result of caring for someone with generalised myasthenia gravis. 8 of these 14 (57%) said this was to a mild extent; 4 of these 14 (29%) said that it was to a moderate extent; and 2 of these 14 (14%) said that this was to a severe extent. *"At times I feel down because this is someone I love so much and having to watch her go through such problems can be disheartening and I feel down and bad and I wish I could prevent that but it is beyond me. At times I feel it is my fault."* *"Generally being a carer is difficult because sometimes we have no choice. You have to make huge sacrifices. You cannot achieve your dreams. You cannot maintain relationships or friendships and cannot travel around."* *I fell into depression. I had a lot in life I liked to do. Being stuck makes me think a whole lot. I am not getting paid, and I feel that my life is wasting away, and I think too much, and it doesn't get better. Sometimes it is okay and then there is another crisis. I do not want to lose him, but I am scared, and I am stuck. I can't overreact and I have to be gentle and can't show my own side and my own feelings. I can't make him feel that he is making my life pause. No one is there to talk to, and you feel like sometimes social media makes things harder. I see other people doing a whole lot of stuff [such as] working or starting a family. It is really hard."* *"Sometimes I look forward to when my care giving role comes to an end and I can get on with my life. Doing the same thig over and over again sometimes I think about the end of life and is this what life is about. It gives me anxiety."*

	"You have no control of the situation. You just worry because if you had your way you would have your loved one fully well and you could return to your normal life." *"My life turned all of a sudden and I can't get a grip on it at the moment."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	People with MG are on a range of different treatments, which creates two main difficulties: (1) managing the different timings within their day-to-day activities and (2) getting the dosage right between balancing the side effects of steroids and managing MG symptoms. Overall, our focus group showed there are a lot of problems with the management of steroid intake, particularly with prednisolone. Attendees would largely like to reduce their dose but fear the impact of this on their MG. Following a stringent routine for medication intake is incredibly taxing, as the process must be consistent to achieve the most relief from MG symptoms. Ordering prescriptions has no clear sensible system either and demands a lot of time and careful coordination from patients. There is a constant feeling of being dictated by medication and 'living at the mercy of a clock'. Lots of medications must be ordered and collected at alternate times, further contributing to the burden of managing myasthenia. Access to more expensive treatments feels like it is being withheld in place of cheaper options. **<u>Scheduling treatments</u>** In our focus group, there was a lot of frustration at how an individual's treatment schedule inhibits day to day activities. For example, people with MG must consistently be aware of what food they are consuming, and at what time of the day to ensure it doesn't impact their treatments. As a result, socialising where food is involved is very challenging with their meals needing to be regulated to be in time with their medications which feels restrictive for them and the people they are eating with. Further, accessing their treatments is inconsistent with ordering all medications at the same time. One respondent told us: "*It's not just about remembering to take medication in a sort of order, but the ordering itself. Every medication has a different place it can be prescribed from, and the ordering all takes different times*." **<u>Side effects and opinion on steroids and steroid sparing agents</u>** A lot of people with MG are on steroids to reduce inflammation by reducing the production of the autoantibodies that are attacking the neuromuscular system, this is achieved by 'damping down' the activity of the body's immune system. However, getting the dose right to reduce the risk of side effects but to still manage the MG symptoms is tricky and causes a lot of stress for this community. We particularly heard: "*The medication I was put on to start with controlled my symptoms. I saw a consultant a month later who thought he found some weakness in one of my arms. The protocol was to increase prednisolone. My intuition was that it had been more down to being unable to eat for alternative reasons. The increase to steroid did not help*

	physically but stressed me mentally. I explained this to him and he was very good. It's a risky business when you want to trust your own intuition about your body even when it goes against what a consultant is recommending." Side effects from non-steroidal immunosuppressants such as Azathioprine have also been reported by respondents, with one saying: "*I did have to come off Azathioprine as it impacted my blood, liver and kidney functions*."

8. Is there an unmet need for patients with this condition?	People with MG struggle to balance their treatments with symptom management and undertaking their day-to-day activities such as work and socialising. As we have demonstrated this has negatively impacted their mental health as well, which clearly shows the need for new treatments to reduce this burden of care. The accessibility to new treatments is an additional problem for people with MG. Sometimes it can feel like the cost to NHS outweighs a beneficial outcome to them. As spoken by an attendee: "*I have hated prednisolone since the day they put me on it. I was convinced it was not making a difference. I was on 60 mg and have had to fight for a reduction. I'm now on 3 mg but also taking a cocktail of others. Then there is the side effects of the medication you take to reduce the side effects of prednisolone. I've found even the most empathetic of doctors find IVIG is too expensive. Rituximab really changed my life, and I would like another round of it but there is a feeling that it is being held back because of the expense. I just wonder why it feels like sometimes the doctors don't listen to you, don't fiddle with medications that do work. I knew Rituximab wouldn't be immediately effective, but after 6 months it was like magic. I was feeling so much better I felt I was in remission*." In addition, there appears to be a reluctance to deviate from treatments that work in favour of trying alternative approaches that might give an improved result. One attendee said: "*My GP will not prescribe me mycophenolate, so I have to get it prescribed by my consultant at the hospital and have to make a long car journey. GP is happy to prescribe 100 mg of prednisolone. GPs don't seem to have necessarily as much comfort with immunosuppressive agents which makes life harder sometimes*." People with myasthenia who are taking immunosuppressive drugs are at high risk of being severely affected by infections, such as Covid19. Their immune systems are "dampened down" and so cannot respond effectively to opportunist infections.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Myasthenia gravis is an autoimmune disease caused by autoantibodies to components of the neuromuscular junction. Antibodies to the acetylcholine receptor are found in over 80% of patients, with a smaller number of other patients having detectable antibodies to other neuromuscular proteins such as MuSK. Myasthenia is a difficult to control chronic disease. Many patients may have myasthenic crisis brought on by infection, stress, and other causes both known and unknown. There is no cure, but the symptoms of a proportion of patients can be controlled using a range of drugs including steroid and steroid replacement drugs. Some patients can have their symptoms controlled by these drugs, however the symptoms in a significant proportion of patients are hard to control, and these patients face a prolonged period on steroids with the danger of the many known medical side effects of long-time steroid usage and are prone to “myasthenic crisis”, when their condition may suddenly become severe and life threatening. Patients with myasthenia, do not like taking steroids. They are worried about the medical side effects of steroids including low resistance to infections, weight gain, possible onset of other disorders (diabetes, osteoporosis), and sleep and mood problems including depression. Reducing dosage brings on the fear and possibility of a loss of control of in their symptoms and an increase possibility of myasthenic crisis. Rozanolixizumab is neonatal Fc receptor blocker with proven efficacy and safety in its assessment for use to treat myasthenia gravis. The MycarinG study used multiple patient reported outcomes (RPOs) to report the improvement of symptoms and outlook for candidates with either AChR-positive or MuSK-positive antibodies. The enrolment of MuSK-positive patients in this trial is a significant advantage for the myasthenia community, as there are few therapeutics, even amongst the new wave of medicines, that involve this subgroup. The MycarinG study was the largest of its time and enrolled 200 patients. Within this study, Rozanolixizumab showed clinically meaningful improvement across multiple RPOs in both dosage groups (7 mg/kg and 10 mg/kg). It was also administered subcutaneously throughout this study, which is beneficial over intravenous (IV) administration as it is easier to access and maintain. This advantage is significant for myasthenia patients as it will make it easier for them to access the therapy from home or if they do attend a clinic, it will take less time to complete compared to IV administration. Therapy from home removes the burden of travel and financial costs associated with this, as well as reducing any potential lost working hours to attend hospital appointments. It is also more comfortable for patients and less stressful.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The most likely clinical disadvantage of this drug (and other related monoclonal-engineered drugs) is its non-selective mode of action. Blocking the neonatal Fc receptor will result in an increase in the degradation of all circulating antibodies, good as well as bad. In certain cases, it may lay the patient open to infection. However, this is true of other forms of immunosuppressive drugs too, and so the patient will need to be monitored and be aware of this possibility. With this in mind, the MycarinG study reported no severe, serious, or opportunistic infections during the course of the trial. The other significant disadvantage is the cost of the drug, which will be very high. Our members appreciate the cost is higher than the day-to-day cost of tablets, but suggest that long-term steroid usage is not cheap and leads to other medical conditions that also require treatment which have a cost to the NHS and society too.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As stated previously, Rozanolixizumab has been trialled and reported positive outcomes for MuSK antibody-positive myasthenia gravis patients. This is a subgroup of MG patients who have significant unmet needs in addition to those with AChR antibody-positive MG. We welcome a therapeutic with a proven impact for this group.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Myasthenia is a very variable and fluctuating disorder. Gender-based differences in MG onset change based on age, with early onset MG being more common in women while men tend to present with MG between the ages of 40-70. With this in mind, there are some gender and ethnicity predispositions, but these are irrelevant to the treatment the patient receives. The needs of particular treatment regimes in individual patients will be administered as to their personal needs at the time, by their own physician and is independent of gender or ethnicity.

Other issues

13. Are there any other issues that you would like the committee to consider?	Nothing else to add.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Myasthenia Gravis (MG) is an autoimmune condition that can affect anyone, regardless of age or gender. It is characterised by muscle fatigue, which often worsens throughout the day. If left untreated, MG can result in swallowing and breathing difficulties. The significance of associated health implications is highlighted by the fact that two in five survey respondents were admitted to hospital within the first year of their diagnosis. • MG has a wide-ranging impact on the lives of people living with the condition and their families. Survey data showed that MG not only affects individuals physically, but also impacts them emotionally, socially and financially. • Currently, people with MG take a range of different treatments to manage their symptoms. This presents several challenges. 1. Lots of people with MG take steroids, such as prednisolone, to increase muscle strength and reduce inflammation. Some patients can have their symptoms controlled by these drugs. However, a significant proportion of patients find their symptoms are hard to control, and they therefore face a prolonged period on steroids. For people living with hard to control MG, it can be difficult to balance getting the right dosage of steroids to help manage their symptoms against concerns about the potentially extensive and serious medical side effects of prolonged use of steroids. Reducing steroid dosage may lead to loss of control of symptoms and an increased possibility of myasthenic crisis. Both steroid-related side effects and loss of control of symptoms would have cost and resource implications for the NHS. 2. To manage the symptoms of MG as well as possible requires consistent medication intake and therefore a stringent treatment schedule. The research found that this resulted in frustration at how the need for such a medical intake routine can negatively impact an individual's ability to carry out day-to-day activity and can feel overwhelming. There is a need for a new treatment to reduce this burden of care. • Rozanolixizumab works by reducing IgG levels and has been trialled in both AChR and MuSK antibody-positive MG patients. In theory, it should also work with other antibody-positive patients (such as LRP4). The MycarinG study proved the safety and efficacy of Rozanolixizumab for these patients and reported significant improvement across several PRO scales when compared to the placebo group. • We recognise that cost may be prohibitive to Rozanolixizumab being used as a frontline drug, but emphasise that it could meet a significant unmet need that exists for MG patients throughout the country. The is a distinct need for targeted therapeutics in myasthenia for patients who do not respond well to standard therapy. For these patients, there is little relief from their symptoms and the risk of crisis is higher. They desperately need a treatment that is tuned to their disease.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists
3. Job title or position	Consultant Neurologist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	Association of British Neurologists Advisory Group
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	. Treat more effectively and safely patients with seropositive generalised myasthenia gravis (MG); in more detail, the main aim includes: 1. Improve symptoms characteristic of MG, in particular severe ocular, bulbar, limb and respiratory muscle fatigable weakness alone or in combination, which do not respond fully to standard immunosuppressive treatment and corticosteroids. 2. To improve symptoms if patients have significant side effects of such treatments and or become dependent on the chronic regular use of treatments that are supposed to be used only in acute settings (i.e. intravenous immunoglobulins [IVIG] and plasma exchange [PLEX]). 3. Reduce comorbidities so often associated with the disease as a result of long-term steroid and immunosuppression therapy, the most frequent being diabetes, hypertension, osteoporosis, cataracts, mental health problems obesity and cancers, particularly lymphomas and skin cancer. 4. Reduce subsequent health problems related to the vascular risk factors from corticosteroid therapy (e.g. stroke, ischemic heart disease, kidney dysfunction) 5. Reduce hospital admission directly related to MG crisis and MG exacerbations. 6. Reduce hospital admissions related to the consequences of complications of the disease and the treatment such as organ dysfunction/failure, infections, fractures, infections and frailty. Some of the infections result from immunosuppression. 7. Improve ability of patients to be independent fulfil their family commitments, be able to attend academic, social and professional activities appropriate for their age, skills, experience and their training and cultural background. 8. Prevent and reduce specific and general disability, prolonged or frequent sick leave, early retirement and dependence , including the psychological consequences of chronic disease. This would also potentially reduce the impact on families including allowing partners or children to participate in education or the workforce rather than act as carers. 9. In some cases, to reduce mortality related to direct MG serious crisis when ventilation is required. Even in long term respiratory and bulbar muscle weakness there is a high level of disability and it comes witha high risk of fatal complications such as venous thromboembolism including that related to immobility or use of intravenous catheters for IVIG or PLEX.

	The aim is NOT to replace all the current standard therapies, which are effective and safe in a good proportion of patients, if we treat promptly. As part of this, we should be able to use other advanced treatments such as anti-CD20 therapies as earlier as possible knowing that their efficacy is much higher if given early. The aim is to treat a small proportion of patients who we, experts, have significant difficulty treating safely after using the best current treatments.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in functional abilities: 2-point or greater improvement on MG-ADL score Reduction of symptoms and neurological deficits: change in QMG >3, MGC >3 Reduction of admissions for MG crisis, including ITU admissions and rescue treatment Reduction in chronic and acute IVIG and PLEX treatments Reduction need for use of non-invasive ventilation Reduce admissions because complications of treatment – falls and fractures, stroke, severe infections, pulmonary embolism Improve general health, level of fitness and ability to be independent and have a good quality of life
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there remains a group of patients with highly refractory MG who do not do well on existing therapies, either due to complications of treatment or insufficient response.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	For the majority of patients, they are still treated with long-term standard therapies, which rely heavily on steroid therapy and oral immunosuppression (azathioprine, mycophenolate or methotrexate), often in combination. Some patients are suitable for thymectomy. Severe refractory cases are sometimes managed with regular IVIG or PLEX, an inappropriate use of what should be an acute treatment. In more recent years, rituximab or similar drugs have been used as second or third line treatment in patients who do not tolerate or are inadequately treated on standard immunosuppression. These are most effective given early in the disease course.
9a. Are any clinical guidelines used in the	No. The 2015 ABN endorsed clinical practice guide is out of date and requires revision.

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, there is a pathway, which in general works, but is dependent on 1. Patients being willing to travel to specialist clinics 2. Workforce issues common across the NHS There is broad consensus between MG specialists across the UK about what constitutes good care and the "hub and spoke" model of neurology care in the UK facilitates dissemination of good practice and referral to specialist clinics within regions.
9c. What impact would the technology have on the current pathway of care?	. Given the MDT structure that would be required for implementation of ever more complex treatment pathways, this may well bring benefits to MG patients who are not necessarily suitable for this therapy. If well structured, nationally and at local levels, and well resourced, the current pathways of care can become much more reliable, harmonised, patient orientated, improving patient care and being cost-effective.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used through myasthenia specialist clinics and MDT arrangements as are the other more advanced therapies currently Some myasthenia care is undertaken at a local level currently and it would not be anticipated that this drug would be available in that setting
10a. How does healthcare resource use differ between the technology and current care?	The self-injected nature of the treatment is similar to some existing newer therapies for MG, although others are infusion therapies It does not require frequent blood monitoring in contrast to other current therapies We would anticipate a lower use of healthcare resource by patients with refractory MG as with availability of this and the other newer therapies for MG used appropriately by MG specialists, admissions and hospital visits by patients with MG could be reduced by 80% or more.
10b. In what clinical setting should the technology be used? (For example,	Only in the context of specialised neuromuscular clinics and with MDT discussions and MDT agreement.

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	1. Training for patients to self-inject 2. Implementation of vaccines pre-treatment. 3. Resourced MDT teams in expert centres: in many regions these exist but the newer advanced therapies for refractory patients will make these essential. 4. Dissemination of education for other neurologists to guide referrals (what patients, when, to where)
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	No doubt about the impact of this and similar treatments. It has an extremely high, meaningful benefit, and is very safe. The testimony of patients who have accessed the therapy on the trials is striking.
11a. Do you expect the technology to increase length of life more than current care?	1. As this group of severe refractory patients are those at high risk of respiratory and bulbar exacerbations/crises it will be life-saving as each hospital and particularly ICU admission comes with a risk of severe morbidity and mortality 2. The complications of treatments which are immunosuppressive but not very effective in the eligible group of patients are life threatening and life shortening. The drug, could change the long term effects of chronic general immunosuppression and steroid treatment improving healthy and absolute length of life. This applies also to the elderly who with other co-morbidities have a higher rate of complications from steroid and other immunosuppressive therapy.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. 1. Many patients on current therapies suffer of significant side effects of treatments, particularly steroids but also oral immunosuppression and even rituximab if given after chronic immune suppression. This could be prevented if advanced treatments are used earlier and there were available options for treating those with refractory and severe disease. The complications include weight gain, diabetes, osteoporosis, heart disease, mental health problems, skin cancers, infections and affect everyone at any age, reducing significantly health-related quality of life. In the trials of this and similar drugs, over 50% of patients had their background medication fully weaned and many could reduce the medication 2. The side effects of new treatments are much fewer and less significant if patients are well prepared medically (vaccinations) and trained well to inject their treatment.

	3. The quality of life impact of poorly controlled MG is very significant including respiratory, bulbar, ocular, mobility issues and exercise intolerance in every muscle restricts all daily activities. This medication has improved all aspects of the disease in trials. There is also the psychological impact of a poorly controlled chronic disease which with earlier and better control should be reduced. 4. Hospital admission have a huge impact on physical and mental health – preventing these should also improve quality (and quantity) of life
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	1. The patients should only be treated if they have seropositive MG, and within that group those who have currently detectable antibodies will probably be most likely to benefit. 2. From a safety point of view, this medication may be less suitable for those with immuno deficiency, particularly hypogammaglobulinemia for example which can be associated with thymoma (Good syndrome), or long-term treatment with rituximab. These might be more suitable for complement inhibitors.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This drug (and others in its class) are very easy to use by patients, with simple training and monitoring for self injection If anything monitoring is less frequent and onerous than on the traditional immunosuppressive drugs such as azathioprine. The key requirements are that there should be the workforce; MDT teams and specialist clinics for patients to be able to access these therapies and supervise the reduction in other therapies to ensure that full benefits are realised

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting: Vaccinations prior to starting Acetylcholine receptor antibodies/anti-MuSK antibodies- checked that positive at some point as the treatment is only suitable for seropositive MG, and also preferably before starting treatment Immunoglobulin levels will be checked prior to and, as needed during, treatment, for example if intercurrent infections occur. Clinical reviews to ensure effectiveness for individuals as per standard care in MG specialist clinics – this medication has a rapid effect and so the decision to continue or stop treatment can be made quickly.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I do not think so.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the	This is a member of the new class of anti-MG drugs specifically targeting the Fc domain of IgG antibodies including the acetyl choline receptor antibodies or anti-MuSK antibodies which cause MG

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	This (and similar drugs) is definitely a step change in the MG management history. This is a therapy which targets molecules involved in the pathogenic mechanisms of the disease. They are safe and easy to use.
16b. Does the use of the technology address any particular unmet need of the patient population?	See answers above. Within the unmet needs of the patients, this medication will provide stability and predictability (fewer fluctuations of symptoms), will improve their general health and mental health (those who suffer the disabling muscle weakness and in addition obvious facial and body changes related to steroids and immunosuppression) and will provide longer and heathier life.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	According to data from the clinical trials, the adverse events are minor compared to those associated with standard therapies and complications of the disease.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, although the great majority of the patients in the clinical trials had very severe disease, in need of ventilation. These are the hardest to treat patients so the benefit in those patients would apply to all with

	refractory MG, even if not requiring ventilation. The pathology is the same even if no ventilatory requirement. Their demographics and background treatments were similar to those in our cohorts.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes were measured in the trials and consist of: 1. Efficacy: Objective MG specific scales- MG-ADL as primary outcome, MGC, QMG scores as secondary outcomes 2. Safety. Adverse outcome recording: treatment emergent adverse events also Columbia suicide severity rating scale 3. The ability to reduce underlying medication 4. Use of rescue therapy or time to rescue therapy: none required during the trial 5. Overall quality of life- patient-reported outcomes: Myasthenia Gravis Symptoms Patient reported outcome, patient global impression of severity, patient global impression of change.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes: significant reduction in IgG (total and subclass) concentrations and reduction in specific antibodies (AChR and MuSK) which mirrored clinical improvement.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	unclear

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes, equality of access to better care must be achieved by. 1. Ensuring pathways for referrals to expert centres are well organised, well-resourced and well known across UK. 2. Patients who struggle to access healthcare should be referred and supported to attend expert centres for assessments. Those economically deprived or living in remote areas should not be denied treatments. Given the advantageous safety profile, the use of virtual consultations and relevant documentation to prevent travel may be possible as experience with these treatments grow.
21b. Consider whether these issues are different from issues with current care and why.	They are not very different. Good treatments should be the ultimate aim for every patient regardless where and who they are. So, measures to improve their access to prompt diagnosis and adequate treatments are important. Although the initial treatment may be started by non-specialised neurologists, a clear pathway should be in place to facilitate discussions and advice from experts early in the disease course with review depending on clinical progress.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• There are unmet needs in the management of seropositive MG, especially for patients who have severe and refractory disease or suffer significant side effects and complications of standard therapies, or have significant co-morbidities preventing the use of stand treatments • New, targeted therapies, such as Rozanolixizumab have proved meaningful and substantive prolonged benefit, with safe profile. They allow reduction of other immunotherapies (steroids, immunosuppression and IVIG and PLEX) and thus improve MG and health related QoL in patients with gMG. • This treatment is not a replacement for early therapies except in very severe cases. They have now clear indications, following results of clinical trials and their use under certain schemes. • Rozanolixizumab is one of the life changer and life saver new target therapies, which allow improvement of health-related quality of life and effectively a return to normal life. Given its current high price, it is to be used in highly selected patient groups who have not responded or have intolerable side effects on existing therapiesThey have a fast onset of action and clear measurable clinical benefit, which is known to persist while on treatment, indicating a long-term and prolonged effect. Equally, it will allow quick identification of patients who do not respond to such treatments, helping to improve their care by offering them different treatments. • The MDT and specialist clinic structure required to assess for this therapy may well have advantages for the treatment of those with MG more generally by (i) improve national pathways for MG referrals to expert centres so patients have equal access to MDT reviews, ideally in person, and treatment options discussed; (ii) improve the access to anti-CD20 to earlier stages of the disease (as disease modifying treatment) and (iii) stop the use of regular chronic IVIg and PLEX because of the previous lack of better options for these severely refractory patients.

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Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with myasthenia gravis or caring for a patient with myasthenia gravis. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Monday 05 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with myasthenia gravis.

Table 1 About you, myasthenia gravis, current treatments and equality

1. Your name	Abuk Mabil
2. Are you (please tick all that apply)	☒ A patient with myasthenia gravis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with myasthenia gravis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Myaware & MDUK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with myasthenia gravis? **If you are a carer (for someone with myasthenia gravis) please share your experience of caring for them**	At 19years old and a student at university, I experienced a number of debilitating eye symptoms – double vision with a drooping eyelid. It was a long process until I was finally diagnosed with ocular myasthenia gravis around when I was 22yrs old. It was a long process (3 years) between onset of symptoms to diagnosis which had a huge impact on my life as a young adult Due to mg, I had to quit university after 2 years as I was unable to continue my studies. I experienced a brief period of remission whilst I was pregnant with my daughter (aged 24), but after her birth, my symptoms returned into full blown generalised myasthenia gravis. This presented as weakness in my neck, arms, legs, foot & ankle. It also affected my speech and swallowing at times. I was unable to properly care for myself or my daughter, requiring twice daily carers visits and support from adult social services. I had to move into the living room as I was unable to manage the stairs in my home. This had a significant and detrimental impact on my mental health. The sudden loss of independence and struggle to accept my disability. Over the years, I have also required support from talking therapies and mental heath services due to depression and anxiety, caused to some extent by my diagnosis. I was referred to Oxford Hospitals as my previous trust were unable to get my symptoms under control and I should be moved under a specialist consultant. For a number of years, I worked my way through a number of medicines and therapies to try managing my symptoms. I never managed full remission and

	almost accepted that I will always live with some level of disability for the rest of my life. I was able to return to full time work by the age of 26years, however that was supported with additional funding through PIP and a blue badge as my mobility was still affected. I have been fortunate to work with supportive employers that helped me manage my condition and demonstrate some relative flexibility to support me staying within the workforce. It did however have a long term detrimental effect in career progression, as I still had no university degree qualifications, and the roles I was suitable for were limited due to my inability to travel too far or on public transport for work. Whilst well enough to work, my life (any my daughters) was still severely limited due to the myasthenia gravis. The fatigue meant most evening and weekends were for recovery to ensure I was ready to go again the next week. My daughter, by the age of 7/8 was registered as a young carer and had dedicated support to ensure she could go out and enjoy extracurricular activities, when I was unable to do so. Following several falls, one of the most serious was down a flight of stairs, causing a serious wound to the back of my head, I was moved by the council into a ground floor flat on medical grounds. I grew incredibly anxious about walking outside on uneven surfaces, and would avoid going out if I was unsure I could park close to the site or had to walk a distance without anywhere to sit and take a break. Adult social services conducted an assessment and provided a number of tools and adaptions to try to maintain by independence and safety at home. I found this process very distressing, as it further cemented the idea that I wouldn't ever feel well again.

	Slowly over the years, my world became very small. I didn't really socialise, most of my adult contact came through work. Due to weakness in my hands, I lost the ability to knit or type for any real length of time. I struggled with most self-care tasks – doing my own hair was particularly upsetting to me as I had been braiding and styling my own hair since I was 13yrs old. I once got into a bath after a long day, and was so weak, I was unable to get myself out. I had to call out the emergency services and sat in a bath for over 6 hours before the ambulance could attend to get me out. I did not have a bath for a very long time after that incident. Whilst the mestinon was a tried and tested medication, it came with side effects which meant I hand to be very mindful of timing and ensure I had access to it at all times. These (not inconspicuous) brown bottles were everywhere in my home, car, work lockers. I couldn't be spontaneous with my activities as I was controlled by my medication schedule. Plasma exchange was probably the most effective rescue treatment. Prior to the current trial, I was probably an inpatient for 7 days in Oxford up to twice a year. The effects of plasma exchange were variable and often rather short lasting. I was also offered and treated with IVIG at various points of my journey – the difficulty again was poor venous access and variable, often minimal response to the treatment.
7a. What do you think of the current treatments and care available for myasthenia gravis on the NHS?	7a. I think there are lots of current treatments for mg, but for some (like the immunosuppressants) it takes a very long time for impact to be felt, if it works at all. Trying to find the right combination of medications that specifically work for me/the

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	individual can be laborious and time intensive. Also, quite demoralising at times when improvement is slow and/or limited. The treatments I was offered prior to my current clinical trial • Mestinon • Azathioprine • Prednisolone • Mycophenolate • IVIG • Plasma exchange 7b. I know and feel very fortunate that I was able to have access to clinical specialists and a treatment centre that offer all of these options. I think now my view is these previous treatments (for me) are rather "old fashioned" as there has been a real expansion in drugs and interventions to treat MG than ever before. I am also aware that people respond very differently to the drugs, so I am aware when I share my experience on some of the drugs I've tried with others living with mg, that it is a personal one, and not everyone will have the same response. I also believe there is huge variation and inequity to access of current effective treatments for patients across the country.
8. If there are disadvantages for patients of current NHS treatments for myasthenia gravis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Some side effects of the medication below; • Mestinon – moderate gastrointestinal side effects. Sometimes severe enough for bladder and bowel incontinence. • Azathioprine – excessive nausea and fatigue • Prednisolone – significant detrimental effect on my mental and physical health leading to a severe mental health crisis and weight gain.

	• Mycophenolate – no significant side effects, however constant and routine blood monitoring required, which was difficult to schedule around work and childcare commitments. • IVIG – limited benefit experienced but required a lot of travel and I have poor veins which made daily access difficult. Often required inpatient stay • Plasma exchange – required 7day inpatient stay due to requiring femoral vein access. Overall, with all the different treatments, I never reached a level of remission or feeling of "wellness" that I was aware was possible since starting this trial. The impact of the inpatient stays was detrimental not only to my mental health, but also that of my daughter. Having to find childcare that could facilitate my daughter getting to school with overnight stays was difficult and also very expensive. When I was unable to drive, the NHS would have to provide patient transport from my home to hospital (circa 50miles) to facilitate my inpatient stay. I was unable to be spontaneous with my activities/schedules as they revolved around my medication timetable. I never reached a level of remission, which meant I was reliant on disability benefits for a number of years as well. Whilst I was fortunate that MG allowed me to have a medical exemption certificate for my medications – there were times that I was taking up to 4/5 different drugs multiple times a day to manage my mg. It would have put an additional financial burden on me if I had to fund these medications personally.

9a. If there are advantages of rozanolixizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does rozanolixizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I cannot comment as I am not a patient that has tried rozanolixizumab.
10. If there are disadvantages of rozanolixizumab over current treatments on the NHS please describe these. For example, are there any risks with rozanolixizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I cannot comment as I am not a patient that has tried rozanolixizumab.
11. Are there any groups of patients who might benefit more from rozanolixizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I believe this treatment would benefit patients that has struggled to achieve an appropriate/decent level of remission on traditional treatment options. Patients that struggle to attend inpatient attendances for IVIG/Plasma exchange due to travel/work/caring commitments.
12. Are there any potential equality issues that should be taken into account when considering myasthenia gravis and rozanolixizumab? Please explain if you think any groups of people with this condition are particularly disadvantage	Whilst not directly a protected characteristic, I think its important to note the socioeconomic status of patients with MG.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	People from a BAME backgrounds/disabled/women (esp. with caring responsibilities) are more likely to be in lower paid roles, or unable to have the flexibility and finances to attend frequent hospital appointments. Frequent inpatient stays, hospital appointments and poorly controlled MG has had a significant impact on my educational progression and career path to date. I am not sure how we ensure equity of access to this drug for some of the issues I described above.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

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

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Lois Woods, Senior Research Assistant, Evidence Synthesis and Information Specialist Fay Chinnery, Research Fellow, Health Economics Neelam Kalita, Senior Research Fellow, Health Economics David Alexander Scott, Principal Research Fellow, Statistics Geoff Frampton, Principal Research Fellow, Evidence Synthesis
Correspondence to	Dr Geoff Frampton Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
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Dr Saif Huda, Consultant Neurologist, The Walton Centre NHS Foundation Trust Liverpool.

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Declared competing interests of the authors and advisors

The authors and Dr Garcia Reitboeck declare that they have no conflicts of interest.

Dr Huda is a principal investigator for the MOG001 study investigating the effectiveness of rozanolixizumab for relapsing myelin oligodendrocyte glycoprotein antibody disease (MOGAD); he is also involved in a review of neuromyelitis optica spectrum disorder (NMOSD)/MOGAD data registries that is sponsored by UCB Pharma (manufacturer of rozanolixizumab). Dr Huda confirms that he has not worked on rozanolixizumab research projects for myasthenia gravis.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Lois Woods critically appraised the clinical effectiveness systematic review and drafted the report and is the project co-ordinator; Fay Chinnery critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Scott critically appraised the indirect treatment comparisons and drafted the report; Geoff Frampton critically appraised the clinical effectiveness systematic review and indirect treatment comparisons, drafted the report and is the project guarantor.

Table of Contents

LIST OF TABLES

LIST of FIGURES

LIST OF ABBREVIATIONS

Ab+	Antibody-positive
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase inhibitor
AChR	Acetylcholine receptor
AE	Adverse event
AIC	Academic in confidence
AWTCC	All Wales Therapeutic and Toxicology Centre
BNF	British National Formulary
CCP	Clinical commissioning policy
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
EAMS	Early Access to Medicine Scheme
ECM	Established clinical management
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
FcRn	Neonatal fragment crystallizable receptor
FDA	U.S. Food & Drug Administration
gMG	Generalised myasthenia gravis
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life

HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IgG	Immunoglobulin G
IPD	Individual patient level data
IST	Immunosuppressant therapy
ITT	Intent to treat
IVIg	Intravenous immunoglobulin
MAIC	Matched-adjusted indirect comparison
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite score
MGFA	Myasthenia Gravis Foundation of America
MG-QoL15r	Myasthenia Gravis Quality of Life 15-item scale revised
MGS-PRO	Myasthenia Gravis Symptoms Patient Reported Outcomes
MGII	Myasthenia Gravis Impairment Index
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intent to treat
MSE	Minimum symptom expression
MuSK	Muscle specific tyrosine kinase
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
PLEX	Plasma exchange
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QMG	Quantitative Myasthenia Gravis scale
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
RS	Randomised set
SAE	Serious adverse event
SCIg	Subcutaneous immunoglobulin

SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 List of the Key Issues identified by the EAG

Issue number	Summary of the issue	Report sections
1	Inappropriate standard of care comparator	2.3 / 4.2.4 / 6
2	Relevance of the overall trial populations to patients with refractory generalised myasthenia gravis	2.3 / 3.2.1.2.2 / 3.3
3	Relevance of the overall trial populations to patients who are AChR antibody-positive and MuSK antibody-positive	3.2.5.10.3
4	Appropriateness of alternative sources of response outcomes in relation to placebo effect	3.3 / 3.4 / 3.5 / 4.2.6.1
5	Response timepoint for all treatments	4.2.8.1
6	Resource use for chronic IVIg and PLEX therapy	4.2.8.1 / 4.2.8.3
7	Subsequent treatment following discontinuation of the index treatment	4.2.8.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are listed in section 1.7 and their cumulative effect on the company's base case ICER is shown in Table 2. We discuss these differences in section 1.3 and section 1.5.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

After submitting their evidence, the company informed NICE of an error in their NMA, affecting the rate of responders for rozanolixizumab, zilucoplan and efgartigimod. The company provided a revised version of their economic model, which includes the updated referent response rate of [redacted] and response rates for rozanolixizumab, zilucoplan and efgartigimod using a 2-point improvement in MG-ADL (Table 22).

The company's revised base case deterministic cost-effectiveness results for rozanolixizumab compared with efgartigimod, intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg), plasma exchange (PLEX) and zilucoplan are shown in Table 2. Rozanolixizumab provides an increase of 0.1914 QALYs at an additional cost [redacted] compared with IVIg/SCIg and provides an increase of 0.1906 QALYs at an additional cost [redacted] compared with standard of care (which is a basket of therapies: corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, and pyridostigmine). Rozanolixizumab [redacted]

The EAG requested the company to provide a version of the model that included standard of care as a comparator, with an option to include IVIg and PLEX within the standard of care arm (Clarification Question B2). The company did not provide this analysis, so we have created a standard of care arm using the functionality within the company's model. Using the company's revised base case, comparing rozanolixizumab with standard of care (the basket of therapies that includes corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, and pyridostigmine; and excludes IVIg and PLEX) results in an ICER of [redacted] per QALY (Table 2). The EAG note that the company did not include the cost of standard of care treatments (corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine) within the costs for the targeted therapies (rozanolixizumab, efgartigimod, IVIg/SCIg, PLEX and zilucoplan).

Table 2 Company updated base case results for rozanolixizumab, pairwise results, including PAS

Technologies	Total		Incremental vs. rozanolixizumab		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Rozanolixizumab	[redacted]	8.2293	-	-	-
IVIg/SCIg	[redacted]	8.0379	[redacted]	0.1914	[redacted]
Efgartigimod	[redacted]	8.2120	[redacted]	0.0173	[redacted]
PLEX	[redacted]	8.0950	[redacted]	0.1343	[redacted]
Zilucoplan	[redacted]	8.1418	[redacted]	0.0875	[redacted]
SoC (excl. IVIg/SCIg and PLEX)	£462,281	8.0387	[redacted]	0.1906	[redacted]

Source: adapted from CS Erratum March 2024 Table 69.
Excl.: excluding; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; PLEX: plasma exchange; QALY: quality adjusted life year; SCIg: subcutaneous immunoglobulin; SoC: standard of care

1.3 The Decision Problem: summary of the EAG's key issues

Issue 1 Inappropriate standard of care (SoC) comparator for patients with refractory generalised myasthenia gravis.

Report section	Section 2.3 (Decision Problem); section 4.2.4, section 6 (economic analysis)
Description of issue and why the EAG has identified it as important	The comparators used in the company's Decision Problem and economic model are inconsistent with the NICE scope. According to the NICE scope, standard of care (SoC) includes corticosteroids and immunosuppressants with or without intravenous immunoglobulin (IVIg) or plasma exchange (PLEX), i.e., an overall 'basket' of care. However, the company have included IVIg and PLEX as separate comparators. The EAG do not consider this to appropriately reflect SoC for patients with refractory generalised MG in England, which is the population specified in the company's Decision Problem.
What alternative approach has the EAG suggested?	The EAG's clinical experts advised that both IVIg and PLEX are used as chronic (i.e., maintenance) therapies for refractory patients as part of established clinical management (ECM). Some centres use IVIg as chronic therapy for refractory patients, but other centres (with a strict protocol for IVIg use) use PLEX instead.

	In our economic model base case, patients in the comparator arm receive the EAG's definition of ECM: 43.8% of patients receive IVIg along with the basket of other standard treatments (corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine; proportions shown in Table 20); 14.6% of patients receive PLEX plus the basket of other standard treatments, and 41.6% of patients receive only the basket of standard treatments. The data source for the proportions of patients receiving chronic IVIg and PLEX is the patient cohort in the efgartigimod Early Access to Medicine Scheme (EAMS),[1] which the EAG consider to be comparable to the patient group of interest for rozanolixizumab in the current appraisal. We conducted scenario analyses exploring the effect of different proportions of patients receiving IVIg and PLEX treatment within ECM.
What is the expected effect on the cost-effectiveness estimates?	Using the EAG's definition of ECM as the comparator decreases the ICER from [redacted] per QALY compared with SoC (obtained from the company's revised model), to [redacted] per QALY for rozanolixizumab versus ECM.
What additional evidence or analyses might help to resolve this key issue?	Further clinical opinion to clarify the proportions of patients with refractory generalised MG in England receiving chronic IVIg and PLEX treatment, and the proportion of this patient group who would be eligible to receive chronic IVIg or PLEX but receive neither.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Relevance of the overall trial populations to patients with refractory generalised myasthenia gravis

Report section	Section 2.3 (Decision Problem); section 3.2.1.2.2 (MycarinG population); section 3.3 (network meta-analysis populations)

Description of issue and why the EAG has identified it as important	The population specified in the company's Decision Problem is patients with AChR antibody-positive or MuSK antibody-positive generalised myasthenia gravis (MG) who are refractory to prior therapies. Clinical evidence for the efficacy of rozanolixizumab in a refractory population is more limited than for the broader generalised MG population specified in the NICE scope due to a smaller sample size and lack of statistical testing. The company's pivotal MycarinG trial (rozanolixizumab versus placebo) includes a relatively small (N=[redacted]) post-hoc refractory subgroup making up [redacted] of the randomised trial population while the RAISE trial of zilucoplan and the ADAPT trial of efgartigimod (comparators in the company's Decision Problem) contained 50% and 63% refractory patients respectively (although refractory was not defined in precisely the same way as in the Decision Problem in either comparator trial, and in ADAPT refractory patients were not reported as a subgroup). The EAG's clinical experts suggested that the overall randomised population of the MycarinG trial could be broadly reflective of refractory generalised myasthenia gravis patients in England, and we note that the randomised population and refractory subgroup in the trial generally experienced [redacted] treatment effects.
What alternative approach has the EAG suggested?	The EAG requested the company to conduct an NMA indirect comparison of rozanolixizumab against zilucoplan restricted to all refractory patients (both AChR antibody-positive and MuSK antibody-positive) and another NMA restricted to refractory patients who are AChR antibody-positive only (Clarification Question A11). However, the company state that no NMA could be conducted in the subgroup of patients with refractory generalised MG due to insufficient data, lack of a defined subgroup in the comparator trials or small sample size, and the introduction of further heterogeneity (Clarification Response A11). The EAG accept there may be data limitations but a systematic feasibility assessment would have clarified this.
What is the expected effect on the cost-effectiveness estimates?	Uncertain
What additional evidence or analyses might help to resolve this key issue?	Clinical consensus on whether each of the full-trial populations of the MycarinG, RAISE and ADAPT trials are reflective of patients with refractory generalised MG who would be seen in NHS clinical practice.

Issue 3 Relevance of the overall trial populations to patients who are AChR antibody-positive and MuSK antibody-positive

Report section	Section 3.2.5.10.3 (MycarinG subgroup analyses)
Description of issue and why the EAG has identified it as important	The company's Decision Problem states that rozanolixizumab is intended as an add-on to standard therapy for adult patients with AChR or MuSK antibody-positive generalised MG. However, the pivotal trial (MycarinG) primarily included patients who were AChR antibody-positive, with only a minority representation of MuSK antibody-positive patients (placebo n=8, 11.9% and rozanolixizumab ~7 mg/kg n=5, 7.6%). Patients with MuSK and AChR antibodies are expected to respond differently to treatments (section 2.2.1) as was demonstrated in the MycarinG trial (section 3.2.5.10.4). However, there is uncertainty around the response outcome for MuSK antibody-positive patients due to the very small subgroup size. The EAG are unclear whether the overall MycarinG trial population or the AChR subgroup is most appropriate for decision making. The overall trial population does approximate the relative proportions of MuSK and AChR antibody-positive patients likely to be seen in NHS clinical practice but may not accurately reflect clinical efficacy in the very small MuSK antibody-positive subgroup. Conversely, the AChR antibody-positive subgroup is likely to characterise clinical efficacy for most patients seen in clinical practice but excludes MuSK antibody-positive patients. The choice of population for decision making has implications for the availability of evidence, since the trials of comparator therapies vary in whether they include a defined AChR antibody-positive overall trial population (RAISE trial of zilucoplan which could be compared to the AChR antibody-positive subgroup of MycarinG) or include a defined AChR antibody-positive subgroup (ADAPT trial of efgartigimod which could be compared to the AChR antibody-positive subgroup of MycarinG). The comparator trials do not permit any comparisons specifically for MuSK antibody-positive patients.
What alternative approach has the EAG suggested?	Uncertainty may not be easily resolved for the MuSK antibody-positive patients as the population is so small.

	However, to increase certainty in the results for the AChR antibody-positive subgroup for the comparison of rozanolixizumab against zilucoplan the EAG requested indirect treatment comparisons (network meta-analysis, NMA, and matching-adjusted indirect comparison, MAIC) restricted to the AChR-positive subgroup of refractory patients in the MycarinG and RAISE trials. The company declined to conduct the NMA and MAIC as the appraisal for zilucoplan is still ongoing and thus, if/when approved, they consider that zilucoplan will not have been adopted for a long enough time to be considered part of the established management (Clarification Responses A11b and 13b). Whilst the EAG's requested analyses were intended to maximise the available evidence for decision making for the AChR antibody-positive subgroup, this does not address the question of whether this subgroup is the most appropriate unit of evidence for decision making in clinical practice.
What is the expected effect on the cost-effectiveness estimates?	Uncertain
What additional evidence or analyses might help to resolve this key issue?	Expert opinion on whether the overall trial population of MycarinG and the comparator trials would adequately reflect treatment efficacy across both MuSK antibody-positive and AChR antibody-positive patients or whether it would be more appropriate to focus on the AChR antibody-positive subgroup given the limited data available for MuSK antibody-positive patients.

Issue 4 Appropriateness of alternative sources of response outcomes in relation to the placebo effect

Report section	Sections 3.3 / 3.4 / 3.5 (critique of methods and results of the indirect treatment comparisons); 4.2.6.1 (economic model)

Description of issue and why the EAG has identified it as important	The company conducted NMAs which provide MG-ADL response odds ratios for comparisons of rozanolixizumab, efgartigimod and zilucoplan against placebo (albeit for overall trial populations rather than the potentially relevant subgroups noted in Key Issues 2 and 3). The NMAs do not account for the heterogeneity of placebo response rates, which were 31% and 30% respectively in the trials of rozanolixizumab and efgartigimod and, [redacted] for zilucoplan based on a 2-point improvement. To account for the placebo effect heterogeneity the 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]. The EAG consider this to be an inappropriately high response rate relative to the range of placebo responses observed in the trials. Moreover, the company do not explain the rationale for their calculation, which involved converting the odds ratios to relative risks then multiplying them by the referent placebo response rate. The company do not discuss how this calculation models the placebo effect or consider any assumptions that the calculation is based on. The resulting estimates of response rates when this calculation is applied in the economic model are inconsistent with expected values: the modelled response rate for zilucoplan ([redacted]) is [redacted] than that reported in the RAISE trial (73%), the modelled response rate for rozanolixizumab ([redacted] is [redacted] than that reported in the MycarinG trial (72%), and the modelled response rate for efgartigimod ([redacted]) is [redacted] than that reported in the ADAPT trial (68%). (NB the reported response rates were for a ≥2 point improvement in MG-ADL except in the RAISE trial which used a ≥3 point improvement – the 73% reported in RAISE would be higher if a ≥2 point improvement had been used). We note that the response rates from the NMAs are subject to additional uncertainty that is not reflected in these response rates, as the NMAs do not account for heterogeneity in the baseline characteristics of the included trials, as well as some other limitations (see section 3.4.2). Due to a lack of placebo-controlled trials, response rates for IVIg and PLEX are not available from the company's NMAs for the MG-ADL response outcome. The company instead derived the IVIg and PLEX response rates from a trial by Barth et al.[(2)]: 51% and 57%, respectively (and assumed the response rate for subcutaneous immunoglobulin (SCIg) is the same as the IVIg response rate). The Barth et al. trial[(2)] enrolled 84 patients in Canada who appeared to have refractory generalised MG although they were not explicitly defined as such. We are uncertain how representative this population would be of patients who are seen in UK clinical practice.

What alternative approach has the EAG suggested?	We sought the advice of two clinical experts who agreed that the company's modelled response rates for rozanolixizumab, efgartigimod and zilucoplan differ from expectation. The experts were also able to provide 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. We prefer to use the response rates for rozanolixizumab (72%), efgartigimod (68%) and zilucoplan (73%) based on results from the MycarinG, ADAPT and RAISE trials, respectively. This approach does not capture relative treatment effectiveness but provides estimates of response which the EAG's clinical experts agreed are more plausible than those calculated by the company. We also prefer to use the alternative response rates for IVIg and PLEX suggested by our clinical experts, because these are more likely to reflect UK clinical practice than estimates obtained from the Barth et al. trial. The EAG's approach does not utilise response rates from the NMAs due to the uncertainties noted above in the company's approach and with the NMAs themselves (see section 3.4.2). However, we requested additional analyses from the company, including matching-adjusted indirect comparisons (MAICs) to explore ways of accounting for heterogeneity in the NMAs (see section 3.3.2). The MAICs themselves have limitations as noted in section 3.4.2.
What is the expected effect on the cost-effectiveness estimates?	Using the trial response rates for rozanolixizumab, efgartigimod and zilucoplan, and a response rate of 70% for IVIg and PLEX reduces the ICER from [redacted] to [redacted] per QALY for rozanolixizumab compared with SoC. Comparing rozanolixizumab directly with IVIg, efgartigimod, PLEX and zilucoplan: rozanolixizumab [redacted] and results in an ICER of [redacted] per QALY versus IVIg.
What additional evidence or analyses might help to resolve this key issue?	In practice, neither the company's nor the EAG's approaches fully address all the uncertainties relating to the placebo effect. Opinions differ on the cause(s) of placebo effects in generalised MG trials, although regression to the mean due to the fluctuations in MG symptoms has been suggested as a likely contributor. Although the EAG's clinical experts agreed that the trial-based response estimates are more plausible than the company's estimates, these do not explicitly account for the observed placebo effects and their heterogeneity across trials. Consideration could be given to whether any scenario analyses could be conducted to reduce uncertainty in the response estimates, e.g. by assuming that the placebo response applies only to the placebo trial arms or applies also to active trial arms to clarify the boundaries of the uncertainty. Further clinical advice regarding response rates to IVIg and PLEX for patients with refractory generalised MG would be helpful, as the EAG obtained clinical advice from only two clinical experts.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 5 Using a response assessment timepoint of six weeks for all treatments

Report section	Section 4.2.8.1
Description of issue and why the EAG has identified it as important	The treatment response assessment timepoints used in the model are the time of the primary outcome assessment from the clinical trials for rozanolixizumab, efgartigimod and zilucoplan; and are assumptions for IVIg and PLEX (Table 22). Clinical advice to the EAG was that it would be reasonable to assess all interventions at 6 weeks, especially rozanolixizumab and efgartigimod, which have the same mechanism of action.
What alternative approach has the EAG suggested?	We use a response assessment timepoint of six weeks for all treatments.
What is the expected effect on the cost-effectiveness estimates?	This change has no effect on the ICER results for rozanolixizumab compared with IVIg and PLEX, because the response assessment timepoints for IVIg and PLEX do not change. Rozanolixizumab [redacted]
What additional evidence or analyses might help to resolve this key issue?	Further clinical advice about the most appropriate timepoint to assess response to treatment.

Issue 6 Resource use for chronic IVIg and PLEX therapy

Report section	Section 4.2.4
Description of issue and why the EAG has identified it as important	Treatment costs for chronic IVIg therapy are applied every 3 weeks and treatment costs for chronic PLEX are applied every 4 weeks in the company's base case. The EAG do not consider this reflects clinical practice in England. Clinical advice to the EAG was that IVIg is usually given every 4-8 weeks, that the interval can be extended to 12 weeks, and very rarely to 16 weeks, depending on patient response. All experts also explained that PLEX is usually administered every 4-8 weeks.
What alternative approach has the EAG suggested?	Based on our expert advice, we apply chronic IVIg and PLEX treatment costs every 6 weeks.
What is the expected effect on the cost-effectiveness estimates?	These changes result in ICER results of [redacted] per QALY for rozanolixizumab compared with IVIg, and [redacted] per QALY for rozanolixizumab compared with PLEX.

What additional evidence or analyses might help to resolve this key issue?	Further clinical opinion on how frequently patients with refractory generalised MG receive chronic IVIg and PLEX therapy.

Issue 7 Subsequent treatment following discontinuation of the index treatment

Report section	Sections 4.2.6.8 and 4.2.8.1
Description of issue and why the EAG has identified it as important	Refractory generalised MG is a condition that requires lifelong management. If patients do not respond, or lose response to a particular treatment, they are likely to go on to receive an alternative therapy. However, the model does not account for any subsequent treatments patients may receive after discontinuing rozanolixizumab or the comparators.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Clinical advice regarding potential subsequent treatments for patients who discontinue their index therapy. Modelling treatment discontinuation engines for each comparator within the economic model.

1.6 Other issues: summary of the EAG's view

The EAG identified other issues in the cost effectiveness evidence, but we do not consider these to be key issues as they have little impact on the model results. Details of our preferred assumptions are in section 1.7.

In previous technology appraisals for generalised MG there was uncertainty around the relevance of rituximab as a comparator. The EAG's clinical experts do not believe rituximab is a relevant comparator for patients with generalised MG who are AChR antibody-positive, because evidence for rituximab efficacy in this patient group is lacking and the other available comparators (efgartigimod, IVIg, PLEX and zilucoplan) are much faster acting.

However, our clinical experts explained that patients with generalised MG and MuSK antibodies do often respond well to rituximab. The EAG consider it likely that patients with

MuSK antibodies will be offered rituximab earlier in their treatment pathway and so would only be offered rozanolixizumab therapy if they did not respond to rituximab.

We note, rituximab is not listed as a comparator in the NICE scope nor in the company's Decision Problem, which the EAG agree is appropriate.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG's critique of the company's model (discussed in section 5.3) and the scenarios described in section 6.1, we have identified several aspects of the company's revised base case with which we disagree. Our preferred model assumptions are:

- Using established clinical management (SoC including IVIg and PLEX) as the comparator, with 43.8% of patients receiving IVIg; 14.6% of patients receiving PLEX; 41.6% of patients receiving neither;[1] all patients receive the cheaper standard therapies (Table 20) (EAG report section 6.1). However, we acknowledge there is uncertainty regarding the proportions of IVIg and PLEX used in established clinical management. We have conducted scenarios comparing rozanolixizumab directly to efgartigimod, IVIg, PLEX and zilucoplan using our base case (Table 39).
- Using a response rate of 70% for IVIg and PLEX (which produces a response rate of 40.88% in the established clinical management arm, when 43.8% of patients receive chronic IVIg and 14.6% of patients receive chronic PLEX) and trial response rates for rozanolixizumab, efgartigimod and zilucoplan.
- Using a response timepoint of 6 weeks for all treatments.
- Correcting the PLEX administration cost and removing zilucoplan administration costs after cycle 2.
- Applying the treatment and administration costs for chronic IVIg and chronic PLEX every 6 weeks, instead of every 3 and 4 weeks, respectively.

We also include the cost for standard of care treatments (specifically the proportions of corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate and pyridostigmine) in the costs for the company's Decision Problem comparator therapies (rozanolixizumab, IVIg/SCIg, efgartigimod, PLEX and zilucoplan), because this cost is included in the established clinical management arm we programmed into our base case. However, as this cost is common to all arms it has no effect on the ICER.

The EAG's preferred assumptions result in an ICER of [redacted] per QALY for rozanolixizumab compared with established clinical management (Table 3).

Table 3 Cumulative effect of the EAG's preferred model assumptions, rozanolixizumab versus established clinical management

Assumption	Cumulative ICER £/QALY
Company revised base case (SoC only, excluding IVIg and PLEX from ECM)	[redacted]
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	[redacted]
Using 70% response rates for IVIg and PLEX (giving a 40.88% response rate in the ECM arm) and trial response rates for rozanolixizumab (72.0%), zilucoplan (73.1%) and efgartigimod 68.0%)	[redacted]
Using a response assessment time point of 6 weeks for all treatments	[redacted]
Correcting PLEX and zilucoplan administration costs	[redacted]
Applying chronic IVIg treatment and admin costs every 6 weeks	[redacted]
Applying chronic PLEX treatment and admin every 6 weeks	[redacted]
EAG base case	[redacted]
ECM: established clinical management; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IVIg: intravenous immunoglobulin; MG-ADL: Myasthenia Gravis Activities of Daily Living score; PLEX: plasma exchange; QALY: quality-adjusted life-year; SoC: standard of care.	

The EAG did not identify any technical calculation errors in the company's economic model. For further details of the exploratory and sensitivity analyses undertaken by the EAG on our base case, see section 6.2.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from UCB Pharma on the clinical effectiveness and cost effectiveness of rozanolixizumab for treating antibody-positive generalised myasthenia gravis. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

After submission, the company identified an error in the NMA and the EAG received a corrected NMA Report, an updated model, and a CS Erratum on 25th March 2024. Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 28th March 2024. Responses from the company via NICE were received by the EAG on 22nd April 2024 and 29th April 2024, and these can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on generalised myasthenia gravis

The CS accurately describes myasthenia gravis (MG) as a chronic autoimmune disease caused by antibody-mediated destruction of the neuromuscular junction (NMJ) (CS sections B.1.3.1 and B.1.3.1.2). MG affects muscle function and control in patients and severity is classified using the Myasthenia Gravis Foundation of America (MGFA) classification, classes I-V: class I refers to ocular disease, classes II to IV refer to generalised disease involving other muscles impacting mobility, breathing, and swallowing (CS section B.1.3.1), and class V refers to myasthenic crisis requiring intubation with or without mechanical ventilation.[3]

2.2.1.1 Autoantibody status in myasthenia gravis

Approximately 80% to 90% of MG patients have autoantibodies that bind to the acetylcholine receptors (AChR) of the NMJ, about 3% to 7% have autoantibodies that bind to muscle specific tyrosine kinase (MuSK), and about 10% do not have AChR or MuSK autoantibodies detected (CS section B.1.3.1.1; NICE Scope). One of the EAG's clinical experts explained that the proportion of MG patients with MuSK autoantibodies in the UK is only around 2% due to the genetic and geographic variation of the autoantibody type which is more prevalent in women in their thirties and increases in prevalence towards the Equator. The main differences between AChR antibody-positive and MuSK antibody-positive patients are that

MuSK antibody-positive patients tend to have more severe bulbar symptoms (relating to swallowing) and generalised weakness, including crises,[4-6] and are more likely to develop refractory disease[7]. One of the EAG's clinical experts said that MuSK anti-body positive patients initially present with more severe disease.

2.2.1.2 Refractory myasthenia gravis

As explained in the company's Decision Problem (see section 2.3 below), this appraisal focuses on adult patients with refractory AChR antibody-positive or MuSK antibody-positive generalised MG (CS section B.1.1).

2.2.1.2.1 Definition of refractory MG

The Association of British Neurologists (ABN) myasthenia gravis management guidelines (2015) do not include a definition of refractory MG.[8] Various definitions in the scientific literature have been summarised as follows: failure to respond adequately to conventional treatment; severe or intolerable adverse effects from immunosuppressive or symptomatic therapy; inability to reduce immunosuppressive therapy without clinical relapse or need for ongoing rescue therapy e.g. intravenous immunoglobulin (IVIg) or plasma exchange (PLEX); comorbid conditions restricting use of conventional therapies; or frequent myasthenic crises even while on immunosuppressive and symptomatic therapy.[9] The company definition of refractory MG comprises uncontrolled disease despite standard treatment (inadequate response to $\geq$2 prior MG therapies, after acetylcholinesterase inhibitors (AChEIs)) and the patient is being treated with or considered for additional therapy such as IVIg or PLEX (Decision Problem CS section B.1.1). The EAG's clinical experts agreed that the company's definition of refractory is appropriate, although one expert noted that it does not include a disease severity score threshold which might be expected as in clinical practice successful treatment is when symptoms are reduced leading to a low disease severity measure score (see also section 3.2.1.2.2).

2.2.1.2.2 Epidemiology of refractory MG

The company estimate that around 19,053 people are living with MG in England.[10] CS section B.1.3.1.1 states that around 15% of patients with generalised MG are refractory to standard therapy,[7, 11] which is consistent with other reports of between 5% and 20% in the scientific literature,[12-15] and with the estimated proportions of refractory patients in the practices of the EAG's clinical experts.

2.2.1.2.3 Prognostic factors for refractory patients

Prognostic factors for generalised MG, confirmed by one of the EAG's clinical experts, are MG autoantibody status (patients with MuSK antibodies have a more severe disease

course), age at diagnosis, disease severity at diagnosis, and presence of thymoma (although patients do not need thymoma to have a thymectomy and so prior thymectomy is not a reliable way of interpreting prognosis). The EAG's clinical experts noted that refractory patients who have received maximal doses of corticosteroids and immunosuppressants are more likely to become resistant to further treatment. Refractory patients are more likely to have developed comorbidities as side effects of long-term corticosteroid use, such as obesity, diabetes, dyslipidaemia, hypertension, etc, which may influence their prognosis. However, one expert said that not all refractory patients have comorbidities, and refractory patients can be young or old. Another expert said that refractory MG patients are most commonly female with an early age of MG onset, anti-MuSK antibodies, and thymomas.[16] Patients with refractory disease are more likely to experience exacerbations (a sudden worsening of symptoms requiring hospitalisation) and myasthenic crises (severe muscle weakness requiring intubation and/or mechanical ventilation) (MGFA class V), and more likely to be hospitalised than those without refractory disease. [14]

2.2.1.2.4 Disease burden for refractory patients

The CS discusses the clinical and treatment burden of MG, impact on quality of life and the effects of poor symptom control on patients in CS section B.1.3. Specifically, disease symptoms and clinical burden of generalised MG are discussed in CS section B.1.3.1.3. In addition, the EAG note evidence from the 2017 Muscular Dystrophy UK re-audit of unplanned hospital admissions in patients with neuromuscular disease reported that MG and other neuromuscular junction disorders were the most common reason for admission (121 admissions) amounting to 1878 hospital bed days and 30% of the intensive therapy unit bed days in a 30-month period;[17] and evidence from the UK Clinical Practice Research Datalink (CPRD) of primary care records which suggests people with refractory generalised MG experience a greater treatment burden than those who are not refractory.[18]

2.2.2 Background information on rozanolixizumab

Rozanolixizumab (brand name Rystiggo®) is a neonatal fragment crystallizable receptor (FcRn) inhibitor, and its mechanism of action is described in CS Table 2 and CS Figure 1. According to the Summary of Product Characteristics (SmPC), rozanolixizumab is indicated as an add-on to standard therapy for the treatment of generalised MG in adult patients who are AChR antibody-positive or MuSK antibody-positive.[19]

Patients receive a short (up to 18 minutes) subcutaneous infusion of rozanolixizumab via a syringe driver once per week for six weeks (CS Table 2). This is one treatment cycle; further treatment cycles are dependent on clinical evaluation and as such will vary by patient. Estimates of the number of treatment cycles per year vary from an average annualised

number of cycles per patients of [redacted] (company estimate based on the results of the pivotal MycarinG trial, CS Table 2) and up to a maximum of five cycles (based on the MycarinG trial protocol FDA review section 6.3.2)[20] Each dose is weight-based, and the licensed dose is ~7 mg/kg (CS section B.2.3.1).

The rozanolixizumab infusion is administered in an outpatient centre or hospital setting (CS Table 2). The ongoing MG0020 (NCT05681715) study evaluating two different self-administration methods implies potential for self-administration in the future.[21] One of the EAG's clinical experts noted that self-administration could be possible with training, but it is not suitable for all patients, e.g. the elderly, and inability to self-administer could require community or home care input. Although the study is irrelevant to this appraisal (it has no relevant efficacy outcomes), if self-administration is implemented this could have implications for longer-term costs.

2.2.3 The current treatment pathway

The CS describes the current treatment pathway for MG in CS section B.1.3.2.2. According to CS Figure 3, patients with generalised MG are initially treated with acetylcholinesterase (AChE) inhibitors (usually pyridostigmine) with the addition of corticosteroids if they are not effective. Thymectomy is an option for patients aged under 45 years, although effectiveness may not be seen for up to a year. Thymectomy is not suitable, however, for MuSK antibody-positive patients. Non-steroidal immunosuppressive therapies (ISTs) are added to these treatments if patients are non-responsive, and/or to try to reduce the corticosteroid dose. Patients who remain with active disease despite immunosuppression are considered refractory. Treatment can differ for patients with MuSK autoantibodies as they tend to not respond to acetylcholinesterase inhibitors (AChEIs) and may still need high doses of steroids alongside any non-steroidal ISTs. The EAG's clinical experts said that MuSK antibody-positive patients may be offered rituximab early on or they may be controlled on high doses of steroids only with resultant side-effects.

Both refractory and non-refractory generalised MG patients can experience exacerbations or myasthenic crises (refractory patients experience these events more frequently) for which the treatment is IVIg or PLEX. This is usually referred to as rescue therapy to distinguish it from chronic (i.e. maintenance) use of IVIg or PLEX.

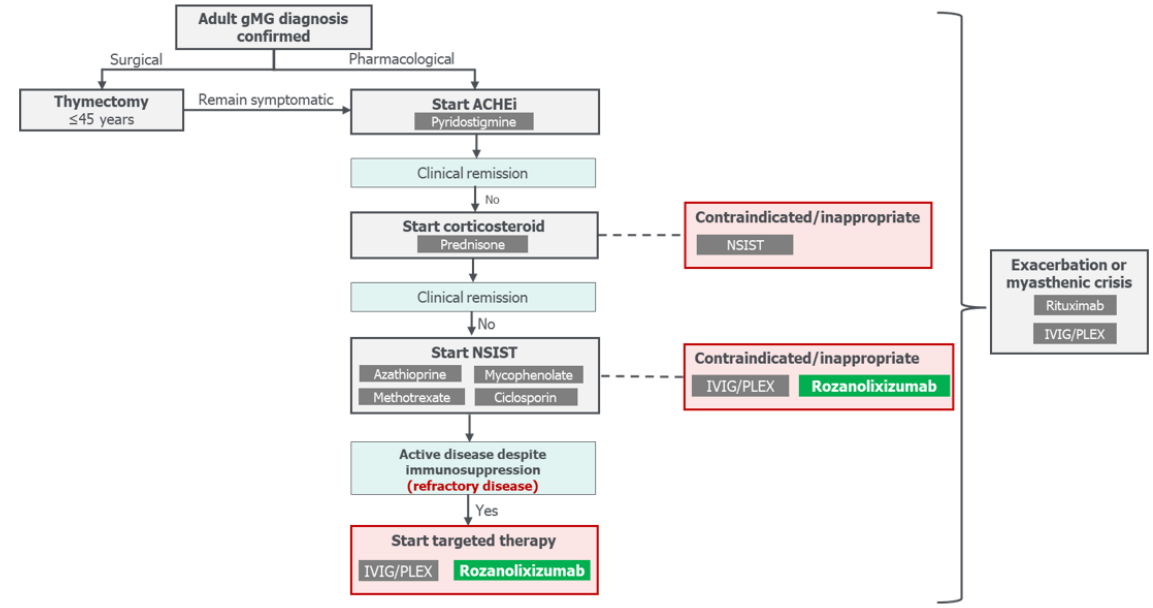
CS Figure 3 shows that if a patient has refractory disease (i.e. active disease despite immunosuppression) then they would start therapy with either IVIg or PLEX. This corresponds with IVIg or PLEX as part of inpatient management for MG patients in hospital

in the ABN MG guidelines,[8] and the commissioning policy for immunoglobulin use in England which specifies the circumstances where IVIg and/or PLEX may be used chronically for refractory patients.[22] This is off-label use of IVIg and PLEX as neither are licensed for use in MG.

2.2.4 Positioning of rozanolixizumab in the treatment pathway

The company position rozanolixizumab as an add-on to standard therapy for adults with refractory AChR antibody-positive or MuSK antibody-positive generalised MG (CS section B.1.3.4), and this is in accordance with the SmPC,[19] as noted above in section 2.2.2, except that the SmPC does not restrict its use to refractory MG patients.

The position of rozanolixizumab in the treatment pathway is shown in CS Figure 4, reproduced below in Figure 1.



Source: Reproduction of CS Figure 4.

gMG: generalised myasthenia gravis; IST: immunosuppressant therapy; IVIg: intravenous immunoglobulin; NSIST: non-steroidal immunosuppressant therapy; PLEX: plasma exchange

Figure 1 Proposed positioning of rozanolixizumab for refractory gMG

Rozanolixizumab is positioned at two points in the treatment pathway:

- When non-steroidal ISTs are contraindicated or inappropriate and IVIg or PLEX would be indicated. This is illustrated in CS Figure 4 as being prior to the refractory disease stage and therefore outside of the company's definition of refractory. However, the EAG consider this is appropriate because there would be no further

options at this stage apart from rituximab (off-label), or IVIg or PLEX, which are the therapies that a refractory population would be eligible for.

- When refractory disease is diagnosed and IVIg or PLEX therapy is being used or considered, which is in keeping with the company indication for refractory patients for this appraisal.

CS Figure 4 only shows use of rituximab as a rescue therapy. It is unclear how the position of rozanolixizumab would affect the use of rituximab for the treatment of MuSK antibody-positive patients. The EAG's clinical experts advised that rituximab is often administered to MuSK antibody-positive patients 'early on', although exactly when was not specified. It is therefore unclear whether rozanolixizumab would be indicated for MuSK antibody-positive patients for whom early-administered rituximab has failed or whether rituximab would be a comparator with rozanolixizumab for these patients. (NB use of rituximab is off-label and does not feature in current guidelines).

Rozanolixizumab is not intended to replace the use of IVIg or PLEX as rescue therapy, i.e., as therapy for exacerbation or myasthenic crisis.

EAG conclusion on the condition and treatment pathway

The company have accurately described generalised MG and the treatment pathway in the CS. Rozanolixizumab is positioned as an alternative treatment to IVIg or PLEX for refractory disease and for when non-steroidal ISTs are contraindicated.

2.3 Critique of the company's definition of the Decision Problem

Table 4 summarises the Decision Problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this.

The company's Decision Problem is consistent with the NICE scope with two exceptions (a narrower population and a difference of interpretation of the standard of care comparator), and the MuSK antibody-positive subgroup introduces uncertainties, as explained in Table 4 above:

- **Population:** The CS focuses on a subgroup of patients with refractory generalised MG. This is narrower than the population specified in the NICE scope and the marketing authorisation for rozanolixizumab which are not limited to refractory patients. The uncertainty around how well the available clinical evidence reflects the refractory population of patients with generalised MG is described in Key Issue 2 in section 1.4 above.
- **Comparator:** The CS does not include all standard of care treatments as defined in the NICE scope. The company compares rozanolixizumab against PLEX and rozanolixizumab against IVIg separately instead of comparing rozanolixizumab against the combined comparator specified in the NICE scope, i.e. standard of care (including ISTs with or without IVIg or PLEX). The EAG preferred interpretation of the standard of care comparator is described in Key Issue 1 in section 1.3 above.
- **Subgroups:** The CS includes MuSK antibody-positive patients as a subgroup which is consistent with the NICE scope but, due to its very small sample size and because these patients are known to respond differently to treatments, the inclusion of this subgroup in the evidence could introduce uncertainties, see Key Issue 3 in section 1.4 above. Additionally, we are uncertain whether rituximab is a relevant comparator for this subgroup, although evidence would be limited.

Table 4 **Summary of the Decision Problem**

	Final scope issued by NICE	Company's Decision Problem	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	There is a 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. Both IVIg and PLEX are a burden to the patient and costly to the healthcare system. Refractory gMG is associated with a substantial clinical and economic burden vs non-refractory disease. In addition, adult patients with AChR or MuSK Ab+ refractory gMG are those who clinicians are expected to prioritise as per the label granted by the EMA and approved by the MHRA.	The company's Decision Problem population is limited to refractory patients which is a subset of the population specified in the NICE scope and enrolled in the company's pivotal trial (MycarinG). The EAG's clinical experts agree that the company's rationale for focusing on refractory patients is appropriate. However, the company's network meta-

		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		analyses (NMAs) that compared rozanolixizumab against zilucoplan or efgartigimod were based on whole-trial populations which included both refractory and non-refractory patients. This deviation from the Decision Problem is noted by the EAG as a Key Issue (Key Issue 2). NMAs focusing on the refractory subgroup were requested by the EAG but have not been provided (Clarification Response A11). The Decision Problem population consists of AChR Ab+ and MuSK Ab+ patients. This

				is consistent with the populations in the NICE scope (which is not limited to any specific antibody type) and the MycarinG trial (which included patients positive for either anti-AChR or anti-MuSK antibodies). Subgroup analysis of AChR Ab+ and MuSK Ab+ patients is therefore appropriate – see EAG comments on the company's subgroup analyses below.
Intervention	Rozanolixizumab	Rozanolixizumab	Not applicable	The intervention is consistent with the NICE scope and the indication specified in the SmPC.
Comparators	• Efgartigimod (subject	• Efgartigimod (subject	• It is anticipated that efgartigimod and zilucoplan will be approved for use in refractory patients with gMG (subject to NICE evaluation)	The company's comparators are

	to NICE evaluation) • Zilucoplan (subject to NICE evaluation) • Ravulizumab (subject to NICE evaluation) • Standard of care without rozanolixizumab (including ISTs [a] [including rituximab] with or without IVIg or PLEX)	to NICE evaluation) • Zilucoplan (subject to NICE evaluation) • IVIg • PLEX	• IVIg/PLEX (added to corticosteroids and ISTs [b]) is the current SoC in patients who are refractory to treatment; therefore IVIg and PLEX are relevant comparators for this submission • NICE was unable to make a recommendation on ravulizumab due to withdrawal of the evidence submission by the company • Rituximab was not included as comparator as it is not licensed in the UK for gMG and has not been robustly studied in the target population. Furthermore, NHSE CCP and AWTCC expert opinion recommend its use at different points of the clinical pathway [b] and [redacted] [c]	appropriate with two exceptions: (i) The company have excluded standard of care as specified in the NICE scope, i.e. "including ISTs (including rituximab) with or without IVIg or PLEX". Instead of modelling PLEX and IVIg as part of standard of care (per the NICE scope) the company have modelled them separately. The EAG and our clinical experts believe this misrepresents clinical practice and we have raised this as a Key Issue (Key Issue 1). (ii) The company's justification for excluding

				rituximab is appropriate for AChR antibody-positive patients. However, the EAG's clinical experts suggested that rituximab is more efficacious in MuSK Ab+ patients than AChR Ab+ patients. Rituximab may therefore be relevant as a comparator for the MuSK Ab+ subgroup, although this subgroup is small in size and the company have not analysed it separately (see EAG comment on subgroup analyses below). The company's citation of the zilucoplan EAG report here is

				inaccurate as that report refers only to AChR Ab+ patients.
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. It is unclear why the number of, and reasons for, hospitalisation/emergency room visits were reported for MG0007 (CS B.2.6.2.4) but not for MycarinG. The sources for the number and duration of hospitalisations are provided in CS Table 67.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.			The company's approach to the economic analysis is consistent with the specifications

	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			of the NICE scope.
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • adults with autoantibodies against AChR • adults with autoantibodies against MuSK • adults with severe MG needing IVIg or PLEX	None	• The data from the clinical trials included patients with autoantibodies against AChR or MuSK. The population with anti-MuSK antibodies is small in the trial, introducing considerable uncertainty. The clinical results are presented for the individual subgroups in Section B.2.7.4; however, the economic modelling considers the overall trial population. • The overall population in the submission already includes adults with severe MG needing IVIg or PLEX, so it is not treated as a subgroup. When the MycarinG primary efficacy endpoint was assessed in patients with MG-ADL score >5 at Baseline (see Section B.2.7), the results were consistent with the overall population, thus a scenario economic analysis for this subgroup was not performed.	Whilst the EAG agree with the company that the MuSK Ab+ subgroup is very small (placebo 11.9%, rozanolixizumab 7.6%) we note that MuSK Ab+ patients exhibited a consistently larger treatment effect than those who were AChR Ab+, for the changes from baseline in MG-ADL score (CS Table 37), MGC score (CS Table 38), and QMG score (CS Table 39) Given these differences, the EAG are uncertain whether it is appropriate to pool together

				AChR Ab+ and MuSK Ab+ patients and we have raised this as a Key Issue for further consideration (Key Issue 3). The company did not consider analysing the AChR Ab+ subgroup separately in their ITCs which would have reduced uncertainty in interpretation, (note that although the MuSK Ab+ subgroup is small, the AChR Ab+ subgroup is, conversely, large). Regarding the company's second bullet point, the EAG agree that the company's Decision Problem

				already reflects a population group with severe MG.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisatio	There is geographic variability in treatment availability and access to specialist centres, which introduces inequality among patients with MG in terms of access to care. The introduction of rozanolixizumab will improve equity of access to treatment, as its administration does not require	Not applicable	The EAG agree that these are appropriate considerations, although the company have not provided any quantitative supporting data.

	n granted by the regulator.	highly specialised equipment or training. Home administration by a healthcare professional may be considered for patients who have tolerated administration of rozanolixizumab in the clinic.		

AChEI, acetylcholinesterase inhibitor; AChR, acetylcholine receptor; AWTCC, All Wales Therapeutic and Toxicology Centre; CCP, clinical commissioning policy; EMA, European Medicines Agency; EQ-5D, EuroQoL 5-Dimensions instrument; gMG, generalised myasthenia gravis; IST, immunosuppressant therapy, IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MHRA, Medicines and Healthcare Products Regulatory Agency; MGS-PRO, Myasthenia Gravis Symptoms Patient Reported Outcomes instrument; MuSK, muscle-specific kinase; NHSE, National Health Service England; QALY, quality-adjusted life year; PLEX, plasma exchange; PSS, Personal Social Service; SoC, standard of care.

[a] ISTs (including mycophenolate) are not currently licensed for MG in the UK;

[b] From NHSE CCP[23] and AWTCC[24] clinical expert opinion on rituximab in gMG;

[c] From EAG report on zilucoplan[25]

Source: Reproduction of CS Table 1 with EAG comments added.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's methods of evidence review

The company carried out a systematic literature review (SLR) to identify studies of the clinical effectiveness of rozanolixizumab and other treatments in patients with MG. Information on the SLR is provided in CS section B.2.1 and CS Appendix D, and in a separate company SLR update report dated January 2024. Details of the same SLR are also provided in a company network meta-analysis (NMA) report (version 1.2 March 2024).

The SLR searches used a broad set of search terms and were up to date when received by the EAG, covering the period from database inception to 1st May 2023 in an original search and from May 2023 to 24th January 2024 in an update search. Eligibility criteria for the SLR are inconsistent between the CS and the separate company SLR update report but this is a minor issue and otherwise the methods of the SLR for randomised controlled trials (RCTs) appear appropriate (Appendix 9.1). The company searches have not missed any relevant RCTs; however, no systematic search was conducted to check whether any non-randomised studies of comparators might be relevant for unanchored indirect treatment comparisons (ITCs) conducted by the company. The company's ITCs also have other limitations e.g. lack of heterogeneity assessment, which are discussed in sections 3.3 to 3.4 of this report.

The company conducted two other SLRs, one for studies of cost-effectiveness, costs and resource use; and another for studies of health-related quality of life (discussed in cost-effectiveness sections 4.1 and 4.2.7.1 of this report respectively).

3.2 Critique of the studies included and the company's analyses of these

3.2.1 Included studies

The clinical effectiveness SLR identified 80 studies from the original search, of which 47 RCTs aligned with the definition of generalised MG used in RAISE (the pivotal zilucoplan trial), and eight RCTs (prioritised from 60 studies) from the update search of which only one was new to the overall SLR (CS Figures 5 and 6). Therefore 48 RCTs were prioritised as relevant, and they were categorised according to MG severity (CS section B.2.1.1). Five studies evaluated rozanolixizumab; their eligibility for inclusion is discussed in CS section B.2.2 and below.

Two of the five trials that evaluated rozanolixizumab were included in the CS:

- MycarinG (MG0003), the pivotal company-sponsored completed phase III RCT, and
- MG0007, the open-label extension RCT evaluating longer-term safety and efficacy of two doses of rozanolixizumab.

The EAG agree that the remaining three studies evaluating rozanolixizumab that were identified in the SLR but not included in the CS were excluded appropriately:

- UP0018 phase I safety study in healthy volunteers.
- MG0002 phase II study.[26] The company explain that it does not inform the economic model (CS section B.2.2.), but do not state what SLR exclusion criteria this study meets. The EAG note that only the first part of the trial is comparative with placebo, for only three once-weekly doses and the dosing schedule does not correspond with the later studies MycarinG and MG0007. Thus, it does not provide informative evidence additional to MycarinG and we agree with its exclusion from the clinical efficacy evidence.
- MG0004 extension study to MycarinG. This study was terminated early due to the burden for patients of once-weekly visits to the study centre for 52 weeks for treatment administration. Participants (n=60) transferred to the MG0007 trial. MG0004 does not inform the economic model; however, safety results are reported in CS Appendix F.1.2. This appropriate and the EAG refer to the MG0004 study in the safety results section of this report only.

3.2.1.1 Study characteristics

The MycarinG trial compared two doses of rozanolixizumab (~7 mg/kg or ~10 mg/kg) against placebo, and in the MG0007 extension study participants were re-randomised to either the ~7 mg/kg or ~10 mg/kg dose of rozanolixizumab. Thus, MycarinG is the only relevant RCT that has compared rozanolixizumab against placebo. MycarinG and MG0007 are described in CS section B.2.3.1 and summarised in the sections below.

3.2.1.1.1 MycarinG (MG0003) trial

MycarinG was a 14-week, phase III, multicentre, double-blind, placebo-controlled RCT. The trial was international, including the US, Japan and Europe. There were no UK sites. Key features are summarised in Table 5 below.

Table 5 MycarinG trial design

Study characteristic	Key details
Population	Patients with generalised MG, including both AChR antibody-positive and MuSK antibody-positive participants as pre-planned subgroups.
Key eligibility criteria	• Age ≥18 years • MGFA class II-IVa • MG-ADL score ≥3 (with ≥3 points from non-ocular symptoms) • QMG score ≥11 • Under consideration for additional treatment, e.g. IVIg or PLEX
Post-hoc analysis subgroup for DP: Refractory patients	Defined as: uncontrolled disease despite standard treatments, i.e., inadequate response to ≥2 prior MG therapies (after AChEIs), and an additional therapy such as IVIg or PLEX is being administered or considered.
Sample size	**Randomised population:** N=200 (rozanolixizumab ~7 mg/kg: n=66; rozanolixizumab ~10 mg/kg: n=67; placebo: n=67). **Refractory subgroup**: N=[redacted] (rozanolixizumab ~7 mg/kg: n=[redacted]; rozanolixizumab ~10 mg/kg: n=[redacted]; placebo: n=[redacted]). **AChR Ab+ subgroup**: N=179 (rozanolixizumab ~7 mg/kg: n=60; rozanolixizumab ~10 mg/kg: n=60; placebo: n=59). **MuSK Ab+ subgroup:** N=21 (rozanolixizumab ~7 mg/kg: n=5; rozanolixizumab ~10 mg/kg: n=8; placebo: n=8).
Intervention	Six once-weekly subcutaneous infusions of rozanolixizumab (either ~7 mg/kg or ~10 mg/kg) as an add-on to standard care, which comprises one treatment cycle. Mock infusions were administered if participant IgG levels dropped below 1g/L or if IgG levels were between ≥1 and <2g/L and the patient experience persistent or recurrent infection. Permitted concomitant medications: oral corticosteroids, methotrexate, mycophenolate mofetil, cyclosporine, azathioprine, cholinesterase inhibitors, and tacrolimus.
Comparator	Six once-weekly subcutaneous infusions of placebo as an add-on to standard care.
Duration	Six-week treatment period followed by an 8-week observation period. Study is complete.
Primary outcome	Change from baseline to Day 43 (end of the 6-week treatment period) in MG-ADL score.
Key secondary outcomes	Change from baseline to Day 43 in MGC, QMG, MGS-PRO scales for bulbar weakness, physical fatigue, and muscle weakness fatiguability; and MG-ADL responder rate at Day 43.
Other outcomes	See outcomes assessment in section 3.2.3 of this report.

Source: CS section B.2.3.1, CS Table 1, CS Appendix E.1.1, E.1.2, E.1.3.
Ab+: antibody-positive; AChEIs: acetylcholinesterase inhibitors; AChR: acetylcholine receptor; DP: company Decision Problem ; IVIg: intravenous immunoglobulin; MG: myasthenia gravis; MG-ADL: Myasthenia Gravis Activities of Daily Living score; MGC: Myasthenia Gravis Composite score; MGFA: Myasthenia Gravis Foundation of America; MGS-PRO: Myasthenia Gravis Symptoms Patient Reported Outcomes; MuSK: muscle-specific tyrosine kinase; PLEX: plasma exchange; QMG: Quantitative Myasthenia Gravis score.

The EAG have not identified any key issues with the study design of MycarinG, although we note that the trial is relatively short (14 weeks) relative to the lifelong condition of MG. Therefore, there is little evidence to support discussion of long-term efficacy or treatment effect waning of rozanolixizumab.

Three of the population subgroups reported for MycarinG are of key interest:

- Refractory patients (post-hoc subgroup). This subgroup is aligned with the company's Decision Problem. However, we are uncertain whether this subgroup or the whole trial population best reflects the refractory generalised MG population in clinical practice (see Key Issue 2 in section 1.4) which is relevant to the company's ITCs. NB the CS refers to this subgroup as study participants who have a history of ≥2 prior MG specific therapies and does not repeat the part of the definition where an additional therapy such as IVIg or PLEX is being administered or considered because this repeats the original trial eligibility criteria.
- MuSK antibody-positive patients (pre-specified subgroup). MuSK antibody-positive patients respond differently to treatments and therefore separate subgroup analysis is valuable. As MuSK is a rare MG autoantibody type (section 2.2.1.1), the subgroup sample size is, expectedly, small (21 patients across all trial arms; 10.5% of the randomised population), although proportionally larger than in clinical practice in the UK (where approximately 2% of patients with generalised MG have the MuSK antibody type). However, the small subgroup size imposes uncertainty in the interpretation of the subgroup results and their generalisability to clinical practice (see Key Issue 3 in section 1.4).
- AChR antibody-positive patients (pre-specified subgroup). This subgroup is comparable with the trial populations for comparator MG interventions that have included AChR antibody-positive patients (e.g. RAISE for zilucoplan and ADAPT pre-specified subgroup for efgartigimod), and the sample size for this subgroup in MycarinG is robust.

3.2.1.1.2 MG0007 trial

MG0007 was an open label, randomised observational extension study that evaluated the efficacy and safety of further cycles of rozanolixizumab treatment at the two different doses (~7 mg/kg or ~10 mg/kg). The study was completed in January 2024; however, the latest data cut provided by the company for this submission is July 2022 so the EAG do not have access to the full results. In the CS, results are reported for up to [redacted] treatment cycles. A cycle consists of a six-week treatment period, followed by a 16-week observation period, and then a non-treatment period that continues until the start of the next cycle or the end of study assessment.

Participants entered MG0007 after completing the MycarinG observation period, or if they required rescue therapy during the observation period of MycarinG they could choose either to receive IVIg or PLEX and discontinue the trials or to rollover into MG0004 or MG0007 and receive rozanolixizumab (Clarification Response A1). Participants from the terminated MG0004 study, which was also an extension study of MycarinG noted in the included studies section 3.2.1 above, were also eligible to enter MG0007.

Participants were re-randomised to either rozanolixizumab ~7 mg/kg (n=79) or rozanolixizumab ~10 mg/kg (n=78) on entering either MG0004 or MG0007; participants who were re-randomised in MG0004 used the last dosage received in MG0004 as their dose in MG0007. Out of 167 enrolled participants in MG0007, [redacted] received at least one dose of the study drug and were included in the safety set on which the safety and efficacy analyses relevant to this submission were performed.

Mock infusions were not necessary in MG0007 as treatment arms were not blinded and the dose could be reduced or temporarily discontinued due to reduced IGg levels along with other reasons. (further details in are CSR section 8.1 and Clarification Response A3).

Dose switching was permitted at the beginning of a treatment cycle at the investigator's discretion (CSR section 3.5.1). [redacted] study participants switched dose during their time in the study (CS section B.2.10.1.3). [redacted] participants switched from rozanolixizumab ~7 mg/kg to ~10 mg/kg in cycles subsequent to cycle 1, and [redacted] participants switched from rozanolixizumab ~10 mg/kg to ~7 mg/kg in cycles subsequent to cycle 1 (Clarification Response A3). This is sufficient to confound the effect of the two doses. For example, when participants are analysed in their randomised set it could make the lower dose appear more effective than it is: the extension study results for the ~7mg randomised group, which included those switching to ~10 mg to gain effect, may be more optimistic than would be expected when rozanolixizumab is used at only the ~7

mg/kg dose in practice. Dose switching will not be possible in practice as the ~7mg /kg dose is the only licensed dose. However, the results reported in CS section B.2.6.2.2 group the study participants according to actual dose received within each study cycle which reduces the risk of confounding by dose but increases the risk of confounding by imbalances in patient characteristics since random patient allocation no longer applies.

Subgroup analyses: There was no analysis of a refractory subgroup in MG0007. However, results are reported for several outcomes for the MG autoantibody subgroups: AChR antibody-positive (rozanolixizumab ~7 mg/kg n=[redacted]; and rozanolixizumab ~10 mg/kg n=[redacted]); and MuSK antibody-positive (rozanolixizumab ~7 mg/kg n=[redacted]; and rozanolixizumab ~10 mg/kg n=[redacted]) (CS Table 14).

To conclude, the CS provides relatively limited data for MG0007 compared to the intended duration of the trial as per use of the interim data cut from July 2022; additionally, results for up to ([redacted] of treatment) are reported whereas results from further cycles are described as consistent but not reported (CS section B.2.6.2.1); there is confounding due to dose-switching. Nonetheless, MG-ADL response data from MG0007 informs assumptions for continued response in the economic model (section 4.2.6.2 below).

3.2.1.2 Participants' baseline characteristics in MycarinG

3.2.1.2.1 Overall trial population

Baseline characteristics for all study participants for each trial arm are reported in CS Tables 10, 11 and 12.

The EAG's clinical experts confirmed that the overall trial population generally reflects MG patients in UK clinical practice, with some minor exceptions. The trial inclusion criteria did not have an upper age limit, but the EAG's clinical experts noted that they are likely to see older patients in clinic and that the trial only included five Black patients (Black patients tend to have a more severe disease course).

There are slight differences between arms in: age at initial diagnosis (participants were slightly younger at diagnosis in the placebo group, age 41.4 years, compared to the rozanolixizumab ~7 mg/kg group, age 46.6 years); sex (there were more females in the placebo group (70.1%) compared to the rozanolixizumab ~7 mg/kg group (59.1%)); and in MGFA class (there were more MGFA class IIIa participants in the placebo group (41.8%) compared to the rozanolixizumab ~7 mg/kg group (31.8%) with the balance made up in the lower MGFA classes IIa and IIb, thus the placebo group included participants with more

severe disease according to MGFA class. One of the EAG's clinical experts noted a floor effect in the MGFA classes – that it is harder to see treatment effects when the disease is mild – although they do not consider any of the differences in patient characteristics between trial arms sufficiently large to be likely to introduce any bias.

3.2.1.2.2 Relevance to a refractory population

CS Table 12 reports that [redacted]/200 ([redacted]) of participants in MycarinG were treatment refractory according to the trial definition (≥2 prior MG specific therapies, see Table 5 and section 3.2.1.1.1 above). The MycarinG trial therefore contains [redacted] proportion of refractory participants compared to the generalised MG population in clinical practice (5% to 20%, section 2.2.1 above).

One of the EAG's clinical experts noted that a disease severity score was not part of the definition of 'refractory' whereas in clinical practice successful treatment reduces symptoms, leading to a lower PRO score (e.g., MG-ADL <5, represents controlled disease). However, the mean (SD) baseline MG-ADL score for the overall trial population was 8.3 (3.4) which [redacted] the mean MG-ADL score ([redacted]) for the refractory subgroup (CS Table 11 and CS Appendix Table 30 respectively), and our experts confirmed this is appropriate for refractory disease. The trial's subgroup for MG-ADL score ≥5 shows [redacted] of participants had an MG-ADL score ≥5 in the overall trial population and the post-hoc refractory subgroup: 86.5% and [redacted] respectively. Additionally, the trial eligibility criteria include the participant either receiving or being considered for IVIg or PLEX, meaning that the overall trial population is likely to be reflective of a refractory population, or one that is contraindicated or intolerant to other MG treatments.

Baseline characteristics for the refractory subgroup of participants, those who in addition to original trial eligibility criteria had at baseline received ≥2 prior MG treatments, are reported in CS Appendix E.1.3 Tables 29, 30 and 31. Most of the participant characteristics are [redacted] to those of the overall trial population with the exception that [redacted] participants had undergone thymectomy in the refractory group ([redacted]) than in the overall trial population (41.5%). One of the EAG's clinical experts would have expected a higher proportion of MuSK antibody patients in the refractory subgroup as these patients are more likely to have severe disease.

The EAG's clinical experts confirmed that the population in the refractory subgroup is generally reflective of refractory patients in clinical practice. They noted that there were more prior myasthenic crises in the placebo group ([redacted]) compared to the rozanolixizumab ~7 mg/kg group ([redacted]), but that this would probably be unlikely to affect subsequent treatment

response. The EAG note that slightly more participants in the rozanolixizumab ~7 mg/kg group had thymectomy ([redacted]) compared to the placebo group ([redacted]). The difference between treatment groups for females that was seen in the overall trial population is not seen in the refractory subgroup where the groups are more balanced: [redacted] females in the placebo group and [redacted] females in the rozanolixizumab ~7 mg/kg group. Overall, we conclude that the balance of participant characteristics is at low risk of introducing bias.

EAG conclusion on study and patient characteristics in the included studies

The EAG have not identified any key issues with the study design of MycarinG and it provides data for relevant subgroups: refractory, MuSK antibody-positive, and AChR antibody-positive patients. The [redacted] of patient baseline characteristics (and the [redacted] of the results, see section 3.2.5) of the overall population compared to the refractory subgroup is supportive of using the results of the overall trial population of MycarinG to draw inferences about clinical efficacy of rozanolixizumab in refractory patients. Dose-switching in the MG0007 extension trial introduces confounding and therefore uncertainty in the efficacy results.

3.2.2 Risk of bias assessment

The company assessed the risks of bias for the MycarinG and MG0007 trials using criteria according to the checklist for RCTs in the 2015 NICE single technology appraisal user guide (CS Appendix D.2).[27] The EAG agree that the company's critical appraisal approach is appropriate and we assessed the trials using the same criteria. The company and EAG assessments are provided below in Appendix 9.2.1 (MycarinG) and Appendix 9.2.2 (MG0007).

EAG conclusion on risk of bias in the included studies

We judged the MycarinG trial to be mainly at low risk of bias, although with some uncertainty around how missing data were accounted for in the intention to treat analysis (i.e. an unclear risk of bias relating to missing data). In contrast, we judged the MG0007 open-label extension trial to have a high risk of bias on account of its open-label design, the lack of a placebo control group, and because dose-switching between the ~7mg/kg and ~10mg/kg rozanolixizumab arms was not adjusted for.

3.2.3 Outcomes assessment

The main aim of treatment for MG is to control a patient's symptoms, and therefore the main clinical outcomes use instruments which measure disease symptom and severity, and

health-related quality of life (HRQoL). Response was defined as achievement of specified threshold changes in scores on the MG-ADL, MGC, QMG and MGS-PRO instruments.

3.2.3.1 Disease symptom and severity measures

Several measures of disease symptoms and severity and HRQoL were used in the MycarinG and MG0007 trials and included in the CS (see Table 6 below). Here we outline the measures used for the primary outcome, secondary outcomes, and the EQ-5D utility measure (an 'other', i.e. not primary or secondary, outcome which informs the company's economic evaluation). Two of these outcomes, the MG-ADL response rate and the MG-ADL score change from baseline to Day 43, are also reported for the company's indirect treatment comparisons (see section 3.5).

Myasthenia Gravis Activities of Daily Living (MG-ADL). The MG-ADL asks eight questions about talking, chewing, swallowing, breathing, ability to brush teeth or comb hair, ability to arise from a chair, double vision, and eyelid droop. The questions are each scored 0-3, with 0 representing normal ability and 3 representing maximum impairment, giving a total score ranging from 0 to 24, with higher scores indicating greater disease severity. The MG-ADL is entirely patient-reported and relatively quick to use. The MCID is 2 points.[28, 29]

Myasthenia Gravis Composite score (MGC). The MGC is a 10-item scale comprised of both patient-reported outcomes (for speech, chewing, swallowing and respiratory function) and physician measured outcomes (to evaluate ocular, neck and proximal limb muscles using quantitative tests and spirometry). Items are weighted so that a maximum score for worst respiratory function is worth more points than the maximum score for worst eyelid strength. The total score ranges from 0 to 50 and higher scores indicate more severe disease. The MCID is 3 points.[30]

Quantitative Myasthenia Gravis scale (QMG). The QMG has 13 items that measure endurance or fatiguability, each scored 0 to 3, giving a total score ranging from 0 to 39, with higher scores indicating greater disease severity. The QMG scale is based on a physical examination requiring a dynamometer and spirometer and can take up to 25 minutes to complete, therefore it is used mostly in research rather than clinical practice. The MCID is 2 or 3 points.[28]

Myasthenia Gravis Symptoms – Patient Reported Outcomes (MGS-PRO). The MGS-PRO comprises 42 items across five scales: ocular-, bulbar-, and respiratory muscle weakness; physical fatigue; and muscle weakness fatiguability. It involves a more detailed

assessment of muscle weakness across different muscle groups than other available PRO measures. Each MGS-PRO scale has a score range from 0 to 100 with a higher result indicating more frequent and severe symptoms. The scores are rated on a 7-day recall period. Each scale is designed to stand alone from the others. In MycarinG the company used the bulbar muscle weakness, physical fatigue, and muscle weakness fatiguability scales as secondary outcomes, which the company justify as reflective of the symptoms that are more common and relevant to the trial's target population (Clarification Response A4). The remaining scales for ocular weakness and for respiratory weakness were 'other' trial outcomes, for which the results are reported for completeness in Clarification Response A4. An MCID has not been established.[31, 32]

Myasthenia Gravis Quality of Life 15 revised version (MG-QoL15r). The MG-QoL15r has 15 items relating to mobility (9 items), symptoms (3 items), and contentment and emotional wellbeing (3 items). Each item is scored 0 to 2, with total scores ranging from 0 to 30, and higher scores indicating worse quality of life. The MG-QoL15r has improved psychometric properties compared to the original version of the instrument (MG-QoL15). However, an MCID has not been established.[28]

EQ-5D-5L index and visual analogue scale (VAS) scores. EQ-5D results from the pooled treatment arms in MycarinG are used in the economic model, and the VAS scores are summarised briefly in the CS (CS section B.2.6.1.3).

Myasthenia Gravis Impairment Index (MGII). The MGII is a validated questionnaire that measures MG disease severity using 22 patient-reported items and six clinical examination items. Total scores range from 0 to 84 and higher scores indicate more severe impairments. The questions have a 2-week recall period. The total score can be divided into two sub-scores, ocular (eight items) and generalised (20 items). The MGII total score has an MCID of 5.5.[33, 34]

The MG-ADL, QMG and MGC are widely used instruments for assessing patients with MG. The MGS-PRO and MGII instruments are not widely used in clinical practice, confirmed by the EAG's clinical experts. The EAG's clinical experts agreed that the outcome measures reported in the CS are appropriate and the thresholds are clinically appropriate as they meet the published minimum clinically important difference (MCID) for these instruments where they have been established. Using all these measurement instruments together gives an overview of the full range of symptoms experienced by MG patients as well as reflecting the patients' and physicians' perspectives when reporting symptoms.

3.2.3.2 Other clinical effectiveness outcomes

Time to clinically meaningful improvement is an outcome in the NICE scope and in MycarinG this was measured as median time (days) to MG-ADL response (≥2 points improvement) (CS section 3.2.5.8).

Hospitalisation is an outcome in the NICE scope but the company state this data was not captured in the clinical trials (CS Table 1), although some data are reported for MG0007 (CS section B.2.6.2.4; safety section 3.2.5.12.3 below).

3.2.3.3 Safety outcomes

The CS reports a summary of all treatment emergent adverse events, serious adverse events, and those leading to treatment discontinuation in MycarinG, MG0007 and MG0004, and for a pooled analysis of MycarinG and MG0007 to evaluate repeated cycles of treatment. Relevant adverse events of special interest (Hy's Law and liver injury) were assessed. Overall, the safety outcomes are reported comprehensively and the EAG have not identified any issues with the way in which they were assessed.

EAG conclusion on outcomes assessment

The CS reports a broad selection of appropriate disease symptom and severity measures to determine treatment response in the MycarinG trial, but only MG-ADL response and MG-ADL change from baseline are reported for the indirect treatment comparisons (except for comparison against IVIg for which only QMG response and QMG change from baseline are reported). Several measures of HRQoL are also reported including EQ-5D which was used in the economic model. The safety outcomes are comprehensive.

3.2.4 Statistical methods of the included studies

3.2.4.1 Analysis populations

3.2.4.1.1 MycarinG trial

The CS uses the Randomised Set (RS) to provide an intention to treat (ITT) analysis of all randomised participants in MycarinG, which the EAG consider is appropriate.

3.2.4.1.2 MG0007 trial

The CS uses the Safety Set (SS) – all randomised participants who received at least one dose of rozanolixizumab – however a modified ITT analysis was not carried out because the CS reports results from the Safety Set according to actual dose received within a study cycle

due to substantial (permitted) dose-switching (section 3.2.1.1.2). The ~7 mg/kg indicated licensed dose of rozanolixizumab is relevant to this appraisal therefore it is necessary to observe the results for this group separately from the ~10 mg/kg dose. No adjustments were made to account for dose-switching and the EAG consider the results are confounded. No statistical testing was planned for this study (CS Table 18).

3.2.4.2 Sample size calculation

3.2.4.2.1 MycarinG trial

The company used a complex algorithm to calculate the sample size which was determined to be between 150 and 240 participants to achieve 90% power (CS Table 19). A total of 200 participants were randomised and overall, the EAG consider MycarinG is likely to be adequately powered to detect statistically significant differences between the trial arms according to the company's calculations.

3.2.4.2.2 MG0007 trial

No formal sample size calculation was performed (CS Table 18).

3.2.4.3 Methods to account for multiplicity

3.2.4.3.1 MycarinG trial

The primary outcome and five of the six secondary outcomes (i.e., not including MG-ADL response) were subject to a parallel gatekeeping testing procedure with a truncated Hochberg test (CSR section 4.6 and Bril et al. 2023).[35] This is a strong method for controlling the overall family-wise error rate,[36] although there are insufficient details reported to know if it was carried out appropriately. No justification is provided for not including the MG-ADL response outcome in the testing procedure.

3.2.4.3.2 MG0007 trial

Only the rozanolixizumab ~7mg/kg arm of MG0007 is relevant for clinical efficacy inferences in this technology appraisal. Multiplicity of comparative statistical tests is therefore not an issue.

3.2.4.4 Statistical analysis of outcomes

3.2.4.4.1 MycarinG trial

Efficacy analyses were adjusted for using appropriate covariates: baseline MG-ADL score, geographic region, and randomisation stratification factors (MG-specific antibody type, i.e.,

AChR or MusK) (CS Table 18), however whether the analyses would be sensitive to the inclusion of other covariates is not discussed.

The EAG note that appropriate general approaches are used for analysis: analysis of covariance approach based on a mixed model with repeated measures for continuous change-from-baseline outcomes (CS Tables 20 to 25), and logistic regression to provide an odds ratio for the dichotomous MG-ADL response outcome (CS Table 26).

3.2.4.4.2 MG0007 trial

Only the rozanolixizumab 7mg/kg arm of MG0007 is relevant for clinical efficacy inferences in this technology appraisal. Statistical comparisons between the trial arms (i.e., ~7mg/kg versus ~10mg/kg) are therefore not applicable.

3.2.4.5 Handling of missing data

3.2.4.5.1 MycarinG trial

Three analysis strategies were employed in the MycarinG trial for handling missing data arising from intercurrent events (rescue medication use or withdrawals due to treatment-emergent adverse events):

- a hypothetical and treatment policy strategy, used for the primary analysis of continuous outcomes (i.e. score changes from baseline), with intercurrent events treated as missing data from the point of the intercurrent event onwards;

- a treatment policy strategy used as a sensitivity analysis for continuous outcomes in which all data were included in the analysis irrespective of whether intercurrent events occurred,

- a composite strategy used as a sensitivity analysis for continuous outcomes where intercurrent events were considered treatment failures and imputed with a worst-case score; and used as the primary analysis for dichotomous outcomes, i.e. response rates, with intercurrent events treated as non-response.

Several imputation approaches were used to obtain missing intercurrent events data and missing outcome score data to enable intention to treat analysis to be conducted and to perform sensitivity analyses around different data missingness assumptions. The analysis strategies and imputation approaches are summarised in Appendix 9.3 of this report.

The analysis strategies and imputation methods employed by the company in MycarinG are broadly appropriate. However, we note the following limitations: no quantitative data were provided to verify the assertion in the CS section B.2.12.2 that the results of the sensitivity analyses are similar to those of the primary analyses; the reference group for the Jump-to-Reference approach is not specified; results reported in the CS show that some data were missing, without explanation, after imputation (CS Tables 20 to 25); there is insufficient information in the CS and CSR to judge whether the imputation methods were implemented correctly.

3.2.4.5.2 MG0007 trial

The approach for handling missing data in MG0007 summarised in CS Table 18 is consistent with the approach reported in the Statistical Analysis Plan (SAP).

Only the rozanolixizumab ~7mg/kg arm of MG0007 is relevant for clinical efficacy inferences in this technology appraisal. Statistical comparisons between the trial arms (i.e. ~7mg/kg versus ~10mg/kg) are therefore not applicable.

The EAG note several inconsistencies and limitations in the approach to handling missing data in MG0007. Those of greatest relevance to the MG-ADL score change from baseline outcome, which is the only data from MG0007 used to inform the economic model (for continued response), are: methods for handling missing data refer to the missing data from individual items within the PRO scores, not any data missing due to intercurrent events; each PRO was handled differently with different missing data thresholds for deciding to apply imputation (apart from MG-ADL and QMG which followed the same imputation rules); MG-ADL score imputation methods are based on averages of available scores which would overestimate statistical precision and risk introducing bias.

3.2.4.6 Sensitivity and post-hoc analyses

3.2.4.6.1 MycarinG trial

Sensitivity analyses relating to missing data assumptions are summarised in section 3.2.4.5.1 above and Appendix 9.3.

Subgroup analyses: All subgroup analyses were descriptive, and no statistical testing was carried out (CS section B.2.7.3). As such, results of the pre-specified subgroup analyses by baseline MG antibody type (AChR or MuSK) are reported for the changes from baseline in MG-ADL, QMG & MGC in CS Tables 37 to 39, and results of the subgroup analyses for the MG-ADL, MGC and QMG response rates are provided only as a brief narrative description in CS section B.2.7.4.1. The CSR provides forest plots of the results of the subgroup analyses

by other trial baseline characteristics for the continuous change from baseline outcomes (CSR Figures 8-2, 8-8 and 8-9), but not for the response rate outcomes.

Refractory subgroup: As this is a subgroup analysis, the EAG assume that the statement in CS section B.2.7.3 also applies to the post-hoc analysis of the refractory subgroup (≥2 prior MG therapies (not including AChEIs)). The results reported for the changes from baseline in the MG-ADL, QMG, and MGC scores (CS Tables 40 to 42) and for MG-ADL, QMG, and MGC response rates (CS Tables 43 to 45) include descriptive statistics to show mean score changes (for score changes from baseline), odds ratios (for response rates), and the difference versus placebo. No statistical testing was planned or reported.

3.2.4.6.2 MG0007 trial

Brief narrative summaries are provided for the results of the pre-specified subgroup analyses relevant to the NICE scope (MG antibody type: AChR or MuSK) for the changes from baseline in scores of the MG-ADL, QMG, MGC, and three MGS-PRO scales (CS section B.2.7.4.3). No further subgroup analyses are reported in the CS, and there was no refractory subgroup analysis for MG0007.

EAG conclusion on study statistical methods

We find the statistical approaches for MycarinG and MG0007 to be generally appropriate, however, there were several limitations around the handling of missing data for both trials, and although there was no statistical testing was planned for MG0007 there was no method to account for the dose-switching. Therefore, we should be cautious when interpreting any results that are observed to have missing data.

3.2.5 Efficacy results of the intervention studies

In this section we provide results for the placebo group and the licensed rozanolixizumab dose group (~7 mg/kg) only as this dose is the company's intended indication for rozanolixizumab. Results for the rozanolixizumab ~10 mg/kg dose group are reported in the CS, and we have included them in the safety results section of this report (section 3.2.5.12).

3.2.5.1 MG-ADL score change from baseline to Day 43

The MG-ADL score change from baseline to Day 43 was the primary outcome of the MycarinG trial. The change from baseline to Day 43 during each treatment cycle was an outcome in MG0007, although the main outcomes in MG0007 focused on assessments of safety (CS Table 18).

3.2.5.1.1 MycarinG trial

Table 7 below summarises the results for MG-ADL score change from baseline at Day 43. In the randomised set (overall trial population), the MG-ADL score decreased overall at day 43 in both trial arms. The decrease was only clinically meaningful (≥2.0) in the rozanolixizumab ~7 mg/kg trial arm (-3.370) and the difference from the placebo arm was statistically significant.

In the refractory subgroup, the MG-ADL score [redacted] at Day 43 in [redacted], and this was [redacted] in the rozanolixizumab ~7 mg/kg trial arm, [redacted] than for the randomised set.

Table 6 MG-ADL score change from baseline to Day 43 in MycarinG (randomised set and refractory subgroup)

Analysis	**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) -2.586 (-4.091 to -1.249) p=<0.001
Refractory subgroup [a] Mean [SD]	[redacted]	[redacted]	LS mean (97.5% CI) [redacted]
Sources: CS sections B.2.6.1.1, B.2.7.4.2. [a] post-hoc analysis; refractory defined as ≥2 prior treatments (not including acetylcholinesterase inhibitors). CI: confidence interval; LS: least squares; SD: standard deviation; SE: standard error.			

Various sensitivity analyses performed to account for missing doses, missing scores, and the impact of COVID-19, are not reported in the CS, some are reported descriptively in the CSR and they are described as [redacted] of the primary analysis (CSR section 8.1.2). The analysis for the randomised set using study participants who received all 6 weekly doses up to Day 43 is reported for the ~7 mg/kg rozanolixizumab dose as: [redacted] (CSR section 8.1.2).

3.2.5.1.2 MG0007 trial

A consistent and clinically meaningful reduction in MG-ADL score was achieved by study participants in both rozanolixizumab trial arms for up to [redacted] cycles of treatment (CS section B.2.6.2.2). It is unclear why results from cycle 5 are not reported because the CS mentions

that there were five cycles for other outcomes although it only reports a range and not the results for individual cycles. Participants receiving the rozanolixizumab ~7 mg/kg dose achieved a mean reduction in MG-ADL score between [redacted] points across up to [redacted] cycles (CS Table 29). There is some missing data, range: [redacted] missing per cycle.

Results from MG0007 are reported by grouping study participants by actual dose received during each cycle (CS Table 29 footnote) instead of by randomised treatment allocation, therefore the results are confounded due to dose-switching (section 3.2.1.1.2). This applies to all outcomes reported for MG0007 in the CS. Results from MG0007 are illustrative of continued effectiveness of rozanolixizumab but due to high risk of bias in the study design they are subject to uncertainty.

The MG-ADL score CFB from cycle [redacted] of MG0007 contributes to the economic model assumptions for continued response (section 4.2.6.2 and CS section B.3.3.4). This cycle showed [redacted] in MG-ADL total score compared to the other cycles, however, it had the smallest sample size of all the cycles ([redacted]) with [redacted] participants missing. Therefore, the data informing the model is from treatment cycle with the least robust data from a trial at high risk of bias and we believe the assumption for continued response with rozanolixizumab should be interpreted with caution.

3.2.5.2 MG-ADL response (≥2 points from baseline) at Day 43

The proportion of MG-ADL responders (improvement ≥2 points from baseline) at Day 43 was a secondary outcome in both MycarinG and MG0007 trials.

3.2.5.2.1 MycarinG trial

In the randomised set (overall trial population), the proportion of MG-ADL responders at Day 43 in the ~7 mg/kg rozanolixizumab dose and placebo arms were 68.2% and 28.4% respectively, and this was statistically significant; the refractory subgroup showed [redacted] proportions of responders ([redacted]% and [redacted]% respectively), see Table 7 below.

Table 7 MG-ADL response at Day 43 in MycarinG (randomised set and refractory subgroup)

Analysis	Rozanolixizumab ~7 mg/kg (RS N=66; refractory N=[redacted])	Placebo (RS N=67; refractory N=[redacted])	Difference
Randomised set	(n=66) 45 (68.2)	(n=67) 19 (28.4)	OR (95% CI); p-value 5.765 (2.100 to 14.882); p<0.001

Responders, n (%)			
Refractory subgroup [a] Responders, n (%)	[redacted]	[redacted]	OR (97.5% CI); p-value [redacted]
Sources: CS Table 26, CS B.2.7.4.2 and CS Table 43. [a] post-hoc analysis; refractory defined as ≥2 prior treatments (not including acetylcholinesterase inhibitors). CI: confidence interval; OR: odds ratio; RS: randomised set.			

The confidence intervals are wide for both the refractory subgroup and the randomised set, however both of the results are statistically significant.

3.2.5.2.2 MG0007 trial

The proportion of MG-ADL responders at Day 43 of each treatment cycle was consistent in both rozanolixizumab trial arms for up to [redacted] cycles of treatment; with participants receiving the rozanolixizumab ~7 mg/kg dose achieving a responder rate of [redacted] for each of the [redacted] cycles consecutively (CS Table 35). It is unclear why the results from the [redacted] cycle are not reported. These results from MG0007 show [redacted] compared to MycarinG, however they are subject to uncertainty due to high risk of bias in the study design and from dose-switching.

3.2.5.3 MGC score change from baseline to Day 43

The MGC score change from baseline to Day 43 was a secondary outcome in MycarinG and MGC score change from baseline to Day 43 during each treatment cycle was a secondary outcome in MG0007.

3.2.5.3.1 MycarinG trial

Results for the overall trial population (randomised set) show that for participants receiving the rozanolixizumab ~7 mg/kg dose, the decrease in MGC score was both clinically meaningful (LS mean -5.930 points compared to the 3 points threshold for MCID) and statistically significant compared to placebo, see Table 8 below.

Results for the refractory subgroup also show that the rozanolixizumab ~7 mg/kg dose [redacted] the MGC score [redacted] and was [redacted] than placebo, see Table 8 below.

Table 8 MGC score change from baseline to Day 43 in MycarinG (randomised set and refractory subgroup)

Analysis	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) -5.930 (0.916)	(n=62) -2.029 (0.917)	LS mean (95% CI) -3.901 (-6.634 to -1.245) p=<0.001
Refractory subgroup [a] Mean [SD]	[redacted]	[redacted]	LS mean (97.5% CI) [redacted]
Sources: CS sections B.2.6.1.2 (CS Table 21) and B.2.7.4.2 (CS Table 41). [a] post-hoc analysis; refractory defined as ≥2 prior treatments (not including acetylcholinesterase inhibitors). CI: confidence interval; LS: least squares; RS: randomised set; SD: standard deviation; SE: standard error.			

3.2.5.3.2 MG0007 trial

A consistent and clinically meaningful reduction in MGC score was achieved by study participants in both rozanolixizumab trial arms for up to [redacted] cycles of treatment (CS section B.2.6.2.2). Participants receiving the rozanolixizumab ~7 mg/kg dose achieved a mean reduction in MGC score between [redacted] points across up to [redacted] cycles (CS Table 30).

3.2.5.4 MGC response at Day 43

MGC response at Day 43 was an 'other' outcome in MycarinG and response at Day 43 for each treatment cycle was an 'other' outcome in MG0007; results are also reported for the refractory subgroup for this outcome. Response was defined as ≥3.0 points improvement from baseline.

3.2.5.4.1 MycarinG trial

In the randomised set (overall trial population), the proportion of MGC responders at Day 43 in the ~7 mg/kg rozanolixizumab dose arm was higher than the proportion of responders in the placebo arm: 60.9% compared to 40.6% respectively (CS section B.2.6.1.3). In the refractory subgroup, the proportion of MGC responders at Day 43 in the ~7 mg/kg rozanolixizumab dose arm was [redacted] the proportion of responders in the placebo arm: [redacted] compared to [redacted] respectively (CS Table 44). As an 'other' trial outcome these results were not tested statistically, but the proportions of MGC responders are [redacted] for the overall trial population and the refractory subgroup.

3.2.5.4.2 MG0007 trial

For the first [redacted] treatment cycles, the proportions of MGC responders at Day 43 for the rozanolixizumab ~7mg/kg group were [redacted] (CS section B.2.6.2.3). These results from MG0007 show [redacted] compared to MycarinG, however they are subject to uncertainty due to high risk of bias in the study design and from dose-switching.

3.2.5.5 QMG score change from baseline to Day 43

The QMG score change from baseline to Day 43 was a secondary outcome in MycarinG and the change from baseline to Day 43 during each treatment cycle was a secondary outcome in MG0007.

3.2.5.5.1 MycarinG trial

Results for the randomised set (overall trial population) show that for participants receiving the rozanolixizumab ~7 mg/kg dose, the decrease in QMG score was both clinically meaningful (LS mean -5.398 points compared to the 3 points threshold for MCID) and statistically significant compared to placebo, see Table 10 below.

Results for the refractory subgroup show that the rozanolixizumab ~7 mg/kg dose [redacted] the QMG score by [redacted] and was [redacted] than placebo, see Table 9 below.

Table 9 QMG score change from baseline to Day 43 in MycarinG (randomised set and refractory subgroup)

Analysis	**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) -5.398 (0.679)	(n=62) -1.915 (0.682)	LS mean (95% CI) -3.483 (-5.614 to -1.584) p=<0.001
Refractory subgroup [a] Mean [SD]	[redacted]	[redacted]	LS mean (97.5% CI) [redacted]
Sources: CS sections B.2.6.1.2 (CS Table 22) and B.2.7.4.2 (CS Table 42). [a] post-hoc analysis; refractory defined as ≥2 prior treatments (not including acetylcholinesterase inhibitors). CI: confidence interval; LS: least squares; RS: randomised set; SD: standard deviation; SE: standard error.			

3.2.5.5.2 MG0007 trial

A consistent and clinically meaningful reduction in QMG score was achieved by study participants in both rozanolixizumab trial arms for up to [redacted] cycles of treatment (CS section B.2.6.2.2). Participants receiving the rozanolixizumab ~7 mg/kg dose achieved a mean reduction in QMG score between [redacted] points across up to [redacted] cycles (CS Table 31). These results from MG0007 show a [redacted] compared to MycarinG, however they are subject to uncertainty due to high risk of bias in the study design and from dose- switching.

3.2.5.6 QMG response at Day 43

QMG response at Day 43 was an 'other' outcome in MycarinG and response at Day 43 for each treatment cycle was an 'other' outcome in MG0007; results are also reported for the refractory subgroup for this outcome. Response was defined as ≥3.0 points improvement from baseline.

3.2.5.6.1 MycarinG trial

In the randomised set (overall trial population), the proportion of QMG responders at Day 43 in the ~7 mg/kg rozanolixizumab dose arm was higher than the proportion of responders in the placebo arm: (54.7%) compared to (39.1%) respectively (CS section B.2.6.1.3).

In the refractory subgroup, the proportion of QMG responders at Day 43 in the ~7 mg/kg rozanolixizumab dose arm was [redacted] the proportion of responders in the placebo arm: [redacted] compared to [redacted] respectively (CS Table 45). As an 'other' trial outcome these results were not tested statistically, but the results for the QMG response for the refractory subgroup show [redacted] in the rozanolixizumab arm, and [redacted] in the placebo arm, compared to the randomised set.

3.2.5.6.2 MG0007 trial

For the first [redacted] treatment cycles, the proportions of QMG responders at Day 43 for were [redacted] (CS section B.2.6.2.3). These results from MG0007 show a [redacted] compared to MycarinG, however they are subject to uncertainty due to high risk of bias in the study design and from dose-switching.

3.2.5.7 MGS-PRO scores change from baseline to Day 43

Change from baseline to Day 43 for the MGS-PRO scales "Muscle Weakness Fatiguability", "Physical Fatigue", and "Bulbar Muscle Weakness" were secondary outcomes in MycarinG, and MGS-PRO score change from baseline to Day 43 during each treatment cycle for

"Muscle Weakness Fatiguability", "Physical Fatigue", and "Bulbar Muscle Weakness" were secondary outcomes in MG0007.

3.2.5.7.1 MycarinG trial

Table 10 below shows that participants receiving the rozanolixizumab ~7 mg/kg dose achieved greater improvement than placebo in each of the reported MGS-PRO scores, and that this was statistically significant.

Table 10 MGS-PRO score changes from baseline in MycarinG (randomised set)

Outcome	Rozanolixizumab ~7 mg/kg (RS N=66)	Placebo (RS N=67)	Difference LS mean (95% CI); p-value
"Muscle Weakness Fatiguability" LS mean (SE)	(n=65) -23.029 (3.034)	(n=62) -10.588 (3.034)	-12.441 (-21.804 to -4.089); p=<0.001
"Physical Fatigue" LS mean (SE)	(n=65) -19.287 (3.046)	(n=62) -10.637 (3.051)	-8.650 (-18.058 to -0.134); p=0.012
"Bulbar Muscle Weakness" LS mean (SE)	(n=65) -14.839 (2.406)	(n=62) -3.519 (2.397)	-11.320 (-18.958 to -4.998); p=<0.001
Sources: CS section B.2.6.1.2 (CS Tables 23, 24 and 25). CI: confidence interval; LS: least squares; RS: randomised set; SE: standard error.			

Change from baseline to Day 43 for the remaining MGS-PRO scales "Respiratory Muscle Weakness" and "Ocular Muscle Weakness", 'other' outcomes in MycarinG, are reported in Figures 2 and 3 of Clarification Response A4: at Day 43 both rozanolixizumab groups showed a score change of around [redacted] for both "Respiratory Muscle Weakness" and "Ocular Muscle Weakness" and this is interpreted as showing [redacted] in score change from baseline compared to placebo which showed [redacted] (exact figures for mean change not reported).

It is unclear by how much the reduced MGS-PRO scores are clinically meaningful as there is no published MCID nor is any threshold discussed in the CS.

3.2.5.7.2 MG0007 trial

Consistent improvements (reductions) were seen in the mean "Muscle Weakness Fatiguability" scores (range [redacted]), the mean "Physical Fatigue" scores (range

[redacted]), and the mean “Bulbar Muscle Weakness” scores (range [redacted]) for the first [redacted] treatment cycles (CS Tables 32, 33 and 34).

3.2.5.8 Time to MG-ADL response

Time to MG-ADL response (≥2 points improvement) was an ‘other’ outcome in both MycarinG and MG0007. Time to response was only reported for the MG-ADL response outcome.

3.2.5.8.1 MycarinG trial

Median time to MG-ADL response in MycarinG was 16 days (97.5% CI 13 to 23 days) for the rozanolixizumab ~7 mg/kg group and could not be determined for the placebo group (CS Table 27).

3.2.5.8.2 MG0007 trial

For the rozanolixizumab ~7 mg/kg group results for the first [redacted] cycles were [redacted]: the median number of days to MG-ADL response was [redacted] days respectively (CS Table 36). These results from MG0007 show a [redacted] time to response compared to MycarinG, however they are subject to uncertainty due to high risk of bias in the study design and from dose-switching.

3.2.5.9 HRQoL outcomes

MG-QoL15r, MGII, and EQ-5D-5L score change from baseline at Day 43 were ‘other’ outcomes in MycarinG; and MG-QoL15r and EQ-5D-5L score change from baseline at Day 43 for each treatment cycle were ‘other’ outcomes in MG0007.

3.2.5.9.1 MycarinG trial

The change from baseline to Day 43 in MG-QoL15r score showed a higher mean (SD) decrease in participants who received the rozanolixizumab ~7 mg/kg dose (-4.0 (6.1)) compared to those who received placebo (-1.3 (4.3)) (CS section B.2.6.1.3).

The change from baseline to Day 43 in MGII score showed a higher mean (SD) decrease in participants who received the rozanolixizumab ~7 mg/kg dose (-12.4 (16.5)) compared to those who received placebo (-3.4 (10.4)) (CS section B.2.6.1.3).

The change from baseline to Day 43 in EQ-5D-5L VAS score showed a higher mean (SD) increase in participants who received the rozanolixizumab ~7 mg/kg dose (12.2 (19.9)) compared to those who received placebo (6.1 (18.2)) (CS section B.2.6.1.3).

These ‘other’ HRQoL outcomes were not statistically tested, and there were some missing data for MGII, meaning that the HRQoL results are subject to uncertainty. But the results of the HRQoL outcomes do suggest that rozanolixizumab did generally achieve greater improvement of quality of life compared to placebo.

EQ-5D-5L data inform the economic model and the company supplied further details of the EQ-5D-5L VAS results in Clarification Response A5, summarised in Table 11 below. The EAG also requested the EQ-5D index score results in Clarification Request A5 but they were not provided. The derived crosswalk utility data was provided (not requested) in Clarification Response A5 for the randomised set but it did not include comparative data by treatment group (i.e., rozanolixizumab compared to placebo) as it is used for the HRQoL mapping process for the economic model.

Table 11 EQ-5D-5L VAS score change from baseline to Day 43 for MycarinG (randomised set and refractory subgroup)

Analysis	Rozanolixizumab ~7 mg/kg (RS N=66; refractory N=[redacted])	Placebo (RS N=67; refractory N=[redacted])	Difference
Randomised set Mean (SD)	(n=[redacted]) 12.2 (19.9)	(n=[redacted]) 6.1 (18.2)	Not reported
Refractory subgroup [a] Mean (SD)	[redacted]	[redacted]	Not reported

Sources: CS section B.2.6.1.3; Clarification Response Tables 2 and 4.
[a] post-hoc analysis; refractory defined as ≥2 prior treatments (not including acetylcholinesterase inhibitors).
RS: randomised set; SD: standard deviation.

3.2.5.9.2 MG0007 trial

The mean EQ-5D VAS score change from baseline at Day 43 for the rozanolixizumab ~7 mg/kg group ranged from [redacted] to [redacted] in the first [redacted] cycles (Clarification Response Table 5), which differs from the mean EQ-5D VAS score change from baseline results reported at any study visit during the first [redacted] cycles in the CS (range [redacted]; CS section B.2.6.2.3). Both sets of results show [redacted] scores.

Consistent improvements (decreases) were seen in the MG-QoL15r score change from baseline at Day 43 (range [redacted]) for the first [redacted] treatment cycles (CS section B.2.6.2.3).

Both the EQ-5D and MG-QoL15r results from MG0007 are subject to uncertainty due to high risk of bias in the study design and from dose-switching.

3.2.5.10 Subgroup analyses

3.2.5.10.1 Prespecified subgroups

Prespecified subgroup analyses evaluated the primary and continuous secondary efficacy outcomes in MycarinG for different age ranges, sex, region, MG-specific autoantibodies (AChR antibody-positive and MuSK antibody-positive), duration of disease, MGFA disease class, thymectomy, MG-ADL category (<5, ≥5), duration of disease at baseline, MGFA class at baseline, thymectomy at baseline, MG baseline medications, and weight (CS section B.2.7.1). Where results were available for subgroups with sufficient sample sizes, the subgroup results were [redacted] with the results in the randomised set (CSR sections 8.1.3 and 8.2.7). An exception was a [redacted] in the MuSK antibody-positive subgroup for the change from baseline to Day 43 in both QMG and MGC scores (CS section B.2.7.4.1), however the sample size is too small to make any certain inferences.

3.2.5.10.2 Patients with refractory generalised MG

Results of the post-hoc analysis of refractory participants (those who had received ≥2 prior MG-specific treatments not including acetylcholinesterase inhibitors) in MycarinG are directly relevant to the refractory population described in the company's Decision Problem and are reported above in the clinical efficacy results section (see section 3.2.5).

3.2.5.10.3 Patients with severe generalised MG

The NICE scope specifies a subgroup of adults with severe MG needing IVIg or PLEX. The company state that as the overall trial population includes these patients they are not treated as a subgroup (CS Table 1). However, the primary outcome in MycarinG, the MG-ADL score change from baseline at Day 43, is reported for a pre-specified subgroup of participants with baseline MG-ADL ≥5 which according to the EAG's clinical experts would reflect those with moderate to severe MG. As shown in Table 12, rozanolixizumab ~7 mg/kg was [redacted] in the more severe MG group (i.e. MG-ADL ≥5) compared to the overall trial population.

Table 12 MG-ADL score change from baseline to Day 43 in MycarinG for the randomised set and subgroup with baseline MG-ADL score ≥5

Analysis	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
Source: CS Tables 20 and 37 CI: confidence interval; LS: least squares; RS: randomised set; SD: standard deviation; SE: standard error.			

In MG0007, the CS reports that improvements in MG-ADL score were generally consistent with the results in the randomised set for all subgroups, but no quantitative results are reported for the subgroup with MG-ADL score ≥5 in the CS (CS section B.2.7.4.3). The CSR reports that [redacted] reductions in MG-ADL score occurred in this subgroup for [redacted] cycles but does not give a breakdown of the data by trial arm.

3.2.5.10.4 Patients with AChR or MuSK autoantibodies

AChR antibody-positive and MuSK antibody-positive participants are pre-specified subgroups in the MycarinG trial and are listed as relevant subgroups in the NICE scope.

3.2.5.10.4.1 MycarinG trial

Results for the AChR and MuSK antibody-positive subgroups are reported in the CS, CSR, and trial publication, and we have summarised them in Table 13 below.

Table 13 AChR antibody-positive and MuSK antibody-positive subgroup results compared to the randomised set (overall trial population) in MycarinG

Analysis	Rozanolixizumab ~7 mg/kg (RS N=66; AChR Ab+ N=[redacted]; MuSK Ab+ N=[redacted])	Placebo (RS N=67; AChR Ab+ N=[redacted]; MuSK Ab+ N=[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*** -2.586 (-4.091 to -1.249) p=<0.001
AChR Ab+ Mean (SD)[a] LS mean (SE)[b]	[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)[a] LS mean (SE)[b]	x [redacted] (n=NR) -7.28 (1.94)	x [redacted] (n=NR) 2.28 (1.95)	***LS mean (97.5% CI)*** Not tested -9.56 (15.25 to -3.87)
MGC score change from baseline at Day 43			
Randomised set LS mean (SE)	(n=65) -5.930 (0.916)	(n=62) -2.029 (0.917)	***LS mean (95% CI); p-value*** -3.901 (-6.634 to -1.245) p=<0.001
AChR Ab+ Mean (SD)	[redacted]	[redacted]	Not tested
MuSK Ab+ Mean (SD)	[redacted]	[redacted]	Not tested
QMG score change from baseline at Day 43			
Randomised set LS mean (SE)	(n=65) -5.398 (0.679)	(n=62) -1.915 (0.682)	***LS mean (95% CI); p-value*** -3.483 (-5.614 to -1.584) p=<0.001
AChR Ab+ Mean (SD)	[redacted]	[redacted]	Not tested
MuSK Ab+ Mean (SD)	[redacted]	[redacted]	Not tested
Responders at Day 43 (MG-ADL ≥2 point improvement, MGC/QMG ≥3 point improvement)			
Randomised set MG-ADL, n/N (%) MGC, n/N (%) QMG, n/N (%)	 45/66 (68.2) 39/66 (60.9) 35/66 (54.7)	 19/67 (28.4) 26/67 (40.6) 25/67 (39.1)	***OR (95% CI); p-value*** 5.765 (2.100 to 14.882); p<0.001 Not tested Not tested
AChR Ab+ MG-ADL, n/N (%) MGC, n/N (%) QMG, n/N (%)	[redacted]	Not reported Not reported Not reported	Not tested Not tested Not tested
MuSK Ab+ MG-ADL, n/N (%) MGC, n/N (%) QMG, n/N (%)	[redacted] [c] [redacted] [c] [redacted] [c]	[redacted] [redacted] [redacted]	Not tested Not tested Not tested

Source: CS Tables 20, 21, 22, 26, 37, 38, 39, CS section B.2.6.1.3, Bril et al. 2023[35].
[a] source: CS. [b] source: trial publication Bril et al. 2023[35].
[c] source: CS section B.2.6.1.3, percentage calculated by EAG.
Abbreviations: 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.

The MuSK antibody-positive subgroup receiving the ~7 mg/kg rozanolixizumab dose achieved the [redacted] clinically meaningful decrease in MG-ADL score at Day 43 ([redacted]). However, the sample size for this subgroup is very small and therefore the result is uncertain.

The summary results tables referred to in section 8.3.2 of the CSR were not provided to the EAG.

3.2.5.10.4.2 MG0007 trial

Results of the subgroup analyses for AChR antibody-positive and MuSK antibody-positive patients for the change in MG-ADL were generally consistent with those of the overall study population, [redacted] the results for the MuSK antibody-positive subgroup showed [redacted] from baseline in MG-ADL score than the overall study population for cycles [redacted] (CS section B.2.7.4.3). The explanation for this pattern is unclear. The 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 these results should be interpreted with caution.

3.2.5.11 Safety outcomes

The CS reports safety results from the MycarinG, MG0007 and (terminated) MG0004 trials in CS sections B.2.6.2.4 (hospitalisations), B.2.10 (adverse events) and Appendix F (adverse events in further detail, including for the refractory subgroup and a pooled analysis of MycarinG and MG0007). We have summarised the key adverse events information here.

3.2.5.11.1 Exposure

MycarinG trial. Median duration of treatment was 36.0 days for all treatment groups, but it is not reported for each treatment arm so we cannot tell if exposure differed between treatment arms. Three mock infusions were received by two participants in the ~7 mg/kg group and four mock infusions were received by two participants in the ~10 mg/kg group (CS section B.2.10.1.1). Mock infusions enabled continuation of blinding of patients when treatment with rozanolixizumab was temporarily discontinued because immunoglobulin levels fell below 2 g/L. Due to the mock infusions actual exposure to rozanolixizumab is less than that reported.

MG0007 trial. In MG0007, at the interim (latest available) data cut (July 2022) the median (range) of treatment cycles was [redacted] (CS section B.2.10.1.3).

MG0004 trial. The mean duration of exposure was similar for both treatment groups: [redacted] and [redacted] weeks for the rozanolixizumab ~7 mg/kg and ~10 mg/kg groups respectively. Due to dose-switching exposure to the ~7mg/kg dose was higher than to the ~10 mg/kg dose (CS Appendix F.1.2).

3.2.5.11.2 Adverse events

MycarinG trial. The proportion of treatment emergent adverse events experienced by study participants was higher in the rozanolixizumab ~7mg/kg and ~10mg/kg groups (81.3% and 82.6%) than in the placebo group (67.2%); similarly, the proportion of treatment emergent

adverse events related to the study drug or placebo received was higher in the rozanolixizumab groups (50.0% and 56.5%) than in the placebo group (32.8%). However, few of the treatment emergent adverse events were severe or resulted in permanent withdrawal of treatment, and these proportions were similar across all study groups (CS Table 50). The most common treatment emergent adverse events were headache, diarrhoea, pyrexia, nausea and arthralgia (CS Table 51).

The refractory subgroup in MycarinG and the Safety Set (overall trial population) generally experienced [redacted] of treatment emergent adverse events and study drug related treatment emergent adverse events (CS Appendix F.1.1). For the refractory subgroup, participants in the rozanolixizumab ~10 mg/kg dose group experienced more severe and more serious treatment emergent adverse events than both the placebo and ~7 mg/kg dose groups (CS Appendix Table 32). Headache, diarrhoea and pyrexia were the most common treatment emergent adverse events (CS Appendix F.1.1).

MG0007 trial. There was no increase in the incidence of treatment emergent adverse events in any of the categories reported from cycle to cycle (CS section B.2.10.1.3). CS Table 55 shows that there were lower proportions of participants experiencing events in the rozanolixizumab ~7 mg/kg (licensed dose) than in the ~10 mg/kg dose group for: any treatment emergent adverse event (~7 mg/kg [redacted]; 10 mg/kg [redacted]); serious adverse events (~7 mg/kg [redacted]; 10 mg/kg [redacted]); events resulting in discontinuation from the study (~7 mg/kg [redacted]; 10 mg/kg [redacted]); events resulting in permanent withdrawal from rozanolixizumab (~7 mg/kg [redacted]; 10 mg/kg [redacted]); and severe treatment-emergent adverse events (~7 mg/kg [redacted]; 10 mg/kg [redacted]). Headache was the most frequently reported treatment emergent adverse event, and comparable for both rozanolixizumab dose groups (~7 mg/kg [redacted]; 10 mg/kg [redacted]) (CS Table 56).

3.2.5.11.3 Adverse events of special interest

MycarinG trial. There were no cases of potential Hy's Law according to the trial definition nor any cases of potential drug-induced liver injury (CS section B.2.10.1.1); CS Table 53 reports the elevated liver function test events none of which were considered related to the study drug.

MG0007 trial. There were no cases of potential Hy's Law. [redacted] study participants had elevated liver function tests; the CS does not report whether these instances were determined to be related to the study drug except that [redacted] were consistent with Gilbert's syndrome (CS section B.2.10.1.3).

3.2.5.11.4 Hospitalisations

The company state in their Decision Problem that the number and duration of hospitalisations were not captured in the clinical trials (CS Table 1). However, for MG0007, the CS reports that the proportion of participants experiencing at least one hospitalisation or emergency room visit was [redacted] in the rozanolixizumab ~7 mg/kg trial arm and [redacted] in the rozanolixizumab ~10 mg/kg trial arm. The most frequent reasons for hospitalisation or emergency room visit were adverse events or 'study disease' (which we assume to mean myasthenia gravis crises or exacerbations); none were determined to be related to lack of efficacy of treatment (CS section B.2.6.2.4).It is unclear why hospitalisations were not reported for MycarinG.

3.2.5.11.5 Mortality

No deaths were reported during the MycarinG trial (CS section B.2.10.1.1). In the MG0007 trial, [redacted] reported in the rozanolixizumab ~7 mg/kg trial arm due to pneumonia and [redacted] reported in the rozanolixizumab ~10 mg/kg trial arm due to COVID-19 and COVID-19 pneumonia. None were considered treatment-related (as considered by the investigator) (CS section B.2.10.1.3).

3.2.5.11.6 Anti-drug antibodies

The CS reports results of monitoring for treatment-induced antidrug antibodies (CS section B.2.10.1.1). The occurrence of antidrug antibodies in MycarinG and MG0007 trial participants was also considered in the FDA review (section 14.4) which raised no safety concerns.[20] However, one of the EAG's clinical experts noted that there is not enough long-term data to fully understand the impact of antidrug antibodies related to the administration of rozanolixizumab. The European Medicines Agency Public Assessment Report (EPAR) for rozanolixizumab does, however, raise concerns about the incidence of antidrug antibodies and neutralising antibodies because the safety data is not adequate to show the effect of immunogenicity with long-term treatment.[37]

3.2.5.11.7 MG0004

The most frequently reported treatment emergent adverse event was headache (in [redacted] and [redacted] of participants in the rozanolixizumab ~7 mg/kg and ~10 mg/kg groups respectively), followed by diarrhoea, decreased blood immunoglobulin G, nausea, pyrexia and urinary tract infection. Treatment-emergent adverse events were mostly mild or moderate in intensity. [redacted] participants experienced treatment emergent adverse events that led to discontinuation from the study, due to myasthenia gravis in [redacted] participants and congestive cardiac failure in the [redacted]. There were no deaths, no anaphylactic or serious

hypersensitivity reactions, and no new safety signals reported (CS section B.2.10.2 and CS Appendix F.1.2).

3.2.5.11.8 Pooled analysis

The company report a pooled analysis, that included data from MycarinG and MG0007 only, to assess the safety profile and tolerability of repeated cyclic treatment with rozanolixizumab that are reported in CS Appendix F.1.3. Repeated cycles of treatment were not observed to increase the incidence of treatment emergent adverse events, adverse events of special interest nor hypersensitivity reactions (CS section B.2.10.3). The EAG did not observe any new safety signals in the data provided.

EAG conclusion on safety results

The trial data for MycarinG, MG0007, MG0004, and the pooled analysis of MycarinG and MG0007 appear to show good tolerability of rozanolixizumab for the ~7 mg/kg dose although headaches are notable. The EAG agree that the safety results for the post-hoc refractory subgroup are similar to those seen in the overall trial population in MycarinG. The long-term effects of rozanolixizumab on antidrug antibodies and immunoglobulin levels, and more rare events such as aseptic meningitis (an identified risk in the EPAR), cannot be addressed by the relatively short-term trial data.

3.2.6 Pairwise meta-analysis of intervention studies

As noted in section 3.2.1 above, only one RCT compared rozanolixizumab against placebo. Pairwise meta-analysis would therefore not be justified nor feasible. No RCTs comparing rozanolixizumab against zilucoplan, efgartigimod, IVIg or PLEX are available and so the company utilised indirect treatment comparisons to perform some of those comparisons, as described in the following sections.

EAG conclusion on pairwise meta-analysis

Pairwise meta-analysis was, appropriately, not conducted by the company.

3.3 Critique of studies included in the indirect treatment comparisons

The company provided two types of indirect treatment comparison (ITC). The CS reports network meta-analyses (NMAs). Due to limitations of the NMAs the EAG requested that the company consider alternative ITC methods such as matching-adjusted indirect comparisons (MAICs) (Clarification Question A13). MAICs were provided by the company in their clarification response, as described further below.

The NMAs and MAICs provided by the company were conducted on the full trial populations which include both refractory and non-refractory patients and patients with both types of MG autoantibodies (i.e. AChR and MuSK). The EAG requested the company to explore subgroup analyses in the NMAs for refractory patients and those who were both refractory and had AChR antibodies, to investigate whether outcomes differed between these groups (Clarification Question A11). The company explained in their clarification response that insufficient data are available to analyse these subgroups in NMAs. Whilst the EAG agree, we note that a subgroup analysis of refractory patients in the MAIC comparison of rozanolixizumab against zilucoplan could be feasible but was not considered by the company.

3.3.1 Rationale for the NMAs

In the absence of head-to-head trials, NMAs were conducted to enable rozanolixizumab to be compared against the comparator therapies relevant to this appraisal. The company report their NMAs in the following sources:

- CS section B.2.9 reports NMAs for comparisons of rozanolixizumab against efgartigimod and zilucoplan for the outcomes of MG-ADL response (defined as a ≥2-point improvement in the score) and MG-ADL score change from baseline. The response outcome (CS Table 48) is presented as the probability of response for each individual treatment. Due to a lack of placebo-controlled trials with relevant outcomes the CS does not report any NMA results for IVIg or PLEX.
- A CS Erratum, together with a corrected version of a company NMA Report, was provided to the EAG by the company on 25th March 2024 to correct an unspecified error in MG-ADL response rates. The EAG compared the uncorrected and corrected NMA Report versions and deduced that the wrong cutoff for MG-ADL improvement in the MycarinG trial (≥3 points instead of ≥2 points) had been used in their original MG-ADL response analysis (Table 5 of their original NMA Report). The correction was implemented appropriately.

The CS Erratum and the corrected NMA Report supersede the information reported in section B.2.9 of the original CS. The EAG's critique of the NMA methods is therefore based on the information in the CS Erratum and the corrected NMA Report.

3.3.2 Rationale for the MAICs

The NMAs conducted by the company do not account for any heterogeneity in the baseline characteristics of the included trials, or heterogeneity of placebo effects across the included

trials (section 3.3.4.1 below). The EAG requested that the company explore alternative ITC analysis methods such as MAICs to account for the heterogeneity of trial baseline characteristics (Clarification Question A13).

In response to Clarification Question A13 the company provided MAIC analyses for the comparison of rozanolixizumab against efgartigimod and the comparison of rozanolixizumab against IVIg. Two company MAIC Reports, one for each analysis, were provided with the clarification response. The company declined to conduct a MAIC for the comparison of rozanolixizumab against zilucoplan. The company's rationale for excluding zilucoplan from the MAIC analysis was based solely on the timescale for the NICE appraisal of zilucoplan (ID4008) which is such that NICE have not yet made a final recommendation for zilucoplan. This is not a valid reason for excluding zilucoplan since this comparator is relevant to the NICE scope. The company's rationale is also inconsistent, since they have not excluded efgartigimod as a comparator (the NICE efgartigimod appraisal (ID4003) has also not yet reached a final recommendation).

The comparison of rozanolixizumab against efgartigimod was based on an anchored MAIC, matching the MycarinG trial (rozanolixizumab versus placebo) to the ADAPT trial (efgartigimod versus placebo). This method uses the trial placebo arms as a common comparator, preserving the benefits of randomisation in the contributing trials so that the placebo response can be captured, and the risk of confounding reduced.

The comparison of rozanolixizumab against IVIg used an unanchored MAIC because no trials with a common comparator are available. For this MAIC the company matched the rozanolixizumab arm of the MycarinG trial to the IVIg arm of the trial reported by Barth et al. 2011.[(2)] However, the Barth et al. 2011 trial did not report MG-ADL outcomes. The company instead report QMG response and QMG change from baseline for this MAIC analysis. The QMG outcomes do not inform the economic model and the company have not reported QMG outcomes for any other NMA or MAIC analyses.

In summary, only one MAIC analysis has been provided that could inform the economic analysis, i.e. the comparison of rozanolixizumab against efgartigimod that reports the MG-ADL response rate odds ratio and the change from baseline in MG-ADL score. However, the company do not discuss the MAIC results in the context of the economic analysis.

3.3.3 Identification, selection and feasibility assessment of studies for ITC

3.3.3.1 Identification of studies for inclusion in NMAs

The selection process for identifying trials eligible for inclusion in the NMAs is reported in CS Appendix D.1. Searches were conducted in May 2023 and updated in January 2024. As noted in section 3.1 above, we consider the methods of searching generally appropriate. A total of 48 trials that align with the population of the MycarinG trial were identified, as listed in CS Appendix Table 10. Of these, CS Appendix Tables 11 and 12 (which duplicate each other) show that 35 trials were excluded, mainly due to not having relevant therapies or outcomes. However, Table 3 in the corrected NMA Report shows that 41 trials were excluded, as the company had excluded a further six trials because they were phase II trials (the company do not explain why one further trial was excluded, but we assume this was because it was only reported in a conference abstract, and it did not assess MG-ADL). After the selection process, six phase III trials were eligible for inclusion in NMAs (Table 4 in the corrected NMA Report). These six trials cover six therapies (rozanolixizumab, efgartigimod, zilucoplan, eculizumab, ravulizumab, rituximab). No placebo controlled RCTs of IVIg or PLEX were identified in the searches.

The EAG and our clinical experts believe that all relevant randomised controlled trials that could be eligible for NMAs have been identified by the company. However, we disagreed with the company's approach to excluding the phase II trials and requested the company to provide a scenario analysis including both phase II and III trials (Clarification Question A10). In their response the company did not provide a scenario analysis but listed several reasons for not including specific phase II trials. The EAG do not agree with the company's arguments, and the company did not apply these systematically to investigate the feasibility of including individual phase II trials. However, we agree that the exclusion of phase II trials is unlikely to substantively affect uncertainty in the NMA results, given the other limitations of the NMAs noted above.

3.3.3.2 Identification of studies for inclusion in MAICs

The MAIC Reports provided by the company in response to Clarification Question A13 refer to a systematic literature review which identified 73 studies that qualified for inclusion, citing an unreferenced separate technical report. The EAG are uncertain why this number is different to the 80 'prioritised' studies referred to in the company's SLR (CS Appendix D.1.2.1). The MAIC Reports describe a feasibility assessment for the MAICs, but this refers to the ranking and prioritisation of the trial characteristics in the analysis rather than establishing the eligibility of the trials for inclusion in MAICs. The trial selection process for

the MAICs is therefore unclear. Regarding the two types of MAIC conducted by the company:

- The anchored MAIC approach requires RCTs with a common comparator. These trials had already been appropriately identified by the company in their study selection process for the NMAs. We therefore believe that all relevant trials that could be considered for anchored MAIC analysis (i.e. the MycarinG and ADAPT trials) have been considered.

- The unanchored MAIC approach can compare any two individual study arms or cohorts that report sufficient methodological details. However, the company's study 'prioritisation' process (CS Appendix D.1.2.1) did not include observational studies. The company do not discuss the selection of studies for unanchored MAIC analysis, and we are uncertain whether there might be relevant single-arm studies that the company have not identified that could be included in alternative unanchored MAICs.

3.3.4 Clinical heterogeneity assessment

3.3.4.1 Heterogeneity assessment for NMAs

The company provide a brief narrative discussion of the heterogeneity of the trial baseline characteristics in CS section B.2.9.3.2 and in their response to Clarification Question A12, acknowledging that there is heterogeneity in patient-reported outcomes, disease duration and the timing of treatment cycles. The company also acknowledged in their response to Clarification Question A15 that there is heterogeneity in the placebo effect across the trials, but they do not explain this or conduct any analyses to explore its impact on cost-effectiveness results. Differing explanations for the placebo effect have been proposed.[38-40] The EAG requested that the company consider approaches such as MAIC to adjust for the baseline imbalances in trial characteristics (Clarification Question A13).

3.3.4.2 Heterogeneity assessment for MAICs

Table 3 in both MAIC Reports shows that there are some differences in the inclusion/exclusion criteria between the MycarinG and comparator trials (i.e. the ADAPT trial on efgartigimod and the Barth et al. 2011 trial on IVIg). Differences in the inclusion/exclusion criteria cannot be adjusted for but some of the resulting differences in trials' baseline characteristics may be adjusted for by the MAIC methodology, subject to data availability, to reduce the clinical heterogeneity between trials.

The MAIC Reports state that a feasibility assessment was conducted, involving two named key opinion leaders who ranked the trial baseline characteristics in terms of their importance for influencing MG-ADL and QMG outcomes. An initial list of 18 baseline characteristics was considered in the ranking exercise. Ten characteristics were subsequently included in the anchored MAIC for efgartigimod whilst 13 were included in the unanchored MAIC for IVIg, but the role of the ranking exercise in achieving these sets of baseline characteristics for analysis is unclear.

The company followed the NICE Decision Support Unit (DSU) guidance on indirect comparisons.[41] Section 3.3 of the MAIC Reports correctly state that trials included in anchored MAIC analyses should be matched on treatment effect modifiers whilst trials included in the unanchored analyses should be matched on all baseline characteristics (i.e. effect modifiers and prognostic variables). According to the MAIC Reports, effect modifiers were identified through univariate analysis; however, no details or results of this analysis are provided and the company do not explain which of the trial baseline characteristics they regard as being prognostic factors or effect modifiers.

Table 4 in the efgartigimod MAIC Report shows that 10 baseline characteristics were considered for matching the rozanolixizumab and efgartigimod arms, and all of these were included in the matching (MAIC Report section 4.2.1). The EAG are not aware of any other baseline characteristics of the MycarinG and ADAPT trials that the trials could potentially be matched on. We note that some prognostic factors, such as history of myasthenic crisis or exacerbation, or disease severity at diagnosis, were not reported in both trials and therefore could not be included. Table 8 in the MAIC Report shows that the post-matching baseline characteristics are identical to those of ADAPT for all of the 10 matched characteristics but the company do not comment on this and the EAG are uncertain whether these data are correct. We note that the baseline characteristics from the MycarinG trial before matching do not precisely match those reported in the trial publication, but no explanation is provided. Overall, it is difficult to be certain how successful matching was based on the information provided in the MAIC Report due to these ambiguities and the relatively low effective sample size post-matching.

Table 4 in the IVIg MAIC report states that 6 of 13 included baseline characteristics were selected for matching in the comparison of rozanolixizumab against IVIg based on the standardised mean difference of each characteristic between the MycarinG and Barth et al. 2011 trials. However, it is not obvious how the selected characteristics relate to the reported standardised mean differences. As noted above, the Barth et al. 2011 trial did not report MG-

ADL response or change from baseline. This MAIC is therefore not informative for the current appraisal and we do not critique it further in this report.

3.3.5 Risk of bias assessment for studies included in the indirect comparisons

We judged the MycarinG trial to be at low risk of most types of bias, but with an unclear risk of bias relating to missing outcomes data (section 3.2.2).

The EAG for the technology appraisal of zilucoplan (ID4008) considered the RAISE trial to have a low risk of bias for most trial aspects, except for an unclear risk of bias relating to missing outcomes data (ID4008 EAG Report).

The EAG for the technology appraisal of efgartigimod (ID4003) considered the ADAPT trial was at low risk of bias for the primary outcome and was probably at low risk of bias for the other outcomes (ID4003 EAG Report).

The company's unanchored MAIC is potentially at risk of bias due to the lack of a placebo comparator group to mitigate against confounding, although the direction and magnitude of any bias is uncertain.

EAG conclusion on the studies included in the indirect comparisons

Overall, we believe the company have identified all relevant trials for their NMA and anchored MAIC analyses, but it is unclear whether all relevant studies have been identified for the unanchored MAIC analysis. The company do not comment whether any non-randomised studies on IVIg or PLEX that report MG-ADL outcomes exist that could be relevant to their unanchored MAIC analysis. Overall, the trials included in the company's NMAs and MAICs were judged to have low risk of bias.

3.4 Critique of the indirect comparisons

3.4.1 Data inputs

The NMA data inputs are listed in Tables 5 to 7 of the company's corrected NMA Report. The company provided sufficient information in their WinBUGS code (Clarification Response A9) for the EAG to rerun the NMA analyses and confirm that they were implemented correctly.

Data inputs and statistical code for the MAIC analyses were not provided with the company's MAIC Reports in Clarification Response (A13). The EAG therefore cannot confirm whether the MAIC analyses were implemented correctly.

3.4.2 Statistical methods for the indirect comparisons

3.4.2.1 NMAs

The NMAs were conducted using a Markov chain Monte Carlo Method under a Bayesian framework in R software, using noninformative prior distributions. The overall statistical approach to the NMAs for the binary outcome (MG-ADL response) and continuous outcome (MG-ADL change from baseline) is appropriate.

The company conducted both fixed and random effects analyses and state that the fixed-effect model was preferred because the networks generally consisted of only one trial per direct comparison (CS section B.2.9 and corrected NMA Report). The EAG reran the fixed and random-effects NMAs and found them to give similar point estimates, deviance information criterion (DIC), and residual deviance (thus very similar leverage plots), albeit with markedly wider 95% credible intervals (CrIs) in the random-effects analyses. We confirm that the NMA results reported by the company are from the fixed-effect analyses. The wide CrIs of the random effects models will overestimate heterogeneity in small evidence networks as it is not possible to accurately estimate the between-study standard deviation so we agree with the company's focus on the fixed effect model. However, the fixed effect model would underestimate uncertainty unless the included studies are estimating the same treatment effect, which we believe is an unlikely assumption. Alternative analysis approaches to account for heterogeneity, such as using an informative prior distribution,[42] were not considered by the company.

3.4.2.2 MAICs

The company's approach to the MAIC analyses is described in section 3.3.1 of each MAIC Report. The analyses were conducted in R, but the R analysis package(s) used are not reported. The company's statistical approach for conducting the MAICs appears broadly appropriate, but is subject to limitations:

- Due to the lack of statistical code and input data the EAG could not verify that the MAICs were implemented correctly.
- The company did not conduct any analyses to investigate the sensitivity of the MAIC results to the variables included in matching.

3.4.3 Summary of EAG's critique of the Indirect comparisons

- We believe all relevant placebo-controlled trials have been identified for the company's NMAs and anchored MAIC analyses.
- The company report NMA comparisons of rozanolixizumab against zilucoplan and efgartigimod. The NMAs have limitations because they do not adjust for heterogeneity of baseline characteristics of the included trials (the company did not explore whether an informative prior could account for the between-trial heterogeneity) and do not account for the placebo effect (the networks are too small to facilitate adjustment for placebo heterogeneity using meta-regression).
- The NMA results refer only to phase III trials since the company declined to include phase II trials. However, we expect this omission to have limited influence on results relative to the other uncertainties in the indirect treatment comparisons.
- MAICs can adjust for heterogeneity in trial baseline characteristics, subject to adequate matching. MAICs are therefore useful as a sensitivity analysis to explore heterogeneity in the ITC outcomes. However, MAICs can only adjust for the placebo effect if the variables which are matched are those that explain the placebo effect – but this information is unknown.
- The company conducted an anchored MAIC of rozanolixizumab against efgartigimod. but declined to conduct an anchored MAIC comparing rozanolixizumab against zilucoplan despite this being feasible. We disagree with the company's rationale for omitting the zilucoplan comparison.
- Due to a lack of placebo-controlled trials, we agree that it was not feasible for the company to conduct NMAs or anchored MAICs for comparisons of rozanolixizumab against IVIg or PLEX. Instead, the company conducted an unanchored MAIC of rozanolixizumab against IVIg. The unanchored MAIC is not very informative for the current appraisal since the comparator trial (Barth et al. 2011[(2)]) did not report MG-ADL response or change from baseline which are the key clinical efficacy parameters that inform the economic analysis.
- The company did not investigate whether any single-arm studies could be included in unanchored MAIC analyses to enable comparisons against IVIg or PLEX for the MG-ADL outcomes.
- The NMA and MAIC analyses were conducted on the overall trial populations and do not consider any of the subgroups (refractory, AChR+. MuSK+) - see Key Issue 2 (refractory subgroup) and Key Issue 3 (autoantibody subgroups) in section 1.4 for further discussion.

3.5 Results from the indirect comparisons

Below we summarise the results from the company's NMAs and MAICs, although these are subject to uncertainties due to the limitations described above (section 3.4.3) that are not captured within the credible intervals.

3.5.1 NMA results

The company provided NMA results for two outcomes: the MG-ADL response rate and the change from baseline in MG-ADL score. Other outcomes that may be helpful for clinical efficacy interpretation, such as QMG, MGC, and MG-QoL15r, that were reported in the MycarinG trial, and in NMAs in previous NICE technology appraisals for generalised MG, were not included in the company's NMAs.

3.5.1.1 MG-ADL response

The MG-ADL response rates from NMAs where response was defined as a ≥2 point improvement in the MG-ADL score (primary analysis) and a ≥3 point improvement in the MG-ADL score (scenario analysis) are shown in Table 14.

Table 14 MG-ADL response rates from the company's corrected NMAs

NMA comparison	Odds ratio (95% CrI) for MG-ADL response rate	
	Response defined as ≥2 point improvement	Response defined as ≥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]

CrI, credible interval.
[a] This comparison is not used in the company's economic model.
[b] This comparison is used in the company's economic model, with response defined as a ≥2 point improvement in the MG-ADL score.
Source: Figures 3 and 4 in the corrected NMA Report

3.5.1.2 MG-ADL change from baseline

The changes from baseline in the MG-ADL score as reported in the corrected NMA Report are shown for relevant comparisons in Table 16**.**

Table 15 MG-ADL changes from baseline from the company's corrected NMAs

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]
CrI, credible interval. [a] Change from baseline to the primary assessment timepoint of the study. Source: Figure 6 in the corrected NMA Report	

3.5.2 MAIC results

The company provided MAIC results in their response to Clarification Question A13. As noted above, the company declined to include the comparison of rozanolixizumab against zilucoplan in an anchored MAIC. Results are available for the following analyses:

- Anchored MAIC comparing rozanolixizumab against efgartigimod, for MG-ADL response (section 3.5.2.1) and MG-ADL change from baseline (section 3.5.2.2).
- Unanchored MAIC comparing rozanolixizumab against IVIg, for QMG response and QMG change from baseline. As this analysis does not report MG-ADL outcomes, and as no other MAIC analyses report QMG outcomes for comparison, we do not report the results here (see IVIg MAIC Report Table 9).

3.5.2.1 MG-ADL response

For the anchored MAIC comparing rozanolixizumab (Week 4 assessment) against efgartigimod (Week 4 assessment) the odds ratio (95% CrI) for the rate of responders (defined as a ≥2 point improvement in the MG-ADL score) is [redacted] ([redacted] to [redacted]). This odds ratio from the MAIC is larger than that obtained from the NMA (Table 15 above), but the NMA and MAIC results are [redacted] significant. A post hoc sensitivity analysis of the MAIC that used the Week 6 assessment for rozanolixizumab also gave a statistically [redacted] result.

3.5.2.2 MG-ADL change from baseline

For the comparison of rozanolixizumab (Week 4 assessment) against efgartigimod (Week 4 assessment) the mean (95% CrI) treatment difference in the change from baseline in MG-ADL score was [redacted] ([redacted] to [redacted]). The efgartigimod MAIC Report confirms that the result is [redacted] significant. A post hoc sensitivity analysis that used the Week 6 assessment for rozanolixizumab also gave a statistically [redacted] result.

3.6 Conclusions on the clinical effectiveness evidence

Rozanolixizumab at the licensed ~7 mg/kg dose is effective versus placebo in both a statistically significant and clinically meaningful way.

The rozanolixizumab efficacy results for the MuSK antibody-positive subgroup in MycarinG had a [redacted] response than the randomised set for all measured outcomes. MuSK antibody-positive patients are rare, hence the small sample size making these results uncertain (Key Issue 3 in section 1.4).

The AChR antibody-positive subgroup exhibited a potentially clinically meaningful response with rozanolixizumab (however, outcomes were not tested for statistical significance for the subgroup analyses). The AChR antibody-positive subgroup in MycarinG corresponds directly with the trial populations for the comparator interventions efgartigimod and zilucoplan which either had a defined AChR antibody-positive subgroup (ADAPT trial) or an overall AChR antibody-positive trial population (RAISE trial). NMAs or MAIC scenario analyses limited to AChR antibody-positive participants could more accurately characterise the relative effectiveness of rozanolixizumab in this population group, although the company did not conduct these (section 3.4.3).

Evidence from the company trials is relatively short-term compared to the life-long condition of generalised MG. This has implications for longer-term treatment using rozanolixizumab and there is uncertainty around the extent of treatment discontinuations, antidrug antibodies, treatment waning, use of subsequent treatments, and longer-term safety.

Evidence from the MG0007 extension study illustrates continued efficacy of rozanolixizumab treatment, but the trial 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 the results are uncertain. The uncertainty is a concern because MG0007 informs the assumption for continued response for the economic model (section 4.2.6.2).

Using data from the overall population of MycarinG and MG0007 as a proxy for a refractory generalised MG population in the economic model means that the population in the company Decision Problem is not the population in the economic model (Key Issue 2 in section 1.4). We believe that the overall trial population in MycarinG is probably a suitable proxy for the refractory subgroup in MycarinG and that using the data from the overall trial population in the economic model to support cost-effectiveness in the indicated refractory population is appropriate (participant characteristics section 3.2.1.2.2 and efficacy results

section 3.2.5). However, the refractory population in MycarinG was analysed in a post-hoc subgroup analysis and is therefore more prone to bias than a pre-specified subgroup.

The NMAs are subject to several key uncertainties, summarised in section 3.4.3 above, including that they do not account for between-trial heterogeneity in baseline characteristics or placebo responses. Results for the only MAIC comparison relevant to the economic model show there is no statistically significant difference in the odds of MG-ADL response for treatment with rozanolixizumab compared to efgartigimod (section 3.5.2). However, the MAIC analysis does not adjust for the placebo effect and has other uncertainties (sections 3.3.4.2 and 3.4.2.2). We do not have a complete picture of the overall clinical efficacy of rozanolixizumab compared to other interventions because the company have focused on MG-ADL outcomes only and declined to provide a MAIC for rozanolixizumab compared to zilucoplan for MG-ADL outcomes.

4 COST EFFECTIVENESS

4.1 Company's review of the cost-effectiveness evidence

The company conducted a systematic literature review (SLR) on economic evidence of treatments for patients with generalised MG (CS Appendix G). Databases were searched on 01 May 2023, with searches finalized in February 2024. The review identified twelve studies containing economic evaluations; most of them (n=9) were conference abstracts. Of these, three studies assessed myasthenic crisis, two studies each assessed refractory MG and MG with exacerbations, while the remaining five studies did not provide much information on disease type. Two of the identified economic evaluations were HTA appraisals: one assessed refractory gMG with or without AChR antibodies (ADAPT trial), and the other assessed adult patients with refractory gMG who were AChR antibody positive (REGAIN trial). The REGAIN study assessed the efficacy of eculizumab versus placebo and the ADAPT trial compared efgartigimod with placebo. The company do not discuss these appraisals any detail. No studies were identified for rozanolixizumab.

EAG conclusions on cost-effectiveness searches:

Overall, we view the company's searches were appropriate. The two HTA appraisals identified in the company's search are pertinent to the current appraisal.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The company's economic model fulfils the requirements of NICE's reference case (Table 17)

Table 16 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, direct patient effects are included (section 4.2.5)
Perspective on costs	NHS and PSS	Yes (section 4.2.5)
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes (section 4.2.2); the cost-effectiveness results are presented for pairwise analysis.

Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes (lifetime) (section 4.2.5)
Synthesis of evidence on health effects	Based on systematic review	Yes (section 4.2.7)
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes (section 4.2.7)
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes (section 4.2.7)
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes (section 4.2.7)
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes (severity modifier does not apply, CS B.3.6 and section 7)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes (section 4.2.8)
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes (section 4.2.5)
Source: EAG assessment based on the company submission		

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company describe the structure and key features of their model in CS Section B.3.2.2. Additionally, they summarised the model assumptions in CS Table 68, the parameters in CS Sections B.3.3 to B.3.5 and CS Tables 59 to 67. The model is a seven-state cohort state-transition model, developed in Microsoft Excel®: see Figure 2. The Markov model has a cycle length of 2-weeks and a 52.5 -year time horizon (effectively lifetime from a starting baseline age of 51.8 years). Costs and QALYs are discounted at an annual rate of 3.5% and the analyses are conducted from the perspective of the NHS and Personal Social Services (PSS). The clinical effectiveness data were informed by the MycarinG trial, described earlier in section 3.2.1 and later in section 4.2.6.

The company's model consists of six active health states, and a death state, these are defined in CS Table 57. Patients enter the model in the 'uncontrolled on high dose steroids and ISTs' health state. Those meeting the definition for treatment response (a ≥2 points decrease in MG-ADL score) transition to the 'response' state at the response assessment timepoints (which differ by treatments as shown in CS Table 59). These patients can then transition to the 'continued response' state (with ongoing improvement in MG-ADL score), the 'stable response' state (no change in MG-ADL score), or the 'loss of response' (an increase, i.e., worsening of MG-ADL scores). Within each of the active health states, patients can experience exacerbations, crises, or death. Detailed discussion of the clinical parameters and patients' transition through the health states are given in section 4.2.6 below. The key model assumptions, summarised in CS Table 68, are:

- Treatment response rate, informed by an NMA, is applied in each model cycle up until the time of response assessment. After this point, patients in the 'Uncontrolled on high dose steroids and ISTs' are assumed to not respond and discontinue treatment.
- Transition from exacerbation to crisis is treated independently of treatment received.
- Patients in the 'Uncontrolled on high dose steroids and ISTs' health state are assumed to not experience disease worsening over time.
- Patients are assumed to experience the same risk of mortality as the general population unless they experience a myasthenic crisis.
- Only patients in the 'Continued response' and 'Stable response' health states receive active treatment.
- End of life costs are included as a one-off cost that is borne by the healthcare provider

To estimate utilities, the company used EQ-5D-5L data obtained from the MycarinG trial and mapped to EQ-5D-3L using the Hernandez-Alava et al. (2017) algorithm,[43] in line with the NICE reference case. Costs were sourced from standard UK sources. For further discussion on utilities and costs, see sections 4.2.7 and 4.2.8 below, respectively.

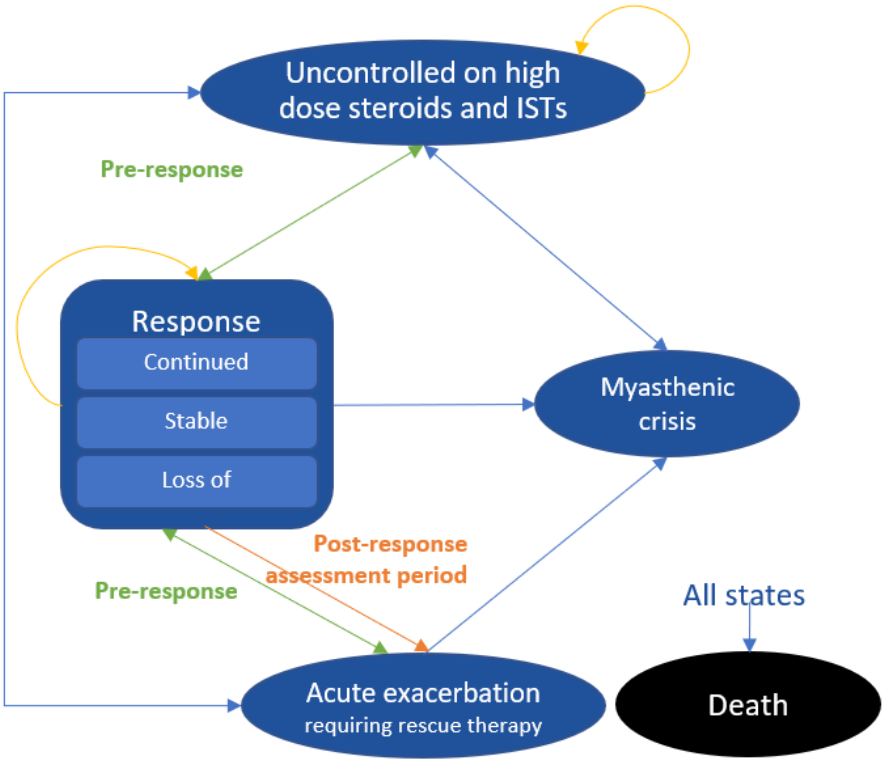


Figure 2 Company's model structure

Source: CS Figure 12

EAG conclusions on the model structure

We view that the overall model structure is appropriate and reflective of the patient pathway, based on our clinical experts' opinion. The structure is the same as the one used for an ongoing NICE appraisal on zilucoplan (ID4008) but differs from the one used for the other ongoing appraisal on efgartigimod (ID4003); the latter used MG-ADL score bands, crisis, and death as health states. However, the current model does not account for subsequent treatments (discussed later in section 4.2.6.8). We are uncertain whether this is clinically plausible as refractory MG is a condition that requires lifelong management. Therefore, patients discontinuing any active treatments may be eligible for chronic IVIg or PLEX, or any NICE-approved treatment for refractory generalised MG.

4.2.3 Population

The CS states that the anticipated marketing authorization of rozanolixizumab is for use as an add-on to standard therapy for treating adult patients with AChR or MuSK antibody-positive generalised MG. In the current appraisal, patients who have AChR or MuSK antibody-positive generalised MG and are refractory to treatment are included in the economic model. However, the company use the baseline characteristics of the full trial population from MycarinG in their base case model, reproduced below in Table 18. They justified their choice of these baseline characteristics based on a post-hoc analysis of a subgroup of participants in MycarinG who received ≥2 prior MG specific therapies. This subgroup showed similar outcomes to the overall MycarinG population. Comparing these characteristics with those of the MycarinG AChR antibody-positive subgroup and MuSK antibody-positive subgroup, we note some differences (see Table 18). However, these are unlikely to have any significant impact on the overall cost-effectiveness results.

Table 17 Modelled population characteristics

Characteristic	Used in the company model for refractory patients (obtained from the MycarinG whole population)	MycarinG AChR+ patients	MycarinG MuSK+ patients
Mean age, years	51.80	52.24	48.3
Female, %	60.50%	57.05%	80.9%
Mean weight, kg	81.15	-	-
Mean MG-ADL score at start	8.30	[redacted]	[redacted]
Baseline BMI (kg/m^2)	27.83	-	-

EAG conclusions on model population

Clinical advice to the EAG was that the patient characteristics in the company's model, based on the MycarinG trial population, are broadly reflective of the patients with refractory disease who would be treated with rozanolixizumab in England. Although it is clinically observed that the incidence of generalised MG is bimodal by age, there is insufficient data to estimate results for subgroups based on age of onset. The EAG conducted scenario analyses using the population characteristics from two subgroups: generalised MG patients with AChR antibodies, and generalised MG patients with MuSK antibodies (see section 6 below).

4.2.4 Interventions and comparators

The economic model evaluates the intervention, rozanolixizumab, against four comparators:

- Efgartigimod
- Zilucoplan
- Chronic intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg)
- Chronic plasma exchange (PLEX)

The CS describes the intervention in CS Section B.1.2 and we discuss the intervention and its intended use in practice earlier in Section 2.2 of this report. The dosing regimen of rozanolixizumab is consistent with that used in the MycarinG trial, and the anticipated approved posology in the EU product label. In practice, rozanolixizumab is intended to be used as an add-on to a basket of standard care therapies (henceforth, referred to as the "standard basket"), which does not include IVIg or PLEX. However, within the company's analyses, the standard basket is excluded from both the intervention and the comparator arms (these are discussed below). We consider this as a reasonable simplification as the treatments within the standard basket are cheap and their impact across the two arms is likely to cancel out. Nonetheless, for completeness, we include the standard basket across all the treatment arms in the EAG analyses, see section 6.

The NICE scope states the following comparators for this appraisal:

- SoC arm (comprising immunosuppressive therapies i.e., referred to as standard basket)
- SoC arm (comprising immunosuppressive therapies i.e., standard basket) with IVIg or PLEX
- Efgartigimod (subject to NICE approval)
- Ravulizumab (subject to NICE approval)
- Zilucoplan (subject to NICE approval)

The company deviated from the NICE scope: the economic model excluded SoC (comprising immunosuppressive therapies) as a comparator (as explained earlier in section 2.3). In response to the EAG clarification question B2, the company argued that as rozanolixizumab is intended to mainly displace IVIg or PLEX in clinical practice, they consider these treatments as the most relevant comparators in this appraisal.

We do not view this as an appropriate reflection of clinical practice in England. Clinical opinion to the EAG is that both IVIg and PLEX are used in patients with refractory generalised MG as part of standard of care. While some centres use IVIg for regular chronic therapy, there are other centres (with a strict protocol for IVIg use) that instead use PLEX for treating these patients. Furthermore, a proportion of refractory patients could potentially receive neither of these therapies. To reflect this, we conducted a scenario analysis wherein

patients in the comparator arm receive a blended comparator (henceforth, referred to as the "Established Clinical Management (ECM)" arm), which is a combination of a proportion of patients receiving the standard basket only (shown in Table 20), a proportion receiving IVIg along with the standard basket and a proportion receiving PLEX along with the standard basket of treatments. This is informed by a recent study by Moniz Dionisio et al. that reported the real-world experience of using efgartigimod in patients with generalised MG in the UK (n=48).[1] We view that this patient cohort in the efgartigimod Early Access to Medicine Scheme (EAMS) is comparable to the patient group of interest for rozanolixizumab in the current appraisal. We discuss this study and the percentage split of the patients across these three groups within the ECM arm are
discussed in section 6 below.

Consultation with our clinical experts indicates that while the composition of drugs within the standard basket used in the company's model (shown in Table 19) is broadly reflective of current clinical practice in England, fewer people would receive tacrolimus and cyclosporine and more would receive mycophenolate instead. Using revised percentages of patients receiving these drugs has a limited impact on the ICER because of the low drug prices, and the costs are cancelled out when used in all comparator arms, including the ECM comparator arm alongside IVIg and PLEX.

Table 18 Standard of care treatments included in the company model

Treatment	Patients receiving treatment
Corticosteroids	63.2%
Azathioprine	17.8%
Mycophenolate mofetil	19.0%
Cyclosporine	7.5%
Tacrolimus	5.7%
Methotrexate	2.3%
Pyridostigmine	80.5%
Source: Company's economic model	

EAG conclusions on intervention and comparators

We disagree with the comparators included in the company's economic analyses. Our key concerns are:

- SoC is excluded as a comparator, this deviates from the NICE scope.
- The CS compared rozanolixizumab directly with IVIg and PLEX separately. These pairwise comparisons do not reflect clinical practice. Based on our expert opinion, we view that in clinical practice the patient population with refractory generalised MG receives both IVIg and PLEX as part of standard of

care, with a proportion potentially receiving neither of these therapies and only the standard basket. This is not reflected in the company's analysis.

To address the above issues and reflect UK clinical practice, we conducted scenario analyses including a blended comparator (ECM) where a proportion of patients (43.8%) received IVIg plus the standard basket, a proportion (14.6%) received PLEX plus the standard basket and the remaining 41.6% receiving only the standard basket, based on the efgartigimod EAMS cohort. This has a significant impact on the overall cost-effectiveness results. Further details are in section 6 below.

4.2.5 Perspective, time horizon and discounting

The company's model appropriately uses a lifetime horizon to reflect the condition of generalised MG. Their analyses take the perspective of the NHS and PSS, which aligns with the NICE manual for health technology evaluations.[44] Costs and outcomes (life years and QALYs) are discounted at 3.5%.

4.2.6 Clinical parameters

The key clinical parameters and sources used in the company's economic analysis are presented in Table 20 below.

Table 19 Key clinical parameter sources for the company's economic model

Parameter	Sources
MG-ADL Response rates	NMAs and published literature
Efficacy (MG-ADL reduction)	NMAs and published literature
Time on treatment	Assumption
Clinical event: Exacerbation	Published literature
Clinical event: Crisis	
Mortality	ONS Life tables and published literature
Transitional probabilities	All the clinical parameters listed in this table
Source: produced by the EAG	

4.2.6.1 Response rate

The odds ratios for MG-ADL response rates (discussed earlier in Table 15 within section 3.5 of this report) inform the transition probabilities of patients moving from the "uncontrolled on high dose steroids and ISTs" to the "response" health state. The company base case model uses these odds ratios obtained from the NMA to estimate the response rates for rozanolixizumab, zilucoplan, and efgartigimod. As discussed earlier in section 3.5, 'response' in the NMAs was defined as a ≥2-point improvement in the MG-ADL score. This point

improvement used in the rozanolixizumab trial (MycarinG) aligns with the efgartigimod trial (ADAPT), but not with the zilucoplan trial (RAISE) that uses a ≥3-point improvement in the MG-ADL score. We note that the model is currently not designed to consider the comparative evidence directly, but instead via placebo through a 'referent response rate', which we discuss below.

Treatment specific response rates for rozanolixizumab, zilucoplan and efgartigimod were obtained from the odds ratio from the NMA by applying the following steps:

- First, odds ratios obtained from the NMA for rozanolixizumab versus placebo ([redacted]), efgartigimod versus placebo ([redacted]), and zilucoplan versus placebo ([redacted]) were converted to relative risks, using the formula stated in CS Section B.3.3.1 and reproduced below

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

t is the comparator treatment with known OR versus the referent treatment

- The relative risks were then applied to the referent response rate to estimate each treatment's response rate. The CS states that the referent response rate, estimated at [redacted], was calculated as the average response rate across the studies used in the NMAs. The following formula was used to estimate the treatment specific response rates from the referent response rate and relative risks

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

Using the above approach, the response rates for rozanolixizumab, zilucoplan and efgartigimod were estimated to be [redacted] and [redacted] respectively.

The response rates for IVIg and PLEX were not available from the NMAs and were instead obtained from a study by Barth et al.[2] These response rates were converted to odds ratios using the referent response rate. Table 21 summarises the treatment specific response rates.

There are several key limitations to the Barth et al. study data. The study was conducted in Canada, with uncertain relevance to UK patients; the study population was not explicitly defined as having refractory MG (patients were described as having moderate to severe MG with a QMG score >10.5); the response was reported as a ≥3-point improvement in QMG score because the MG-ADL response outcome was not available from the study; and no confidence intervals or standard errors were provided with the response rates.

The company applied the response rates until the 'response assessment time point', which represents the waiting period to see if a patient responds to the treatment. The timepoints for the company's base case were obtained from the trial endpoints associated with each of the comparators (see Table 21). The EAG note that the company back calculated the odds ratios for IVIg and PLEX using response rates from the study by Barth et al. After the response assessment time point, patients who have not responded discontinue treatment. The model assumes no patients transition from the 'uncontrolled on high dose steroids' health state to the 'response' health state after the response assessment timepoint. The company acknowledged response was assumed to be constant across treatments, although this may not reflect rozanolixizumab and efgartigimod, which are both dosed cyclically and therefore response to these treatments can potentially wax and wane during a treatment cycle.

Table 20 Odds ratio, response rates and timepoints applied in the company revised base case

Treatment	Odds ratio	Response rate	Response assessment time point (weeks)
Rozanolixizumab	[redacted]	[redacted]	6
Zilucoplan	[redacted]	[redacted]	12
Efgartigimod	[redacted]	[redacted]	10
IVIg/SCIg	1.04	51.01%	6
PLEX	1.33	57.01%	6

Source: Company's revised economic model and their response to Clarification Questions B4 and B5.

Note: Odds ratios for rozanolixizumab, zilucoplan and efgartigimod (column 2) are obtained from the company's NMAs. The rates for PLEX and IVIG were back calculated from the response rates obtained from the study by Barth et al. The ORs were then converted to the response rates by applying the referent reference rate (which is [redacted] and calculated as average response rate across the studies used in the NMA). These response rates (column 3 above) inform the transition probabilities.

EAG conclusions on the modelled response rate

The company's model uses odds ratios obtained from the comparison of rozanolixizumab, zilucoplan and efgartigimod against placebo in the NMA which were converted to response rates for these treatments. It does not consider comparative evidence directly but via placebo through the referent response rate, which is an average placebo response. We view the estimated referent response rate is implausible at [redacted] as the placebo response rates in MycarinG, RAISE and ADAPT trials were 31%, [redacted] and 30% respectively. Further limitations of the NMA are discussed in section 3.2.5 above. In response to clarification question A13, the

company conducted a MAIC that provided pairwise comparative evidence, using the MG-ADL outcome, for rozanolixizumab against efgartigimod. The MAIC providing comparative evidence for rozanolixizumab against IVIg did not report the MG-ADL outcome, and MAICs for rozanolixizumab against zilucoplan or against PLEX were not provided. The EAG could not incorporate the MAIC output into our analyses due to pragmatic reasons as the model would require significant adaptation. Because of the limitations associated with the outputs from the indirect comparisons (NMA and MAIC), we prefer to use the response rates for rozanolixizumab, zilucoplan and efgartigimod from the MycarinG, RAISE and ADAPT trials respectively, shown in Table 22 and applied in EAG analyses reported in section 6 below. We validated these response rates with our clinical experts. We also validated the company's reported treatment response rates with our clinical experts. Two experts commented that, in general, most patients (about 70%) would respond to IVIg and PLEX. We explored the impact of this assumption in a scenario analysis, see section 6.

With respect to the response assessment timepoint, our clinical experts noted that in clinical practice, treatment effects are seen (and maintained) much earlier, after 1-2 weeks, and patients are often assessed 3-4 weeks after starting IVIg or PLEX. Clinical advice to the EAG, reported in the EAG report on zilucoplan,[25] was that assessing PLEX after 6 weeks (as proposed by the company) may be inappropriate, because patients may have responded and lost response by that time. We conducted a scenario analysis to explore the impact of assessing response after three weeks for all treatments; further details are in section 6.1 below.

Table 21 Alternative inputs for the response rates and timepoints used by the EAG

Treatment	Response rate	Response assessment time point (weeks)
Rozanolixizumab	72%	6
Zilucoplan	73%	6
Efgartigimod	68%	6
IVIg/SCIg	70%	6
PLEX	70%	6
Source: Response rates for rozanolixizumab, zilucoplan and efgartigimod are obtained from the clinical trial publications[35, 45, 46]; response rates for IVIg and PLEX and the response assessment timepoints for all the treatments based on EAG expert clinical opinions.		

4.2.6.2 Efficacy (MG-ADL reduction)

The company use the change in MG-ADL score (a decrease in score indicates an improvement in the disease) to assess treatment response. The baseline MG-ADL score used in the model is the mean baseline score for the patients in the MycarinG trial, MG-ADL 8.3, indicating that patients have severe disease. The speed and magnitude of symptom improvement, as well as the sustained response level, were obtained by tracking MG-ADL scores over time where patients could experience the following:

- Initial response (as shown above in section 4.2.6.1)
- Continued response, meaning MG-ADL scores continue to fall over time.
- Stable response, meaning MG-ADL scores remain stable over time.
- Loss of initial treatment response, meaning MG-ADL scores decrease initially and then start increasing over time.

The above trajectories of the MG-ADL scores are captured by the three health states in the model: continued response, stable response, and loss of response (shown in Figure 2 above). The company made the following assumptions for applying the MG-ADL scores across the health states:

- All responders in each treatment arm are assumed to have the same treatment-specific MG-ADL score until the response assessment timepoints, thereby assuming equivalence to a stable response.
- After the response assessment timepoint, of those patients who respond to treatment and progress to the response health state, [redacted] are assumed to have a stable response, [redacted] are assumed to lose response, and the remaining [redacted] are assumed to have a continued response. These assumptions are based on the opinion of two clinical experts consulted by the company. Clinical advice to the EAG verified these assumptions.
- The model assumes patients who lose response slowly return to the baseline MG-ADL score over a period of 14 weeks of response assessment. This time-period is based on the time taken for patients to return to a QMG score similar to their baseline after switching treatments in the phase 2 eculizumab clinical trial,[47] which the company applied to the immature discontinuation data from MycarinG and MG0007. For these patients, the model assumes that the MG-ADL score worsens linearly back to the baseline MG-ADL score.

[redacted]Table 23 summarises the average MG-ADL score change from baseline used in the company's revised model. These estimates are applied to the 'controlled response state' of the Markov trace. CS section B.3.3.4 states that the estimates for the stable response for

rozanolixizumab, zilucoplan and efgartigimod were obtained from the NMA and that for IVIg and PLEX from Barth et al.[2]

The estimates for the stable response (see column 3 in Table) were used to calculate the continued response (see column 4 in Table 23) by applying a [redacted] increase in change from baseline MG-ADL score. CS section B.3.3.4 states that the estimate ([redacted] was obtained from the difference between the highest CFB MG-ADL score in MG0007 ([redacted] cycle 4) and the change from baseline MG-ADL score reported for the primary endpoint of MycarinG (-3.22). The EAG could replicate this calculation. In the uncontrolled response state, the average MG-ADL score did not change from baseline in the company's model.

Table 22 Change in MG-ADL score from baseline used in the company's revised model

Treatments	Loss of response	Stable response	Continued response
Rozanolixizumab	0.00	[redacted]	[redacted]
Zilucoplan	0.00	[redacted]	[redacted]
Efgartigimod	0.00	[redacted]	[redacted]
IVIg/SCIg	0.00	[redacted]	[redacted]
Plasma exchange	0.00	[redacted]	[redacted]

Source: CS Appendix N and Company Erratum

EAG conclusions on change from baseline MG-ADL score

We have concerns with the company's estimates applied for the change in MG-ADL score from baseline, due to the uncertainties inherent in the NMAs from which these estimates are obtained (as discussed earlier in section 3.5). Furthermore, the company used the open-label extension study MG0007 to inform the percentage change to estimate the continued response. We have concerns about this study as it is a single study with no placebo arm and involved patients' switching between treatments (for further discussion, see section 3.2.1.1.2).

4.2.6.3 Clinical events

Two clinical events were modelled as separate health states: exacerbation and myasthenic crisis. The company obtained the exacerbation and myasthenic crisis annual event rates from a study by Abuzinadah et al[48], reproduced below in Table 24.

Table 23 Annual clinical event rates

Health states	Exacerbation	Myasthenic crisis	Source
Response	0.244	0.023	Abuzinadah et al. 2021
Uncontrolled	0.651	0.062	A relative risk of 2.67 (obtained from the same source as above) was applied to the rates in the response state.
Source: reproduction of CS Table 61			

The company also accounted for patients who might experience an exacerbation, but further worsen to a crisis, by applying a 2-week event rate of 0.184 to those patients in the exacerbation health state.

EAG conclusions on the clinical event rates

Overall, we agree with the company's approach to modelling the two clinical events.

4.2.6.4 Time on treatment

In the economic model, patients receiving rozanolixizumab and responding to a treatment will receive that treatment for the rest of their lifetime. Those who do not respond or who lose their initial response at the response assessment time point (and do not experience a crisis, or an exacerbation, or die) discontinue treatment due to lack of efficacy and move to the uncontrolled health state, with a return to their baseline MG-ADL score.

4.2.6.5 Adverse events

Adverse events (AEs) were excluded from the company's base case model as none of them met the inclusion criteria for serious AEs with an incidence ≥5% in the MycarinG trial.

4.2.6.6 Mortality

General population mortality adjusted for age and gender was appropriately implemented in the economic model. In addition, the model assumed 4.47% patients in the crisis health state would die within 2 weeks.

4.2.6.7 Transition probabilities

All the clinical parameters discussed in the above sub-sections informed the transition probabilities for the Markov trace. The model did not apply time-dependent transitional probabilities, but the number of patients at the start and end of a period was used to estimate these probabilities, which were then applied over the model time horizon. The company updated their transition probabilities in their revised economic model, submitted as erratum as part of their Clarification Response.

EAG conclusions on time on treatment, adverse events, mortality, and transition probabilities

We agree with the company's approach to modelling time on treatment, adverse events, and transition probabilities. Concerning mortality, we acknowledge that the literature on the mortality associated with generalised MG is limited. Therefore, it may be reasonable to use UK general population mortality as background mortality due to lack of other data. However, advice from the clinical experts indicates that there is likely to be excess mortality associated with the condition, related to the chronic therapies. As an example, use of corticosteroids may be associated with higher hip fractures which may, in turn, increase the risk of mortality.

4.2.6.8 Subsequent treatments

The economic model does not account for subsequent treatments. The company assumes that patients in the 'Uncontrolled on high dose steroids and ISTs' either do not respond or lose their initial response to treatment, and therefore stop receiving treatment due to lack of efficacy. We have concerns about this assumption. Refractory MG is a condition requiring lifelong management; therefore, patients discontinuing from rozanolixizumab, zilucoplan or efgartigimod may be eligible for chronic IVIg or PLEX treatment. Applying costs for subsequent treatments within the economic model is likely to impact the overall cost-effectiveness results. For example, adding subsequent costs to rozanolixizumab arm would reduce the incremental costs compared to ECM, resulting in increase of ICER for rozanolixizumab versus ECM. However, adding subsequent treatment costs to rozanolixizumab, zilucoplan and efgartigimod arms may not influence the cost-effectiveness results for rozanolixizumab versus efgartigimod or rozanolixizumab versus zilucoplan due to similar costs.

EAG conclusions on subsequent treatments

The EAG disagree with the company's assumption that patients who discontinue treatment do not receive any subsequent treatment. Currently, the model does not account for the impact of subsequent treatments on the overall cost-effectiveness results. Whether this is reflective of clinical practice warrants further discussion as including the costs and health benefits of subsequent treatments is likely to influence overall cost-effectiveness results.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature review of existing health-related quality of life (HRQoL) studies in generalised MG and report their search and findings in CS Appendix H. Ninety-five studies were found in the search that met the population, intervention, comparator, and study design inclusion criteria. Of these, four reported utilities among patients with MG using EQ-5D and SF-6D. The utilities for the overall MG population were obtained from using the EQ-5D index and ranged from 0.68 to 0.8. We note that a recent study by Dewilde et al.[49] that estimated HRQoL of people with MG using the MyRealWorld(MRW)-MG and POPUP observational datasets. Briefly, POPUP is a multinational digital study that recruited 9000 members of the public in eight countries (US, Canada, UK, Italy, Spain, Germany, The Netherlands, and Belgium). In contrast, MRW is a digital, prospective, observational, longitudinal multi-country study, conducted among 1859 adults diagnosed with MG from nine countries (US, UK, Canada, Italy, Germany, Spain, France, Denmark, and Japan), with an aim to provide a comprehensive real-world, long-term view of the impact of MG in a large, diverse cohort of people diagnosed with MG. Dewilde et al.[49] reported an EQ-5D-5L value of 0.468 for patients with severe disease (i.e., MG-ADL ≥ 10) in the UK. We use this value for the EQ-5D baseline value in our scenario analyses shown in section 6.1.

4.2.7.2 Study-based health related quality of life

HRQoL data from the MycarinG trial were used to estimate utilities in the model. EQ-5D-5L data were collected at baseline and at Day 43. The EQ-5D-5L data from the trial were mapped onto EQ-5D-3L using the method designed by Hernandez-Alava et al. (2017).[43]

4.2.7.3 Health related quality of life data used in cost-effectiveness analysis

Utility values based on EQ-5D-5L scores from the MycarinG trial were used in a repeated measures regression model and fitted for all patients in the trial. For this regression model, treatment arms were pooled. The company's base case utility regression model included baseline EQ-5D and MG-ADL scores as independent variables, as shown in Table 25 below.

Table 24 Regression parameters for utility equation

Parameter	Estimate	SE	p value
Baseline EQ-5D	0.6327		
Intercept [β0]	0.2024	0.02819	<0.0001
Coefficient of baseline EQ-5D (β1)	–0.2794	0.04162	<0.0001
Coefficient of MG-ADL score (β2)	–0.0221	0.002664	<0.0001

Source: Reproduced from CS Table 63

The model did not explore any alternative regression specifications, including additional covariates of baseline BMI, disease duration and exacerbation or crisis. The company did not report any method or information for covariate selection. Therefore, the EAG are unable to verify the company's regression model.

The economic model applies an appropriate age- and gender- adjustment to the overall utility, based on the regression algorithm designed by Ara and Brazier (2010).[50]

4.2.7.4 Disutilities for adverse events and clinical events

The economic model does not include any adverse events, as discussed earlier in section 4.2.6.5. The company obtained the disutility for an exacerbation from the REGAIN trial for eculizumab. They applied a weighted average disutility for the expected duration of the event (see Table 26). The patients are then assumed to incur the average utility across the response and uncontrolled health states, weighted by the proportion of patients in each health state for the remaining length of a cycle (2.2 days). After an exacerbation, patients are assumed to return to one of the three response subgroups to continue treatment until the response assessment timepoint. At that point, if patients lose response, then they are assumed to discontinue treatment and transition to the uncontrolled health state.

The company applied a disutility for patients experiencing myasthenic crisis that was also obtained from the REGAIN trial. This disutility is applied for the full model cycle in which a patient transitions into a crisis health state; the company assumes a crisis lasts for 14 days (see Table 26). Patients transition to the uncontrolled health state following successful treatment for a crisis.

Table 25 Disutilities for clinical events

Clinical event	Disutility	Duration (days)
Exacerbation	-0.20	11.80
Myasthenic crisis	-0.39	14.00

Source: Disutilities for the clinical events were obtained from the REGAIN trial

4.2.7.5 Disutilities for caregiver burden

The company's economic model does not capture the effect of generalised MG on caregiver disutilities. The company discuss the potential impact in CS section B.1.3.1.5 within the Economic burden section, and in CS section B.1.3.3.3 Unmet need.

EAG conclusions on HRQoL

Overall, we consider the company's approach for modelling utilities to appropriate but have some concerns. The company did not provide any regression statistics in either the CS or in the economic model to show whether adding or removing alternative covariates improves the fit of the regression model. Our experts considered that the duration of a crisis is underestimated in the company model and suggested patients are likely to spend three weeks in crisis. The EAG note that CS section B.1.3.1.3 states 20% of patients experiencing a crisis would be ventilated beyond one month in the ICU. We conducted a scenario analysis to explore the impact of this assumption, reported in section 6.1 below. Furthermore, we explored the impact of using a baseline EQ-5D estimate of 0.468 based on the study by Dewilde et al.,[51] also shown in section 6.1. Lastly, the EAG consider it appropriate to not include caregiver disutilities in the model.

4.2.8 Resources and costs

The company conducted a systematic literature review to identify the sources of costs and resource use used in the model. Further details are in CS Section B.3.5.1, CS Appendices I, G1.1 and G1.2. Briefly, they identified 63 studies of which only two were based in England[52, 53] and one was based in the UK.[54] In addition, the company surveyed UK clinical experts with experience of treating patients with generalised MG to obtain costs and resource use estimates relevant to the UK setting.

The economic model included the following healthcare resource use and costs, which we discuss in the following sub-sections of this report:

- Drug acquisition and administration
- Routine care
- Vaccination costs (for patients receiving zilucoplan)
- Management of clinical events

EAG conclusions on the company's searches

The EAG consider the company to have searched appropriate databases and conference proceedings, we have no concerns about their search strategy, and we believe it is unlikely that any key studies have been missed. We view that appropriate sources have been used to inform the unit costs in the model.[55, 56] The EAG were not provided with information concerning the number of clinical experts who advised the company, or their affiliations. Uncertainty remains concerning the geographical coverage of the clinical expertise sought by the company and whether the clinicians

worked in specialist centres or not, which could determine their access to, and experience with, IVIg/SCIg and PLEX treatment.

4.2.8.1 Drug acquisition

Rozanolixizumab is given as weekly subcutaneous infusions for 6 weeks (one treatment cycle), which is repeated as needed. CS Table 65 shows the unit costs associated with each treatment in the economic model. Rozanolixizumab dosage is based on patient weight:

- <50 kg = 280 mg
- ≥50 kg to < 70 kg = 420 mg
- ≥70 kg to < 100 kg = 560 mg
- ≥100 kg = 840 mg

The model uses a weighted net price of [redacted] per mg for rozanolixizumab, after applying the PAS discount of [redacted]. The weighted price is based on the distribution of patients in the different weight bands who received different doses of rozanolixizumab, based on the company's assumed launch posology. In their economic model, the company uses the price for a 560mg vial of rozanolixizumab (i.e., the dose for patients weighing ≥70 kg to < 100 kg). The EAG note that, of the participants in the MycarinG trial:

- 6% weighed less than 50kg
- 31% weighed ≥50 to <70kg
- 42% weighed ≥70 to <100kg
- 22% weighed 100kg or more

We consider the company's assumed weighted price for rozanolixizumab to be reasonable.

The CS states approximately 90% of patients in the clinical trials had treatment-free intervals of 4–13 weeks between cycles, while 10% of patients had a treatment-free interval of less than 4 weeks. The average annualised number of cycles per patient was [redacted]. Instead of including breaks in treatment costs for rozanolixizumab in their economic model, the company take the total annual cost of [redacted] treatment cycles of rozanolixizumab ([redacted]), divide this by the number of model cycles in the year (26) and apply a standard per cycle treatment cost of [redacted] (i.e., every two weeks). The EAG consider this approach to be reasonable.

For the comparators, IVIg/SCIg is given every three weeks at a dose of 1000mg/kg , PLEX is administered every four weeks and zilucoplan is given daily, based on patient weight (CS Table 65).

- <56 kg: 16.6 mg dose

- ≥56 to <77 kg: 23 mg dose
- ≥77 kg: 32.4 mg dose

The model uses a weighted list price of [redacted] per mg for zilucoplan.

In practice, efgartigimod is given weekly at a dose of 10mg/kg for four weeks, with six weeks off treatment. However, rather than including breaks in treatment costs in their base case, the company take the total annual cost of five treatment cycles of efgartigimod (£262,789), divide this by the number of model cycles in the year (26) and apply a standard per cycle treatment cost of £10,107 (i.e., every two weeks). As for rozanolixizumab above, the EAG consider this approach to be reasonable. The costs of the comparator treatments in the first, second and subsequent model cycles in the company's base case are shown below in Table 27.

Efgartigimod and zilucoplan are subject to patient access scheme (PAS) discounts and results including these data will (subject to confirmation of the PAS discounts) be presented in a separate confidential addendum to this report.

Table 26 Costs associated with the treatments in the company's base case

Treatment	Weighted price per mg	Cost in model cycle 1 or 2	Cost in subsequent model cycles
Rozanolixizumab[a]	[redacted]	[redacted]	[redacted]
IVIg/SCIg	£0.07	£3,716	£3,716
Efgartigimod	£16.42	£10,107	£10,107
Plasma exchange	£2,587	£6,469	£5,861
Zilucoplan	[redacted]	[redacted]	[redacted]

Source: Adapted from CS Table 65
[a] Costs include the PAS discount
IVIg: intravenous immunoglobulin; mg: milligram ; SCIg: subcutaneous immunoglobulin

Clinical advice to the EAG was that it would be reasonable to assess all interventions at 6 weeks, especially rozanolixizumab and efgartigimod, which have the same mechanism of action. Our clinical experts explained that IVIg is generally given every 4-8 weeks. One expert typically gives IVIg every 8-12 weeks, depending on patient response, and stated that giving IVIg every 3 weeks was too frequent. Our experts also explained that PLEX is usually administered every 4-8 weeks, but that giving patients PLEX treatment every 8 weeks is rare. We apply the costs for IVIg and PLEX every 6 weeks in our base case (section 6.2). Our experts commented that most patients (about 70%) would respond to IVIg and about 70% would respond to PLEX. Our experts also highlighted that it would be very unusual for a patient not to respond to either IVIg or PLEX.

The company weight the cost of immunoglobulin as 50% IVIg and 50% subcutaneous immunoglobulin (SCIg) as they anticipate use of SCIg to increase in the future. Our clinical experts also expect use of SCIg to increase unless other treatment options for generalised MG become available. We investigated the effect of using 100% SCIg in a scenario analysis, as reported in section 6.1 below.

4.2.8.2 Drug administration

CS Table 66 presents details of the administration costs used in the model. Rozanolixizumab is administered as a short subcutaneous infusion (CS section B.3.5.2.1 states the infusion lasts up to 18 minutes), and administration costs were assumed to cover 60 minutes of nurse time on treatment initiation, which is reduced to 30 minutes in subsequent model cycles.

Efgartigimod and IVIg are given as infusions, for which the EAG consider the company have used appropriate NHS reference costs. The EAG note the subcutaneous formulation for efgartigimod has been approved, which can be injected by the patient or carer. We explore the use of subcutaneous administration by applying an alternative administration cost strategy in a scenario analysis i.e., the first two subcutaneous injections are given by a nurse in hospital (£41), then administration is free for the subsequent cycles.

Zilucoplan is a self-administered subcutaneous injection given once a day using a pre-filled syringe. The CS states the administration cost (subcutaneous injection; £41; 60mins, Band 5 hospital nurse) was applied as "*one-off costs associated with the cost of training patients to self-inject the treatment in future model cycles. The healthcare system was assumed not to incur any costs for self-injections in subsequent cycles*." However, the EAG note that the £41 administration cost is being applied in all model cycles in the company's base case. We removed this administration cost for zilucoplan after cycle 2 in our base case (section 6).

The company use the NHS reference cost SA44A (single plasma exchange; £910) for PLEX, applying a per cycle cost of £303.33 (i.e., every 2 weeks). However, PLEX treatment is given every four weeks in the company's base case (CS Table 65). The EAG consider the per cycle PLEX administration cost in the company's base case to be too low. Consequently, the per cycle PLEX administration cost should be £455. We prefer to apply PLEX maintenance and administration costs every 6 weeks, which makes the PLEX admin cost £303.33 in our base case.

4.2.8.3 Resource use

Costs and resource use for patients with a) uncontrolled disease, b) responding to treatment, c) transitioning through an exacerbation or d) a crisis, are presented in CS Table 67. Consultation with our experts indicated several differences in the company's assumptions for resource use when compared to the current clinical practice in England. Our experts' suggestions are shown below in Table 28 and Table 29 and we tested the cumulative effect of these differences in a scenario analysis (section 6.1).

Clinical advice to the EAG was that generalised MG patients with MuSK antibodies would likely have 20-30% increased resource use compared with patients with generalised MG who do not have MuSK antibodies. However, our clinical experts also explained that the number of generalised MG patients in the UK with MuSK antibodies is very low (<2% of the generalised MG patient population UK-wide, and <5% of the generalised MG patient population in London), so we have not conducted any scenario analyses, but consider this noteworthy.

Table 27 Health state resource use and unit costs (all treatments except PLEX), alternatives suggested by EAG clinical advisors (in bold and underlined)

Resource	Health state			
	Frequency of resource use and length of stay			
	Uncontrolled	Response	Exacerbation	Myasthenic crisis
GP visits [57]	13.62	9.53	**0.20**	0.06
Visit to other Healthcare Professionals	11.47	6.89	**0.40**	0.32
Outpatient hospital visits	7.10	4.77	**0.40**	**0.00**
Presenting at ER	0.44	**0.10**	**0.60**	1.00
Hospital stay (with ICU, cost per critical care period)	0.13	0.07	**0.10**	1.00
Hospital stay (no ICU, cost per day)	1.40, length of stay: 1.19 days	0.75, length of stay: 1.19 days	0.33, length of stay: 7.50 days	1, length of stay: **21** days

Source: Adapted from CS Table 67

Abbreviations: ER, emergency department; GP, general practice; ICU, intensive care unit; IVIg, intravenous immunoglobulin; PLEX, plasma exchange.

Table 28 Health state resource use and unit costs (PLEX), alternatives suggested by EAG clinical advisors (in bold and underlined)

Resource	Health state			
	Frequency of resource use and length of stay			
	Uncontrolled	Response	Exacerbation	Myasthenic crisis
GP visits	13.62	9.53	**0.40**	0.06
Visit to other Healthcare Professionals	11.47	6.89	**0.80**	0.32
Outpatient hospital visits	7.10	4.77	**0.30**	**0.0**
Presenting at ER	0.44	0.33	**0.70**	1.00
Hospital stay (with ICU, cost per critical care period)	0.13	0.07	**0.10**	1.00
Hospital stay (no ICU, cost per day)	1.40, length of stay: 1.19 days	0.75, length of stay: 1.19 days	0.33, length of stay: 7.50 days	1, length of stay: **21** days

Resource	Health state			
	Frequency of resource use and length of stay			
	Uncontrolled	Response	Exacerbation	Myasthenic crisis
Source: Adapted from CS Table 67 Abbreviations: ER, emergency department; GP, general practice; ICU, intensive care unit; IVIg, intravenous immunoglobulin; PLEX, plasma exchange.				

4.2.8.3.1 Subsequent therapy

Refractory generalised MG is a condition that requires lifelong management. We consider it likely that if patients do not respond, or lose response, to a particular treatment, they would go on to receive an alternative therapy (please see section 3.2.1.1.1). We note that the costs and health benefits patients may receive from any subsequent treatments following discontinuation from rozanolixizumab or comparators have not been costed into the economic model. We raise this as a Key Issue in section 1.5.

4.2.8.4 Adverse event resource use

The company's base case does not include adverse event costs, because no adverse events were considered to meet the inclusion criteria of serious adverse events with an incidence ≥5% in the MycarinG trial. Overall, we consider excluding adverse event costs in either arm as a conservative assumption favouring the comparator.

EAG conclusion on resources and costs

The EAG note the variation in treatment-free intervals experienced by the patients receiving rozanolixizumab in the clinical trials. We explore a scenario where patients receive four cycles of rozanolixizumab per year (six weeks on treatment, eight weeks off) in our analyses (section 6.1).

Clinical advice to the EAG was that IVIg and PLEX can be given every 4-8 weeks, and we apply the costs for chronic IVIg and chronic PLEX every 6 weeks in our base case. We consider the administration costs for rozanolixizumab, efgartigimod and IVIg to be suitable, but disagree with how the company have implemented the administration costs for zilucoplan and PLEX. We conducted scenario analyses to explore our assumptions (described in section 6.1).

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company report their base case incremental cost-effectiveness analysis results for rozanolixizumab versus efgartigimod, IVIg/SCIg, PLEX and zilucoplan in CS Table 69, using the PAS discount price for rozanolixizumab and list prices for all other treatments. Efgartigimod and zilucoplan are also subject to PAS discounts and the results including these will be presented in a separate confidential addendum to this report, subject to confirmation of the two PAS discounts.

After submission of their evidence, the company informed NICE of an error in their NMA, affecting the rate of responders for rozanolixizumab, zilucoplan and efgartigimod. The company provided a revised version of their economic model, which includes the updated referent response rate of [redacted] and response rates for rozanolixizumab, zilucoplan and efgartigimod using a 2-point improvement in MG-ADL (Table 21).

All results in this section use the PAS discount of [redacted] applied to the list price for rozanolixizumab, which reduces the total costs for rozanolixizumab. The company's revised base case results are presented in CS Erratum March 2024 Table 69. The EAG was able to reproduce these new results by updating the referent response rate and odds ratios within the economic model. Table 30 presents the company's base case results using the revised model received as part of the company's update. The pairwise ICER for rozanolixizumab compared with IVIg/SCIg is [redacted] per QALY; [redacted].

Table 29 Revised company base case results, pairwise results

Technologies	Total		Incremental vs. rozanolixizumab		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Rozanolixizumab	[redacted]	8.2293	-	-	-
IVIg/SCIg	[redacted]	8.0379	[redacted]	0.1914	[redacted]
Efgartigimod	[redacted]	8.2120	[redacted]	0.0173	[redacted]
PLEX	[redacted]	8.0950	[redacted]	0.1343	[redacted]
Zilucoplan	[redacted]	8.1418	[redacted]	0.0875	[redacted]

Source: adapted from CS Erratum March 2024 Table 69.
QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; PLEX: plasma exchange; SCIg: subcutaneous immunoglobulin; SoC: standard of care

5.1.1 Deterministic sensitivity analyses

The company report deterministic sensitivity analysis (DSA) results in the form of tornado diagrams, showing the top 10 most influential parameters. The comparison of rozanolixizumab versus efgartigimod, zilucoplan, IVIg and PLEX are shown in CS Erratum March 2024 Figure 15 – Figure 18, and Tables 74 – Table 77, respectively. CS Erratum March 2024 Appendix N reports the input parameters used in the company's deterministic sensitivity analysis. The range of variation for the input parameters was based on published standard errors where available, or a range of +/- 20%. The company consider the net monetary benefit to be the most appropriate primary outcome for the DSA rather than the ICER, stating that the latter may produce extreme values that could cause issues with interpretation. The company use a threshold of £30,000 in their net monetary benefit calculations, which the EAG consider to be appropriate.

For the comparison between rozanolixizumab and efgartigimod, the ICER is most influenced by the annual exacerbation rate and the percentage of patients showing a stable response to treatment. The average patient weight has the greatest effect on the ICER for rozanolixizumab compared with zilucoplan and compared with IVIg/SCIg, because the total drug costs of both rozanolixizumab and zilucoplan are dependent on patient weight. When compared with PLEX, the ICER is mostly strongly influenced by the percentage of patients showing a stable response to treatment.

5.1.2 Scenario analyses

The company's scenario analyses using their revised base case are reported in CS Section B.3.10.3 and CS Erratum March 2024 B.3.10.3 and shown below in Table 31. The company initially investigated three scenarios:

1. Using the average weight of the refractory population with generalised MG from the MycarinG clinical trial ([redacted]) in place of the base case value of 81.15kg.
2. Using the same response assessment time-point across all the treatments, i.e., 6-weeks from MycarinG trial.
3. Using a responder rate of 70% for IVIg and PLEX, based on clinical expert opinion from the EAG report on zilucoplan.[25]

The company provided results of an additional scenario analysis, using a responder definition of ≥3-point improvement in MG-ADL score, in the CS Erratum March 2024 document. The EAG were unable to reproduce the results of this extra scenario using the data provided in the CS Erratum. The scenario analyses, using the company's revised base case, are shown in Table 31, results for scenario 4 are reproduced from CS Erratum March 2024 Section B.3.10.3. Using a responder rate of 70% for IVIg had the greatest effect on the

ICER for rozanolixizumab compared with IVIg/SCIg, reducing it to [redacted] per QALY (scenario 3). Rozanolixizumab [redacted].

Table 30 Company scenario analyses results, pairwise comparison, revised base case

Scenario		Treatment	ICER(£/QALY)
1	Refractory population weight: [redacted] from the MycarinG clinical trial	Rozanolixizumab	-
		IVIg/SCIg	[redacted]
		Efgartigimod	[redacted]
		PLEX	[redacted]
		Zilucoplan	[redacted]
2	6-week response assessment time point for all treatments	Rozanolixizumab	-
		IVIg/SCIg	[redacted]
		Efgartigimod	[redacted]
		PLEX	[redacted]
		Zilucoplan	[redacted]
3	Responder rate of 70% for IVIg and PLEX	Rozanolixizumab	-
		IVIg/SCIg	[redacted]
		Efgartigimod	[redacted]
		PLEX	[redacted]
		Zilucoplan	[redacted]
4	MG-ADL probability of response (3-point improvement in MG-ADL responder definition)	Rozanolixizumab	-
		IVIg/SCIg	[redacted]
		Efgartigimod	[redacted]
		PLEX	[redacted]
		Zilucoplan	[redacted]

Source: Adapted from CS Section B.3.10.3 and CS erratum March 2024 B.3.10.3
QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; PLEX: plasma exchange; SCIg: subcutaneous immunoglobulin

5.1.3 Probabilistic sensitivity analyses

The company reports their probabilistic sensitivity analysis results from 1000 iterations of a Monte-Carlo simulation, using the revised base case, in CS Erratum March 2024 Table 72 and shown below in Table 32. The cost-effectiveness scatterplot is depicted in CS Erratum March 2024 Figure 13 and reproduced in Figure 3 below. The pairwise ICER per QALY gained is reported as [redacted] per QALY versus IVIg/SCIg. [redacted]. The company present the variation between the original base case and probabilistic sensitivity analysis (PSA) results in CS Erratum March 2024 Table 73. The company considers the PSA results align

with their base case results. However, the EAG note a difference of over £120,000 per QALY between the revised PSA and the revised base case ICERs for rozanolixizumab compared with IVIg: [redacted] per QALY and [redacted] per QALY, respectively. We reran the PSA, which produced an ICER of [redacted] per QALY for rozanolixizumab compared with IVIg, indicating a high degree of uncertainty in the input parameters used in the probabilistic sensitivity analysis (reported in CS Erratum March 2024 Appendix O.1).

Table 31 Company probabilistic sensitivity analyses, pairwise results, revised base case

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Rozanolixizumab	[redacted]	8.2225	-	-	-
IVIg/SCIg	[redacted]	8.0206	[redacted]	0.2019	[redacted]
Efgartigimod	[redacted]	8.1896	[redacted]	0.0329	[redacted]
PLEX	[redacted]	8.0919	[redacted]	0.1306	[redacted]
Zilucoplan	[redacted]	8.1501	[redacted]	0.0724	[redacted]

Adapted from CS erratum March 2024 Table 72
Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SCIg, subcutaneous immunoglobulin;

Uncertainty in the ICER calculation is further demonstrated by the cost-effectiveness scatter plots for rozanolixizumab versus comparators (Figure 3). The EAG noted a bimodal distribution in the zilucoplan scatter plot, which the company explained in their response to clarification question B8. Patients mean weight is included in the probabilistic sensitivity analysis and values are sampled from the log-normal distribution based on the mean weight. For some iterations, the probabilistic average weight is less than 77 kg, reducing the dose of zilucoplan from 32.4 mg to 23 mg. Because of this shift, the drug cost of zilucoplan decreases significantly, leading to the observed bimodal distribution. The company performed a scenario excluding patient weight from the PSA, and the bimodal distribution is no longer observed (Company response to Clarification Question B8 Figure 8).

[redacted]. Consequently, the company present their willingness-to-pay (WTP) analysis using incremental net monetary benefit results. At a WTP threshold of £30,000 per QALY gained, the incremental net monetary benefit result for rozanolixizumab versus comparators is [redacted] compared with IVIg/SCIg, [redacted] compared with efgartigimod, [redacted] compared with PLEX and [redacted] compared with zilucoplan, indicating that rozanolixizumab

[redacted].

Figure 3 Scatterplot of PSA results (cost-effectiveness scatter plot), company revised base case

Abbreviations: IVIg, intravenous immunoglobulin; QALY, quality-adjusted life year; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SCIg, subcutaneous immunoglobulin.
Source: CS erratum March 2024 Figure 13

5.2 Model validation and face validity check

5.2.1 Company model validation

The company's approach to validating their model is described in CS section B.3.13. The company also provided a Technical Quality Control report from Index Match Ltd (Health economics consultancy), who assessed two cost-effectiveness models in generalised MG that had been built by Mtech Access for the company:

1. Chronic treatment of generalised MG (with zilucoplan)
2. Acute treatment of generalised MG exacerbations (with rozanolixizumab)

The quality control checks were completed by an independent health economist, using a proprietary checklist to identify common mistakes. The checks included:

- 'Black box' tests to verify that model calculations aligned with a priori expectations.
- 'White box' tests (on a sheet-by-sheet basis) to validate formulae
- Assessing Excel Visual Basic for Applications (VBA) code critical to the functioning of the model for errors.

Furthermore, the company consulted clinical experts in generalised MG based in the UK to validate the clinical parameters used in the model (listed in CS section B.3.3.6). The CS states that these themes were tested in additional clinician interviews and the company held an advisory board in the UK in September 2023, focussing on the refractory patient population (CS B.3.4.6.2).

EAG conclusion on the company's model validation

The company's clinical expert opinion covered all the important model inputs. However, we were not provided with information concerning the number of clinical experts who advised the company, or their affiliations. We find the Technical Quality Control report to be thorough for both models presented but note that the rozanolixizumab model was for acute treatment of generalised MG exacerbations. We consider the model provided as part of the current CS to be the zilucoplan model for chronic generalised MG that has been adapted for rozanolixizumab, and that this approach is reasonable.

5.2.2 EAG model validation

The EAG conducted a range of tests to verify model inputs, calculations, and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses
- Checking individual equations within the model ('white box' checks)
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks)

5.2.3 Company corrections to the company model

The company's corrections to their original model are described in section 5.1 above, and Table 33 shows the cumulative effect of each of these changes on the ICER. The EAG were able to replicate the results of the company's revised base case after applying the changes made to correct the error in the original base case.

Table 32 Cumulative changes to the company's original base case, rozanolixizumab versus comparators, pairwise results

No.	Scenario description	Cumulative change to ICER (£/QALY)			
		IVIg/SCIg	Efgartigimod	PLEX	Zilucoplan
Original company base case		[redacted]	[redacted]	[redacted]	[redacted]
1	Use updated odds ratios and response rates (CS erratum March 2024 Table 59)	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case		[redacted]	[redacted]	[redacted]	[redacted]
Source: Company results reproduced by the EAG as part of the model check					

5.2.4 EAG corrections to the company model

Other than the issues raised by the EAG in the Clarification Question stage of this appraisal, we did not identify any technical calculation errors in the company's economic model.

As part of the EAG's Clarification Question B1, the company were asked to provide a version of the model that included standard of care as a comparator, with an option to include proportions of patients on IVIg or PLEX within standard of care. The company did not conduct this analysis and maintained that it was appropriate to compare IVIg and PLEX to rozanolixizumab separately. The EAG have endeavoured to code a standard of care arm that includes proportions of patients receiving IVIg and PLEX (discussed earlier in section 4.2.4 and referred to as 'established clinical management'; ECM) within the company's revised model. We discuss this in section 6 of this report and have raised it as a Key Issue for further consideration (see Key Issue 1 in section 1.3).

5.3 EAG summary of key issues and additional analyses

The EAG's observations on key aspects of the company base case are presented below (Table 34). We investigated these uncertainties through additional scenario analyses, described in section 6.1.

Table 33 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment on the company's approach	EAG analyses
Population characteristics			
Percentage female Initial MG-ADL score Patient age Patient weight	ModelSetUp tab	We agree. Our clinical expert advised us that a MG-ADL score of 8.3 is representative of patients with refractory gMG.	No change. We conducted scenarios using alternative patient characteristics (see Table 19) and increasing the average MG-ADL score at the start to 10.3 (≥ 2 points change in MG-ADL score was considered clinically meaningful in MycarinG)
Comparator			
Comparator	CS section B.3.5.2 and CS Table 65	The EAG do not consider it appropriate to compare rozanolixizumab with IVIg and PLEX separately, because we do not consider this reflects clinical practice in England for patients with refractory generalised MG. Instead, across the patient population, a proportion receive IVIg and a proportion receive PLEX. The EAG note a recent publication describing therapies received by patients in the efgartigimod Early Access to Medicine Scheme (EAMS) cohort, which we consider to be a reasonable approximation of the patient group rozanolixizumab is intended for.[1]	The EAG prefer to 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 SoC, based on EAMS cohort data.[1]
Clinical parameters			
Treatment response rates – all treatments	CS erratum March 2024 Table 59	We disagree. The company used data from their NMA for the rozanolixizumab, zilucoplan and efgartigimod response rates and derived the IVIg and PLEX response rates from Barth et al.[2] Clinical advice to the EAG was that about 70% of patients respond to both IVIg and PLEX treatment. Our experts also thought a response rate of [redacted] for zilucoplan was low.	We prefer to use the alternative response rates for IVIg and PLEX suggested by our clinical experts and to use response rates for rozanolixizumab, zilucoplan and efgartigimod based on the MycarinG, RAISE and ADAPT trials, respectively (Table 23).

Parameter	Company base case	EAG comment on the company's approach	EAG analyses
Time to treatment response		We disagree. Our experts noted that these treatments are fast-acting and that a response timepoint of 6 weeks would be appropriate for all of them.	We prefer to use 6 weeks for the response timepoint for all treatments. We explore using 3 weeks in a scenario analysis, based on clinical advice to the EAG given in the EAG report on zilucoplan.[25]
Change in MG-ADL score	CS Table 60	We disagree. The company use data from the MG0007 trial to inform the rozanolixizumab stable response data. Due to the biases in this study, we view the company are taking an optimistic approach for rozanolixizumab. We are uncertain of the source of the CFB scores for the remaining treatments. However, we cannot provide a scenario analysis because we do not have alternative data. This item is an unresolved uncertainty.	No change.
Transition probabilities	CS section B.3.3.4	The company assume that of those patients in the response health states, [redacted] had loss of response, [redacted] had continued response, and [redacted] had stable response. We agree.	No change.
Adverse events	CS section B.3.4.5	We agree. The company excluded adverse events.	No change.
Utilities			
Health state utilities	CS Table 63	We agree. The EAG note a recent paper providing utilities for people in the UK with severe gMG that are calculated from two observational data sets (MyRealWorldMG and POPUP).[49]	No change. We explore the utilities from MyRealWorldMG and POPUP in a scenario analysis.
Clinical event disutilities	CS section B.3.4.6.1	We agree	No change
Resource use and costs			

Parameter	Company base case	EAG comment on the company's approach	EAG analyses
Number of annualised cycles of rozanolixizumab per patient ([redacted] cycles)	CS section B.3.2.8	We agree. Clinical advice to the EAG was 4 cycles a year would be reasonable (6 weeks of treatment and approx. 8 weeks of respite is 14 weeks, resulting in ~4 cycles of treatment per year).	No change. We explore using 4 cycles of rozanolixizumab a year in a scenario analysis.
Administration costs	CS Table 66	We disagree. • The model uses NHS reference cost SA44A for PLEX administration, applying £303.33 every model cycle (i.e. every 2 weeks). However, the elective unit cost for SA44A is £910. PLEX is given every 4 weeks in the company's base case, so PLEX admin costs should be £455 per cycle. • CS Table 66 says zilucoplan admin "*Costs were applied as one-off costs associated with the cost of training patients to self-inject the treatment in future model cycles. The healthcare system was assumed not to incur any costs for self-injections in subsequent cycles*." But the £41 admin cost is applied in all subsequent cycles in the model.	• We prefer to use £455 per cycle for PLEX admin costs. • We prefer to remove the zilucoplan administration cost from subsequent treatment cycles (i.e., after cycle 2). • We note that the subcutaneous formulation of efgartigimod has now been approved, which can be carer- or self-injected. We conduct a scenario using similar pricing to zilucoplan i.e., the first 2 injections are given by a nurse (£41), and no admin costs are applied in the remaining cycles.
IVIg treatment costs	CS Table 65	Costs for chronic IVIg therapy were applied every 3 weeks in the model. Clinical advice to the EAG was that chronic IVIg is given 4-8 weeks.	We prefer to apply chronic IVIg costs every 6 weeks.
PLEX treatment costs		Treatment costs for PLEX were applied every 4 weeks in the model. Clinical advice to the EAG was that PLEX is given every 4-8 weeks.	We prefer to apply chronic PLEX costs every 6 weeks.
Resource use; SoC treatment costs; and duration of myasthenic crisis	CS Table 67; ModelSheet! DrugCostsDetail_Popup!; ModelSheet! Utilities!	We agree. Our clinical experts suggested alternative resource use by health state (Table 29 and Table 30). Clinical advice to the EAG was that there is very little use of cyclosporine and tacrolimus in the UK; mycophenolate is used more often instead. Our experts suggested alternative percentages of	No change. We explore the combination of using the suggested alternative resource use, different proportions of SoC (4% tacrolimus, 4% cyclosporin, 4% methotrexate; 25% mycophenolate) and extending the duration of a

Parameter	Company base case	EAG comment on the company's approach	EAG analyses
		SoC drugs and also advised us that a myasthenic crisis would last 21 days.	myasthemic crisis to 21 days in a scenario analysis.
Use of SCIg	CS B.3.5.2.1	We agree. The model weights the immunoglobulin cost based on 50% use of IVIg and 50% of SCIg to anticipate the increase in use of SCIg.	No change. We explore using 100% SCIg in a scenario analysis.

AE: adverse event; CFB: Change from baseline; CQ: Clarification Questions; CTCAE: Common Terminology Criteria for Adverse Events; ECM: Established clinical management; ICU: intensive care unit; IVIg: intravenous immunoglobulin; MG-ADL: Myasthenia Gravis Activities of Daily Living score; PLEX: plasma exchange; s.c.: subcutaneous; SCIg: subcutaneous immunoglobulin; SmPC: Summary of Product Characteristics; SoC: standard of care.

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted additional scenario analyses on the company's revised base case to explore the issues described in section 5.3 and to investigate other areas of uncertainty not included in the company's scenario analyses (Table 35).

We note a recent study by Moniz Dionisio et al. that reported the real-world experience of using efgartigimod in patients with generalised MG in the UK (n=48).[1] In the EAG's opinion, this patient cohort in the efgartigimod Early Access to Medicine Scheme (EAMS) is comparable to the patient group of interest for rozanolixizumab in the current appraisal, because:

- Patients in EAMS had AChR antibody-positive generalised MG
- The average age was 49.2 years (21.0 – 75.0 years, SD = 14.2)
- Most patients (75%) were female
- Most patients (66.7%) had a disease duration of over 10 years
- All patients had utilized at least one non-steroidal immunosuppressant treatment in the past, and the average number tried prior to efgartigimod was 2.6 (range 1 - 6)

The EAG note that the average MG-ADL score at baseline of patients in the EAMS cohort was 11.2 (5-19, SD = 3.2). The average MG-ADL score of patients entering the economic model is 8.3 (derived from participants in the MycarinG trial). However, clinical advice to the EAG was that a MG-ADL score of 8 is representative of patients with refractory generalised MG. One expert noted that the MG-ADL score concerns the severity of the disease, whereas 'refractory' denotes a failure or intolerance to drugs, which implies ongoing severity despite treatment. Our expert added that a MG-ADL score of 8.3 would be in line with refractory disease. Consequently, we consider using data from the EAMS cohort to be reasonable.

Before the introduction of the EAMS scheme, clinical consensus was achieved with UK MG clinicians that efgartigimod use in EAMS would be reserved for patients with refractory disease who had not responded to ≥ 2 non-steroidal immunosuppressant agents, those who were intolerant or ineligible for such therapies, and those patients who were dependent on IVIg and PLEX.[1]

We observe that at the time of initiating efgartigimod treatment, 43.8% of patients in the EAMS cohort were receiving chronic IVIg treatment,14.6% of patients were receiving chronic

PLEX treatment, and 41.6% of patients were receiving neither.[1] The EAG are unsure why so many patients in the EAMS cohort did not receive regular IVIg or PLEX therapy, the reasons may include: lack of availability, contraindications, inability to tolerate the treatment, being physically unable to receive the therapy (venous access problems in the case of PLEX, for example), or the patient had received the treatment in the past and not responded to it. Alternatively, patients may have been receiving IVIg and PLEX therapy, but as rescue treatment rather than chronic therapy.

We conducted a scenario analysis (scenario 4, Table 35) that involved 43.8% of patients receiving IVIg, 14.6% of patients receiving PLEX and 41.6% of patients receiving neither; all patients receive the basket of standard treatments (shown earlier in Table 19). Using this blended standard of care (i.e., established clinical management) as a comparator reduces the ICER from [redacted] per QALY (obtained versus the basket of standard treatments alone) to [redacted] per QALY. However, further clinical advice is needed regarding the proportion of patients with refractory generalised MG receiving IVIg and PLEX in England (Key Issue 1 in section 1.3 of this report).

Rozanolixizumab is [redacted], shown in Table 19).

Rozanolixizumab [redacted], except for scenario 9 and scenario 13. When four cycles of rozanolixizumab are given per year (scenario 9), the ICER result is [redacted] per QALY, because [redacted]. The model is also sensitive to the frequency at which PLEX treatment is given. If PLEX treatment and administration costs are applied every six weeks instead of every four weeks (scenario 13), the ICER result is [redacted] per QALY, because in this scenario [redacted]. Rozanolixizumab [redacted].

Table 34 EAG scenario results, company's revised base case, pairwise results

No.	Scenario description	Pairwise ICER (£/QALY), rozanolixizumab vs comparator				
		IVIg/SCIg	Efgartigimod	PLEX	Zilucoplan	SoC [a]
Company revised base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	Population characteristics from the AChR Ab+ MycarinG population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Population characteristics from the MuSK Ab+ MycarinG population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Increase initial MG-ADL score to 10.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	Include IVIg and PLEX in SoC: 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[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	Using 70% response rates for IVIg and PLEX; trial response rates for rozanolixizumab (72%), zilucoplan (73%) and efgartigimod (68%); [redacted][c] response rate for SoC[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Use 3 weeks for the response timepoint for all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	Use 6 weeks for the response timepoint for all treatments (company scenario)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	Use utilities from MyRealWorldMG and POPUP for people in the UK with severe gMG[(49)]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	Use 4 cycles of rozanolixizumab per year instead of [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	Applying PLEX administration costs every 4 weeks and removing zilucoplan administration costs after cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	Applying administration costs for the s.c. formulation of efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

No.	Scenario description	Pairwise ICER (£/QALY), rozanolixizumab vs comparator				
		IVIg/SCIg	Efgartigimod	PLEX	Zilucoplan	SoC [a]
12	Applying chronic IVIg treatment costs every 6 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	Applying chronic PLEX treatment costs every 6 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	Apply costs for alternative resource use, SoC proportions and myasthenic crisis duration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	Apply costs for 100% SCIg use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] SoC excludes IVIg and PLEX, unless stated in the scenario description.
[b] The ICERs change from the base case because, the costs for the SoC standard basket (Table 20) are now included in the comparator arms
[c] This scenario uses the company's referent response rate as a proxy for the SoC response rate
gMG: generalised myasthenia gravis; HCP: healthcare professional; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IVIg: intravenous immunoglobulin; MG-ADL: Myasthenia Gravis Activities of Daily Living score; PLEX: plasma exchange; QALY: quality-adjusted life-year; s.c.: subcutaneous; SCIg: subcutaneous immunoglobulin; SoC: standard of care

6.2 EAG's preferred assumptions

Based on the EAG's critique of the company's model (discussed in section 5.3) and the scenarios described in section 6.1, we have identified several aspects of the company's revised base case with which we disagree. Our preferred model assumptions are:

- Using established clinical management (SoC including IVIg and PLEX) as the comparator, with 43.8% of patients receiving IVIg; 14.6% of patients receiving PLEX; 41.6% of patients receiving neither;[1] all patients receive the cheaper standard therapies (Table 19) (EAG report section 6.1). However, we acknowledge there is uncertainty regarding the proportions of IVIg and PLEX used in established clinical management. We have conducted scenarios comparing rozanolixizumab directly to efgartigimod, IVIg, PLEX and zilucoplan using our base case (Table 38).
- Using a response rate of 70% for IVIg and PLEX (which produces a response rate of 40.88% in the established clinical management arm, when 43.8% of patients receive chronic IVIg and 14.6% of patients receive chronic PLEX), and trial response rates for rozanolixizumab, efgartigimod and zilucoplan
- Using a response assessment timepoint of 6 weeks for all treatments
- Correcting the PLEX administration cost and removing zilucoplan administration costs after cycle 2
- Applying the treatment and administration costs for chronic IVIg and chronic PLEX every 6 weeks, instead of every 3 and 4 weeks, respectively

We also include the cost for standard of care treatments (specifically the proportions of corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate and pyridostigmine) in the costs for the company's Decision Problem comparator therapies (rozanolixizumab, IVIg/SCIg, efgartigimod, PLEX and zilucoplan), because this cost is included in the established clinical management arm we use for our base case. As the cost for standard of care treatments is common to all arms, it has no effect on the ICER.

Table 36 shows the cumulative effect of each of these changes on the company's base case ICER and Table 37 gives detailed results (breakdown of total costs and QALYs) of the EAG's base case. The EAG's preferred assumptions result in an ICER of [redacted] per QALY for rozanolixizumab compared with established clinical management.

Table 35 Cumulative effect of the EAG's preferred model assumptions, rozanolixizumab versus established clinical management

Assumption	Incr. Costs	Incr. QALYs	Cumulative ICER £/QALY
Company revised base case (SoC only, excluding IVIg and PLEX from ECM)	[redacted]	0.191	[redacted]
+ 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	[redacted]	0.191	[redacted]
+ 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%)	[redacted]	0.163	[redacted]
+ Using a response assessment time point of 6 weeks for all treatments	[redacted]	0.161	[redacted]
+ Correcting the PLEX administration cost and removing zilucoplan administration costs after cycle 2	[redacted]	0.161	[redacted]
+ Applying chronic IVIg treatment and administration costs every 6 weeks	[redacted]	0.161	[redacted]
+ Applying chronic PLEX treatment and administration every 6 weeks	[redacted]	0.161	[redacted]
EAG base case	[redacted]	**0.161**	[redacted]

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

6.2.1 Probabilistic sensitivity analysis

The results for the PSA using the EAG's preferred assumptions are shown in Table 37. The mean probabilistic ICER is similar to the deterministic result. However, there is considerable variability in the PSA results, as shown by the incremental cost and QALYs scatterplot (Figure 3).

Table 36 Deterministic and probabilistic results for rozanolixizumab compared with established clinical management, EAG base case

Analysis	Treatments	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£ per QALY)
Deterministic	Rozanolixizumab	[redacted]	8.19	-	-	-
	ECM	£519,763	8.03	[redacted]	0.16	[redacted]
PSA	Rozanolixizumab	[redacted]	8.14	-	-	-
	ECM	£516,974	7.99	[redacted]	0.15	[redacted]

ECM: Established clinical management; ICER: incremental cost-effectiveness ratio; Incr: incremental; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; SoC: standard of care.

[redacted]

Figure 4 Scatterplot of PSA results (cost-effectiveness scatter plot), EAG base case

6.3 Scenario analyses conducted on the EAG's preferred assumptions

Using the EAG's preferred assumptions, the ICER result for rozanolixizumab compared with IVIg is [redacted] per QALY and rozanolixizumab [redacted]. However, we do not consider efgartigimod, zilucoplan, IVIg or PLEX to be appropriate comparators and prefer to use established clinical management as our comparator arm. We present the results of scenario analyses using our base case for rozanolixizumab compared with established clinical management in Table 38.

We explored different proportions of patients receiving IVIg and PLEX therapy (i.e., all patients receive one of the active treatments) in the established clinical management arm and note that the model is sensitive to these changes, because IVIg and PLEX are expensive treatments. Increasing the proportions of patients who receive chronic IVIg and

PLEX therapy (and where all patients receive one or other treatment) in the established clinical management arm substantially decreases the ICER to [redacted], depending on the proportions of patients receiving each treatment (scenarios 1, 2 and 3).

The model is also sensitive to the frequency with which the treatments are given. [redacted] the number of rozanolixizumab cycles from [redacted] to four per year (scenario 6) increases the ICER from [redacted] per QALY to [redacted] per QALY, because total costs for rozanolixizumab are [redacted], thus [redacted] incremental costs. Similarly, increasing the frequency with which chronic IVIg or PLEX treatment is given (scenarios 7 and 8) decreases the ICER, because total costs for IVIg or PLEX in the established clinical management arm are increased, thus reducing incremental costs.

Table 37 Scenario results for rozanolixizumab versus established clinical management, EAG base case

No.	Scenario description	ICER (£/QALY)		
		Incr. costs	Incr. QALYs	ICER
EAG base case		[redacted]	0.161	[redacted]
1	ECM: 80% of patients receive IVIg; 20% of patients receive PLEX; 0% of patients receive neither; all patients receive the cheaper standard therapies	[redacted]	0.122	[redacted]
2	ECM: 50% of patients receive IVIg; 50% of patients receive PLEX; 0% of patients receive neither; all patients receive the cheaper standard therapies	[redacted]	0.122	[redacted]
3	ECM: 20% of patients receive IVIg; 80% of patients receive PLEX; 0% of patients receive neither; all patients receive the cheaper standard therapies	[redacted]	0.122	[redacted]
4	Company response rates for rozanolixizumab, zilucoplan, efgartigimod, IVIg and PLEX (CS erratum March 2024 Table 59) and 50%[a] response rate for ECM	[redacted]	0.188	[redacted]
5	Company response assessment timepoints (CS erratum March 2024 Table 59)	[redacted]	0.163	[redacted]
6	Response timepoint of 3 weeks for all treatments	[redacted]	0.141	[redacted]
7	Use 4 cycles of rozanolixizumab per year instead of [redacted]	[redacted]	0.161	[redacted]
8	Chronic IVIg costs applied every 4 weeks	[redacted]	0.161	[redacted]
9	Chronic PLEX costs applied every 3 weeks	[redacted]	0.161	[redacted]
10	Apply costs for alternative resource use, SoC proportions and myasthenic crisis duration	[redacted]	0.162	[redacted]

[a] This scenario uses the company's referent response rate as a proxy for the ECM response rate
ECM: Established clinical management; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; MG-ADL: Myasthenia Gravis Activities of Daily Living score; NMA:, network meta-analysis; PLEX: plasma exchange; QALYs: quality-adjusted life years; SCIg: subcutaneous immunoglobulin; SoC: standard of care.

6.4 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost effectiveness of rozanolixizumab compared with efgartigimod, IVIg/SCIg, PLEX and zilucoplan, which includes a simple PAS discount for rozanolixizumab. The EAG consider it to be a well-structured model, which uses rozanolixizumab treatment effectiveness data from the MycarinG trial (MG0003; the company-sponsored phase III RCT, and MG0007 (observational long-term extension study). The EAG did not identify any significant technical calculation errors in the company's original model. However, we identified some inconsistencies in the company model assumptions, which we raised in our clarification questions.

After submitting their evidence, the company informed NICE of an error in their NMA, affecting the rate of response for rozanolixizumab, zilucoplan and efgartigimod. The company provided an erratum (CS Erratum March 2024) with updated cost-effectiveness results and a revised model. These cumulative changes increased their base case ICER from [redacted] per QALY to [redacted] per QALY for rozanolixizumab compared with IVIg/SCIg; rozanolixizumab [redacted] after the changes (Table 33).

The EAG disagree with treating IVIg/SCIg and PLEX as separate comparators. This approach is inconsistent with the NICE scope, and the EAG do not consider this to be an appropriate reflection of established clinical management in England. The EAG prefer to include IVIg and PLEX treatments together with other standard of care therapies and use this 'established clinical management' arm as the comparator. The proportions of patients receiving IVIg and PLEX in established clinical management are based on publicly available data taken from the UK efgartigimod EAMS patient cohort.[1] We acknowledge there may be uncertainty around this estimate of chronic IVIg and PLEX use for patients with refractory generalised MG in England. We highlight this discrepancy as part of Key Issue 1, discussed in section 1.3, and explore alternative proportions of patients receiving IVIg and PLEX in scenario analyses (Table 38).

The EAG's preferred assumptions and their effects are presented in Table 36 in section 6.2. The company's base case ICER result for rozanolixizumab compared with standard of care (excluding IVIg and PLEX) is [redacted] per QALY. Our preferred assumptions result in an ICER of [redacted] per QALY for rozanolixizumab compared with established clinical management (i.e. a standard of care arm that includes IVIg and PLEX treatment). We also conducted a range of scenario analyses on the EAG base case including comparing rozanolixizumab directly with efgartigimod, IVIg, PLEX and zilucoplan (Table 38). The

economic model is most sensitive to the proportions of patients receiving IVIg and PLEX treatment, how frequently patients receive IVIg and PLEX treatment, and to the number of cycles of rozanolixizumab patients receive a year.

7 SEVERITY

CS section B.3.6 states that the company do not anticipate that a severity weighting will be applicable for this rozanolixizumab appraisal. The EAG agree with this assessment, because the absolute and proportional QALY shortfalls for the company and EAG base cases do not meet the thresholds for severity,[44] i.e. all of the scores for the absolute QALY shortfall are below 12, and all scores for the proportional QALY shortfall are lower than 0.85 (Table 39).

Table 38: Summary of QALY shortfall analysis

Analysis	Expected total discounted QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
Company base case vs efgartigimod	15.34	[redacted]	[redacted]	[redacted]
Company base case vs IVIg/SCIg	15.34	[redacted]	[redacted]	[redacted]
Company base case vs PLEX	15.34	[redacted]	[redacted]	[redacted]
Company base case vs zilucoplan	15.34	[redacted]	[redacted]	[redacted]
Company base case vs SoC (excluding IVIg and PLEX)	15.34	[redacted]	[redacted]	[redacted]
EAG base case vs ECM (i.e. SoC including IVIg and PLEX)	15.34	[redacted]	[redacted]	[redacted]

ECM, established clinical management; IVIg: intravenous immunoglobulin; PLEX: plasma exchange; QALYs: quality-adjusted life years; SCIg: subcutaneous immunoglobulin; SoC: standard of care.

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9 APPENDICES

9.1 SLR critique

Summary of the EAG appraisal of the clinical effectiveness review:

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	Company SLR report (January 2024) A.1 Table 29 details the summary protocol for the SLR and 2024 SLR update according to a PICOS framework. This supports the statement in CS Appendix D.1 that the SLR aims to identify the relevant comparators to rozanolixizumab and to inform on the efficacy of pharmacological and non-pharmacological interventions used to treat and manage generalised MG, therefore the scope of the SLR is broader than that of this appraisal. The PICO framework reported in CS Table 5 (CS section B.2.1.1) is probably designed to be more relevant to this submission as it excludes non-pharmacological interventions and surgery, but also incorrectly excludes PLEX.
Were appropriate sources of literature searched?	Yes	The main healthcare databases were searched (MEDLINE and Embase); trials registers: Cochrane CENTRAL, ClinicalTrials.gov, EudraCT; hand searching of specific MG and neuromuscular conferences; the references of systematic reviews and meta-analyses were also checked (CS Appendix D.1.1).
What time period did the searches span and was this appropriate?	Yes	From database inception to May 2023, with an update search from May 2023 to January 2024 (CS Appendix D.1.1). The searches are up to date and the EAG has not identified any more recent studies.
Were appropriate search terms used and combined correctly?	Probably	MEDLINE and Embase were searched simultaneously in Embase.com, but it is not reported whether mapping was applied to the subject headings to ensure both MeSH terms and Emtree terms were used (CS Appendix D.1.1.4). Otherwise, the searches were carried out transparently and appropriately.
Were inclusion and exclusion criteria specified?	Yes	The PICO in CS Table 5 is incorrect (excludes PLEX), however, the company SLR Report

If so, were these criteria appropriate and relevant to the Decision Problem?		(January 2024) Table 2 has broader criteria detailing the original criteria prior to editing the review for this submission.
Were study selection criteria applied by two or more reviewers independently?	Yes	Two independent researchers performed the screening with a third reviewer resolving any discrepancies (CS appendix D.1.2.1).
Was data extraction performed by two or more reviewers independently?	Yes	Two reviewers conducted the data extraction with disputes referred to a third reviewer (CS appendix D.1.2.1).
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	Both the MycarinG and MG0007 trials were assessed using the NICE RCT checklist (CS section B.2.5). The assessments are discussed further in terms of risk of bias in section 3.2.2 of this report.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Yes	Two independent reviewers assessed the MycarinG and MG0007 trials with reconciliation of any differences by a third independent reviewer (CS appendix D.1.2.2).
Is sufficient detail on the individual studies presented?	Yes	Relevant study documents (CSRs and SAPs) and references were provided with the CS. A separate SLR and NMA Report were provided. The NMA Report was limited to reporting only one outcome from the NMAs; the NMA Report was replaced during the appraisal process because the original submission contained an error, also resulting in an updated economic model and a CS Erratum.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Partly	NMAs were conducted to estimate the comparative efficacy of rozanolixizumab, zilucoplan, efgartigimod, IVIg, and PLEX against an averaged placebo response rate of the comparator trials (CS section B.2.9). MAICs were provided for MG-ADL response and MG-ADL score change from baseline for rozanolixizumab versus efgartigimod and for QMG score change from baseline and QMG response for rozanolixizumab versus IVIg, in Clarification Response A13. See sections 3.3 and 3.4 of this report for discussion.
CSR: clinical study report; EudraCT: European Union Drug Regulating Authorities Clinical Trials; ITC: indirect treatment comparison; IVIg: intravenous immunoglobulin; MAICs: matched-adjusted indirect comparisons; MeSH: Medical Subject Headings; NMA: network meta-analysis; PLEX: plasma exchange; RCT: randomised controlled trial; SAP: statistical analysis plan; SLR: systematic literature review.		

9.2 Risk of bias assessment

9.2.1 MycarinG trial

Question	Company response (CS table 19)	EAG response
Was randomisation carried out appropriately?	Yes, an IRT was used for assigning eligible study participants to a treatment regimen based on a predetermined production randomisation and/or packaging schedule provided by the Sponsor (or designee). The randomisation schedule was produced by the IRT vendor. The IRT generated individual assignments for kits of study medication, as appropriate, according to the visit schedule.	Probably yes. The specific method of generating a random sequence using the IRT is not explained in the CS or trial publication, but we assume this would have been appropriate. **Low risk of bias**
Was the concealment of treatment allocation adequate?	Yes, all study participant treatment details, rozanolixizumab treatment group, planned dose, or placebo were allocated and maintained by the IRT system.	Probably yes. The CS and trial publication do not state how the IRT achieved allocation concealment, but we assume this was appropriate. **Low risk of bias**
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, study participant demographics were balanced across treatment groups. Apart from a higher proportion of female study participants in the placebo group (70.1%) compared with the rozanolixizumab ≈7 mg/kg (59.1%) and ≈10 mg/kg (52.2%) groups, and the number of study participants in the <50 kg body weight category, with a lower proportion in the rozanolixizumab ≈10 mg/kg group (1.5%) compared with placebo and rozanolixizumab ≈7 mg/kg (6.0% and 10.6%)	Groups were balanced overall with the following exceptions (placebo versus rozanolixizumab ~7mg/kg): • Age: 50.4 versus 53.2 years • Age at initial MG diagnosis: 41.4 versus 46.6 years • Duration of disease: • 6.8 versus 5.3 years • Sex % female: • 70% versus 59% • MGFA class IIIa: • 42% versus 32% Of these characteristics only age at initial diagnosis is a prognostic factor, so potentially the

		rozanolixizumab trial arm is disadvantaged by including slightly older patients, but the difference is not clinically important according to the EAG's clinical experts (section 3.2.1.2.1). **Low risk of bias**
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, study participants and study staff remained blinded to treatment assignments until after the data had been cleaned, locked, and unblinded.	Partly. Blinding was broken for the implementation of mock infusions when participant IgG levels dropped below the protocol-defined threshold. An unblinded Medical Monitor informed the Investigator, who was therefore also unblinded, and the Investigator could hold the dose until deemed appropriate (Clarification Response A8). This affected four participants: two in each rozanolixizumab group (CS section B.2.10.1.1). The trial publication also states that site pharmacists had access to treatment allocation. **Unclear risk of bias**
Were there any unexpected imbalances in drop-outs between groups?	No. All groups were balanced and there were no un-expected imbalances in drop-outs.	No. The proportion of dropouts and reasons for dropout were balanced across the trial arms. **Low risk of bias**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All outcomes were related to the clinical goals of gMG therapy, and safety.	No. (NB Several outcomes measured and reported for the MycarinG trial were not reported for the company's NMAs. However, the missing outcomes are not required for the economic analysis.) **Low risk of bias**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods	All efficacy analyses were based on the randomized set and treatment assignment at randomization (i.e. intention to treat, not treatment	Yes, for ITT analysis. CS section B.2.4.3 states that efficacy analyses were performed on the Randomised Set (RS) which

used to account for missing data?	received). Intention to treat and missing data and intercurrent events were handled appropriately.	consisted of all study participants who were randomised, using the treatment assigned instead of the actual treatment received. So, we agree that ITT analysis was included. Unclear, for missing data. CS Table 8 shows that 37.3% and 34.8% of patients discontinued the placebo and rozanolixizumab ~7mg/kg arms respectively, however, no explanation is given for how the efficacy analysis of the RS accounted for these missing data. CS Tables 40 to 45 show that for the primary and most key secondary outcomes analysed up to Day 43 only three patients were missing from the analysis from the placebo arm and two were missing from the analysis for the rozanolixizumab ~7mg/kg arm, suggesting that an imputation approach must have been used to recreate almost all of the missing data in these arms. However, no imputation approach is reported and it is unclear why the ITT analysis after imputation was missing the three and two patients respectively. The reasons for discontinuation listed in CS Table 8 were generally balanced between the arms. **Unclear risk of bias**
Sources: partial reproduction of CS Table 19 with added EAG comments and interpretation of risk of bias; trial publication.[35]		

Abbreviations: IRT: interactive response technology; ITT: intention to treat; MG: myasthenia gravis; MGFA: Myasthenia Gravis Foundation of America [class]; NMAs: network meta-analyses; RS: randomised set.

9.2.2 MG0007 trial

Question	Company response (CS table 19)	EAG response
Was randomisation carried out appropriately?	Yes, an IRT is used for assigning eligible study participants to a treatment regimen (as applicable) based on a predetermined production randomisation and/or packaging schedule provided by UCB (or designee). The randomisation schedule is produced by the IRT vendor. The IRT generates individual assignments for kits of study medication, as appropriate, according to the visit schedule. Study participants from MG0003 who completed the EOS Visit are re-randomised in MG0007. Randomisation in MG0007 is to a ratio of 1:1. Study participants from MG0004 are not re-randomised upon entering MG0007 but continue their last treatment regimen received in MG0004 for their first treatment cycle in MG0007. Study participants retain the same 5-digit number assigned at Screening in MG0003 that serves as the study participant identifier throughout the study.	Yes. The study CSR notes use of an interactive response technology (IRT) to perform randomisation. As explained in the column on the left, study participants were re-randomised 1:1 on entry to either MG0004 or MG0007, therefore study participants transferring from MG0004 to MG0007 were not re-randomised twice. **Low risk of bias**.
Was the concealment of treatment allocation adequate?	Yes, this is an OLE study and treatment details (i.e. dose arm) are not blinded. To maintain study integrity, IgG level remains blinded to the study sites and the UCB study team for the first four weeks of the study.	This is an open-label extension study and as such there was no concealment of treatment allocation: therefore, the study is at high risk of bias. **High risk of bias.**
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, study participant demographics were generally balanced between the treatment groups apart from the higher proportion of study participants from North America in	Mostly. As noted in the column on the left there was an imbalance in regional characteristics between the

	the ≈7 mg/kg group (32.9%) compared with the ≈10 mg/kg group (23.1%) and the lower proportion of study participants from Europe in the ≈7 mg/kg group (57.0%) compared with the ≈10 mg/kg group (67.9%).	treatment groups, but these are not prognostic factors. There was a lower proportion of study participants who had undergone thymectomy in the ~7 mg/kg group ([redacted]%) compared to the ~10 mg group ([redacted]). One of the EAG's clinical experts explained that presence of thymoma is a prognostic factor but patients do not need thymoma to have a thymectomy therefore we do not regard this difference as a robust indication of imbalance of a prognostic factor between trial arms. There was a higher proportion of study participants who were MuSK Ab+ in the ~7 mg/kg group ([redacted]%) compared to the ~10 mg group ([redacted]%), and MuSK Ab+ patients are known to have a more severe disease course. However, there was balance across the treatment groups for prognostic factor of age at initial MG diagnosis (~7 mg/kg: [redacted]%; ~10 mg/kg: [redacted]%). Refractory status (≥2 prior MG therapies) is not reported for MG0007. Dose-switching occurred for [redacted]% of participants during the study and this would affect the balance of characteristics across treatment groups, but exactly how it would affect the balance is unknown (CS

		section B.2.10.1.3 reports [redacted]% did not switch dose). **Unclear risk of bias.**
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A. As MG0007 is an open-label study and all study participants received rozanolixizumab ≈7 mg/kg or ≈10 mg/kg.	No. MG0007 is an open-label study and therefore at high risk of bias. **High risk of bias**.
Were there any unexpected imbalances in drop-outs between groups?	No. All groups were balanced and there were no unexpected imbalances in drop-outs.	No. At the time of the interim analysis [redacted]% of participants in the ~7 mg/kg group and [redacted]% of participants in the ~10 mg/kg group had discontinued the study (CS Table 9). Reasons for discontinuation were similar across treatment groups except for discontinuation due to adverse events which was [redacted]% in the ~7 m/kg group and [redacted]% in the ~10 mg/kg group (CS Table 9). It is unclear if the assigned dose affected the discontinuation rate because dose modifications were permitted, i.e., the occurrence of some adverse events could initiate switching from ~10 mg/kg to ~7 mg/kg (CSR 3.5.1). **Unclear risk of bias.**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All outcomes were related to the clinical goals of gMG therapy, and safety.	Some. The primary outcome was safety which is reported in the CS. All efficacy outcomes reported in the CSR are also reported in the CS except for the other MGS-PRO scores for “Respiratory Muscle Weakness” and for “Ocular Muscle Weakness”. The CSR includes hyperlinks to Listings of these results that are not available to the EAG (CSR 9.2.4). Clinical

		experts to the EAG noted that we should be able to see all MGS-PRO results and that ocular manifestations are common to 99% of MG patients as these are the most-used muscles in the body, hence ocular manifestations of gMG are important to consider. **Unclear risk of bias.**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	All efficacy analyses were based on the randomized set and treatment assignment at randomization (i.e. intention to treat, not treatment received). Intention to treat and missing data and intercurrent events were handled appropriately.	Disagree. The efficacy results reported in the CS are reported for the Safety Set (SS) (CS section B.2.4.3). This is appropriate as equivalent to a modified ITT analysis. However, table footnotes for all secondary outcomes in the CS state that study participants [within the SS] were grouped according to the actual dose level received within the study cycle. This is due to dose-switching, described in section 3.2.1.1.2, therefore the modified ITT analysis was subject to confounding. It is unclear how study participants are grouped for the reporting of the 'other' efficacy outcomes. **High risk of bias.**
Sources: partial reproduction of CS Table 19 with added EAG comments and interpretation of risk of bias; study CSR. Abbreviations: CSR: clinical study report; EOS: end of study; FAS: Full Analysis Set; gMG: generalised myasthenia gravis; IRT: interactive response technology; ITT: intention to treat; MG-ADL: Myasthenia Gravis Activities of Daily Living; MGS-PRO: Myasthenia Gravis Symptoms Patient Reported Outcomes; OLE: open-label extension; SS: Safety Set; UCB: UCB Pharma [company].		

9.3 Summary of the approaches for handling intercurrent events and missing outcome data in the MycarinG trial

Outcome	Analysis	Trial population	Analysis strategy for intercurrent events (ICE)	Missingness assumption for scores	Imputation method for ICE and scores	Summary of approach	EAG comment on results
Continuous outcomes (change from baseline) MG-ADL MGC QMG MGS-PRO MG-QoL15r	Primary	RS	Hypothetical & Treatment Policy	MAR	MLE	The primary ITT analysis using the RS	-
	Sensitivity 1	FAS	Hypothetical & Treatment Policy	MAR	MLE	Check of the consistency of FAS and RS analyses	No quantitative results in the CS (section B.2.12.2) or CSR [b]
	Sensitivity 2	RS	Hypothetical & Treatment Policy	MNAR	Jump-to-Reference	Imputes missing data from a reference group [a]	No quantitative results in the CS (section B.2.12.2) or CSR [b]
	Supple-mental 1	RS	Composite	MNAR	Worst-case imputation (trimmed mean approach)	Treats ICE as treatment failures	Not reported in the CS or CSR
	Supple-mental 2	RS	Treatment Policy	Not reported	Not reported for scores	Allows (ignores) ICE	Not reported in CSR
Dichotomous outcomes (response)	Primary	RS	Composite	MNAR	Non-responder imputation	The primary analysis, which treats missing	CSR sections 8.3.2.1, 8.3.2.2 & 8.3.2.3 state an observed

MG-ADL QMG MGC						data as non-responders	cases analysis was also done (not reported in the CS) [c]

CSR, clinical study report; FAS, full analysis set, ICE, intercurrent event; ITT, intention to treat; MAR, missing at random; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite [score]; MG-QoL15r, Myasthenia Gravis Quality of Life 15-item revised; MLE, maximum likelihood estimation; MNAR, missing not at random; QMG, Quantitative Myasthenia Gravis scale; RS, randomised set: SAP, Statistical analysis plan.

[a] Reference group not specified; EAG assume this is the placebo arm of the MycarinG trial.

[b] The version of the CSR provided to the EAG did not include the quantitative results tables for this analysis.

[c] The CSR reports observed cases first and non-responder imputation second, suggesting that the latter was a sensitivity analysis rather than the primary analysis.

Source: CSR sections 6.6.2, 8.1.2, 8.2.6, and CSR Table 6-1; SAP section 8.1.

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **4 June 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3 (page 15) reads: 'The data source for the proportions of patients receiving chronic IVIg and PLEX is the patient cohort in the efgartigimod Early Access to Medicine Scheme (EAMS),[1] which the EAG consider to be comparable to the patient group of interest for rozanolixizumab in the current appraisal.'	Please remove the second half of the sentence ('which the EAG consider to be comparable to the patient group of interest for rozanolixizumab in the current appraisal').	The sentence is incorrect. The EAMS data are not fit to assess rozanolixizumab for two reasons. One, the inclusion criteria for EAMS and MycarinG are not the same. Two, SoC is not a relevant comparator for decision making as rozanolixizumab is expected to be used in place of chronic IVIg/PLEX and a significant proportion of patients in the EAMS cohort were not receiving either IVIg or PLEX.	Not a factual inaccuracy. EAG opinion on the suitability of the EAMS cohort is correctly stated, and the data informs the EAG's preferred blended ECM comparator described in Key Issue 1. No change made.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4 (page 18) reads: 'The company declined to conduct the NMA and MAIC as they asserted that zilucoplan is not a relevant comparator (Clarification Responses A11b and 13b).'	Please change the sentence to: 'The company declined to conduct the NMA and MAIC as the appraisal for zilucoplan is still ongoing and thus, if/when approved, zilucoplan will not have been adopted for a long enough time to be considered part of the stablished management (Clarification Responses A11b and 13b)'.	The sentence does not accurately reflect the company response to Clarification Questions A11b and 13b.	Thank you for highlighting this inaccuracy; wording changed to reflect the company argument more accurately.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4 (page 19) reads: 'The NMAs do not account for the heterogeneity of placebo response rates, which were 31%, 30% and 46% respectively in the trials of rozanolixizumab, efgartigimod and zilucoplan.'	Please change the sentence to: 'The NMAs do not account for the heterogeneity of placebo response rates, which were 31% and 30%, respectively, in the trials of rozanolixizumab and efgartigimod, and [redacted]% for zilucoplan based on a 2-point improvement (NMA report).'	The sentence does not accurately reflect the data presented in the NMA. The placebo response rate of 46% for zilucoplan refers to the 3-point improvement in MG-ADL score (RAISE trial) but the data presented in the NMA were based on a 2-point improvement.	Thank you for highlighting this error, which we have corrected.
Section 1.4 (page 19) reads: 'The EAG consider this to be an inappropriately high response rate relative to the range of placebo responses observed in the trials.'	Please remove the sentence.	The high 'referent' placebo response rate is driven by the placebo response rate for zilucoplan in the NMA ([redacted]%) which is based on a 2-point improvement in MG-ADL score and not a 3-point improvement	Not a factual inaccuracy. The average of the three placebo rates (31%, 30% and [redacted]) is [redacted], which is less than the 'referent' placebo response rate of [redacted] as used in the company's base case. No change made.

Section 4.2.6.1 (page 90) reads: We view the estimated referent response rate is implausible at [redacted] as the placebo response rates in MycarinG, RAISE and ADAPT trials were 31%, 46% and 30% respectively.	Please remove the sentence.	The 'referent' placebo response rate is due to the placebo response rate for zilucoplan reported in the NMA ([redacted]%) which is based on a 2-point improvement in MG-ADL score and not a 3-point improvement	The average of the three placebo rates (31%, [redacted] and 30%) is [redacted], which is less than the 'referent' placebo response rate of [redacted] as used in the company's base case. Hence, the original EAG statement still applies. However, we have corrected the zilcoplan response rate to [redacted] based on a 2-point improvement in MG-ADL score and not a 3-point improvement

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.4 (page 31) reads: 'The company have accurately described generalised MG and the treatment pathway in the CS, but do not comment on whether therapies received by MuSK antibody-positive and AChR antibody-positive patients may differ.'	Please remove the second half of the sentence ('but do not comment on whether therapies received by MuSK antibody-positive and AChR antibody-positive patients may differ'.)	The statement is not correct. The CS (Section B.1.3.2.2, page 31) discusses the classes of therapies for MuSK Ab+ patients and the different positioning of rituximab in MuSK Ab+ vs AChR Ab+ patients.	Thank you for highlighting this oversight; we have changed the text as requested.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.7 (Table 3, page 24) reads: 'Using 70% response rates for IVIg and PLEX (giving a 40.88% response rate in the ECM arm) and trial response rates for rozanolixizumab (68.2%), zilucoplan (73.1%) and efgartigimod (73.0%).'	Please change the sentence to: 'Using 70% response rates for IVIg and PLEX (giving a 40.88% response rate in the ECM arm) and trial response rates for rozanolixizumab (72.0%), zilucoplan (73.1%) and efgartigimod (68.0%)'	The response rates provided in Table 3 do not match those reported in Issue 4 of the EAG report: 'We prefer to use the response rates for rozanolixizumab (72%), efgartigimod (68%) and zilucoplan (73%) based on results from the MycarinG, ADAPT and RAISE trials, respectively'	Thank you for highlighting this discrepancy. Table 3 has been corrected as requested.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2 (page 28) reads: 'Estimates of the number of treatment cycles per year vary from an average of [redacted] cycles (company estimate based on the results of the pivotal MycarinG trial, CS Table 2) […].'	Please change the sentence to: Estimates of the number of treatment cycles per year vary from an average annualised number of cycles per patients of [redacted] (company estimate based on the results of the pivotal MycarinG trial, CS Table 2) […].'	The number presented is the average annualised number of cycles per patient.	Thank you for highlighting this error; we have amended the text as requested.
Section 4.2.8.1 (page 99) reads: 'The average number of cycles per year per patient was [redacted].'	Please change the sentence to: The average annualised number of cycles per patient was [redacted]	The number presented is the average annualised number of cycles per patient.	Thank you for highlighting this error; we have amended the text as requested.
Section 5.3 (Table 34, page 114) reads: 'Number of cycles of rozanolixizumab per year ([redacted] cycles)'	Please change the sentence to: 'Number of annualised cycles of rozanolixizumab per patient ([redacted] cycles)'	The number presented is the average annualised number of cycles per patient.	Thank you for highlighting this error; we have amended the text as requested.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.3 (page 29) reads: 'Thymectomy is an option for patients aged under 45 years, although effectiveness may not be seen for up to a year, and if they remain symptomatic they rejoin the pharmacological treatment pathway.'	Please remove the second half of the sentence ('and if they remain symptomatic they rejoin the pharmacological treatment pathway').	It is inaccurate to say that the patients rejoin the pharmacological treatment pathway as they never leave it, either before, during or after thymectomy.	Thank you for highlighting this error; we have amended the text as requested.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3 (Table 4, page 35) reads: 'It is unclear how the number of duration and hospitalisations were sourced for the economic analysis'	Please remove the sentence.	The sources for the number and duration of hospitalisations are provided in Table 67 of the CS.	Thank you for clarifying this information. We have replaced the erroneous sentence with alternative text in the Justification for amendment column because this is more informative than deleting the sentence.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3 (Table 4, page 35) reads: 'However, results for MG-ADL response were only reported for the MuSK Ab+ subgroup and not for the AChR Ab+ subgroup, and it is unclear why not.'	Please remove the sentence.	The statement is incorrect. The responder rates amongst historical AChR Ab+ participants for MG-ADL, QMG and MG-C scores are reported in Section B.2.7.4.1 (page 103 of the CS). The MG-ADL responder rate in historical AChR Ab+ participants was 69.0%. The sentence in the CS reported the wrong dose of rozanolixizumab (≈10 mg/kg) which might have led to the confusion.	Thank you for confirming that these results reported in the CS are for the ~7 mg/kg dose group. We have removed the sentence.

<table>
<tr>
<td>Section 3.2.5.10.4.1 (Table 13, page 64)
<table><tr><td>AChR Ab+
MG-ADL, n/N (%)
MGC, n/N (%)
QMG, n/N (%)</td><td>
Not reported
Not reported
Not reported</td></tr></table></td>
<td>Please edit the Table as follow
<table><tr><td>AChR Ab+
MG-ADL, n/N (%)
MGC, n/N (%)
QMG, n/N (%)</td><td>
[redacted])

</td></tr></table></td>
<td>The responder rates amongst historical AChR Ab+ participants for MG-ADL, QMG and MG-C scores are reported in Section B.2.7.4.1 (page 103 of the CS).
The sentence in the CS reported the wrong dose of rozanolixizumab (≈10 mg/kg) which might have led to the confusion.</td>
<td>Thank you for confirming that the results reported in the CS are for the ~7 mg/kg dose group. We have updated Table 13 as suggested.</td>
</tr>
<tr>
<td>Section 3.2.5.10.4.1 (page 65) reads:
‘Neither the CS nor the CSR explain why responder rates were reported for the MuSK antibody-positive subgroup and not for the AChR antibody-positive subgroup.’</td>
<td>Please remove the sentence.</td>
<td>The responder rates amongst historical AChR Ab+ participants for MG-ADL, QMG and MG-C scores are reported in Section B.2.7.4.1 (page 103 of the CS).
The sentence in the CS reported the wrong dose of rozanolixizumab (≈10 mg/kg) which might have led to the confusion.</td>
<td>Thank you for confirming that the results reported in the CS are for the ~7 mg/kg dose group. We have removed the sentence.</td>
</tr>
</table>

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3 (Table 4, page 36) reads: 'We also note that for the changes from baseline in MG-ADL and MGC scores a placebo effect is evident only in the AChR Ab+ subgroup..'	Please remove the sentence.	The statement is incorrect. The data reported in Tables 37–39 of the CS do not allow to draw comparisons on the placebo effect in the different subgroups.	Thank you for raising this point. We have removed this sentence.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.3.1 (page 47) reads: 'The trial publication and CS do not list EQ-5D as an outcome although the EQ-5D was a pre-specified exploratory outcome according to the CSR.'	Please remove the sentence.	The statement is incorrect. EQ-5D-5L is listed as an outcome in Document A (Table 3) and listed in Section B.2.6.2.3 of the CS as one of the other efficacy outcomes.	Thank you for highlighting this oversight; we have removed this sentence.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.5.5.2 (page 58) reads: 'A consistent and clinically meaningful reduction in MGC score was achieved by study participants in both rozanolixizumab trial arms for up to [redacted] cycles of treatment (CS section B.2.6.2.2).'	Please change the sentence to: 'A consistent and clinically meaningful reduction in QMG score was achieved by study participants in both rozanolixizumab trial arms for up to [redacted] cycles of treatment (CS section B.2.6.2.2).'	Section 3.2.5.5 discusses the changes from Baseline in QMG score.	Thank you for highlighting this error, this has been corrected.
Section 3.2.5.5.2 (page 58) reads: 'Participants receiving the rozanolixizumab ~7 mg/kg dose achieved a mean reduction in MGC score between [redacted] points across up to [redacted] cycles (CS Table 31).'	Please change the sentence to: Participants receiving the rozanolixizumab ~7 mg/kg dose achieved a mean reduction in QMG score between [redacted] points across up to [redacted] cycles (CS Table 31).'	Section 3.2.5.5 of the CS discusses the changes from Baseline in QMG score and the data presented in the sentence are the changes in QMG score across treatment cycles.	Thank you for highlighting this error, this has been corrected.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.5.9.2 (page 61) reads: 'Both sets of results show [redacted] scores, but it is unclear why the reported results differ as both report the safety set analysis (CS B.2.6.2.1 and Clarification Response Table 5).'	Please remove the second half of the sentence ('but it is unclear why the reported results differ as both report the safety set analysis (CS B.2.6.2.1 and Clarification Response Table 5)).'	Section B.2.6.2.3 of the CS reports the 'mean increase (improvement) from Baseline in EuroQol visual analogue scale at any visit during the treatment periods of the first five treatment cycles', while Table 5 in the Clarification response reports the mean change from Baseline to Day 43.	Thank you for explaining the difference. We have removed the second half of the sentence as requested, and for clarity we have inserted the text in italics below, "mean EQ-5D VAS score change from baseline results reported *at any study visit during* ~~for~~ the first five cycles"

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4 (page 21) reads: 'Using the trial response rates for rozanolixizumab, efgartigimod and zilucoplan, and a response rate of 70% for IVIg and PLEX reduces the ICER from [redacted] to [redacted] per QALY for **zilucoplan** compared with SoC.'	Please change the sentence to: 'Using the trial response rates for rozanolixizumab, efgartigimod and zilucoplan, and a response rate of 70% for IVIg and PLEX reduces the ICER from [redacted] to [redacted] per QALY for rozanolixizumab compared with SoC.'	The wrong treatment is reported in the sentence.	Thank you for highlighting this discrepancy. The text has been corrected as suggested.
Section 5.3 (Table 34, page 112) reads: 'The EAG do not consider it appropriate to compare **zilucoplan** with IVIg and PLEX separately, because we do not consider this reflects clinical practice in England for patients with refractory generalised MG.'	Please change the sentence to: 'The EAG do not consider it appropriate to compare rozanolixizumab with IVIg and PLEX separately, because we do not consider this reflects clinical practice in England for patients with refractory generalised MG.'	The wrong treatment is reported in the sentence.	Thank you for highlighting this discrepancy. The text has been corrected as suggested.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.1 (page 69) reads: 'However, no odds ratios for comparisons between rozanolixizumab and the other treatments are provided.'	Please change the sentence to: 'While odds ratios for comparisons between rozanolixizumab and the other treatments were not provided in section B.2.9, they were presented in the NMA report'.	The statement is not correct. The odds ratios were provided in the NMA report.	Thank you for highlighting this error. We have deleted the whole sentence to correct the error more concisely.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.5.2 (page 79) reads: 'For the comparison of rozanolixizumab (Week 4 assessment) against efgartigimod (Week 4 assessment) the mean (95% CrI) treatment difference in the change from baseline in MG-ADL score was [redacted]). There appears to be a typographic error in the 95% CrI but the efgartigimod MAIC Report confirms that the result is [redacted] significant.'	Please change the sentences to: 'For the comparison of rozanolixizumab (Week 4 assessment) against efgartigimod (Week 4 assessment) the mean (95% CrI) treatment difference in the change from baseline in MG-ADL score was [redacted]). The 95% CrI values were swapped in the CS but the efgartigimod MAIC Report confirms that the result is [redacted] significant.'	The CrI values reported in the CS were swapped.	Thank you for clarifying the correct CrI values. We have swapped the values to display them correctly and, for conciseness, removed mention of the typo.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3 (page 14) 'The EAG do not consider this to appropriately reflect SoC for patients with refractory generalised MG in England, which is the population specified in the company's Decision Problem.'	Please remove the sentence.	As per clinical opinion and detailed in the company submission and the response to Clarification Question B2, rozanolixizumab is anticipated to be used for refractory patients who are being treated or considered for IVIg/PLEX. Based on the commissioning policy for the use of immunoglobulins, IVIg/PLEX may be considered for patients who have failed standard treatments, including steroids and immunosuppression.	Not a factual inaccuracy, the EAG's opinion is correctly stated. No change made.

Section 4.2.4 (page 86) reads: 'In response to the EAG clarification question B2, the company argued that IVIg or PLEX is standard of care in refractory patients, and they compare rozanolixizumab directly with IVIg and PLEX separately.'	Please change the sentence to: 'In response to the EAG clarification question B2, the company argued that rozanolixizumab is expected to be used in patients considered for IVIg/PLEX (i.e. patients with active disease despite standard treatments) and chronic IVIg/PLEX is standard of care in refractory patients. Thus, they compare rozanolixizumab directly with IVIg and PLEX as rozanolixizumab is intended to displace these treatments.'	The company response to Clarification Question B2 was not presented accurately.	Thank you for highlighting this, we have reworded the sentence to more accurately reflect Clarification Response B12.

Issue 18

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>Section 4.2.4 (Table 18)
<table>
<tr><th>Characteristic</th><th>Used in the company model for refractory patients (obtained from the MycarinG whole population)</th><th>Mycarin G AChR+ patients</th><th>Mycarin G MuSK+ patients</th></tr>
<tr><td>Mean age, years</td><td>51.80</td><td>52.24</td><td>48.3</td></tr>
<tr><td>Female, %</td><td>60.50%</td><td>57.05%</td><td>78.3%</td></tr>
</table>
</td>
<td>Please change the Table to:
<table>
<tr><th>Characteristic</th><th>Used in the company model for refractory patients (obtained from the MycarinG whole population)</th><th>Mycarin G AChR+ patients</th><th>Mycarin G MuSK+ patients</th></tr>
<tr><td>Mean age, years</td><td>51.80</td><td>52.24</td><td>48.3</td></tr>
<tr><td>Female, %</td><td>60.50%</td><td>57.0%</td><td>80.9%</td></tr>
</table>
</td>
<td>While not specified in the EAG report, the AChR Ab+ and MuSK Ab+ patients characteristics were apparently calculated using the weighted average of the placebo, rozanolixizumab ~7 mg/kg, and ~10 mg/kg cohorts. Based on the data from these three cohorts, the proportion of female participants in the MuSK Ab+ subgroup is incorrect and should be 80.9%.</td>
<td>Thank you for highlighting this. The table has been updated as requested. We have also updated the results for scenario 2 in Table 35 (Population characteristics from the MuSK Ab+ MycarinG population, using the company’s base case) in Section 6.1 of the EAG report.</td>
</tr>
</table>

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.4 (page 86) reads: 'In practice, rozanolixizumab is intended to be used as an add-on to a basket of standard care therapies (henceforth, referred to as the "standard basket").'	Please change the sentence to: 'In practice, rozanolixizumab is intended to be used as an add-on to a basket of standard care therapies (henceforth, referred to as the "standard basket") which does not include IVIg and/or PLEX.'	Please clarify that in this context the basket of standard care does not include IVIg/PLEX as rozanolixizumab is not expected to be used as an add-on to IVIg/PLEX.	Thank you for highlighting this ambiguity. The text has been corrected as suggested.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.1 (page 90) reads: 'In response to clarification question A13, the company conducted MAICs which provided pairwise comparative evidence for rozanolixizumab against efgartigimod, but not for rozanolixizumab against zilucoplan or against PLEX.'	Please change the sentence to: 'In response to clarification question A13, the company conducted MAICs which provided pairwise comparative evidence for rozanolixizumab against efgartigimod and IVIg, but not for rozanolixizumab against zilucoplan or against PLEX.'	The company also provided a MAIC for rozanolixizumab vs IVIg.	Not a factual inaccuracy. The MAIC providing comparative evidence for rozanolixizumab against IVIg did not report the MG-ADL outcome. We have revised the text to clarify this.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.1 (page 90) reads: 'The EAG could not incorporate the MAIC output into our analyses due to pragmatic reasons as the model would require significant adaptation.'	Please remove the sentence.	It is not accurate to state that the model would require significant adaptation. The company has used the existing model functionality to input the odds ratios obtained from the MAICs in the model and presented the results; thus, it should be possible for these calculations to be verified by the EAG.	We disagree. The company's model is not set up to use odds ratios directly, but requires the use of the referent rate adjustment calculation and odds ratios. The MAICs provided the odds ratio for rozanolixizumab versus efgartigimod. The company model, on the other hand, is set up to use the odds ratios of rozanolixizumab versus placebo, efgartigimod versus placebo, and zilucoplan versus placebo. These are converted to relative risks, which are then applied to the referent response rate to estimate the treatment's response rate, which feeds into the transition probabilities.

Issue 22

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>Section 4.2.6.2 (Table 23) reads:

<table>
<tr><th>Treatments</th><th>Loss of response</th><th>Stable response</th><th>Continued response</th></tr>
<tr><td>Rozanolixizumab</td><td>0.00</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Zilucoplan</td><td>0.00</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Efgartigimod</td><td>0.00</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>IVIg/SCIg</td><td>0.00</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Plasma exchange</td><td>0.00</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Please change the Table to:

<table>
<tr><th>Treatments</th><th>Loss of response</th><th>Stable response</th><th>Continued response</th></tr>
<tr><td>Rozanolixizumab</td><td>0.00</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Zilucoplan</td><td>0.00</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Efgartigimod</td><td>0.00</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>IVIg/SCIg</td><td>0.00</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Plasma exchange</td><td>0.00</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
.
</td>
<td>The data for stable response for zilucoplan, IVIg and PLEX have been inaccurately reported in the EAG report and Table 60 of the CS. The correct response data are found in Appendix N, both in the original CS and in the Erratum.</td>
<td>Thank you for highlighting this. The table is now corrected.</td>
</tr>
</table>

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.2 (page 93) reads: 'We were unable to verify the company's assertion that the estimates for zilucoplan and efgartigimod were obtained from the NMA as no information was provided in the CS.'	Please remove the sentence.	The data on the change from baseline in MG-ADL score from the NMA were presented in Table 48 of the CS (Section B.2.9.3) and in Table 8 of the NMA report.	Thank you for highlighting this. The sentence has been removed.

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.3 (page 93) reads: 'In the model, a lower MG-ADL score is associated with lower probabilities of experiencing the clinical events, indicating that changes in MG-ADL score impact the probability of transitioning to the crisis- and exacerbation- health states.'	Please remove the sentence.	This statement is incorrect as the base case presented by the company assumes that the risk of exacerbation depends on the health state, i.e. whether patients are in an uncontrolled state or a response state.	Thank you for highlighting this. The sentence has been removed.

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.8.1 (page 99) reads: 'The model uses a weighted list price of [redacted] per mg for rozanolixizumab, after applying the PAS discount of [redacted].'	Please change 'list price' to 'net price'.	The correct term in this context is net price.	Thank you for highlighting this discrepancy. The text has been corrected as suggested.

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.1.3 (page 108) reads: 'For some iterations, the probabilistic average weight is less than 77 kg, reducing the loading dose of zilucoplan from 32.4 mg to 23 mg.'	Please change the sentence to: 'For some iterations, the probabilistic average weight is less than 77 kg, reducing the dose of zilucoplan from 32.4 mg to 23 mg.'	There is no loading dose for zilucoplan	Thank you for highlighting this discrepancy. The text has been corrected as suggested.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.1 (Table 35, page 118) reads: 'Using 70% response rates for IVIg and PLEX; trial response rates for rozanolixizumab (72%), zilucoplan (73%) and efgartigimod (68%); 50% response rate for SoC[a].'	Please add a reference for the response rate for SoC.	Please clarify the source of the response rate of [redacted] for SoC.	Not a factual inaccuracy. This scenario uses the company's referent response rate as a proxy for the SoC response rate. To improve clarity, an explanation has been added to the table footer as requested.

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG model (Response tab, cell E17): Response rate for ECM= (43.8%x70%)+(14.6%x70%)=40.88%	Please edit the value to include the response rate to SoC (without IVIg/PLEX). As response rates were based on trial data, the company suggest using the placebo data from clinical trials (i.e. MycarinG) to calculate the SoC response rate and include it in the ECM: Response rate for ECM= [redacted]	The response rate ([redacted]%) for ECM is based on weighted average of the assumed response rate of [redacted]% for IVIg and PLEX. The response rate for SoC (without IVIg and PLEX), which makes up 41.6% of the basket, was not included in the calculations.	Not a factual inaccuracy. We do not agree that 31% of patients in the NHS receiving the standard basket of therapies would respond to them. If patients did respond, they would not be refractory. We conducted a scenario using a [redacted] response rate for the ECM arm, which produced an ICER of [redacted] per QALY for rozanolixizumab compared with ECM, using the EAG's base case.

Section 6.1 (page 24): 'Using a response rate of 70% for IVIg and PLEX (which produces a response rate of 40.88% in the established clinical management arm, when 43.8% of patients receive chronic IVIg and 14.6% of patients receive chronic PLEX) […].'	See above.	See above.	See above
Section 1.7 (Table 3, page 24): 'Using 70% response rates for IVIg and PLEX (giving a 40.88% response rate in the ECM arm) […].	See above.	See above.	See above
Section 6.2 (page 120): 'Using a response rate of 70% for IVIg and PLEX (which produces a response rate of 40.88% in the established clinical management arm, when 43.8% of patients receive chronic IVIg and 14.6% of patients receive chronic PLEX) […].'	See above.	See above.	See above

Section 6.2 (Table 36): +Using 70% response rates for IVIg and PLEX (giving a 40.88% response rate in the ECM arm) […]	See above.	See above.	See above

Issue 29

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Engine (Tab T6, cell AZ5 – when ECM is selected): Cost for ECM= SoC cost+(IVIg cost x[redacted])+(PLEX cost x[redacted])	Please change to: Cost for ECM= (SoC cost x[redacted])+(IVIg cost x[redacted])+(PLEX cost x[redacted]	The cost has been calculated by adding the cost of SoC to the weighted average of IVIg and PLEX; the final cost should be the weighted average of all three components in the basket.	This is not a factual inaccuracy. We assume that all patients in our ECM arm receive SoC, rather than just the percentage not receiving IVIg or PLEX. We ran a scenario applying the costs for SoC to the ECM arm as suggested (for the costs in model cycles 1&2 and for subsequent cycles; Engine Tab T6, cells AZ5 and BA5), which produced an ICER of [redacted] per QALY for rozanolixizumab compared with ECM, using the EAG's base case.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID5092 EAG report: • Section 1.2 (Table 2) • Section 5.1 (Table 30) • Section 6.2 (Table 36) • Section 6.2 (Table 37) • Section 6.3 (Table 38)	Confidential marking differs from company submission.	Please mark all costs, incremental costs and ICERs as confidential. QALYs and incremental QALYs do not need to be marked as confidential.	Confidential marking has been corrected so that: • Rozanolixizumab and zilucoplan total costs are confidential. • All incremental costs are confidential • All ICERs are confidential This is in line with the zilucoplan appraisal and makes as much data as possible transparent, without allowing back calculation of results.

<table>
<tr>
<td>Section 3.2.5.9.2 (page 61)</td>
<td>All cycles numbers should be marked as confidential.</td>
<td colspan="3">The mean EQ-5D VAS score change from baseline at Day 43 for the rozanolixizumab ~7 mg/kg group ranged from [redacted] to [redacted] in the first [redacted] cycles (Clarification Response Table 5), which differs from the mean EQ-5D VAS score change from baseline results reported for the first [redacted] cycles in the CS (range [redacted]; CS section B.2.6.2.3). Both sets of results show i[redacted] scores, but it is unclear why the reported results differ as both report the safety set analysis (CS B.2.6.2.1 and Clarification Response Table 5).</td>
<td>Not a factual inaccuracy. CS section B.2.6.2.3 does not mark the first [redacted] cycles as confidential. Confidentiality marking has been added for all cycles for consistency.</td>
</tr>
<tr>
<td>Section 3.2.5.10.4.1 (Table 13, page 64)</td>
<td>All patient numbers and responder rates for the AChR Ab+ and MuSK Ab+ patient subgroups should be marked as confidential.</td>
<td colspan="3">
<table>
<tr><td>AChR Ab+
MG-ADL, n/N (%)
MGC, n/N (%)
QMG, n/N (%)</td><td>[redacted])</td><td>Not reported
Not reported
Not reported</td></tr>
<tr><td>MuSK Ab+
MG-ADL, n/N (%)
MGC, n/N (%)
QMG, n/N (%)</td><td>[redacted]c
[redacted]c
[redacted]c</td><td>[redacted]
[redacted]
[redacted]</td></tr>
</table>
</td>
<td>The N value is not confidential and is reported transparently in CS Table 11. All other confidentiality marking has been added as requested.</td>
</tr>
</table>

<table>
<tr>
<td>Section 4.2.3 (Table 18)</td>
<td>Baseline mean MG-ADL scores in AChR Ab+ and MuSK Ab+ subgroups should be marked as confidential.

The baseline BMI of the MycarinG whole population does not need to be marked as confidential.</td>
<td>
<table>
<tr><td>Mean MG-ADL score at start</td><td>8.30</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Baseline BMI (kg/m^2)</td><td>27.83</td><td>-</td><td>-</td></tr>
</table>
</td>
<td>Confidential marking has been added and removed as requested.

Additional confidential marking was removed for the other baseline characteristics obtained from the MycarinG whole population for mean age, female, mean weight, and mean MG-ADL score.</td>
</tr>
<tr>
<td>Section 4.2.6.1 (table 21)</td>
<td>The response assessment time points do not need to be marked as confidential.</td>
<td>
<table>
<tr><th>Treatment</th><th>Odds ratio</th><th>Response rate</th><th>Response assessment time point (weeks)</th></tr>
<tr><td>Rozanolixizumab</td><td>[redacted]</td><td>[redacted]</td><td>6</td></tr>
<tr><td>Zilucoplan</td><td rowspan="2">[redacted]</td><td rowspan="2">[redacted]</td><td>12</td></tr>
<tr><td>Efgartigimod</td><td>10</td></tr>
<tr><td>IVIg/SCIg</td><td>1.04</td><td>51.01%</td><td>6</td></tr>
<tr><td>PLEX</td><td>1.33</td><td>57.01%</td><td>6</td></tr>
</table>
</td>
<td>Confidential marking has been removed as requested.</td>
</tr>
<tr>
<td>Section 4.2.6.2 (page 91)</td>
<td>The baseline mean MG-ADL score of the MycarinG whole population does not need to be marked as confidential.</td>
<td>The baseline MG-ADL score used in the model is the mean baseline score for the patients in the MycarinG trial, MG-ADL 8.3, indicating that patients have severe disease</td>
<td>Confidential marking has been removed as requested.</td>
</tr>
</table>

Section 5.1.2 (pages 106 and 107)	The responder rate used in the scenario analysis should be marked as confidential.	• Using a responder rate of [redacted] for IVIg and PLEX, based on clinical expert opinion from the EAG report on zilucoplan • Using a responder rate of [redacted] for IVIg had the greatest effect on the ICER for rozanolixizumab compared with IVIg/SCIg, reducing it to [redacted] per QALY (scenario 3).	These responder rates come from clinical expert advice to the EAG. The information is not confidential. Confidential marking not added.
Section 5.1.2 (Table 31)	The responder rate used in the scenario analysis should be marked as confidential.	3 | Responder rate of [redacted] for IVIg and PLEX	The responder rate comes from clinical expert advice to the EAG. The information is not confidential. Confidential marking not added.
Section 5.3 (Table 34, page 112)	The response rate for zilucoplan should be marked as confidential.	Our experts also thought a response rate of [redacted]% for zilucoplan was low.	Confidential marking has been corrected as requested.

Section 6.1 (Table 35, page 118)	The response rates for SoC and IVIg/PLEX should be marked as confidential.	Using [redacted]% response rates for IVIg and PLEX; trial response rates for rozanolixizumab (72%), zilucoplan (73%) and efgartigimod (68%); [redacted] response rate for SoC[a]	Responder rates for IVIg and PLEX come from clinical expert advice to the EAG. The information is not confidential. Confidential marking not added. Confidential marking has been added to the SoC response rate as requested.
Section 6.3 (page 123)	All terms that indicate that the average number of annualised cycles per patient in lower than 4 should be marked as confidential.	[redacted] the number of rozanolixizumab cycles from [redacted] to four per year (scenario 6) increases the ICER from [redacted] per QALY to [redacted] per QALY, because total costs for rozanolixizumab are [redacted], thus [redacted] incremental costs	Confidential marking has been corrected as requested.

Section 9.2.2 (pages 137 and 138)	The proportion of study participants based on region should be marked as confidential.	Yes, study participant demographics were generally balanced between the treatment groups apart from the higher proportion of study participants from North America in the ≈7 mg/kg group (32.9%) compared with the ≈10 mg/kg group (23.1%) and the lower proportion of study participants from Europe in the ≈7 mg/kg group (57.0%) compared with the ≈10 mg/kg group (67.9%).	This data is not marked confidential in CS Table 19 which is the source of the table in section 9.2.2. However, we note that this data is marked as confidential in CS Table 13 for baseline characteristics and where the EAG entered data in the EAG response column of the table in section 9.2.2 we used confidential marking. Confidentiality marking has been added as requested.

Additional EAG amendment to the report made at the FAC stage.

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.2.6.1 (pages 88-90) The limitations associated with the Barth et al. 2011 study have not been communicated.	Addition of a short paragraph in 4.2.6.1: “There are several key limitations to the Barth et al. study data. The study was conducted in Canada, with uncertain relevance to UK patients; the study population was not explicitly defined as having refractory MG (patients were described as having moderate to severe MG with a QMG score >10.5); the response was reported as a ≥3-point improvement in QMG score because the MG-ADL response outcome was not available from the study; and no confidence intervals or standard errors were provided with the response rates.”	The limitations of the Barth et al. 2011 study are clearly communicated in relation to choice of response rates for IVIg and PLEX between published data used in the company model and clinical opinion used in the EAG’s base case.