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:

The following documents were included in the Committee papers for the second Committee meeting, held on 5 November 2025:

1. **Comments on the Draft Guidance from UCB Pharma**:
   a. Draft Guidance Comments
   b. Supporting Information
   c. Supporting Information – Addendum

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. ABN Neuromuscular Advisory Group
   b. Joint submission by Myaware and Muscular Dystrophy UK (MDUK)

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company response to the DG**

The following documents were included in the Committee papers for the third Committee meeting, held on 12 February 2026:

5. **Request for clarification to UCB following the second Committee meeting**

6. **Response from UCB**

7. **External Assessment Group critique of UCB response**

8. **Additional information from the company on the number of exacerbation events**

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

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

Draft guidance comments form

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UCB Pharma Ltd (Company)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Company holding marketing authorisation and submitting the appraisal for rozanolixizumab
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Frank Ababio

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1. Unmet need in refractory MG (Section 3.1 in the draft guidance)	There is an urgent unmet need for a new treatment option for patients with acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) antibody-positive refractory generalised myasthenia gravis (gMG) who are not sufficiently responding to standard therapy, such as corticosteroids (CSs) and non-steroidal immunosuppressants (NSISTs). Currently available treatment options are limited to maintenance intravenous immunoglobulin (IVIg) and plasma

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

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	exchange (PLEX), which are associated with significant treatment burden and adverse events for patients as well as being particularly resource intensive for the National Health Service (NHS). The development of rozanolixizumab began in response to a UCB scientist witnessing first hand the burden and complications his wife experienced with IVIg treatment for a neurological disease. It was this drive to find an alternative way of removing pathogenic antibodies that initiated the development programme in England. Rozanolixizumab is a fast-acting, efficacious, targeted treatment for AChR and MuSK antibody-positive (Ab+) gMG administered as a short subcutaneous infusion, which can be self-administered following training by a healthcare professional, reducing the burden on patients, carers and the healthcare system, with no new significant capital investment or service development required. The treatment landscape in the UK is lagging far behind that of other countries in the European Union (EU) and further afield, e.g. Canada and Australia with similar health technology assessment (HTA) methodologies to the UK, where targeted treatments are already available to patients or recommended for reimbursement. **Widely available therapies for refractory gMG patients in England** The only available treatment options in England for gMG patients who are refractory to standard therapies are regular intravenous courses of IVIg and PLEX. A recent expert elicitation exercise was conducted by the company using Delphi panel methodology with 9 consultant neurologists specialised in treating refractory gMG in the UK, representative of UK neurologists. Of these 9 clinical experts, 8 confirmed that they have access to both IVIg and PLEX as treatment options in their hospitals and the remaining respondent had access to IVIg only. This is also supported by a recent freedom of information request by UCB to 33 NHS trusts on their access to IVIg and PLEX. Of the 30 trusts who responded, 100% have access to IVIg and 83% have access to PLEX (1). However, as mentioned in the draft guidance (DG), IVIg and PLEX both present a significant treatment burden for the patient and are resource-intensive for the NHS. Patients on IVIg and/or PLEX typically attend hospital every 4 weeks, which equates to annual NHS staff time (including consultants, nurses, and administrative support) of [redacted] and [redacted] hours for IVIg and PLEX, respectively, and [redacted] and [redacted] hours of patient time, respectively (2). In addition, allergic reactions, infection, hypotension, nephrotoxicity, venous failure and thrombosis are adverse events associated with the

	use of IVIg and PLEX (3-5). Patient testimony submitted underscores the negative impact of inpatient visits for PLEX treatment on her mental health and on that of her child (pre-committee papers, patient expert perspective (6)). Patients also highlighted the side effects associated with IVIg and PLEX treatment, with one patient expert having to stop treatment due to the permanent catheter causing a blood clot (Section 3.1 DG (7)). The regular hospital visits or stays required for treatment with IVIg and PLEX can also be difficult to fit around work and family commitments, and place a substantial burden on carers (Section 3.1 DG (7)). **Patients with MuSK-Ab+ gMG** Patients with MuSK-Ab+ gMG tend to have more severe bulbar symptoms and generalised weakness, including myasthenic crises, compared with patients with AChR antibody-positive gMG (8, 9). Patients with MuSK antibody-positive gMG do not generally respond to acetylcholinesterase inhibitors (AChEIs) and may require high doses of CSs, in addition to NSISTs, to maintain symptom control. Furthermore, the efficacy of IVIg is usually reduced in patients with MuSK-Ab+ refractory gMG, leaving PLEX as the only available treatment option (8, 9). **Contrast with treatment availability in other countries** As of September 2025, no targeted treatment for gMG has received a positive recommendation from NICE, and access to innovative treatments for gMG is limited to compassionate use schemes, individual funding requests or clinical trials. This contrasts with access to medicines in other disease areas in the UK (e.g. multiple sclerosis and lupus) and to rozanolixizumab for gMG, which was registered in December 2023 in the EU and is accessible or reimbursed since in several countries in the EU (e.g. France, Germany, Italy, Spain, Austria, Belgium, Luxembourg, the Netherlands, Bulgaria and Greece) as well as in countries outside of Europe, countries that all acknowledge the added value these novel targeted treatments bring to patients with gMG. Rozanolixizumab was recommended for reimbursement in Canada in June 2025 (10) and was recommended for listing by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia in March 2025 (11), agencies that both have similar HTA methodology to NICE in the UK. In the recommendation for PBAC, it was stated that IVIg would be displaced by both rozanolixizumab and zilucoplan, and that IVIg and PLEX are the relevant comparators for both targeted treatments (11). In addition,

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	other targeted treatments for gMG, e.g. eculizumab, efgartigimod and ravulizumab, have been available in the EU for up to 8 years (12-14). **Burden of gMG** Patients with gMG experience fluctuating and debilitating symptoms that severely impact all aspects of their lives (15). Living with refractory gMG has a substantial negative impact on all aspects of self care, from washing themselves, brushing their teeth and styling their hair, all of which often need caregiver help. gMG also has a substantial negative effect on the patient's ability to move confidently inside and outside the house, and on long-term education and work, with careers interrupted or ended prematurely (pre-committee papers, patient expert perspective (6)). In addition, patients feel that living with gMG impacts their decision to have a family, which is a protected right in Article 12 of the Human Rights Act (16). Younger patients in particular may feel a sense of loss of life due to restrictions in activity and limitations in life choices (15). In their testimony, the patient expert explained how the loss of independence cause by a diagnosis of MG in her twenties had a strong negative effect on her mental health and how, over the years, 'my world became very small' with limited social interactions (pre-committee papers, patient expert perspective). In a European cross-sectional study, depression and moderate or severe anxiety were reported in 64% and 46% of patients with MG (n=55) (17). In addition, contraindications to therapy during pregnancy and lactation mean women may face a difficult choice between starting a family and managing symptoms of gMG (15). **Unmet need** Patients with refractory gMG are sub-optimally managed with the treatments currently available on the NHS. The consequences for these patients include poor symptom control, as these patients to do not achieve minimal symptom expression (MSE), increased risk of myasthenic crisis (18-20), and the debilitating side effects of corticosteroids (diabetes, osteoporosis, depression and infection, which can trigger a myasthenic exacerbation) (18, 21-24).

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

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	Currently available treatments have a delayed onset of action (usually 6-18 months and up to 2 years to achieve the maximum clinical benefit, usually without achieving MSE), contributing to poor disease control and leaving patients with a high symptom burden and at risk of exacerbation and crisis (18). Treatments currently offered by the NHS for patients with refractory gMG may require patients to travel long distances for treatment at specialist centres, and even stay in hospital for repeat treatment if they live too far away to travel for each session (25, 26), which is burdensome for patients, their families, and the NHS. **Rozanolixizumab as an effective targeted therapy** Rozanolixizumab is a fast-acting, efficacious, targeted treatment for AChR and MuSK antibody-positive gMG administered as a short (up to 18 minutes) subcutaneous infusion, reducing the burden on patients, carers and the healthcare system. Rozanolixizumab is the only treatment currently licensed for patients with both MuSK antibody-positive and AChR antibody-positive gMG. It is also licensed for self-administration via manual push syringe, with a median administration time of 5 minutes, thus providing benefits to both patients and the NHS in terms of time and resource. An analysis based on an average of three experts' estimates of NHS staff time calculated that, if 1,375 of 4,338 patients with refractory gMG receive either rozanolixizumab or zilucoplan instead of IVIg and PLEX over a 5-year period, a total of 9,938 consultant hours, 628,009 nurse hours, and 66,750 hours of administrative support hours were saved (27). In terms of patient time, [redacted] and [redacted] hours per patient per year were saved compared with IVIg and PLEX, respectively. The use of rozanolixizumab as an alternative treatment option to IVIg and PLEX would enable more IVIg (which has a finite supply) and PLEX to be made available to patients with other diseases without proven licensed treatments and free up vital and much needed NHS resources. In addition, not recommending rozanolixizumab and other targeted therapies for reimbursement is effectively leaving those patients with gMG, who are most in need of effective treatment, with burdensome unlicensed therapies as the only treatment choice. The consequence of an approach that focusses on the inevitable uncertainties associated with a comparison with unlicensed expensive treatments associated with very limited data is that patients will be deprived of a new treatment associated with proven clinical benefits and will be required to continue use of unlicensed treatments for which the benefits are uncertain, which will

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

Draft guidance comments form

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	almost certainly never be licensed for use in MG, where the costs (including in terms of NHS resources) are substantial, and where a NICE efficacy and cost-effectiveness appraisal has not been undertaken. **Equity considerations** The NICE manual states that although decisions about the acceptability of the technology as an effective use of NHS resources will consider the degree of certainty around the value for money, the committee will be mindful that there are certain technologies or populations for which evidence generation is particularly difficult, because they are rare diseases and/or the technology is innovative (28). UCB would also like to highlight that a priority of the Rare Disease Action Plan 2024 is to improve access to specialist care, treatments and drugs (29, 30). Furthermore, rozanolixizumab could play a role in achieving one of the three radical shifts named in the NHS Fit for the Future:10 year health plan for England (moving care from hospital to community), by shifting healthcare spending out of hospital with patients treating themselves with rozanolixizumab in their own homes when possible (29). **Conclusion** Rozanolixizumab presents a significant opportunity for patients living with a severe and debilitating disease such as refractory gMG to access an efficacious treatment that reduces the symptom burden, with no new significant capital investment or service development required.
2. How the company sought to address the uncertainties listed in the draft guidance (Section 3.17 in the draft guidance)	The company would like to emphasise that, given the paucity of data in refractory gMG, a very extensive effort has been made to address the uncertainties listed in the DG, some of which are impossible to answer due to the rarity of the disease and the lack of data for the comparators. IVIg and PLEX are not licensed for the treatment of gMG and there are substantial variabilities in these therapies, e.g. PLEX may be administered centrally or locally and there are a number of IVIg products manufactured by different companies, contributing further to the lack of data available for their use in this indication. This is an issue that may not readily be resolved by UCB or the manufacturer of any new targeted therapy for gMG, as the treatment pathways for gMG in many countries across Europe and beyond now focus on licensed targeted therapies and not IVIg and PLEX.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

	In circumstances where IVIg and PLEX are not licensed for use in gMG, it is questionable at best whether any clinical trial should ethically include such therapies as comparators and in these circumstances, a manufacturer has no option but to attempt indirect treatment comparisons using the limited data available. In addition to the original network meta-analysis (NMA) submitted and previous expert elicitation, the company has presented new evidence that will address some of the uncaptured health benefits of rozanolixizumab. The new evidence submission includes: • Updated cost-effectiveness model that seeks to address subsequent treatments and other uncaptured benefits of rozanolixizumab (Section 3.1 in the supporting document) • An updated systematic literature review to evaluate the efficacy of treatment with IVIg and PLEX in gMG, including both randomised controlled trials and observational studies (Section 2.3 in the supporting document) • New indirect treatment comparison methodologies (bivariate NMA [bvNMA] and baseline risk-adjusted [BLRA] NMA) (Sections 2.4 and 2.5 in the supporting document) • An expert elicitation exercise to clarify the positioning of rituximab in the treatment pathway for patients with AChR and MuSK antibody-positive gMG (Section 2.2 in the supporting document) • A Delphi panel to determine the proportion of index treatment and subsequent treatment (Section 3.1.6 in the supporting document) • The final results from the extension phase of MG0007 for rozanolixizumab (Section 2.1 in the supporting document) • Data from MG0007 on the proportion of patients reaching MSE on rozanolixizumab (Sections 2.1.2.10 and 3.1.5 in the supporting document).

Please return to: **NICE DOCS**

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

Draft guidance comments form

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	UCB have also conducted a cost-minimisation analysis versus IVIg and PLEX. To implement this, the efficacy (response rate, change from baseline in MG-ADL score, and proportions of patients in continued, stable and loss of response health states) was assumed to be equal to rozanolixizumab. The results show that, even if the efficacy of rozanolixizumab was equal to that of IVIg and PLEX, rozanolixizumab would still be cost saving versus both treatments. In addition, a cost per responder analysis illustrates that the net cost per responder is £[redacted] less for rozanolixizumab than IVIg and £[redacted] less than PLEX.
3. Use of rituximab in the treatment pathway (Section 3.4 in the draft guidance)	NICE requested that the company undertake expert elicitation to fully understand the use of rituximab in NHS practice, including whether rituximab is currently used and in what proportions of patients, where in the pathway rituximab is used, whether rituximab is used as a subsequent treatment, and any variation in its use in practice. **A structured survey was conducted** The company considered multiple approaches to elicit expert opinion on the use of rituximab in the treatment pathway for gMG, including a Delphi panel, one-on-one interviews, an online survey, and the Sheffield elicitation framework (SHELF). Considering the original time constraints and the need to reach as many experts as possible to provide a comprehensive overview of rituximab use, the company chose to use an anonymous online survey, which is associated with a low risk of bias and can reach multiple clinical experts quickly. A total of 11 identified gMG clinical experts representing the specialist gMG centres in the UK (10 in England and one in Scotland) were contacted and responses were obtained from 100% of these clinicians. **Rituximab is used earlier in the pathway before maintenance IVIg and PLEX, where rozanolixizumab is positioned, and therefore rituximab is not a relevant comparator for rozanolixizumab** All respondents (11, 100%) currently use rituximab to treat MuSK-Ab+ gMG patients in their clinical practice, and 10 (91%) use rituximab in AChR-Ab+ gMG patients. In AChR Ab+ patients, nine (90%) respondents positioned rituximab

	before maintenance IVIg/PLEX, and one (10%) respondent would use rituximab after IVIg/PLEX. In MuSK-Ab+ gMG patients, all respondents would use rituximab before maintenance IVIg/PLEX. Rozanolixizumab would be positioned as an alternative to maintenance IVIg/PLEX, and none of the respondents positioned rituximab here, indicating that rituximab would not be a direct comparator to rozanolixizumab. This is in line with the recently updated Association of British Neurologists (ABN) autoimmune myasthenia gravis management guidelines, which position rituximab ahead of neonatal fragment crystallisable receptor (FcRn) inhibitors (31). The proportion of patients being treated with rituximab in the corresponding population (i.e. the position in the treatment pathway that the respondent chose) varied widely among clinicians, ranging from [redacted] in AChR Ab+ gMG patients and [redacted] in patients with MuSK Ab+ gMG. The experts stated that rituximab use has moved to earlier in the treatment pathway over time (since the publication of RINOMAX study (32)) and is used earlier in patients with explosive-onset disease. **Responses varied greatly on whether rituximab is used as a subsequent treatment** Despite the clinical experts placing rituximab earlier in the treatment pathway than IVIg and PLEX in all but one cases, some experts would also use rituximab as a subsequent treatment following non-response to IVIg, PLEX, and FcRn treatment. However, the responses varied greatly and no firm conclusion could be drawn on the use of rituximab as a subsequent treatment across centres. One respondent stated that it would be highly likely that rituximab would be used before chronic IVIg and PLEX, but that if they failed, rituximab would be trialled again. It is worth noting that, during this survey, each clinician was asked to select one treatment that they would use as subsequent treatment in each scenario (following non-response to maintenance IVIg, maintenance PLEX, and FcRn inhibitor). Therefore, the proportions reported in the supporting document and reference report do not represent the range of treatments likely used as subsequent treatment (which has since been interrogated in further expert elicitation (please see the Delphi panel in point 9), and also only represent the percentage of clinicians providing each response, rather than the proportion of patients taking each treatment. Please refer to Section 2.2 of the supporting document as well as the report submitted as a reference for additional information on the survey methodology and results.

NICE National Institute for Health and Care Excellence

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

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4. The use of a blended standard of care 'basket' as comparator (Section 3.6 in the draft guidance)	**The blended standard of care 'basket' is inappropriate and unreasonable as a comparator for rozanolixizumab** The company maintains that comparison of rozanolixizumab with the blended standard of care 'basket' is inappropriate based on the evidence presented. UCB believes that rozanolixizumab will be used as an alternative treatment option to IVIg and PLEX, in line with the company's proposed target population, clinical expert opinion noted in Section 3.2 of the DG, and the recently updated ABM guidelines (31). The clinicians explained that "rozanolixizumab would be used as an alternative to long-term maintenance IVIg or PLEX, but would not replace rescue use". As such, rozanolixizumab is expected to displace maintenance IVIg and PLEX in clinical practice in refractory patients who have failed standard of care alone. **Rozanolixizumab will displace IVIg and PLEX and should be treated as an alternative to these maintenance therapies** The company's assertion is supported by the clinical expert opinion provided to the Committee, where they explained that "rozanolixizumab would be used as an alternative to long-term maintenance IVIg or PLEX, but would not replace rescue use" (Section 3.2 of the DG). In a recent (August-September 2025) expert elicitation exercise conducted by the company using Delphi panel methodology, all nine responding clinicians agreed that targeted therapy would displace the use of IVIg and PLEX as treatment options. In addition, UK market data show that the majority ([redacted] of switches to unapproved targeted therapies originated from IVIg or PLEX, showing that rozanolixizumab would displace IVIg and PLEX in the majority of cases. The actual market share data collected is likely to be indicative of the broader licensed population for therapies, as opposed to the proposed positioning for reimbursement. Therefore, it would be expected that, if rozanolixizumab were to be recommended for reimbursement, the reimbursement criteria would be followed and that the percentage of patients switching from IVIg and PLEX would be higher. It is also worth noting that the remaining [redacted] of patients were likely to have been about to escalate to treatment with maintenance IVIg or PLEX, meaning that IVIg and PLEX use might have been displaced by the use of an unapproved targeted therapy. UCB have also conducted a database study of claims data in Germany, which shows a declining trend in IVIg use with the introduction of targeted therapies (33), and it is reasonable to expect this trend would be the same if rozanolixizumab were to be recommended for reimbursement in the UK.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

	A pairwise comparison versus IVIg and PLEX is the most appropriate analysis All of this data and expert opinion show that IVIg and PLEX are the only relevant comparators for rozanolixizumab, and that rozanolixizumab would be an alternative option to IVIg and PLEX at the same point in the treatment pathway. In addition, the clinical data that formed the basis for the marketing authorisation for rozanolixizumab and was submitted to NICE is consistent with this position in the treatment pathway. The appropriate economic analysis should therefore comprise pairwise comparisons between rozanolixizumab and IVIg and rozanolixizumab and PLEX. The NICE manual (PMG36) states that pairwise comparisons are relevant and justified when the technology is expected to specifically displace individual comparators, and that cost-effectiveness only needs to be proven against one comparator (28). The pairwise comparison versus IVIg and PLEX is further supported by rozanolixizumab's recommendation from PBAC, where it was stated that IVIg would be displaced by both rozanolixizumab and zilucoplan, and that IVIg and PLEX are the relevant comparators for both targeted treatments (11). The target population for rozanolixizumab is also within the marketing authorisation for rozanolixizumab as add-on to standard treatment for AChR and MuSK antibody-positive gMG (see also Section 3.5 in the draft guidance) (34). Rozanolixizumab would be used as an add-on to standard care, i.e. CSs and NSISTs and not IVIg or PLEX. In fact, administering IVIg alongside an FcRn inhibitor is counterproductive since the FcRn inhibitor will accelerate the clearance of IVIg, which depends on FcRn to prolong the half-life of immunoglobulin G (IgG) antibodies, thus making IVIg ineffective. This is supported by the recently updated ABN guidelines, which recommend a 4-week washout period between IVIg and FcRn therapy to avoid this mechanistic conflict (31). It is important to note that patients receiving IVIg and PLEX would also be receiving some form of background or standard therapy. This is consistent with the committee's conclusion in section 3.6 that "corticosteroids and immunosuppressants should be included in both arms". If rozanolixizumab, IVIg and PLEX are intended to be used as add-on to corticosteroids and NSISTs, then it is reasonable to assume that they are alternative treatment options for patients with gMG for whom standard of care (SoC) only has failed to provide adequate symptom control. Comparing rozanolixizumab against IVIg and PLEX as standalone comparators is no different from other NICE approved medicines that hold marketing authorisation as add-on treatments but were considered by the NICE

appraisal committees as alternative options. A few examples of such treatments have been presented in the table below.

Treatment	Marketing authorisation	NICE recommendation or committee's conclusion
Tezepelumab (TA880)	Tezepelumab is indicated as an **add-on maintenance treatment** in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment	Tezepelumab as an add-on maintenance treatment is **recommended as an <u>option</u>** for severe asthma in people 12 years and over, when treatment with high-dose inhaled corticosteroids plus another maintenance treatment has not worked well enough.
Tirzepatide (TA924)	Tirzepatide is indicated: 1. For the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • **in addition to other medicinal products** for the treatment of diabetes.	The committee concluded that all incremental cost-effectiveness ratios (ICERs) for tirzepatide (all doses) against all comparators were within what NICE considers a cost-effective use of NHS resources. Because of tirzepatide's **positioning as an <u>alternative</u> to glucagon-like peptide-1 receptor agonists (GLP-1 RAs)**, it is recommended in a narrower population than its marketing authorisation.

	Fenfluramine (TA1050)	Fenfluramine is indicated for 'the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) as **an add-on therapy to other antiepileptic medicines** for patients 2 years of age and older'	Fenfluramine is **recommended as an <u>option</u>** for treating seizures associated with Lennox–Gastaut syndrome (LGS), as an add-on to other antiseizure medicines, for people 2 years and over.:

All hospitals with neuroscience centres have access to IVIg and 83% have access to PLEX

The committee noted in section 3.6 that there is a substantial variation in access to IVIg and PLEX and that some centres may not have access to these treatments for their patients. In recognition of this variability, the Evidence Assessment Group (EAG) opted to model the comparator as a basket. UCB submitted a freedom of information request to 33 neuroscience centres in the UK, including all the hospitals considered to be gMG specialist centres (which also covers all hospitals that are expected to be able to prescribe rozanolixizumab if it were to be recommended for reimbursement), to secure an evidence-based picture of any variation in IVIg and PLEX accessibility. A total of 91% of the hospitals responded to the request, including all but one specialist centres. The results show that 100% of the hospitals have access to IVIg and 83% have access to PLEX for the treatment gMG. Additionally, all the gMG centres treating refractory gMG patients are among the top 50 trusts for IVIg use as reported in the MDSAS 2023/2024 report (35). Although the report does not specify IVIg usage for MG by individual trust, it does confirm that these facilities have access to IVIg.

In addition, during the appraisal of zilucoplan (ID4008), the EAG consulted three clinicians who are experts in the treatment of gMG. They unanimously agreed that all patients with refractory gMG would be treated with IVIg or PLEX unless contraindicated (36). Therefore, the rationale behind the EAG and committee preference for a basket of care is contrary to the independently provided information by 30 provider hospitals, clinical expert advice, and Section 3.2 of

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

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	the DG, which states that clinical expert opinion provided to the Committee explained that rozanolixizumab would be used as an alternative to long-term maintenance IVIg or PLEX. **Analyses to show the perversity of the outcome versus the blended basket comparator** To demonstrate that the standard of care 'basket' is not suitable as a comparator, the company explored two scenarios in which hypothetical new versions of IVIg and PLEX have a 10% lower acquisition cost and are 10% more effective than the versions of IVIg and PLEX currently available in the NHS (see supporting information document Section 3.3.5.1). This analysis results in incremental costs for the hypothetical IVIg of £[redacted] and incremental quality adjusted life years of 0.007 versus the standard of care 'basket' as a comparator using the revised EAMS proportions. The resulting incremental cost-effectiveness ratio is £[redacted] per quality adjusted life year. For the hypothetical PLEX versus the standard of care 'basket' comparator, incremental costs are £[redacted] and incremental QALYs are 0.053, resulting in an ICER of £[redacted] per quality-adjusted life year. Both of these ICERs are far above (~[redacted] times for the hypothetical IVIg and ~[redacted] times for the hypothetical PLEX) the top end of the willingness-to-pay threshold accepted by NICE (£30,000 per quality-adjusted life year), and would result in these less costly, more effective versions of IVIg and PLEX to be refused reimbursement, which is clearly an incorrect outcome. The method of blended comparator is therefore not appropriate and would reach the illogical conclusion that a cheaper and more effective version of IVIg or PLEX would not be recommended. Based on this approach, patients with refractory gMG will need to continue using a less effective treatment that costs the NHS more money compared with recommending rozanolixizumab for reimbursement. **Blueteq management** UCB understands the concern that all patients with gMG (and not just those solely receiving or about to receive IVIg or PLEX) could potentially be considered for rozanolixizumab should it be recommended. UCB has proactively engaged with NHS England concerning budget impact mitigation; it is expected that rozanolixizumab will be used following review by a multidisciplinary team (MDT) at a gMG specialist centre and funding approval managed through Blueteq.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

	This is further supported by the recently updated ABN guidelines, where FcRn inhibitors are recommended for specialist centre use only with MDT referral (31). **The overall EAMS cohort includes non-refractory patients and is therefore inappropriate** The EAG based the proportion of people receiving each comparator on the published efgartigimod Early Access to Medicines Scheme (EAMS) patient cohort (37, 38). The company disagrees with applying the composition and proportions of the basket assumptions to this appraisal for rozanolixizumab based on the following points: • Patients with MuSK antibody-positive gMG were not eligible for enrolment in the efgartigimod EAMS (37, 38) • On page 11 of the DG, the EAG noted that ‘‘refractory was defined slightly differently” in the efgartigimod EAMS. The efgartigimod EAMS paper reports that only 77% [n=37] of patients were refractory (37, 38). The population recruited in the efgartigimod EAMS is broader than the population presented in the rozanolixizumab company submission. The entry criteria used in the efgartigimod EAMS is patients with AChR antibody-positive gMG, including but not limited to patients with refractory gMG (37, 38). Therefore, as not all patients were refractory, the population in the efgartigimod EAMS does not match the population under consideration in this single technology appraisal for rozanolixizumab. • As the eligibility criteria for MycarinG required participants to be considered for additional treatment, such as IVIg or PLEX (39), the MycarinG population is more representative of patients with refractory gMG and those that will receive rozanolixizumab in clinical practice than the EAMS cohort. • The publicly available results do not specify the standard of care therapies in the refractory subgroup. In total, 4.2% (n=2) of patients were provided efgartigimod as a bridging treatment which is outside of the proposed positioning of rozanolixizumab. Additionally, ten patients (20.8%) were receiving prednisolone only. It is unclear if or how many of these patients will be eligible for rozanolixizumab as the study does not specify if NSIST options were exhausted in this subgroup. Finally, three patients (6.3%) were reported as having no immunosuppressive/immunomodulatory treatment, but it is unknown if these patients were refractory patients

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

	or otherwise (37). It is unclear how many of these patients would be eligible for rozanolixizumab as it is licensed as an add-on therapy to standard of care. • Furthermore, the proportions of patients receiving IVIg and PLEX in the efgartigimod EAMS are based on the overall study population and not the 77% that were considered refractory. It is therefore reasonable to assume, in the light of the evidence provided, that the proportions used by the EAG to represent the target population of this appraisal (refractory patients receiving IVIg or PLEX) have been underestimated. The company has based the above considerations on the available published data and is unaware of whether the EAG or the committee have relied on any other information for decision making that has not been made available to UCB or other stakeholders involved in this assessment. **Updated model submission** As part of this response, the company has submitted an updated model, with a change log embedded, requested by the committee, that includes in the base case a standard of care basket as subsequent treatment for patients who discontinue due to lack of response to rozanolixizumab and its comparators (IVIg and PLEX) (see point 9).
5. Treatment effect may be overestimated and is uncertain in the long-term (Section 3.7 in the draft guidance)	The open-label extension study (MG0007) was completed on 25 January 2024. The final results from the study demonstrate the consistent efficacy of rozanolixizumab over multiple treatment cycles and its long-term safety in patients with AChR- and MuSK-positive gMG. Patients received a median of [redacted] treatment cycles (range: [redacted] cycles). Repeated cyclic treatment of rozanolixizumab led to consistent and clinically meaningful improvements in myasthenia gravis activities of daily living (MG-ADL), Quantitative myasthenia gravis (QMG), myasthenia gravis-composite (MG-C) and myasthenia gravis symptoms patient-reported outcome (MGSPRO) scores in each treatment cycle. Responses, defined as a ≥2-point reduction in MG-ADL score, were seen as early as Day [redacted] of each treatment cycle, with a median time to MG-ADL response of ~[redacted] in the first [redacted] 6-week treatment cycles. Please see Section 2.1 in the supporting document for additional final results from the open-label extension study.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

6. Dose switching and treatment effect (Section 3.8 in the draft guidance)	The company addressed the question of the proportion of patients that switched dose in the open-label extension study (MG0007) in the response to the EAG clarification questions (Question A3). Dose changes were not allowed in MycarinG, however dose switching was permitted in the open-label extension study at the beginning of each cycle. A total of [redacted] ([redacted] %) of the [redacted] study participants who received rozanolixizumab in the open-label extension study did not switch their dose during study participation. Amongst the [redacted] randomised to the rozanolixizumab ≈7 mg/kg dose, [redacted] ([redacted] %) patients received more than one treatment cycle. [redacted] ([redacted] %) study participants switched to rozanolixizumab ≈10 mg/kg following the first treatment cycle. Amongst the [redacted] randomised to the rozanolixizumab ≈10 mg/kg dose, [redacted] ([redacted] %) patients received more than one treatment cycle. [redacted] ([redacted] %) study participants switched to rozanolixizumab ≈7 mg/kg following the first treatment cycle. Although a small proportion of patients switched doses, treatment effect was based on the dose patients received for each cycle.
7. Updated systematic literature review for IVIg/PLEX (Section 3.10 in the draft guidance)	A systematic literature review (SLR) was conducted in September 2024 to identify all published evidence for IVIg and PLEX (including randomised controlled trials [RCTs], observational studies and other data sources such as single arm and phase 2 studies, as requested by NICE). In total, 11 publications were included: three RCTs and eight observational studies. Of these, six were included in the NMAs since they could link to the network and reported outcomes of change from baseline in MG-ADL or QMG score or response rate using MG-ADL or QMG score, with the bvNMA informing the economic model: • Zinman et al, 2007, an RCT comparing IVIg (n=24) with placebo (n=27) in patients with MG • Barth et al, 2011, an RCT comparing IVIg (n=41) with PLEX (n=43) in patients with MG • Duan et al, 2023, an observational study comparing PLEX (n=62) with lymphoplasmapheresis (n=62) in patients with severe MG • Barnett et al, 2017, an observational study comparing control (n=54) vs prednisone (n=50) vs IVIg/PLEX (n=45) in patients with MG

Please return to: **NICE DOCS**

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

	• Leng et al, 2024 is an observational study comparing PLEX (n=3) with Protein A immunoadsorption (n=4) in patients with MG • NCT02473952, an RCT comparing IVIg (n=30) with placebo (n=32). After the date of the SLR searches, this study was published so was included in the NMA to inform a MG-ADL response rate for IVIg (related to Bril et al, 2024) The full SLR report is provided as a supporting reference along with this document.
8. Bivariate NMA (Section 3.10 in the draft guidance) and treatment response rates (Section 3.13 in the draft guidance)	As stated in point 2, a very extensive effort has been made by the company to address the uncertainties listed in the DG, some of which are impossible to answer due to the rarity of the disease and the lack of data for the comparators. The updated bvNMA analysis (see section 2.4 of supporting document and accompanying report) shows that: • Rozanolixizumab has a [redacted] proportion of responders ([redacted] %) compared with IVIg ([redacted] %) and PLEX ([redacted] %), and has demonstrated a larger improvement from baseline in MG-ADL score [redacted]) when compared with IVIg [redacted]) and PLEX [redacted]) in the bivariate network meta-analysis (and in the matched-adjusted indirect comparison submitted as part of the company response to EAG clarification questions). Despite data limitations causing uncertainty with wide credible intervals, there is general concordance with point estimates across analyses (matched-adjusted indirect comparison, network meta-analysis, bivariate network meta-analysis, and the naive treatment comparison). The BLRA NMA (see also Section 2.5 of the supporting document) showed that the mean estimates for responders and change from baseline in MG-ADL score are very similar to the conventional NMA. In addition, there are no significant changes in the deviance information criteria (DIC) or total residual deviance when compared with the conventional NMA The estimate of beta values shows the non-significance of results based on common and exchangeable models and thus indicates that the placebo response is not statistically significantly difference between the studies.

Please return to: **NICE DOCS**

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

	In conclusion, the results from the bvNMA and the BLRA NMA are similar to the conventional NMA, although the credible intervals are wide due to the small sample sizes and quality of the studies included for IVIg and PLEX.
9. Modelling subsequent treatments (Section 3.12 in the draft guidance)	Formally modelling treatment sequences is impossible and cannot be answered with any certainty due to the rarity of the disease, the highly individualised treatment choices for refractory patients, and the lack of available data. There is great uncertainty around the number of lines of subsequent treatments needed, which treatments clinicians will consider after failure on IVIg/PLEX, and whether lack of response to index treatment will be a treatment effect modifier. However, UCB acknowledges that the validity of a model which did not allow for repeat attempts of treatment and switching of treatment may be challenged. Similarly, a model which kept patients on IVIg or PLEX persistently despite loss of response might also be challenged. Therefore, the company has included subsequent treatment in the base case and modelled it as a basket containing IVIg, PLEX and SoC only. The proportion of patients on each treatment remains constant over time as a steady state (snapshot in time) but would in reality represent patients moving between IVIg, PLEX and standard of care only (described in supporting document Section 3.1.5). The subsequent treatment basket has been assumed to be the same for the intervention and comparator, consistent with the approach described by the committee for TA1069. In section 3.15 of the final draft guidance document of TA1069, “the committee agreed the most reasonable approach would model the same proportions of people having plasma exchange and IVIg in both arms. That would mean that people who stop efgartigimod would have the same sequence of IVIg and plasma exchange as the comparator arm”. UCB also acknowledges the statements (3.12) from patient and clinical experts that gMG requires lifelong management. A recent Delphi panel survey was conducted, including 9 clinical experts in gMG from across England (n=8) and Scotland (n=1). The experts were asked in the first round to provide estimates of subsequent treatments following IVIg and PLEX. They were then provided the mean values of these estimates and were asked whether they agreed. Consensus was achieved in nearly all estimates; please see the supporting reference for full methodology and results.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

	These proportions were then applied to proportions of patients receiving IVIg, PLEX, and SoC (CSs/NSISTs in a revised population from the efgartigimod EAMS study. In this study, only 37 of the 48 patients were classed as refractory. Therefore, 11 patients were removed from the cohort for the purpose of this appraisal, which included three patients receiving no treatment and eight receiving CSs only, all of which are unlikely to be refractory patients and/or would be ineligible for treatment with rozanolixizumab, which is licensed as an add-on treatment. Please see Section 3.3.4.2 of the supporting document for further details on this revised cohort. The results from the two-round Delphi panel survey were recent, robust, and achieved consensus. Therefore, they were preferred to previous other expert elicitation results for subsequent treatment, which is why they were used in the base case. However, scenario analyses were performed to explore different subsequent treatment scenarios: • With subsequent treatment excluded • With the Delphi results weighted by the number of patients treated by each expert • With proportions informed by a separate expert elicitation exercise involving individual interviews with four UK clinical experts in treating gMG, and • With the incorporation of rituximab as a subsequent treatment within the Delphi-obtained proportions. Please see the supporting document for full methods and results.
10. Response assessment timepoint of 6 weeks (Section 3.14 in the draft guidance)	Thank you for your comments. UCB agrees with a response assessment timepoint of 3 weeks for IVIg and PLEX and 6 weeks for rozanolixizumab, as defined in the draft guidance document, and has made the required changes to the cost-effectiveness model.
11. Administration costs of IVIg and PLEX applied every 4 weeks (Section 3.16 in the draft guidance)	Thank you for your comments. UCB agrees with the committee's assumptions and has made the required changes to the cost-effectiveness model.
12. Uncaptured benefits: adverse events (steroid cost and utility)	Patients have testified that treatments for gMG are associated with side effects, which are sometimes severe and life limiting, and it is particularly difficult to manage the side effects of multiple treatments simultaneously (DG Section 3.1).

Please return to: **NICE DOCS**

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

	A substantial proportion of patients with gMG rely on corticosteroids as part of their treatment regimen. Long-term use of CSs is associated with serious adverse effects, including diabetes, obesity, hypertension, osteoporosis, glaucoma, cataracts, and increased susceptibility to infections. These complications compromise patient quality of life and impose significant economic burden not only to patients but to the NHS and social care. UCB believes it is important to quantitatively account for the burden of CSs in terms of cost and quality of life impact to truly reflect the benefits of rozanolixizumab. It is unlikely that the utility decrement associated with corticosteroid use is captured in the EuroQol 5-dimensions (EQ-5D) scores. They are taken from a relatively short-term clinical trial, and are therefore unlikely to capture the longer-term adverse events and comorbidities associated with corticosteroid use and therefore the benefit of a treatment being corticosteroid sparing. In addition, as EQ-5D is a generic measure, it may not be sensitive to some of the utility impacts associated with corticosteroid induced comorbidities, such as weight gain, poor vision, hair loss, and skin disorders as well as some aspects of mental health problems associated with corticosteroids. Due to the rarity of gMG and the paucity of data in this therapy area, data from Sullivan et al (40) and Brexelius et al (41) from systemic lupus in the UK have been used as a proxy to quantitatively estimate the utility impact of steroid use in this appraisal. This is also consistent with the application of corticosteroid costs in the modelling. Please see the supporting information document for further details on how the corticosteroid disutility and costs were calculated and applied.
13. Uncaptured benefits: fatigue	It is unlikely that the full impact of fatigue on uncontrolled patients with gMG is captured in the EQ-5D scores, since EQ-5D is a generic measure. A report by the Office of Health Economics (OHE) suggests that generic measures of health-related quality of life (HRQoL) may fail to reflect what matters to patients by not capturing symptoms such as fatigue (42). In addition, the EQ-5D may miss changes in quality of life (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 (42). 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 (43, 44).

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

	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 (45-52). The DG cites highly variable and unpredictable fatigue experienced by patients with gMG, and that gMG substantially affects daily activities and the person's ability to work (7). Fatigue is also associated with increased depressive symptoms (53). It was shown in MG0003 that physical fatigue, as measured by the MGSPRO 'physical fatigue' score, improved significantly with rozanolixizumab compared with placebo (original submission document, Section B.2.6.1.2), which was maintained through MG0007 (original submission, Section B.2.6.2.2).
14. Uncaptured benefits: convenience with short-duration sc infusion	Patient experts have testified that regular hospital visits or stays with IVIg and PLEX can be difficult to fit around work and family commitments and place a substantial burden on carers (DG Section 3.1). Adverse events are also problematic with one patient expert having to stop treatment with PLEX due to the catheter line causing a blood clot (DG Section 3.1). Expert patients thought that rozanolixizumab, as a short-duration subcutaneous infusion, would be more convenient and could improve adherence (DG Section 3.21) There are benefits to both patients (improved quality of life) and the NHS (reduced healthcare resource utilisation) associated with subcutaneous administration, compared with highly burdensome intravenous administration of treatments such as IVIg and PLEX. PLEX and IVIg are also associated with the risk of rare but life-threatening side effects (such as infection, hypotension with anaphylactic shock, venous access issues, and thrombosis) (3, 4, 54, 55). A study in patients with multiple sclerosis showed that 87.8% of patients preferred subcutaneous administration over intravenous, and 82.9% of patients specified "requires less time in the clinic" as the reason for the preference for subcutaneous administration (56). There remains limited data relating to the difference in utility between intravenous and subcutaneous administration, but of the few studies found, the increment ranges from 0.03 to 0.12 (57-63).

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

15. Uncaptured benefits: incorporation of administration/patient time	Travel time and treatment administration time for IVIg and PLEX are a burden to patients and caregivers as they may interfere with work or family care responsibilities. Administration time for IVIg and PLEX is also burdensome for the NHS as it utilises healthcare resources that could be directed to other patients. A micro-costing approach was used to estimate the time per initial administration and the time per subsequent administration per year for consultants, nurses, administrative support, and patients. It showed that, on average, [redacted] hours of NHS resources (consultant, nurse and administrative support time) per patient per year were required for rozanolixizumab, compared with [redacted] for IVIg and [redacted] for PLEX. This shows that the use of rozanolixizumab will have markedly lower NHS staff time requirements (and costs) compared with IVIg, PLEX. If 1,375 of 4,338 patients with refractory gMG in the UK were to receive rozanolixizumab or zilucoplan instead of IVIg and PLEX over 5 years, 9,938 hours of consultant time, 628,009 hours of nurse time, and 66,750 hours of administrative support would be saved (27). In terms of patient time per year, [redacted] hours were needed for rozanolixizumab, [redacted] for IVIg and [redacted] for PLEX. This is likely to have a large impact on patient quality of life as well as working time productivity.
16. Uncaptured benefits: carer cost and disutilities (Section 3.21 in the draft guidance)	Myasthenia gravis is associated with a significant carer burden. The burden to families of patients with gMG and carers was highlighted by expert patients at the appraisal committee meeting (ACM) on 14 August 2024. Caregiver burden (time spent caring for a patient with gMG) by MG-ADL range, including costs and disutilities, has now been included as an option in the updated model and a scenario has been provided with this option included (please see the supporting document).
17. Uncaptured benefits: societal costs (Section 3.21 in the draft guidance)	In the ACM on 14 August 2024, expert patients and clinicians highlighted how gMG is associated with a societal and humanistic burden as it affects patients' ability to work and spend time with their family and friends. Societal costs for patients (work time lost) by MG-ADL range has now been included as an option in the updated model. The company recommends that expert patients and clinicians are invited to present at ACM2 so that detailed perspectives can be shared on the burden that both generalised myasthenia gravis and the currently available treatments have on patients, carers, and the NHS.

Insert extra rows as needed

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

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Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

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Please return to: **NICE DOCS**

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 25 October 2024. Please submit via NICE Docs.

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Overview of new evidence and modelling updates and results

1. Executive summary

In the draft guidance published by NICE for rozanolixizumab for treating patients with AChR or MuSK antibody-positive generalised myasthenia gravis (gMG), the committee has requested the following:

- Updated cost-effectiveness model that seeks to address subsequent treatments and other uncaptured benefits of rozanolixizumab (Section 3.1)
- An updated systematic literature review to evaluate the efficacy of treatment with IVIg and PLEX in gMG, including both randomised controlled trials and observational studies (Section 2.3)
- New indirect treatment comparison methodologies (bivariate NMA [bvNMA] and baseline risk-adjusted [BLRA] NMA) (Sections 2.4 and 2.5)
- An expert elicitation exercise to clarify the positioning of rituximab in the treatment pathway for patients with AChR and MuSK antibody-positive gMG (Section 2.2)
- A Delphi panel to determine the proportion of index treatment and subsequent treatment (Section 3.1.6)
- The final results from the extension phase of MG0007 for rozanolixizumab (Section 2.1)
- Data from MG0007 on the proportion of patients reaching MSE on rozanolixizumab (Sections 2.1.2.10 and 3.1.5).

This document includes an overview of new evidence for rozanolixizumab (Section 2) referred to in the draft guidance comments form. Section 3 presents updates made to the model following the draft guidance consultation. This document only presents key results and additional details can be found in the supporting files that were submitted (i.e. SLR report, expert elicitation survey, NMA report and log of changes to the CEM, which is embedded in the CEM).

A 13-question survey was designed to elicit clinical expert opinion on the use of rituximab in England in both AChR Ab+ and MuSK Ab+ patients, and on the use of subsequent treatments following maintenance IVIg, maintenance PLEX, and neonatal Fc receptor (FcRn) inhibitors. All 11 MG specialists who responded to the survey used rituximab in NHS clinical practice, although one respondent stated that they did not use it in AChR Ab+ patients. Nearly all respondents would use rituximab before maintenance IVIg and PLEX in both AChR and MuSK Ab+ patients. The experts stated that rituximab use has moved to earlier in the treatment pathway over time (since the RINOMAX study (1)) and is used earlier in patients with explosive-onset disease. None of the respondents would choose to use rituximab at the same point in the treatment pathway where a targeted therapy might be considered as an alternative to maintenance IVIg or PLEX.

A systematic literature review (SLR) was conducted in September 2024 to identify all published evidence for IVIg and PLEX (including randomised controlled trials, observational

studies and other data sources such as single arm and phase 2 studies, as requested by NICE). In total, 11 publications were included: three RCTs and eight observational studies. Of these, six were included in the NMAs and used in the economic model.

The findings of the ITCs conducted (bivariate NMA, baseline risk-adjusted [BLRA] NMA and conventional NMA) all demonstrate that rozanolixizumab is significantly better than standard of care (SoC) alone in patients with gMG. Rozanolixizumab is associated with a numerically larger proportion of treatment responders compared with IVIg and PLEX, and has demonstrated a larger change from baseline compared with IVIg and PLEX (statistically significant versus IVIg). Despite data limitations causing uncertainty in the results with wide credible intervals, there is general concordance with point estimates across the analyses (conventional NMA, bivariate NMA, BLRA NMA, and naive comparison).

Section 3.3 provides the results of the cost-utility analysis utilising the base-case settings described in Section 3.2 as well as the results of scenario analyses. In the base-case, rozanolixizumab [redacted]. The results of the probabilistic sensitivity analysis and scenario analyses were consistent with the base-case. The deterministic sensitivity analysis identified that the price of rozanolixizumab was the largest driver for both comparisons.

The additional analyses discussed in this response were conducted to aid decision making and decrease the uncertainty around the ICER. Given the paucity of data in refractory gMG, UCB have conducted multiple analyses to reduce uncertainty as far as possible with the limited data available. UCB asks that the findings submitted as part of this response are taken into consideration, to avoid a scenario where an efficacious and cost-effective treatment, for a population with a high unmet need, receives a negative decision due to a lack of data on comparator treatments.

There is an urgent unmet need for a new treatment option for patients with acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) antibody-positive refractory generalised myasthenia gravis (gMG) who are not sufficiently responding to standard therapy, such as acetylcholinesterase inhibitors (AChEIs), corticosteroids (CS), non-steroidal immunosuppressants (NSISTs), and /or rituximab. The only available treatment options in England and Wales for gMG patients who are refractory to standard therapies are regular intravenous courses of immunoglobulin (IVIg) and plasma exchange (PLEX). As mentioned in the draft guidance (DG), IVIg and PLEX both pose a significant treatment burden for the patient and are resource-intensive for the healthcare system. Patients on IVIg and/or PLEX typically attend hospital every 4 weeks, which equates to annual NHS staff time commitment (including consultants, nurses, and administrative support) of [redacted] and [redacted] hours for IVIg and PLEX, respectively, and [redacted] and [redacted] hours of patient time, respectively. Patient testimony submitted to this appraisal underscored the negative impact inpatient visits for PLEX treatment had on her mental health and on that of her child (pre-committee papers, patient expert perspective). Patients also highlighted the side effects associated with IVIg and PLEX treatment, with one patient expert having to stop treatment due to the permanent catheter causing a blood clot (Section 3.1 DG).

2. New evidence

2.1. MG0007 final data cut

2.1.1. Methodology

Full details on study design and methodology for MG0007 were provided in the company submission (CS) (Section B.2.3.1), as were patient demographic and baseline characteristics (Section B.2.3.1.1).

2.1.1.1. Patient disposition

As reported in the CS, a total of [redacted] study participants received rozanolixizumab in Cycle [redacted]: [redacted] study participants were allocated to the rozanolixizumab ≈7 mg/kg group and [redacted] to the rozanolixizumab ≈10 mg/kg group (Table 1).

A total of [redacted] study participants completed the study, while the remaining [redacted] discontinued the study permanently. The most common reason for study discontinuation was 'other' ([redacted] study participants), followed by adverse event ([redacted] study participants) and withdrawal by study participant ([redacted] study participants) (Table 1).

Table 1: Patient 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			
Other	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]
Withdrawal by study participant	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; AE, adverse event.
Note: Started study was defined as signing informed consent. Completed study was defined as having completed all phases of the study including the Observation Period and the End of Study Visit.

2.1.2. Efficacy results: Secondary efficacy outcomes

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).

Data for the first four cycles of treatment were presented in the CS (Section B.2.6.2.2).

2.1.2.1. 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 [redacted] and continued through to Day [redacted]. Clinically relevant reductions from baseline in MG-ADL score were consistently observed with repeated cyclic treatment (Figure 1).

Figure 1: MG-ADL score: Mean change from baseline to each scheduled assessment†

[redacted]

Abbreviations: BL, baseline; MG-ADL, myasthenia gravis activities of daily living; RLZ, rozanolixizumab.
† Data taken from pool E1 dataset, study participants having at least two symptom-driven cycles (n=129).

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

Improvements (reductions from Baseline) in the MG-C score were observed at all timepoints through to Day 43 in both rozanolixizumab treatment groups. Clinically relevant reductions from baseline in MG-C score were consistently observed with repeated cyclic treatment (Table 2).

Table 2: MG-C score CFB to Day 43 during each treatment cycle (safety set)

Cycle	Rozanolixizumab ≈7 mg/kg N=[redacted]			Rozanolixizumab ≈10 mg/kg N=[redacted]			Rozanolixizumab total N=[redacted]		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[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 cycle treatment group.
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.

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

Improvements (reductions from Baseline) in the QMG score were observed at all timepoints through to Day 43 in both rozanolixizumab treatment groups. Clinically relevant reductions from baseline in QMG score were consistently observed with repeated cyclic treatment (Table 3).

Table 3: QMG score CFB to Day 43 during each treatment cycle (safety set)

Cycle	Rozanolixizumab ≈7 mg/kg N=			Rozanolixizumab ≈10 mg/kg N=			Rozanolixizumab total N=		
	n	Mean	SD	n	Mean	SD	n	Mean	SD

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 cycle treatment group.
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.

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

Improvements (reductions from Baseline) in MGSPRO "Muscle Weakness Fatigability" score from Baseline to Day 43 were observed in both rozanolixizumab treatment groups. Reductions from baseline in MGSPRO "Muscle Weakness Fatigability" score were consistently observed with repeated cyclic treatment (Table 4).

Table 4: MGSPRO "Muscle Weakness Fatigability" score CFB to Day 43 during each treatment cycle (safety set)

Cycle	Rozanolixizumab ≈7 mg/kg N=[redacted]			Rozanolixizumab ≈10 mg/kg N=[redacted]			Rozanolixizumab total N=[redacted]		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[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 cycle treatment group.
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.

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

Improvements (reductions from Baseline) in MGSPRO "Physical Fatigue" score from Baseline to Day 43 were observed in both rozanolixizumab treatment groups. Reductions from baseline in MGSPRO "Physical Fatigue" score were consistently observed with repeated cyclic treatment (Table 5).

Table 5: MGSPRO "Physical Fatigue" score CFB to Day 43 during each treatment cycle (safety set)

Cycle	Rozanolixizumab ≈7 mg/kg N=[redacted]			Rozanolixizumab ≈10 mg/kg N=[redacted]			Rozanolixizumab total N=[redacted]		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
[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 cycle treatment group.
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.

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

Improvements (reductions from Baseline) in MGSPRO "Bulbar Muscle Weakness" score from Baseline to Day 43 were observed in both rozanolixizumab treatment groups. Reductions from baseline in MGSPRO "Bulbar Muscle Weakness" score were consistently observed with repeated cyclic treatment (Table 6).

Table 6: MGSPRO "Bulbar Muscle Weakness" score CFB to Day 43 during each treatment cycle (safety set)

Cycle	Rozanolixizumab ≈7 mg/kg N=[redacted]			Rozanolixizumab ≈10 mg/kg N=[redacted]			Rozanolixizumab total N=[redacted]		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
[redacted]									

Cycle	Rozanolixizumab ≈7 mg/kg N=[redacted]			Rozanolixizumab ≈10 mg/kg N=[redacted]			Rozanolixizumab total N=[redacted]		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[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 cycle treatment group.
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.

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

Consistently high MG-ADL responder rates were observed with repeated cyclic treatment throughout the first [redacted] treatment cycles (Figure 2). High response rates were observed as early as Day [redacted] (first post Baseline efficacy assessment) and continued to increase to Day [redacted] in each of treatment cycle.

Figure 2: Observed MG-ADL responder rates at Day 43 for cycles 1–9†

[redacted]

† Data taken from pool E1 dataset, study participants having at least two symptom-driven cycles (n=129).
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 treatment cycle

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

Median time to first MG-ADL response was ~2 weeks for the majority of each of the first twelve 6-week treatment cycles (Table 7).

Table 7: Time to MG-ADL response during each treatment cycle (safety set)

Cycle	Rozanolixizumab ≈7 mg/kg N=[redacted]		Rozanolixizumab ≈10 mg/kg N=[redacted]		Rozanolixizumab total N=[redacted]	
	n	Median (95% CI), days	n	Median (95% CI), days	n	Median (95% CI), days
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[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 treatment 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.

2.1.2.9. MG-ADL improvements over time

Across consecutive symptom-driven cycles of rozanolixizumab, improvement from baseline in MG-ADL over time was maintained until end of treatment. Improvements in symptoms with repeated cycles stabilised at approximately a 3-point decrease in MG-ADL compared with baseline (Figure 3).

Figure 3: Mean MG-ADL change from baseline over time in patients who receive consecutive symptom-driven cycles of rozanolixizumab†

† Data taken from pool E3 dataset, study participants having at least two consecutive symptom-driven cycles (n=121).
Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; RLZ, rozanolixizumab; SE standard error.

2.1.2.10. Minimal symptom expression

Minimal symptom expression (MSE) is designed to assess how many study participants become free or virtually free of MG symptoms, defined as achieving an MG-ADL score of 0 or 1 at any time during the Treatment Period and Observation Period (up to 16 weeks). The proportion of study participants achieving MSE across all cycles was [redacted]% (Table 8).

Table 8: Patients achieving MSE in each treatment cycle (Safety set)

Cycle	Rozanolixizumab ≈7 mg/kg N=[redacted]	
	n	MSE achieved, n (%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Cycle	Rozanolixizumab ≈7 mg/kg N=[redacted]	
	n	MSE achieved, n (%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; MG-ADL, myasthenia gravis activities of daily living.
Note: Percentages are based on the number of participants with MG-ADL data in the safety set.
Note: Participants are grouped according to the actual dose level received in the proceeding study cycle.

2.1.2.11. Use of rescue therapy during the study

Rescue therapy during MG0007 was defined as the use of IVIg, PLEX, or intravenous steroids. A total of [redacted] study participants in the rozanolixizumab ≈7 mg/kg group received rescue therapy. [redacted] needed rescue therapy in [redacted] out of the first 12 treatment cycles.

2.1.3. Safety results

2.1.3.1. Exposure to rozanolixizumab

Overall, [redacted] treatment cycles in [redacted] study participants were included in the Safety set. The mean annualised number of infusions was [redacted] and the mean annualised number of treatment cycles was [redacted]. The median time in study was [redacted] months, with [redacted] study participants enrolled in the study for [redacted] year and [redacted] for [redacted] years.

A total of [redacted] study participants received rozanolixizumab ≈7 mg/kg in Cycle [redacted], with [redacted] study participants continuing to receive rozanolixizumab ≈7 mg/kg in subsequent cycles. [redacted] study participants switched to rozanolixizumab ≈10 mg/kg in subsequent cycles.

A total of [redacted] study participants received rozanolixizumab ≈10 mg/kg in Cycle [redacted], with [redacted] study participants continuing to receive rozanolixizumab ≈10 mg/kg in subsequent cycles. [redacted] study participants switched to rozanolixizumab ≈7 mg/kg in subsequent cycles.

No trends were observed regarding the timing of dose switches.

2.1.3.2. Overview of treatment-emergent adverse events

A total of [redacted] treatment-emergent adverse events (TEAEs) were reported in [redacted] study participants. For any TEAEs, serious TEAEs, treatment-related TEAEs, severe TEAEs, TEAEs leading to discontinuation from the study, and TEAEs leading to permanent discontinuation of rozanolixizumab, there was a higher incidence in the rozanolixizumab ≈10 mg/kg group than in the ≈7 mg/kg group (Table 9).

Overall, there was no increase in the incidence of TEAEs in any of the categories reported from cycle to cycle. The incidence of serious adverse events (SAEs) and TEAEs leading to study or study treatment discontinuation remained low (<[redacted]) with repeated cyclic treatment. Within each treatment cycle the incidence of any TEAEs were generally higher in the rozanolixizumab ≈10 mg/kg group than in the ≈7 mg/kg group up to Cycle [redacted]. The numbers of study participants beyond Cycle [redacted] were too low to draw any conclusions.

Table 9: 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 AE	[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]
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; N, number of study participants reporting at least 1 TEAE in that category; 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.

2.1.3.3. Most common TEAEs

Overall, the system organ classes (SOCs) with an incidence ≥[redacted] were infections and infestations ([redacted] study participants) and nervous system disorders ([redacted] study participants).

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. Diarrhoea was the second most frequently reported TEAE ([redacted] and [redacted] in the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg group, respectively), followed by COVID-19 ([redacted] and [redacted] in the rozanolixizumab ≈7 mg/kg and ≈10 mg/kg group, respectively).

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]

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]
Nausea	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Blood immunoglobulin G decreased	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Myasthenia gravis	[redacted]	[redacted]	[redacted]

Abbreviations: ≈, equivalent dose; COVID-19, coronavirus disease 2019; [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.

2.1.3.4. Deaths

In total [redacted] deaths were reported. [redacted] were due to a TEAE ([redacted] events of COVID-19 and [redacted] of cardiac failure) and [redacted] was due to a TEAE (pneumonia) and non-TEAE events (Table 10). All deaths were assessed as not related to rozanolixizumab.

Table 10: Overview of all deaths

Participant	Treatment	Days since first/most recent RLZ infusion	Preferred term
1	Cycle [redacted]; ≈10 mg/kg	[redacted]	COVID-19 (TEAE)
2	Cycle [redacted]; ≈10 mg/kg	[redacted]	COVID-19 pneumonia (TEAE)
3	Cycle [redacted]; ≈7 mg/kg	[redacted]	Pneumonia (TEAE) Acute kidney injury (non-TEAE) Acute respiratory failure (non-TEAE)

Participant	Treatment	Days since first/most recent RLZ infusion	Preferred term
			Cardiac failure (non-TEAE) Acute respiratory distress syndrome (non-TEAE)
4	Cycle [redacted]; ≈10 mg/kg	[redacted]	Cardiac failure (TEAE)
5	[redacted]	[redacted]	Myocardial infarction (non-TEAE)
6	Cycle [redacted]; ≈7 mg/kg	[redacted]	Small cell lung cancer metastatic (non-TEAE)

† The participant enrolled in MG0007 but withdrew from the study due to lack of efficacy.
Abbreviations: ≈, equivalent dose; COVID-19, coronavirus disease 2019; RLZ, rozanolixizumab; TEAE, treatment-emergent adverse event.

2.2. Use of rituximab in the NHS

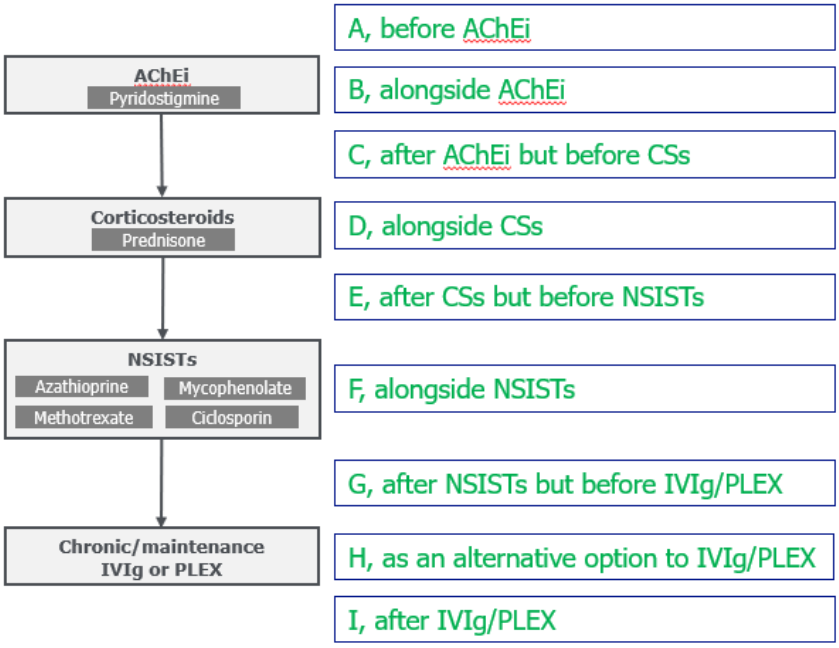
NICE requested that the company undertake expert elicitation to fully understand the use of rituximab in NHS practice, including whether rituximab is currently used and in what proportions of patients, where in the pathway rituximab is used, whether rituximab is used as a subsequent treatment, and any variation in its use in practice. A survey was conducted to gain further insight and clarification on the use of rituximab in England for gMG. The 13-question online survey link was sent to all specialist myasthenia gravis centres in the UK (11 clinicians). Full methodology and results are reported in the supporting report provided as a separate reference.

2.2.1. Respondents and patients

Survey responses were received from all 11 (100%) MG experts in the UK who were sent the survey. There was good representation from different regions of England, including two from Greater London, two from South East, two from East Midlands, one from West Midlands, two from North West and one from North East. One respondent did not disclose the region in which their NHS clinical practice was based; one respondent was from Scotland, which was not an option in the survey so it is assumed that this respondent is from Scotland. The experts treated a mean (range) of approximately 285 (100–600) adult patients per year with gMG, including Myasthenia Gravis Foundation of America (MGFA) classes II to IV and excluding patients with ocular MG only. The mean proportions of these patients who are AChR and MuSK Ab+ were 90% and 5%, respectively. The mean proportion of patients who are refractory, defined for the purpose of the survey as without adequate response to standard treatments (including acetylcholinesterase inhibitors [AChEIs], CSs, and NSISTs), was 12%. The mean proportions of refractory patients who are AChR and MuSK Ab+ were 92% and 5%, respectively.

All respondents (11, 100%) stated that they currently use rituximab to treat gMG patients in their clinical practice. Survey participants were shown a treatment pathway diagram and asked at what stage they would use rituximab for both AChR Ab+ and MuSK Ab+ patients (Figure 4).

Figure 4: Treatment pathway showing options for the position of rituximab use

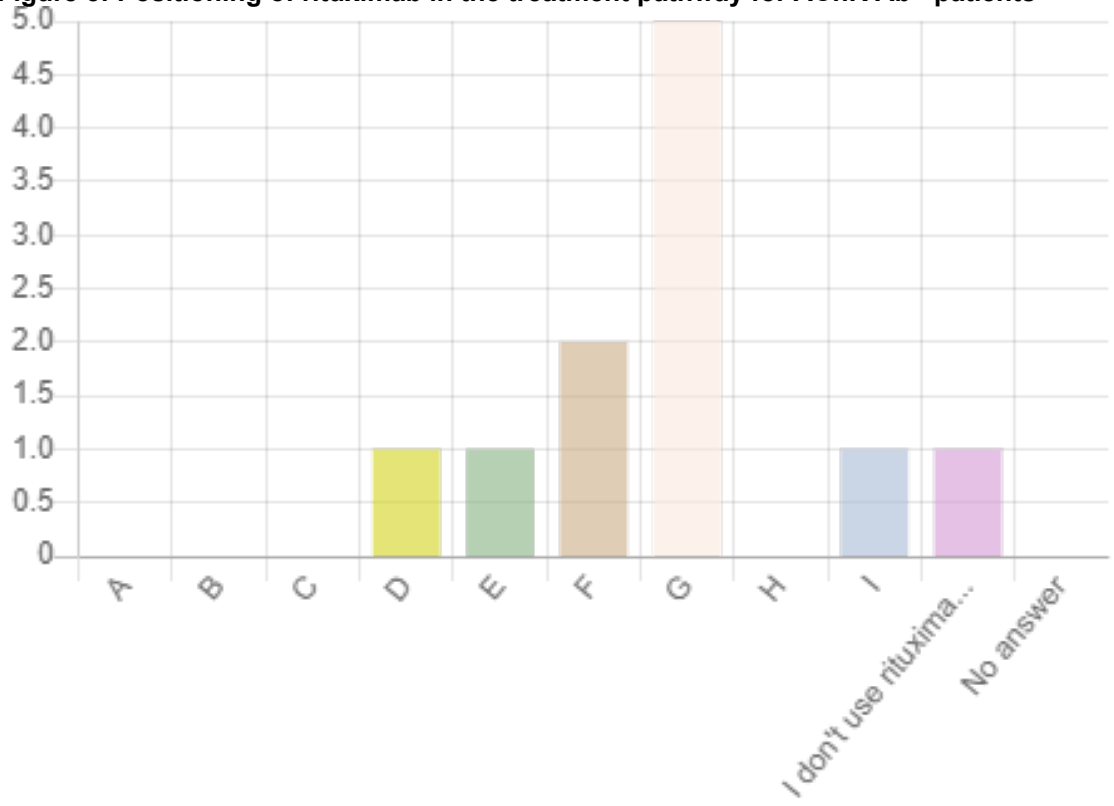


Abbreviations: AChEi, acetylcholinesterase inhibitor; CS, corticosteroid; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant therapy; PLEX, plasma exchange.

2.2.2. AChR Ab+ patients

One respondent stated that they did not use rituximab in AChR Ab+ patients. Amongst the remaining 10 survey respondents, five (50%) would use rituximab at position 'G' (i.e. after NSISTs but before maintenance IVIg/PLEX), one would use rituximab at position I (i.e. after maintenance IVIg/PLEX), and the remaining four (including the respondent from Scotland) all positioned rituximab alongside NSISTs or earlier (before IVIg/PLEX; Figure 5).

Figure 5: Positioning of rituximab in the treatment pathway for AChR Ab+ patients†



† The full response in purple (one respondent) was: 'I don't use rituximab in AChR Ab+ patients'.
Abbreviations: Ab+, antibody-positive; AChR, acetylcholine receptor.

The proportion of patients being treated with rituximab in the corresponding population (i.e. the position in the treatment pathway that the respondent chose) varied widely, between 0 and 90%.

Additional considerations included:

- Rituximab may be used earlier in explosive-onset patients
- Rituximab use has changed over time, moving to earlier in the treatment pathway, depending on comorbidities and explosive-onset
- There has been a change in practice since the RINOMAX study (1) and rituximab is now offered with CSs if patients have been admitted to hospital and/or have required rescue treatment.

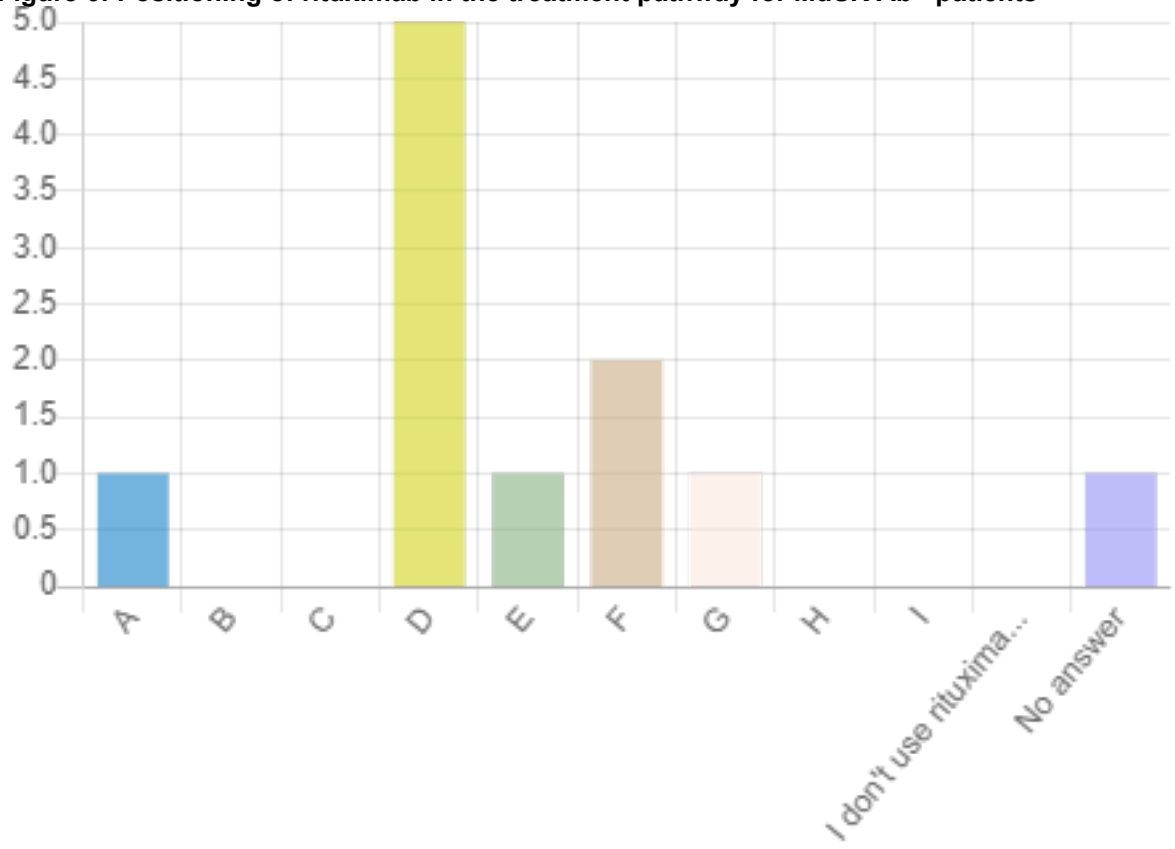
If, in the future, a targeted therapy was to become available, six (55%) respondents (including the respondent from Scotland) would use the targeted therapy before using rituximab, and five (45%) would use the targeted therapy after using rituximab in AChR Ab+ patients. The respondent from Scotland added that this would depend on the mode of action, since the effect of antibodies on the neuromuscular junction is multi-faceted, and focussing on one pathway may not necessarily be the answer to the therapeutic approach.

2.2.3. MuSK Ab+ patients

All the respondents who answered the question on the use of rituximab in MuSK Ab+ patients (n=10) would use it at position G (i.e. after NSISTs but before maintenance

IVIg/PLEX) or earlier, with five (50%) respondents (including the respondent from Scotland) using it alongside CSs (Figure 6).

Figure 6: Positioning of rituximab in the treatment pathway for MuSK Ab+ patients†



† The respondent who answered 'A' added a comment that rituximab would be used very early but after PLEX, and that PLEX is to treat acute bulbar and respiratory symptoms in advance of benefit from rituximab.
Abbreviations: Ab+, antibody-positive; MuSK, muscle-specific kinase.

The proportion of patients being treated with rituximab in the corresponding population (i.e. the position in the treatment pathway that the respondent chose) varied widely, between 0 and 100%.

Additional considerations included:

- Rituximab is very effective in MuSK Ab+ patients
- There are very small numbers of MuSK Ab+ patients
- Rituximab would also be used in explosive-onset patients
- There has been a change in practice following the NHSE commissioning guidelines (2).

If, in the future, a targeted therapy was to become available, four (36%) respondents (including the respondent from Scotland) would use the targeted therapy before using rituximab, and seven (64%) would use the targeted therapy after using rituximab in MuSK Ab+ patients. The respondent from Scotland added that this would depend on the mode of action, since the effect of antibodies on the neuromuscular junction is multi-faceted, and focussing on one pathway may not necessarily be the answer to the therapeutic approach.

2.2.4. Use of rituximab as a subsequent treatment following maintenance IVIg

2.2.4.1. AChR Ab+ patients

When a patient with refractory MuSK Ab+ gMG does not respond to maintenance IVIg, five (45%) respondents would use PLEX as a subsequent treatment, five (45%, including the respondent from Scotland) would use rituximab, and one (9%) would re-treat with IVIg.

2.2.4.2. MuSK Ab+ patients

When a patient with refractory AChR Ab+ gMG does not respond to maintenance IVIg, seven (64%, including the respondent from Scotland) respondents would use rituximab as a subsequent treatment and four (36%) would use PLEX.

2.2.4.3. Response to subsequent treatment

When asked whether the response to the next treatment would be reduced in patients who had previously failed on maintenance IVIg compared with those who had not, four (36%) respondents said yes, three (27%) said no, and four (36%, including the respondent from Scotland) said that they were unsure. The respondent from Scotland commented that it would not be possible to predict response as it cannot be forecasted from phenotype, antibody type, antibody titre or thymus status. Amongst those who stated that the response would be reduced, the reduction was estimated to be between 0 and 60%.

2.2.5. Use of rituximab as a subsequent treatment following maintenance PLEX

2.2.5.1. AChR Ab+ patients

When a refractory AChR Ab+ gMG patient does not respond to maintenance PLEX, five (45%, or 71% of those who provided an answer, including the respondent from Scotland) respondents would use rituximab as a subsequent treatment and two (18%, or 29% of those who provided an answer) would use IVIg. Four respondents did not provide an answer to this question. The respondent from Scotland stated that it would be highly likely that rituximab would be used before chronic IVIg and PLEX, but that if they failed, rituximab would be trialled again.

2.2.5.2. MuSK Ab+ patients

When a refractory MuSK Ab+ gMG patient does not respond to maintenance IVIg, six (55%, or 75% of those who answered the question, including the respondent from Scotland) respondents would use rituximab as a subsequent treatment, one (9%, or 13% of those who answered the question) would use IVIg, and one (9%, or 13% of those who answered the question) would re-treat with PLEX. Three respondents did not provide an answer to the question. The respondent from Scotland stated that it would be highly likely that rituximab would be used before chronic IVIg and PLEX, but that if they failed, rituximab would be trialled again.

2.2.5.3. Response to subsequent treatment

Answers were varied to the question of whether the response to the next treatment would be reduced in patients who had previously failed to respond to PLEX compared with those who had not, with three (27%, or 43% of those who answered the question) respondents saying yes, three (27%, or 43% of those who answered the question, including the respondent from Scotland) saying no, and one (9%, or 14% of those who answered the question) saying that they were unsure. Four respondents did not provide an answer to the question. Amongst

those who stated that the response would be reduced, the reduction was estimated to be between 0 and 80%.

2.2.6. Use of rituximab as a subsequent treatment following FcRn

In total, 10 of the 11 (91%, including the respondent from Scotland) respondents had treated adult patients with gMG with FcRn inhibitors. All 10 respondents, including the respondent from Scotland, had treated with an FcRn inhibitor as part of routine clinical practice (via Early Access to Medicines Scheme [EAMS]), with two respondents saying that they had also treated patients as part of a clinical trial. The mean (range) number of patients treated with FcRn inhibitors was 9 (range, 3–25).

2.2.6.1. AChR Ab+ patients

If FcRn inhibitors were available, and a patient with refractory AChR Ab+ gMG did not respond to the FcRn inhibitor, five (45%, or 63% of those who answered the question) respondents would use rituximab as a subsequent treatment, two (18%, or 25% of those who answered the question) would use IVIg, and the respondent from Scotland (9%, or 13% of those who answered the question) would use PLEX. Three respondents did not provide an answer to the question.

2.2.6.2. MuSK Ab+ patients

If FcRn inhibitors were available, and a patient with refractory MuSK Ab+ gMG did not respond to the FcRn inhibitor, seven (64%, or 88% of those who answered the question) respondents would use rituximab as a subsequent treatment, and the respondent from Scotland (9%, or 13% of those who answered the question) would use PLEX. Three respondents did not provide an answer to the question.

2.2.6.3. Response to subsequent treatment

Answers were varied to the question of whether the response to the next treatment would be reduced in patients who had previously failed to respond to an FcRn inhibitor compared with those who had not, with two (18%, or 25% of those who answered the question) respondents saying yes, three (27%, or 38% of those who answered the question, including the respondent from Scotland) saying no, and 3 (27%, or 38% of those who answered the question) saying that they were unsure. Three respondents did not provide an answer to the question. Of those who stated that the response would be reduced, the reduction was estimated to be between 0 and 60%.

2.2.7. Conclusion

All respondents (11, 100%) currently use rituximab to treat MuSK-Ab+ gMG patients in their clinical practice, and 10 (91%) use rituximab in AChR-Ab+ gMG patients. In AChR Ab+ patients, nine (90%) respondents positioned rituximab before maintenance IVIg/PLEX, and one (10%) respondent would use rituximab after IVIg/PLEX. In MuSK-Ab+ gMG patients, all respondents would use rituximab before IVIg/PLEX. Rozanolixizumab would be positioned as an alternative to maintenance IVIg/PLEX, and none of the respondents positioned rituximab here, indicating that rituximab would not be a direct comparator to rozanolixizumab.

The proportion of patients being treated with rituximab in the corresponding population (i.e. the position in the treatment pathway that the respondent chose) varied widely among clinicians, ranging from 0% to 100%. The experts stated that rituximab use has moved to

earlier in the treatment pathway over time (since the RINOMAX study (25)) and is used earlier in patients with explosive-onset disease.

Despite the clinical experts placing rituximab earlier in the treatment pathway than IVIg and PLEX in all but one cases, some experts would also use rituximab as a subsequent treatment following non-response to IVIg, PLEX, and FcRn treatment. However, the responses varied greatly and no firm conclusion could be drawn on the use of rituximab as a subsequent treatment across centres.

2.3. Systematic literature review on IVIg and PLEX

A systematic literature review (SLR) was conducted in September 2024 to identify all published evidence for IVIg and PLEX (including randomised controlled trials, observational studies and other data sources such as single arm and phase 2 studies, as requested by NICE). In total, 11 publications were included: three RCTs and eight observational studies. Of these, six were included in the NMAs, with the bvNMA informing the economic model:

- Zinman et al, 2007, a randomised controlled trial (RCT) comparing IVIg (n=24) with placebo (n=27) in patients with MG
- Barth et al, 2011, a RCT comparing IVIg (n=41) with PLEX (n=43) in patients with MG
- Duan et al, 2023, an observational study comparing PLEX (n=62) with lymphoplasmapheresis (n=62) in patients with severe MG
- Barnett et al, 2017, an observational study comparing control (n=54) vs prednisone (n=50) vs IVIg/PLEX (n=45) in patients with MG
- Leng et al, 2024 is an observational study comparing PLEX (n=3) with Protein A immunoadsorption (n=4) in patients with MG
- NCT02473952, an RCT comparing IVIg (n=30) with placebo (n=32). After the date of the SLR searches, this study was published so was included in the NMA to inform a MG-ADL response rate for IVIg (related to Bril et al, 2024)

The full SLR report is provided as a supporting reference along with this document.

2.4. Bivariate NMA

A bivariate network meta-analysis was conducted, on recommendation from the committee to consider a multivariate analysis, to obtain estimates of relative differences in studies containing IVIg and PLEX that did not report MG-ADL outcomes so that they could be included in the network. The full methodology and results are included in the report supplied separately as a reference.

2.4.1. Responder outcomes

Responder data gives a percentage of patients achieving a minimum improvement from baseline. In the base case, the outcomes of interest were a ≥2-point improvement in MG-ADL score and ≥3-point improvement in QMG score, both of which are considered clinically meaningful.

A total of 12 studies were included in the responder network; six studies reported both MG-ADL and QMG responder data, five studies reported only QMG responder data at a threshold of ≥3 points of improvement, and one study only reported MG-ADL responder data for ≥3-point improvement.

The results for MG-ADL responder suggest a response probability of [redacted]% for rozanolixizumab, [redacted]% for IVIg and [redacted]% for PLEX. Despite the uncertainty, the results show that rozanolixizumab is significantly better than standard of care, whilst IVIg and PLEX are not.

2.4.2. Change from baseline outcomes:

Data for change from baseline in MG-ADL and QMG scores were assessed separately as continuous outcomes. A total of 18 studies were included in the network; 13 reported change from baseline in both MG-ADL and QMG scores and five studies only reported CFB QMG data.

The results for change from baseline (CFB) in MG-ADL score were [redacted] for rozanolixizumab, [redacted] for IVIg, and [redacted] for PLEX (Table 11). To calculate the total CFB in MG-ADL score, the CFB relative to standard of care was added to the calculated standard of care CFB in MG-ADL score [redacted]). The bvNMA results actually showed a worsening in MG-ADL score with IVIg; therefore, the standard of care value was assumed for IVIg.

Table 11: Change from baseline in MG-ADL score

Treatment	CFB relative to SoC	Total CFB score associated with stable response
SoC	Referent	[redacted]
RLZ	[redacted]	[redacted]
IVIg	[redacted]	[redacted]
PLEX	[redacted]	[redacted]
RTX	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; PLEX, plasma exchange; RTX, rituximab; SoC, standard of care.
* A positive value (worsening, [redacted]) was found so 0 was assumed.

2.5. Baseline risk-adjusted NMA

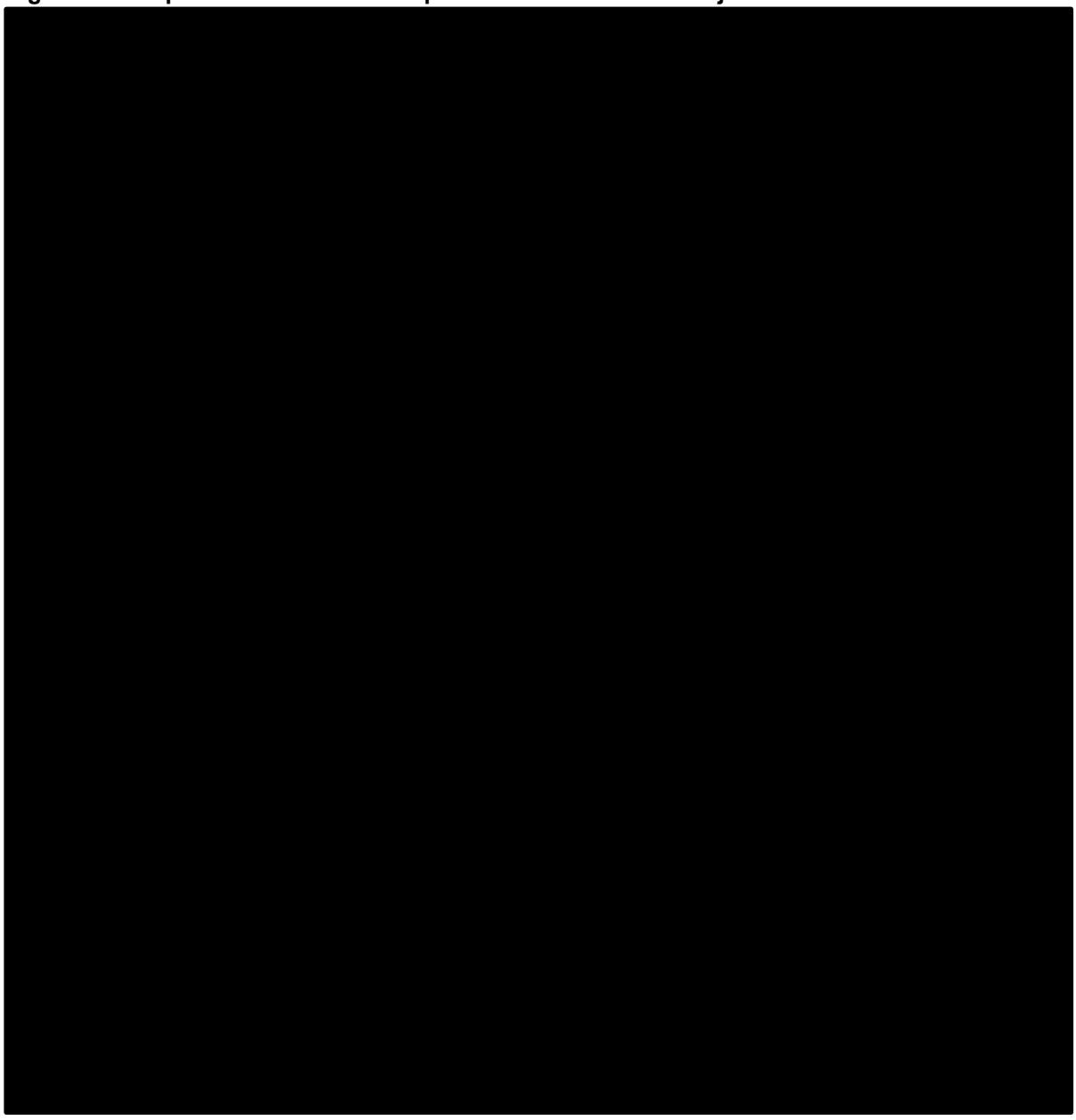
As proposed by the committee, to assess the probable impact of the difference in placebo response, a baseline risk-adjusted (BLRA) NMA was conducted as per the guidelines laid down by Dias et al (3). The primary outcome of interest was a 2-point MG-ADL response.

For MGADL responder outcome, a total of 8 studies (4-10) reported MGADL response at timepoint at which primary endpoint is reported, with no data available for IVIg and PLEX. For CFB MGADL outcome, a total of 13 studies (4-16) reported the data with two studies reporting data on IVIg compared with placebo.

Baseline risk, i.e. placebo response for all the 7 studies were obtained based on number of responders out of total number of patients. The overall mean of log odds based on individual log odds for each study was obtained. This mean acts as the mean covariate value based on which centring of the data is achieved. The analysis results were carried out with three methods for covariate via common covariate, exchangeable, and independent (17). In a common covariate, it is assumed that the covariate is the same for all the treatments whereas in an exchangeable covariate, it is assumed that the covariate is similar but from the same distribution. In the independent covariate, it is assumed that covariates are different and independent from each other. Results based on independent covariate assumption did not converge whereas it may be possible to estimate the exchangeable interaction model in equation with less data (3).

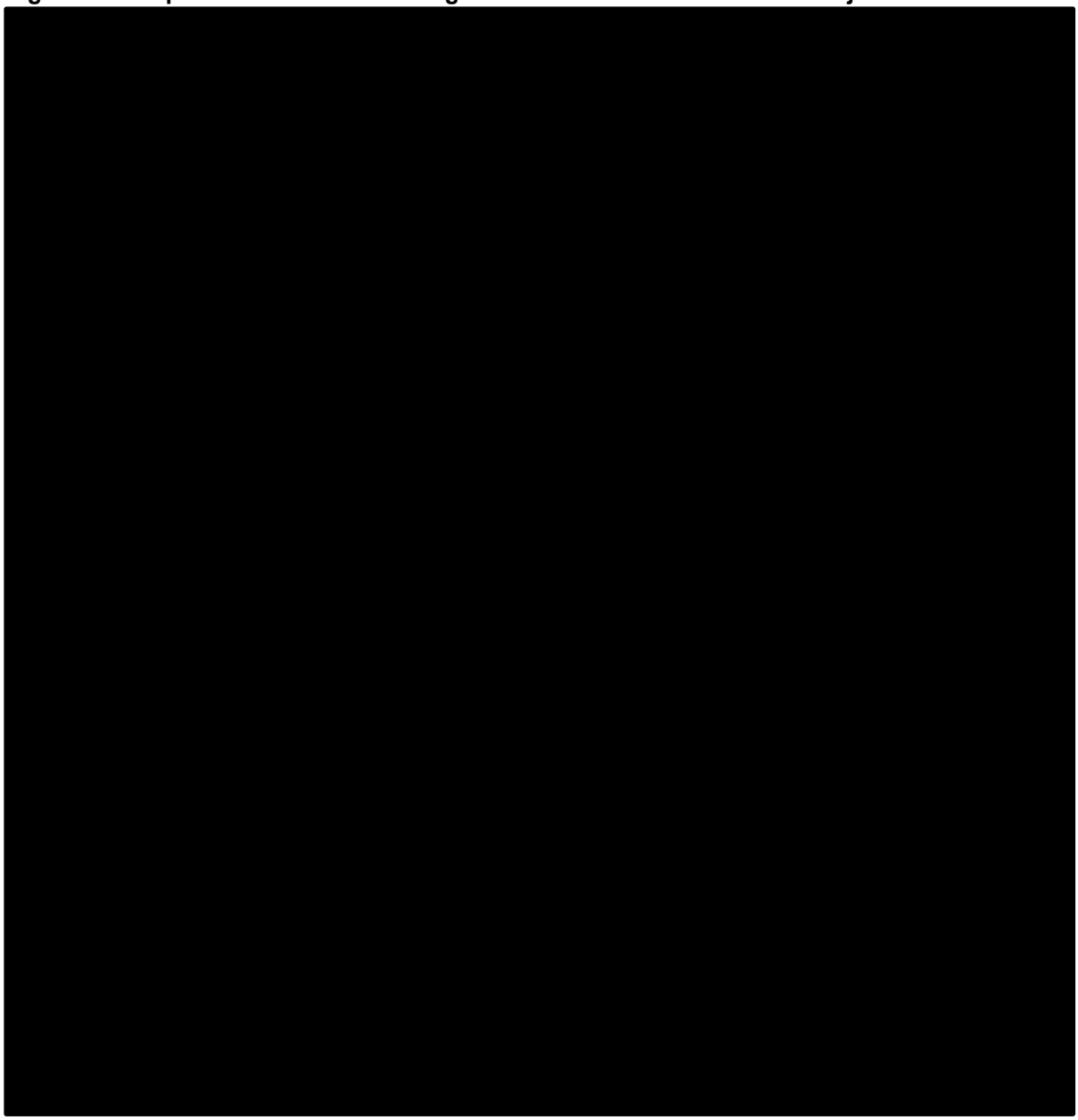
The results for responder odds ratios are shown in Figure 7 and the results for change from baseline in MG-ADL score are shown in Figure 8.

Figure 7: Comparison of MG-ADL responder in baseline risk-adjusted NMA



Abbreviations: MG-ADL, myasthenia gravis activities of daily living; NMA, network meta-analysis.

Figure 8: Comparison of MG-ADL change from baseline in baseline risk-adjusted NMA



Abbreviations: CFB, change from baseline; MG-ADL, myasthenia gravis activities of daily living; NMA, network meta-analysis.

The regression estimate of beta from the NMA indicated that the baseline risk (placebo response) is not statistically significantly different between the studies. The point estimates are comparable to the results from conventional NMA and bvNMA, increasing the confidence in the results. The full methodology and results are included in the report supplied separately as a reference. The results have not been used in the economic model since the networks did not include both IVIg and PLEX studies.

3. Modelling

3.1. Updates to the model

Please refer to the separate supporting document (change log for the cost-effective model) for full description on model methodology, assumptions, inputs and functionality. Adaptations made for this submission are summarised below. A change log has been provided within the economic model, in the yellow 'Updatelog' sheet.

3.1.1. Cost-minimisation analysis

A cost minimisation analysis was undertaken by assuming that the efficacy of all treatments was equal. The response rate and change from baseline in MG-ADL score were set equal to rozanolixizumab for IVIg and PLEX. Disutility and costs for corticosteroid use was removed and no subsequent treatment was assumed.

3.1.2. Response assessment timepoint

The response assessment timepoint used in the model base case is 6 weeks for rozanolixizumab and 3 weeks for IVIg and PLEX, in line with committee's preferred assumption.

3.1.3. Dosing frequency of IVIg and PLEX

The dosing frequency for IVIg and PLEX is applied every 4 weeks in the updated model in line with committee's preferred assumption.

3.1.4. Response rates

The response rates of 75% for rozanolixizumab, 56% for IVIg and 63% for PLEX are from the bivariate NMA (please see Section 2.4).

3.1.5. Minimal symptom expression

Since data are now available from MycarinG on minimal symptom expression (see Section 2.1.2.9), this was assumed to inform the continuous response health state.

Patients with refractory gMG are sub-optimally managed with the treatments currently available on the NHS. The consequences for these patients include poor symptom control, as these patients to do not achieve minimal symptom expression (MSE), have increased risk of myasthenic crisis (18-20), and experience the debilitating side effects of corticosteroids (diabetes, osteoporosis, depression and infection, which can trigger a myasthenic exacerbation) (18, 21-24).

Minimal symptom expression (MSE), as defined by an MG-ADL score of 0 or 1, was used in the model as it is an outcome relevant to patients and is a clinically valid marker of disease severity and treatment response (25-27). The benefit and meaning of MSE to clinicians and patients was further confirmed in expert elicitation interviews conducted in November 2024 (for full details, please see the report provided with this document).

Therefore, excluding it from the model would be disregarding an important benefit of rozanolixizumab versus other treatments. MSE has been used as an evaluation tool for myasthenia gravis treatment goals in recent years, and is used in clinical studies as a patient-relevant outcome (25-27). Clinical expert opinion received by UCB in November 2024 (n=4 clinical experts from the UK) is in agreement with the use of MSE as a clinically

appropriate measure of disease in gMG. The use of more stringent outcomes such as MSE will elevate standard of care and be more clinically meaningful to patients, as patients with MSE tend to feel very well and are able to undertake ordinary daily activities, even work, with few limitations, and the effect of gMG on patients' HRQoL in MSE is minimal.

The proportion of patients with gMG who achieve complete stable remission is low with current treatments available in England and Wales (25). In an analysis of MSE in patients receiving rozanolixizumab in the MycarinG trial, [redacted] (range [redacted]% to [redacted]%) had MSE (see Section 2.1.2.9), meaning that these patients became free or virtually free of MG symptoms. This is an average of all treatment cycles.

MSE data from the rozanolixizumab clinical trial is in line with that from other targeted treatments, such as zilucoplan ([redacted]% of patients achieving MSE) (28) efgartigimod (45.5% of patients achieving MSE) (29) and eculizumab (21.4% of patients achieving MSE) (26).

Expert clinical opinion undertaken in November 2024 (n=4 clinical experts from the UK) suggested that [redacted] and [redacted] of patients with refractory gMG could be expected to achieve MSE on IVIg and PLEX, respectively (Table 12; averages were used in the modelling). Three of the four clinicians said that they would expect no patients on SoC (corticosteroids and immunosuppressants) to achieve MSE, with the fourth saying it would be [redacted] of refractory patients (a very small proportion of patients spontaneously enter remission for unknown reasons). According to the interviewed experts, patients who achieve MSE are expected to remain in MSE whilst on treatment.

Table 12. The proportion of patients expected to achieve MSE with treatment, as estimated by clinical experts

Questions	Expert 1	Expert 2	Expert 3	Expert 4	Mean†
MSE with IVIg					
What proportion of refractory patients receiving IVIg do you expect to reach MSE?	[redacted]	Don't know. Depends on the literature.	[redacted]	[redacted]	[redacted]
MSE with PLEX					
What proportion of refractory patients receiving PLEX do you expect to reach MSE?	[redacted]		[redacted] IVIg and PLEX are interchangeable.	[redacted] Same responses as for IVIg	[redacted]
MSE with SoC					
What proportion of refractory patients receiving SoC do you expect to reach MSE?	[redacted]	[redacted] MSE is not achievable on SoC in refractory patients. A small % might become asymptomatic.	[redacted] If they are refractory, by definition they will not achieve MSE on SoC. Up to 10% of patients do go into remission spontaneously, for reasons unknown.	[redacted] If they are refractory, by definition they will not achieve MSE on SoC.	[redacted]

Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MSE, minimal symptom expression; PLEX, plasma exchange; SoC, standard of care.
† The mean value was calculated by taking the midpoint where a range was given and the upper value when a 'less than' response was given.

MSE data were not included in the original model as the clinical data were not available at that time (had it been available, the original model would have ideally been constructed using MSE). MSE data were incorporated into the updated model by assuming that patients in the continued response health state have reached MSE.

The mean MG-ADL score used for MSE is 0.5 (the average of 0 and 1). It is applied in the model by using a change from baseline in MG-ADL score of 7.8 in the continued response health state, which achieves a 0.5 score from the baseline MG-ADL score in the model of 8.3.

For rozanolixizumab, [redacted] % of patients respond to treatment. Therefore, during each of the two 2-weekly cycles until response assessment time-point, [redacted] % of patients transition from the state of Uncontrolled to one of the three response health states on the rozanolixizumab arm.

The proportions of patients achieving MSE informs the distribution of patients who respond to their first-line treatment across the Continued, Loss of and Stable response levels (Figure 9). [redacted] % of patients who responded to rozanolixizumab achieved MSE.

Therefore, of the [redacted] % of patients who will transition from Uncontrolled to a Response health state by the time response assessment timepoint is reached, [redacted] % will move to "Continued response" (i.e. [redacted] % x [redacted] % = [redacted] % achieving continued response per-cycle).

Previous expert elicitation showed that approximately [redacted] of patients experience loss of response after initially responding. Therefore, [redacted] of patients were assumed to move to the loss of response health state in each treatment arm. The proportion of patients in stable response was calculated as the remainder who aren't in continued or loss of response, i.e. 100% minus percentage in continued response minus [redacted] in loss of response.

Therefore, [redacted] % of responders have a stable response, meaning [redacted] % x [redacted] % transition from Uncontrolled to Stable response per-cycle, and [redacted] x [redacted] % transition from Uncontrolled to Loss of response per-cycle. These transition probabilities apply until the response assessment timepoint, after which point patients are taken off rozanolixizumab and moved to a subsequent treatment.

Figure 9: Distribution of patients who respond to first-line treatment

[redacted]

It is important to note that the inclusion of MSE to inform the proportion of patients in the continued response state does not affect time on treatment, since the proportion of those on loss of response remains the same ([redacted]), and those in the continued and stable response states will all be on treatment. The time on treatment is only dependent on the overall response rate and response assessment timepoint. To illustrate this, the following scenarios have been conducted (Table 13: Effect of MSE and response rate on time on treatment) to calculate time on treatment:

- Including MSE to inform continued response proportions ([redacted] % enter continued response)
- Excluding MSE to inform continued response proportions ([redacted] % enter continued response)
- Response rate decreased by 10% for each treatment
- Response rate increased by 10% for each treatment

Table 13: Effect of MSE and response rate on time on treatment

Treatment	Response rate	Time on treatment (months)			
		Including MSE ([redacted] % enter continued response)	Excluding MSE ([redacted] % enter continued response)	Response rate decreased by 10% for each treatment	Response rate increased by 10% for each treatment
Rozanolixizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVIg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC basket	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Weighted average using the revised EAMS proportions.
§Time on treatment for blended SoC basket is higher than that for IVIg and PLEX due to having a longer time to assessment response (12 weeks versus 3 weeks).

3.1.6. Subsequent treatments

Formally modelling treatment sequences is impossible and cannot be answered with any certainty due to the rarity of the disease, the highly individualised treatment choices for refractory patients, and the lack of available data. There is great uncertainty around the number of lines of subsequent treatments needed, which treatments clinicians will consider after failure on IVIg/PLEX, and whether lack of response to index treatment will be a treatment effect modifier.

However, UCB acknowledges that the validity of a model which did not allow for repeat attempts of treatment and switching of treatment may be challenged. Similarly, a model which kept patients on IVIg or PLEX persistently despite loss of response might also be challenged. Therefore, the company has included subsequent treatment in the base case and modelled it as a basket containing IVIg, PLEX and SoC only. The proportion of patients on each treatment remains constant over time as a steady state (snapshot in time) but would in reality represent patients moving between IVIg, PLEX and standard of care only

UCB believe that the composition of the subsequent treatment basket should be the same irrespective of the treatment received in first line since this basket is applied to patients over

their remaining lifetime from model entry (at the average age of 51.8 years) onwards. Over such a long time horizon, the mix of subsequent treatment that patients receive is expected to converge to the same basket of treatments irrespective of the index treatment received. This approach is consistent with the approach described by the committee for TA1069. In section 3.15 of the final draft guidance document of TA1069, “the committee agreed the most reasonable approach would model the same proportions of people having plasma exchange and IVIg in both arms. That would mean that people who stop efgartigimod would have the same sequence of IVIg and plasma exchange as the comparator arm”. Acknowledging the paucity of data from patients with refractory gMG, UCB believes that experts’ opinion is the most appropriate source to derive the composition of the basket of subsequent treatments. However, it is worth noting that treatment in refractory gMG is highly individualised and can vary from centre to centre; therefore, results should be treated with caution.

A recent Delphi panel survey was conducted, including 9 clinical experts in gMG from across England and Scotland. The experts were asked in the first round to provide estimates of subsequent treatments following IVIg and PLEX. They were then provided the mean values of these estimates and were asked whether they agreed. Consensus was achieved in nearly all estimates; please see the supporting reference for full methodology and results.

These proportions were then applied to the revised EAMS proportions of patients receiving IVIg, PLEX, and SoC (CSs/NSISTs; see Section 3.3.5.2 for details of this population) to give an estimate of subsequent treatments to apply as a steady state across all treatment arms (Table 14).

Table 14. Subsequent treatment steady state proportions

Treatment	Proportion of patients
IVIg	14.05%
PLEX	35.73%
SoC (CSs/NSISTs)	50.22%

Abbreviations: CS, corticosteroid; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant; PLEX, plasma exchange.

The impact of using alternative scenarios of composition of the subsequent treatment basket are explored in Section 3.3.5.4.

3.1.7. Benefit of at-home subcutaneous administration

The “AdminTime” worksheet of the updated model reports the NHS staff and patient time for rozanolixizumab and comparators. Compared with IVIg, rozanolixizumab saves [redacted] hours of NHS staff time and [redacted] hours of patient time per year; for the comparison with PLEX, [redacted] staff hours and [redacted] patient hours are saved (30).

3.1.8. Number of infusions of rozanolixizumab per year

Since the original submission, further data from MycarinG have become available (see Section 2). The mean annualised number of infusions is [redacted], which is calculated from all symptom-driven cycles and the 40 fixed cycles from MG0007 and applied in the model. The annualised number of infusions was deemed to be more accurate in terms of the actual number of infusions received by patients than the annualised number of cycles ([redacted]) and also means that the annual drug cost for rozanolixizumab is consistent regardless of whether

the number of infusions or number of cycles is chosen in the model. However, the annualised number of cycles has been used in a scenario (Section 3.3.5.8).

3.1.9. Duration of exacerbation and crisis

The duration of crisis and exacerbation were amended to 28 days each following expert clinical opinion received (and discussions at ACMs for various gMG appraisals).

3.1.10. Caregiver disutility

The updated model incorporated the parameters for caregiver disutilities, considering the proportion of patients requiring caregiver support according the MD-AGL score ranges and utility decrements reported in previous submissions to NICE for relevant populations (31).

Table 15. Caregiver disutility assumptions

MG-ADL score range		Proportion of patients requiring a caregiver	Utility decrement	Average utility decrement per model cycle
0	1	6%	-0.002	0.000
2	3	10%	-0.002	0.000
4	5	29%	-0.002	-0.001
6	7	40%	-0.045	-0.018
8	9	50%	-0.142	-0.071
10	11	57%	-0.160	-0.091
12	13	74%	-0.160	-0.119
14	24	85%	-0.160	-0.135
Crisis/exacerbation		85%	-0.180	-0.152

Source: National Institute for Health and Care Excellence, 2023 (31).

3.2. Base case inputs and settings

Full details of the methodology can be found in the technical report provided. In this section, a summary of the base-case inputs and model settings is reported.

3.2.1. Model base case settings

<table>
<tr><td>Population</td><td>Refractory gMG population

Table 16. Cohort baseline characteristics
<table>
<tr><th>Patient characteristic</th><th>Mean value</th><th>SD</th><th>Source</th></tr>
<tr><td>The average age of the population at baseline (years)</td><td>51.8</td><td>16.3</td><td>UCB data on file, 2022 (32)</td></tr>
<tr><td>Males, %</td><td>39.5%</td><td>Not reported</td><td>UCB data on file, 2022 (32)</td></tr>
<tr><td>Average MG-ADL score at the start</td><td>8.3</td><td>6.00</td><td>UCB data on file, 2022 (32)</td></tr>
<tr><td>Average weight (kg)</td><td>81.15</td><td>23.88</td><td>UCB data on file, 2022 (32)</td></tr>
<tr><td>Baseline BMI (kg/m^2)</td><td>27.83</td><td>3.4</td><td>UCB data on file, 2022 (32)</td></tr>
</table>
Abbreviations: BMI, body mass index; MG-ADL; Myasthenia Gravis Activities of Daily Living.</td></tr>
<tr><td>Intervention</td><td>Rozanolixizumab</td></tr>
<tr><td>Comparators</td><td>• IVIg
• PLEX</td></tr>
<tr><td>Analysis type</td><td>Cost-utility analysis</td></tr>
<tr><td>Perspective</td><td>NHS and Personal Social Services in England</td></tr>
<tr><td>Discount rate</td><td>3.5% for costs and QALYs</td></tr>
<tr><td>Model type</td><td>State-transition cohort (Markov model)</td></tr>
<tr><td>Health states</td><td>• Uncontrolled on high-dose steroids and ISTs
• Continued response
• Stable response
• Loss of response
• Acute exacerbation
• Myasthenic crisis
• Death</td></tr>
<tr><td>Cycle length</td><td>2 weeks</td></tr>
<tr><td>Time horizon</td><td>Lifetime (48.2 years; calculated as 100 minus average age of population on model entry)</td></tr>
</table>

Abbreviations: gMG, generalized Myasthenia Gravis; IST, immunosuppressive therapies; IVIg, intravenous immunoglobulin; NHS, National Health Service; PLEX, plasma exchange; QALY, quality-adjusted life year.

3.2.2. Efficacy assumptions and inputs

Table 17. Primary response rate and response assessment timepoint

Treatment	Response rate used in the model	Response assessment timepoint used in the model (weeks)	Source
Rozanolixizumab	[redacted]	6	bvNMA
IVIg	[redacted]	3	bvNMA
PLEX	[redacted]	3	bvNMA

Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SE, standard error.

Table 18. Treatment-specific MG-ADL score CFB

Treatment	Continued response	Loss of response	Stable response	Source
Rozanolixizumab	[redacted]	0	[redacted]	bvNMA
IVIg	[redacted]	0	[redacted]	bvNMA
PLEX	[redacted]	0	[redacted]	bvNMA

Abbreviations: CFB, change from baseline; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living profile; PLEX, plasma exchange.

Table 19. Response distribution

	Continued response	Loss of response	Stable response	Source
Rozanolixizumab	[redacted]	5%	[redacted]	MSE rate for rozanolixizumab from MycarinG and extension study (see Section 2.1.2.9)
IVIg	[redacted]	5%	[redacted]	Expert elicitation (see Section 3.1.5)
Plasma exchange	[redacted]	5%	[redacted]	Expert elicitation (see Section 3.1.5)

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

Until the treatment-specific response assessment timepoint, all respondents are assigned the CFB MG-ADL score associated with stable response. From the response assessment timepoint onwards, patients who experience continuous response are assigned the CFB in MG-ADL score associated with continued response, leading to an absolute MG-ADL score of 0.5. For those 5% of respondents assumed who lose response (across all treatments), it is assumed that their MG-ADL score returns to baseline (i.e. [redacted]) linearly over 14 weeks post response assessment timepoint.

Patients who did not respond to index treatment are assumed to receive the basket of subsequent treatment. They will experience a reduction in their MG-ADL score that is conditional on the treatment composition of the basket and associated weighted response rate ([redacted] % under base case composition of the subsequent treatment basket) and weighted MG-ADL score (reduction in score of [redacted] under base case composition of the subsequent treatment basket).

3.2.3. Cost assumptions and inputs

The model assumptions were as follows:

- Vial sharing is excluded
- SoC costs are included with rozanolixizumab, IVIg, and PLEX
- 100% adherence is assumed
- There is a total of 16 infusions per year (annualised) of rozanolixizumab

Table 20. Average costs per cycle

	Weighted cost per mg (£)	Cost per cycle (£)	Annual drug cost (£)	Annual admin. cost (£)	Total annual cost (£)
Rozanolixizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVIg	0.06	2,412.50	62,894.00	19,682.00	82,576.00
Plasma exchange	2,587.45	6,451.26	168,184.25	0.00	168,184.25

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

Table 21. Refractory standard of care (SOC) basket costs

Medication	Bundle composition			Average treatment cost per model cycle (£)	Admin costs per model cycle (£)
	Mean	Lower	Upper		
Azathioprine	17.80%	16.02%	19.58%	5.88	0.00
Cyclophosphamide	0.00%	0.00%	0.00%	0.00	0.00
Cyclosporine	7.50%	6.75%	8.25%	95.59	0.00
Methotrexate	2.30%	2.07%	2.53%	2.20	0.00
Mycophenolate mofetil	19.00%	17.10%	20.90%	6.70	0.00
Corticosteroids	63.20%	56.88%	69.52%	2.42	0.00
Tacrolimus	5.70%	5.13%	6.27%	202.31	0.00
Pyridostigmine	80.50%	72.45%	88.55%	6.36	0.00
Average cost per model cycle (£)				27.72	0.00

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

3.2.3.1. Steroid management costs

The cost of managing steroid use was calculated from a publication by Stirnadel-Farrant et al (33). The uncontrolled health state was assumed to be the cost associated with a 15 mg dose minus the cost associated with no corticosteroids (and therefore removing costs

associated with the disease, lupus) (Table 22). The cost assigned to the stable health state was assumed to be the average of the costs reported for those taking 5–7.5 mg steroid dose and 7.5–10 mg dose, minus the cost with no corticosteroid use. It is assumed that patients in the continued response health state receiving rozanolixizumab would have no steroid-related costs, since expert opinion is that, if a patient achieves MSE on targeted treatment, the clinician would reduce corticosteroid use, eventually stopping it entirely. This is reflected in the draft guidance document, Section 3.21, where it states that "[the clinical experts] explained that people who have rozanolixizumab may be able to reduce their corticosteroid dose. This could lead to fewer corticosteroid-related adverse effects" (34). There is no evidence that corticosteroid reduction or cessation is possible in patients receiving chronic IVIg and PLEX; indeed, it has been reported in a published RCT that there was no statistically significant difference in steroid reduction in patients receiving IVIg versus placebo (35).

Table 22: Cost of steroid complications

Patient group	Costs (£)	Source
No corticosteroids	3,842	(33)
0–5 mg dose of corticosteroids	5,699	(33)
5–7.5 mg dose of corticosteroids	7,884	(33)
7.5–10 mg dose of corticosteroids	9,241	(33)
15 mg dose of corticosteroids	13,929	(33)
Cost assigned to uncontrolled health state	10,087	Cost of 15 mg dose minus cost of no CSs
Cost assigned to stable response health state	4,670.50	Average of 5–7.5 and 7.5–10 mg minus cost of no CSs
Cost assigned to continued response health state with rozanolixizumab	0	Assumption based on clinical opinion
Cost assigned to continued response health state with IVIg and PLEX	4,670.50	Average of 5–7.5 and 7.5–10 mg minus cost of no CSs

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

Table 23. HCRU costs per health state

HCR	Unit cost (£) (range)	Annual health state frequency of resource use					
		Uncontrolled		Stable response		Continued response	
		Mean	Range†	Mean	Range†	Mean	Range†
IVIg	5,942.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	12,937.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GP visit	33.00 (29.70-36.30)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit to other healthcare professionals	52.00 (46.80-57.20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient hospital visits	485.85 (437.26-534.43)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Presenting at an emergency room	278.10 (250.29-305.91)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospital stay (with ICU, cost per critical care period)	11,737.70 (10,563.93-12,911.47)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospital stay (no ICU, cost per day) (1.19 days per stay)	595.42 (535.88-654.97)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of managing steroid use (£)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost for RLZ and refractory SoC (£)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A

Total cost for IVIg and PLEX		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A

Abbreviations: GP, general practitioner; ICU, intensive care unit; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; RLZ, rozanolixizumab; SoC, standard of care; N/A, not applicable.

†In these columns, ranges marked with a dagger are derived from published literature. The unmarked ranges are based on a 10% assumption around the mean.

Table 24. HCRU per event (as detailed in Section 2.4.4.1 of Global CEM technical report)

	Unit cost (£)	Frequency of resource use per event					
		Exacerbation			Myasthenic crisis		
		RLZ/SoC	IVIg	PLEX	RLZ/SoC	IVIg	PLEX
IVIg	5,942.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	12,937.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GP visit	33.00		[redacted]			[redacted]	
Visit to other healthcare professionals	52.00		[redacted]			[redacted]	
Outpatient hospital visits	485.85		[redacted]			[redacted]	
Presenting at emergency room	278.10		[redacted]			[redacted]	
Hospital stay (with ICU, cost per critical care period)	11,737.70		[redacted]			[redacted]	
Hospital stay (no ICU, cost per day) (28 days per stay)	595.42		[redacted]			[redacted]	
Total cost (£)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GP, general practitioner; ICU, intensive care unit; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; RLZ, rozanolixizumab; SoC, standard of care.

3.2.4. Utilities inputs and assumptions

Due to expert clinical opinion and committee meeting discussions during the NICE appraisal for zilucoplan, the duration of exacerbation and myasthenic crisis has been increased to 28 days (Table 25).

Table 25. Clinical event disutility

	Disutility	Duration (days)
Exacerbation	0.20	28.00
Myasthenic crisis	0.39	28.00

The model was also updated to include disutilities associated with the use of corticosteroids. The approach to modelling the disutility of steroids reflects the approach used in the NICE submission for efgartigimod in gMG (36). There are no data available on the costs or utility

values associated with CS use in gMG; therefore, proxy conditions had to be used to incorporate the CS cost and disutility in the model. Two papers were used to derive the disutility of high-dose (≥10 mg/day) and low dose (<10 mg/day) steroids. One paper evaluated the use of steroids in systemic lupus in Sweden (37) and one evaluated the use of systemic steroids in asthma in the US and UK (38). Utility decrements were identified for high and low steroid use by averaging values across the two studies. The decrement for high dose was assigned to patients in the uncontrolled health state and the decrement for low dose was assigned to patients in the stable response health state (Table 26).

Table 26. Annual disutility of steroid use

	Disutility	Duration (days)
Uncontrolled - High-dose (> 10mg/day)	0.18	365.25
Stable response - Low-dose (< 10mg/day)	0.07	365.25
Continued response - no steroid use	0.00	365.25

3.3. Model results and scenario analyses

3.3.1. Base case results (discounted)

The base-case cost-utility analysis results are based on the data, assumptions and structure described in Section 3 and within the global CEM technical report.

Table 27 presents the estimated total costs and QALYs for rozanolixizumab and comparators as well as the pairwise comparison in terms of incremental costs, QALYs, and ICER (£/QALYs). Rozanolixizumab [redacted].

Table 27: Base case results (discounted)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.4151			
IVIg	[redacted]	8.2518	[redacted]	0.1633	[redacted]
Plasma exchange	[redacted]	8.2894	[redacted]	0.1257	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; QALY, quality-adjusted life years.

3.3.2. Cost-minimisation results

Cost minimisation results are shown in Table 28. The results show that, even when we assume that the efficacy is equal across treatments, rozanolixizumab represents the least expensive treatment option.

Table 28: Cost-minimisation results

Technologies	Total		Incremental	
	Costs (£)	QALYs	Costs (£)	QALYs
Rozanolixizumab	[redacted]	8.0205		
IVIg	[redacted]	8.0205	[redacted]	0.00
Plasma exchange	[redacted]	8.0205	[redacted]	0.00

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; QALY, quality-adjusted life years.

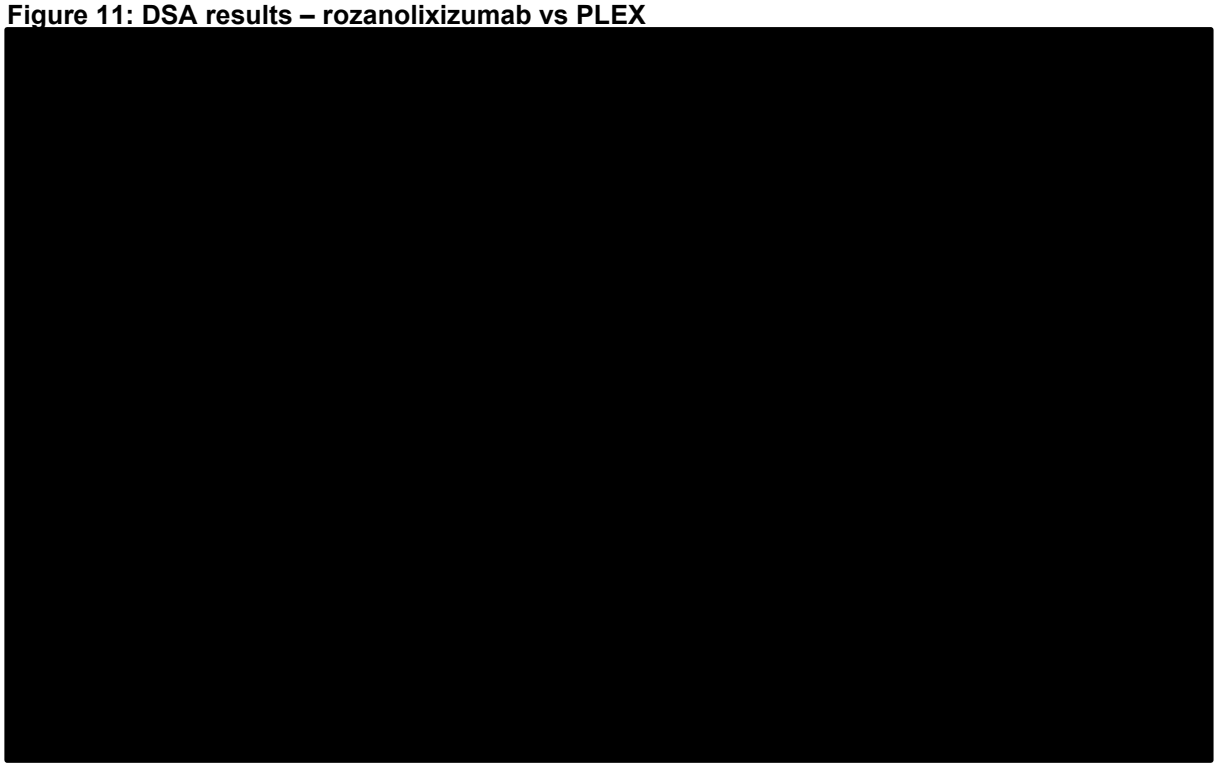
3.3.3. Deterministic sensitivity analysis results

Deterministic sensitivity analysis (DSA) was conducted using extreme range values (for full description please refer to the global CEM tech report). The DSA results in the form of pairwise results are presented in Figure 10 and Figure 11. The largest driver for the analysis versus IVIg is the list price per pack of rozanolixizumab, followed by IVIg resource use during exacerbation and average age of the population (Figure 10). The largest driver for the analysis versus PLEX is also the list price per pack of rozanolixizumab, followed by the annual rate of exacerbation in responders and IVIg resource use during exacerbation (Figure 11).

Figure 10: DSA results – rozanolixizumab vs IVIg

Abbreviations: DSA, deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; ICU, intensive care unit; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year.

Figure 11: DSA results – rozanolixizumab vs PLEX



Abbreviations: DSA, deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; ICU, intensive care unit; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year.

3.3.4. Probabilistic sensitivity analysis results

Full details of the parameters included in the PSA, and their associated distributions, can be found in the global CEM technical report and parameter worksheet of the model. In the PSA all parameters varied 10% around the mean, except parameters informed by the CODA and bvNMA. Results are shown in Table 29 and Figure 12. The ICER scatterplot (Figure 13) shows the cost-effectiveness pairs estimated in each PSA iteration, in terms of incremental costs (y-axis) and incremental QALYs (x-axis). The placement and distribution of these points are reflective of the intervention arm relative to the comparator arm, and the level of uncertainty surrounding the point estimates. The congruence test results for the analysis versus IVIg are shown in Figure 14, and the results versus PLEX are shown in Figure 15.

For the pairwise comparison of rozanolixizumab vs IVIg, the point estimate, determined by the average cost and QALY from the 1,000 iterations, was comparable with the deterministic results, indicating that the outputs of interest may be considered to have converged (i.e. the mean ICER from the PSA has stabilised to the deterministic ICER).

Table 29. Probabilistic sensitivity analysis results (all parameters varied 10% around mean, except parameters informed bvNMA)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.41508			
IVIg	[redacted]	8.25175	[redacted]	0.16	[redacted]

PLEX	[redacted]	8.28942	[redacted]	0.13	[redacted]

Abbreviations: bvNMA, bivariate network meta-analysis; ICER: incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year.

Figure 12. Cost-effectiveness acceptability curve

Abbreviations: IVIg, intravenous immunoglobulin.

Figure 13. Cost-effectiveness plane

Abbreviations: IVIg, intravenous immunoglobulin; QALY, quality-adjusted life years.

Figure 14: Congruence test results versus lVlg

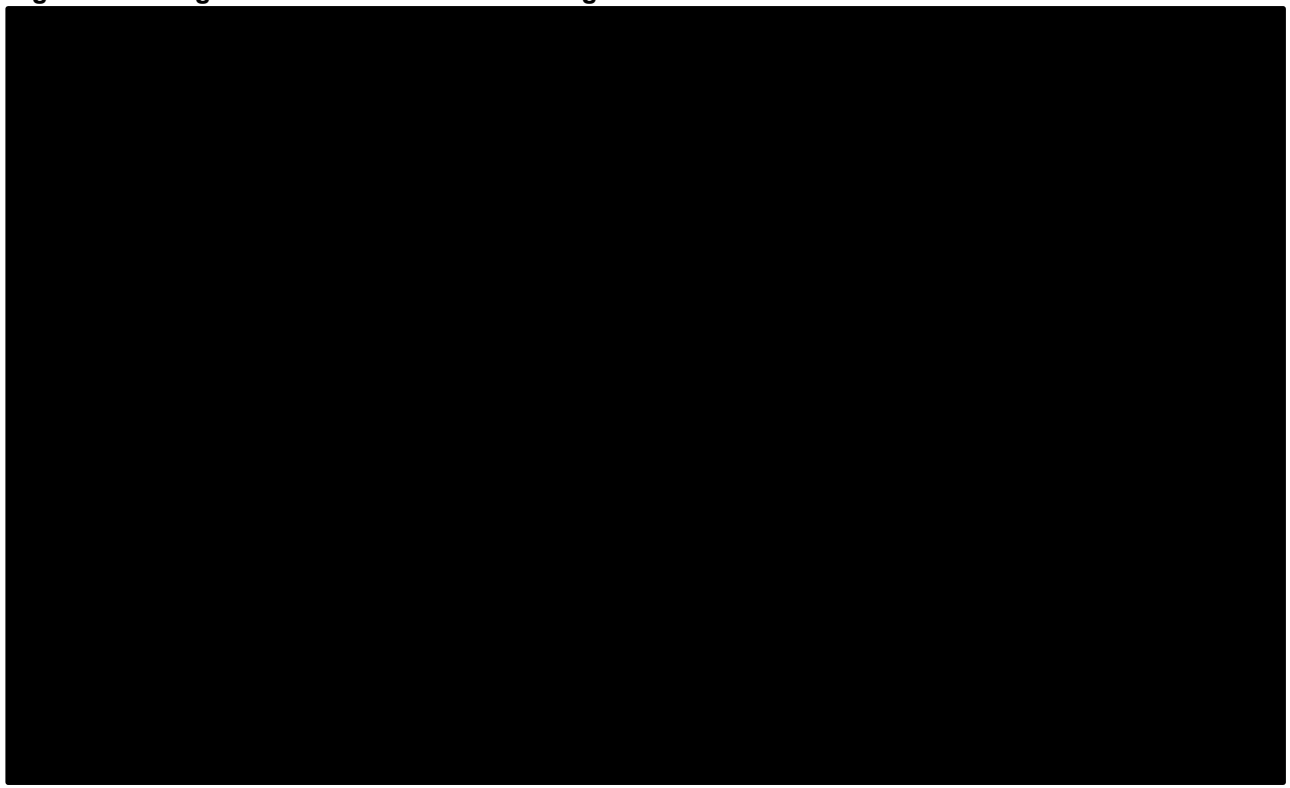


Figure 15: Congruence test results versus PLEX

3.3.5. Scenario analyses

3.3.5.1. Scenarios to understand the appropriateness of the blended SoC basket comparator

Considering that rozanolixizumab is positioned where IVIg or PLEX are being used or considered, UCB would like to clarify the reason that the EAG and the committee think that patients only on standard of care (corticosteroids and NSISTs) should be part of the basket and why patients in this cohort are not receiving IVIg or PLEX. There are three possible reasons for this that the company have identified:

A. Those on SoC only are patients who will never receive IVIg and/or PLEX. If this is the case, then UCB are not suggesting that these patients would be in the target population for rozanolixizumab and would not be eligible for treatment with rozanolixizumab in clinical practice. In this case, the pairwise comparisons with IVIg and PLEX would seem to be the most appropriate. In Table 30, the company have included a blended IVIg/PLEX arm (scenario A), which weights the total costs and QALYs according to the proportions of patients taking IVIg and PLEX on entering the EAMS cohort (21:7, or 75%:25% for IVIg and PLEX, respectively).

B. Those on SoC only are patients who do or will receive IVIg and/or PLEX, but that are having a break from treatment for whatever reason, e.g. drug holidays, AEs, switching due to inadequate response. If this is the case, then it would seem reasonable that this would also apply to patients receiving rozanolixizumab across an extended treatment period, i.e. not all patients would be 'on treatment' and the same proportion of patients would be receiving SoC alone in the rozanolixizumab arm as in the basket of care arm. The company have run two scenarios to illustrate the cost-effectiveness results in this situation, one using the refined refractory EAMS cohort and one using the overall EAMS cohort (Table 31).

C. Those on SoC only are patients who, for some reason, cannot access IVIg or PLEX. In this case, the difference in the cost-effectiveness results (i.e. a high ICER) is due to IVIg and PLEX not being cost-effective versus SoC, but are still used in the NHS. This means that, whilst rozanolixizumab is dominant versus IVIg and the blended arm of patients receiving IVIg and PLEX in clinical practice (Table 30), UCB acknowledges that, like IVIg and PLEX, rozanolixizumab is not cost-effective versus SoC only (and is not positioned at the same point in the treatment pathway). The difficulty of forcing this comparison to a blended SoC basket can be further illustrated by comparing theoretical versions of IVIg and PLEX that are 10% cheaper and 10% more effective than the currently used IVIg and PLEX versus the standard of care basket (Table 32). The ICER results are far above the willingness-to-pay threshold for reimbursement in the NHS, which would lead to cheaper and more effective versions of IVIg and PLEX being not recommended by NICE, meaning the more expensive and less efficacious treatment would remain the standard of care, which is clearly a perverse outcome for patients, being denied an effective treatment in the NHS.

The results for scenario A (blended IVIg/PLEX) were calculated by comparing the rozanolixizumab arm with a weighted average of the IVIg and PLEX arms of 75%:25%,

respectively, i.e. costs and QALYs of the blended arm were calculated as 0.75* costs/QALYs for IVIg + 0.25* costs/QALYs for PLEX (Table 30).

Table 30: Scenario A results: Comparison vs blended IVIg/PLEX arm (75:25)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.415			
Blended IVIg/PLEX arm (75:25)	[redacted]	8.261	[redacted]	0.154	[redacted]

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

In scenario B, patients in both the rozanolixizumab and basket of care arms are assumed to spend some time on SoC only during a long course of treatment. Since there was no combined arm for rozanolixizumab in the model, we produced results for the total costs and QALYs assuming patients received SoC only. We updated the subsequent treatment basket to be 100% SoC to match the assumption for subsequent treatments that was applied in the scenario of rozanolixizumab versus the basket of care, that patients receiving SoC on model entry would remain on SoC as subsequent treatment. The total costs and QALYs for SoC only are shown in Table 31. The costs and QALYs for the rozanolixizumab arm were then weighted to incorporate those patients who would be on SoC only based on the revised EAMS cohort. This means that the rozanolixizumab arm for includes 75.6% of patients on rozanolixizumab and 24.4% on SoC, which is being compared with the standard of care basket of 56.7% IVIg, 18.9% PLEX, and 24.4% SoC (Table 31). It is worth noting that the basket of care is not cost-effective versus SoC (with increased costs of [redacted] but only increased QALYs of 0.0357), illustrating that IVIg and PLEX are not cost-effective but are currently used in the NHS.

Table 31: Scenario B results

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.4151			
SoC (CSs and NSISTs only)	[redacted]	8.221			
Rozanolixizumab arm using proportion on SoC from refractory EAMS cohort (75.6% rozanolixizumab, 24.4% SoC) vs basket of care using proportions from revised EAMS cohort (56.7% IVIg, 18.9% PLEX, 24.4% SoC)					
Rozanolixizumab	[redacted]	8.368			
Basket of care	[redacted]	8.257	[redacted]	0.111	[redacted]

Abbreviations: CS, corticosteroids; EAMS, Early Access to Medicines Scheme; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant therapy; PLEX, plasma exchange; QALY, quality-adjusted life years; SoC, standard of care.

For scenario C, in the comparison of the basket of care with hypothetical versions of IVIg and PLEX that are 10% cheaper and 10% more effective than currently available IVIg and PLEX, the acquisition costs were reduced by 10% while the initial response rates and changes from baseline in MG-ADL score for those in stable response were increased by

10%. This was then compared with the basket of care containing proportions of treatment from the revised EAMS cohort (Table 32).

Table 32: Scenario C results: 10% cheaper and 10% more effective IVIg and PLEX vs revised EAMS basket of care

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Blended SoC basket using revised EAMS proportions†	[redacted]	8.257			
10% cheaper and 10% more effective IVIg	[redacted]	8.264	[redacted]	0.007	[redacted]
10% cheaper and 10% more effective PLEX	[redacted]	8.310	[redacted]	0.053	[redacted]

Abbreviations: EAMS, Early Access to Medicines Scheme; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant therapy; PLEX, plasma exchange; QALY, quality-adjusted life years; SoC, standard of care.
† Comparison with basket of care based on the revised EAMS cohort proportions (56.7% IVIg, 18.9% PLEX, 24.4% SoC).

3.3.5.2. Blended SoC basket comparator

Whilst UCB does not agree that a SoC basket is a relevant comparator and thus it is excluded from the base case, the following scenarios are provided for transparency:

- Basket using revised EAMS proportions
- Basket using revised EAMS proportions incorporating rituximab

For this blended SoC comparator, overall response rates, CFB in MG_ADL score, treatment and administration costs as well as resource use costs associated with clinical events are all computed as weighted averages based on the treatment composition of the basket and treatment-specific costs and efficacy outcomes. Two alternative data sources are used to inform the blended SoC basket comparator and are described below.

Basket using revised EAMS proportions

The EAMS cohort data for efgartigimod requires further analysis to make it relevant to the population appropriate for treatment with rozanolixizumab. Not all patients are considered refractory (n=37/48 are refractory, as presented in the publication), and three patients received no treatment (these patients would not be eligible for rozanolixizumab, as rozanolixizumab is licenced as an add-on therapy and not a monotherapy) and 10 patients are on corticosteroids only (these patients would likely be considered for an NSIST prior to initiation of rozanolixizumab).

Removing these patients from the cohort results in a total of 35 patients. To match the number of refractory patients (n=37), UCB have included two of the patients receiving CSs only, which is a conservative assumption. This leaves a remaining 73% (n=35/48) of patients using IVIg/PLEX in the refractory subgroup (Table 33).

Table 33. Patients receiving subsequent treatments in the reweighted EAMS basket

Treatment	n	N	%
CS only	2	37	5.4
CS & NSIST	27	37	73.0
NSIST only	5	37	13.5
Regular IVIg w CS/NSIST	18	37	48.6
IVIg only	3	37	8.1
PLEX	7	37	18.9

Abbreviations: CS, corticosteroids; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant treatments; PLEX, plasma exchange.

This means that for this scenario, 18.9% of patients were receiving PLEX, 56.7% were receiving IVIg, and the remainder (24.4%) were receiving So (CSs/NSISTs). The costs and efficacy inputs for the blended comparator using the revised EAMS population are shown in Table 34 and Table 35, respectively.

Table 34. Standard of care blended comparator costs: Revised EAMS proportions

Medication	Bundle composition	Average treatment cost per model cycle (£)	Admin costs per model cycle (£)
IVIg	56.7%	[redacted]	[redacted]
PLEX	18.9%	[redacted]	[redacted]
Rituximab	0.00%	[redacted]	[redacted]
SoC	24.4%	[redacted]	[redacted]
Average cost per model cycle (£)		[redacted]	[redacted]

Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SoC, standard of care.

Table 35: Standard of care blended comparator efficacy inputs: Revised EAMS proportions

	Weighted average response rate	Proportion on continued response	CFB in MG-ADL for stable response
SoC blended comparator	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; MG-ADL, myasthenia gravis activities of daily living.

The cost-effectiveness results for rozanolixizumab versus the revised EAMS basket are shown in Table 36.

Table 36: Scenario analysis results: Rozanolixizumab versus revised EAMS basket

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.4151			
Revised EAMS SoC basket	[redacted]	8.2567	[redacted]	0.1584	[redacted]

Abbreviations: EAMS, Early Access to Medicines Scheme; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Basket using revised EAMS proportions including rituximab

An expert elicitation conducted in 2024 confirmed that rituximab would be used in patients with gMG. However, all respondents positioned rituximab in a different position in the pathway to IVIg and PLEX (and therefore the proposed positioning of rituximab), with it nearly always being used earlier in the treatment pathway. Therefore, rituximab should not be considered as a comparator to rozanolixizumab in its own right. However, it could be included in the blended basket comparator as part of the SoC (CSs/NSISTs) component. To incorporate it as part of this scenario, it was assumed that all MuSK-Ab+ patients would receive rituximab as part of the SoC basket. This is because rituximab has been deemed fairly ineffective in AChR Ab+ patients with gMG during the appraisals of efgartigimod and zilucoplan; however, this is a conservative assumption since some consultant neurologists responded in the expert elicitation that they would use rituximab in AChR-Ab+ patients. In MycarinG, 10.5% of patients were MuSK-Ab+; therefore, for this scenario, 10.5% of patients are assumed to receive rituximab as part of the SoC (CSs/NSISTs) portion of the blended basket comparator.

This is applied to the basket by reducing the relative proportion of each component (IVIg, PLEX, and SoC [CSs/NSISTs] equally, i.e., by multiplying each proportion by a factor of (1-0.105) = 0.895. This results in 50.75% of patients receiving IVIg, 16.92% receiving PLEX, 10.50% receiving rituximab, and 21.84% receiving SoC (CSs/NSISTs).

Model inputs used for rituximab are shown in Table 37. The costs and efficacy inputs for the blended comparator using the revised EAMS population are shown in Table 38 and Table 39, respectively. Cost-effectiveness results are shown in Table 40.

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Table 37: Model inputs for rituximab

	Value	Source
Response rate	[redacted]	bvNMA
Change from baseline in MG-ADL score for stable response health state	[redacted]	bvNMA
Response assessment timepoint	52 weeks	Nowak et al (11)
Price	£1.62 per mg	BNF (39)
Proportion in continued response	[redacted]	Average of values for IVIg and PLEX

Abbreviations: bvNMA, bivariate NMA; MG-ADL, myasthenia gravis act8ivities of daily living.

Table 38. Standard of care blended comparator costs: Revised EAMS proportions including rituximab

Medication	Bundle composition	Average treatment cost per model cycle (£)	Admin costs per model cycle (£)
IVIg	50.75%	[redacted]	[redacted]
PLEX	16.92%	[redacted]	[redacted]
Rituximab	10.50%	[redacted]	[redacted]
SoC	21.84%	[redacted]	[redacted]
Average cost per model cycle (£)		[redacted]	[redacted]

Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SoC, standard of care.

Table 39: Standard of care blended comparator efficacy inputs: Revised EAMS proportions including rituximab

	Weighted average response rate	Proportion on continued response	CFB in MG-ADL for stable response
SoC blended comparator	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; MG-ADL, myasthenia gravis activities of daily living.

Table 40: Scenario analysis results: Rozanolixizumab versus revised EAMS basket including rituximab

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.4151			

Revised EAMS SoC basket incl. Rituximab	[redacted]	8.2600	[redacted]	0.1551	[redacted]

Abbreviations: EAMS, Early Access to Medicines Scheme; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

3.3.5.3. Subsequent treatment excluded

Modelling subsequent treatment is usually associated with high risk of uncertainty, particularly in therapy areas where there is no established treatment sequencing. This issue is even more pronounced in rare diseases such as gMG where there is limited data, highly individualised treatment choices in the small sub-population of refractory patients. Therefore, a scenario was conducted where subsequent treatment was removed from the model. In addition, in the model, patients remain on index treatment for a relatively short length of time, so the cost-effectiveness is heavily reliant on the subsequent treatment proportions chosen, which, as discussed, are highly uncertain. The results are shown in Table 41.

Table 41: Scenario analysis results: Subsequent treatment excluded

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	7.9042			
IVIg + SoC	[redacted]	7.7057	[redacted]	0.1984	[redacted]
PLEX + SoC	[redacted]	7.7504	[redacted]	0.1538	[redacted]

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

3.3.5.4. Subsequent treatment proportions

A total of three scenarios were conducted on the proportions of patients receiving subsequent treatment. The first was calculated using weighted means of the responses from the Delphi panel, weighting by the number of refractory patients that each clinical expert was currently treating. Refractory gMG in the Delphi survey was defined as:

- The disease has not responded to adequate treatment with steroids and ≥2 nonsteroidal immunosuppressants or these options are contraindicated or not tolerated, and
- The disease is uncontrolled, as defined by an MG-ADL score of ≥6 or a QMG score of ≥12, and
- Patients are being treated with maintenance IVIg or PLEX, or this is being considered.

The second was calculated by including rituximab as a subsequent treatment, applied in the same way as discussed in Section 3.3.5.2. The third was based on expert elicitation captured during individual interviews with four clinicians (see supporting reference for full methods and results for the expert elicitation). Proportions used for the subsequent treatment steady state are shown in Table 42. Results for each scenario are shown in Table 43.

Table 42: Subsequent treatment steady state proportions for scenarios

Treatment	Proportion of patients		
	Weighted Delphi	Delphi including rituximab	Expert elicitation
IVIg	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]
SoC (CSs/NSISTs)	[redacted]	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]	[redacted]

Abbreviations: CS, corticosteroid; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant; PLEX, plasma exchange

Table 43: Scenario analysis results: Subsequent treatment proportions

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Weighted Delphi proportions					
Rozanolixizumab + SoC	[redacted]	8.4100			
IVIg + SoC	[redacted]	8.2463	[redacted]	0.1637	[redacted]
PLEX + SoC	[redacted]	8.2840	[redacted]	0.1259	[redacted]
Delphi proportions including rituximab					
Rozanolixizumab + SoC	[redacted]	8.4426			
IVIg + SoC	[redacted]	8.2811	[redacted]	0.1614	[redacted]
PLEX + SoC	[redacted]	8.3184	[redacted]	0.1242	[redacted]
Expert elicitation					
Rozanolixizumab + SoC	[redacted]	8.4428			
IVIg + SoC	[redacted]	8.2814	[redacted]	0.1614	[redacted]
PLEX + SoC	[redacted]	8.3187	[redacted]	0.1241	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year; SoC, standard of care

3.3.5.5. Response assessment timepoint

A scenario was conducted setting response assessment timepoint to 3 weeks for all treatment. The results are shown in Table 44.

Table 44: Scenario analysis results: Response assessment timepoint of 3 weeks for all treatments

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	8.3786			
IVIg + SoC	[redacted]	8.2518	[redacted]	0.1268	[redacted]
PLEX + SoC	[redacted]	8.2894	[redacted]	0.0891	[redacted]

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

3.3.5.6. Steroid costs from Lee et al

This scenario uses the costs for corticosteroid management from the EAG of TA10986, sourced from Lee et al (40), inflated to 2022/23 (£342.84 for low dose, £2,448.29 for high dose). Cost estimates were calculated using weighted means, either for long- and short-stay non-elective hospital episodes or for consultant and non-consultant outpatient appointments, sourced from NHS reference costs for 2022/2023 for the scenario analysis using the proportion of patients with intolerable AEs reported in Lee et.al. study, ensuring they are as reflective of real-world activity as possible. These calculations led to a cost for patients with intolerable AEs of £3,110.86. However, due to the limitations of the data from Lee et al, the efgartigimod EAG data was used to apply the high-dose costs to the uncontrolled state, and the low-dose costs to the stable health state.

The Lee et al. study has several key limitations for decision making, including the absence of data on AEs for patients not receiving corticosteroids, which makes it challenging to distinguish between AEs caused by corticosteroids and those associated with gMG. Additionally, the study does not specify the severity of AEs, and many may not meet the threshold for severe AEs (grade ≥3), which are typically considered for costing in NICE appraisals. Unlike the Stirnadel-Farrant et al (2023) study, costs according to dose was not included in the Lee et al study.

Table 45: Scenario analysis results: Steroid costs from Lee et al

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	8.4151			
IVIg + SoC	[redacted]	8.2518	[redacted]	0.1633	[redacted]
PLEX + SoC	[redacted]	8.2894	[redacted]	0.1257	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange QALY, quality-adjusted life years; SoC, standard of care.

3.3.5.7. Excluding steroid disutility

A scenario was conducted to assess the effect of excluding the disutility associated with steroid use. The results are shown in Table 46.

Table 46: Scenario analysis results: Steroid disutility excluded

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	8.6005			
IVIg + SoC	[redacted]	8.4473	[redacted]	0.1533	[redacted]
PLEX + SoC	[redacted]	8.4832	[redacted]	0.1174	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange QALY, quality-adjusted life years; SoC, standard of care.

3.3.5.8. Annualised number of cycles for rozanolixizumab

The base case uses the annualised number of infusions ([redacted]); this scenario explored using the annualised number of cycles ([redacted]) instead, assuming 6 infusions per cycle. The results are shown in Table 47.

Table 47: Scenario analysis results: Annualised number of cycles

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	8.4151			
IVIg + SoC	[redacted]	8.2518	[redacted]	0.1633	[redacted]
PLEX + SoC	[redacted]	8.2894	[redacted]	0.1257	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange QALY, quality-adjusted life years; SoC, standard of care.

3.3.5.9. Using IVIg change from baseline in MG-ADL score from the bvNMA

The result from the bvNMA for change from baseline in MG-ADL score showed an increase (worsening) MG-ADL score for IVIg relative to SoC [redacted]). To be conservative, in the base case it was assumed that IVIg would have the same change from baseline as SoC, i.e. the change in score relative to SoC was 0 and the value used in the model was [redacted].

A scenario analysis was undertaken using the actual value for IVIg from the bvNMA, i.e. [redacted] (=[redacted]). The results are shown in Table 48.

Table 48: Scenario analysis results – using IVIg change from baseline in MG-ADL score from the bvNMA

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	8.4151			

IVIg + SoC	[redacted]	8.2312	[redacted]	0.1839	[redacted]
PLEX + SoC	[redacted]	8.2894	[redacted]	0.1257	[redacted]

Abbreviations: bvNMA, bivariate NMA; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; PLEX, plasma exchange; QALY, quality-adjusted life years; SoC, standard of care.

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I5092 Rozanolixizumab for treating antibody-positive generalised myasthenia gravis

Overview of new evidence and modelling updates and results

Addendum

1. Introduction

In the company response to the draft guidance published by NICE for rozanolixizumab for treating patients with AChR or MuSK antibody-positive generalised myasthenia gravis (gMG), there was a small error due to rounding in the model that had a small impact on the costs of rozanolixizumab. This adjustment has had no or very minor impact on the results. In addition, there was an issue detected in the deterministic (DSA) and probabilistic sensitivity analysis (PSA). For DSA, the net monetary benefit (NMB) analysis for PLEX did not function and required expansion of the named ranges used by VBA code. For PSA, response parameters needed correction in the formulae to draw probabilistic values from assigned distributions. All have been corrected, and updated results are presented here. Details of the corrections in the model are provided in the update log sheet in the model.

As per the original document, the base case remains as [redacted] infusions of rozanolixizumab per year, with a scenario of [redacted] cycles per year. All other inputs and calculations remain correct.

2. Model results and scenario analyses

2.1.1. Base case results (discounted)

Table 1: Base case results (discounted)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.4151			
IVIg	[redacted]	8.2518	[redacted]	0.1633	[redacted]
Plasma exchange	[redacted]	8.2894	[redacted]	0.1257	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; QALY, quality-adjusted life years.

2.1.2. Cost-minimisation results

A cost minimisation analysis was undertaken by assuming that the efficacy of all treatments was equal. The response rate, change from baseline in MG-ADL score, and treatment assessment timepoint were set equal to rozanolixizumab for IVIg and PLEX. The distribution of patients in the continued, stable, and loss of response states were set to KOL opinion (equal across all treatments). Disutility for corticosteroid use was removed and no subsequent treatment was assumed. The cost of managing corticosteroids was set equal to IVIg and PLEX for rozanolixizumab meaning that there was no steroid-sparing effect, i.e. all treatments had a cost associated with managing corticosteroids for the continued response health state.

Cost minimisation results are shown in Table 2. The results show that, even when we assume that the efficacy is equal across treatments, rozanolixizumab represents the least expensive treatment option.

Table 2: Cost-minimisation results

Technologies	Total		Incremental	
	Costs (£)	QALYs	Costs (£)	QALYs
Rozanolixizumab	[redacted]	8.0205		
IVIg	[redacted]	8.0205	[redacted]	0.0000
Plasma exchange	[redacted]	8.0205	[redacted]	0.0000

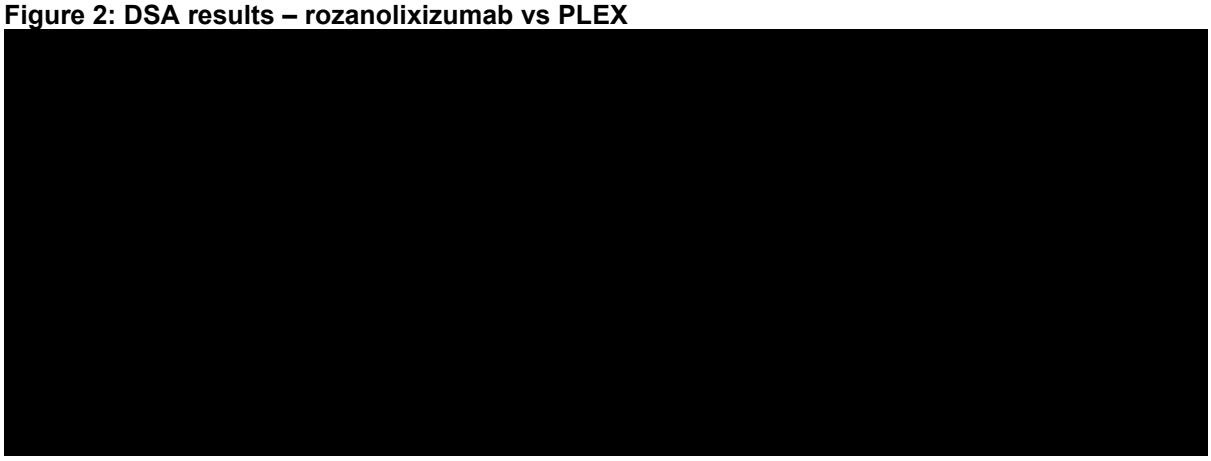
Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; QALY, quality-adjusted life years.

2.1.3. Deterministic sensitivity analysis results

Figure 1: DSA results – rozanolixizumab vs IVIg

Abbreviations: DSA, deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; ICU, intensive care unit; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year.

Figure 2: DSA results – rozanolixizumab vs PLEX



Abbreviations: DSA, deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; ICU, intensive care unit; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year.

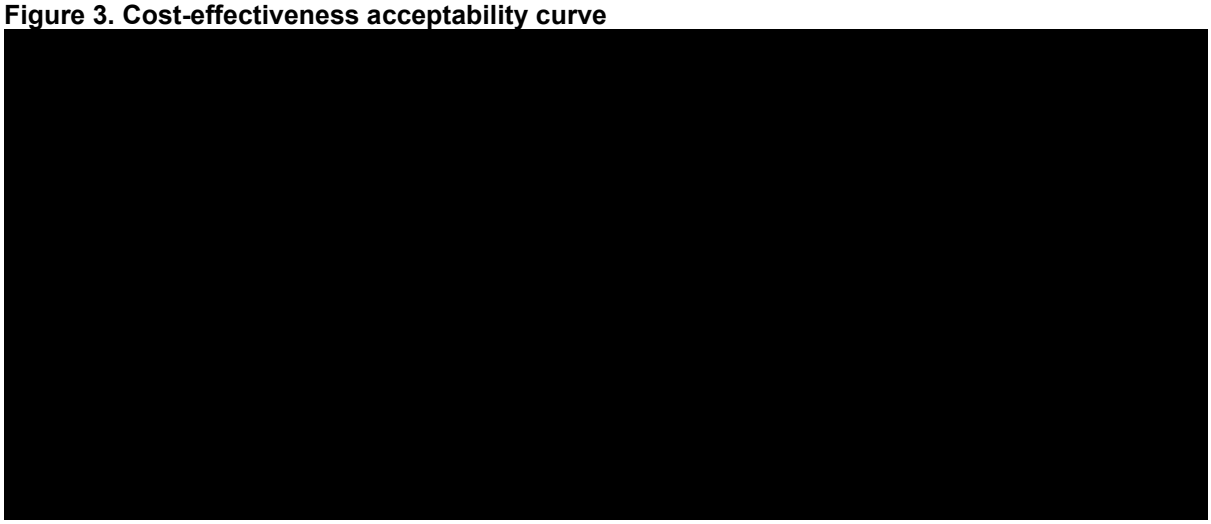
2.1.4. Probabilistic sensitivity analysis results

Table 3. Probabilistic sensitivity analysis results (all parameters varied simultaneously and randomly across 1000 iterations based on predefined probability distributions)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.3567			
IVIg	[redacted]	8.2132	[redacted]	0.14	[redacted]
PLEX	[redacted]	8.2509	[redacted]	0.11	[redacted]

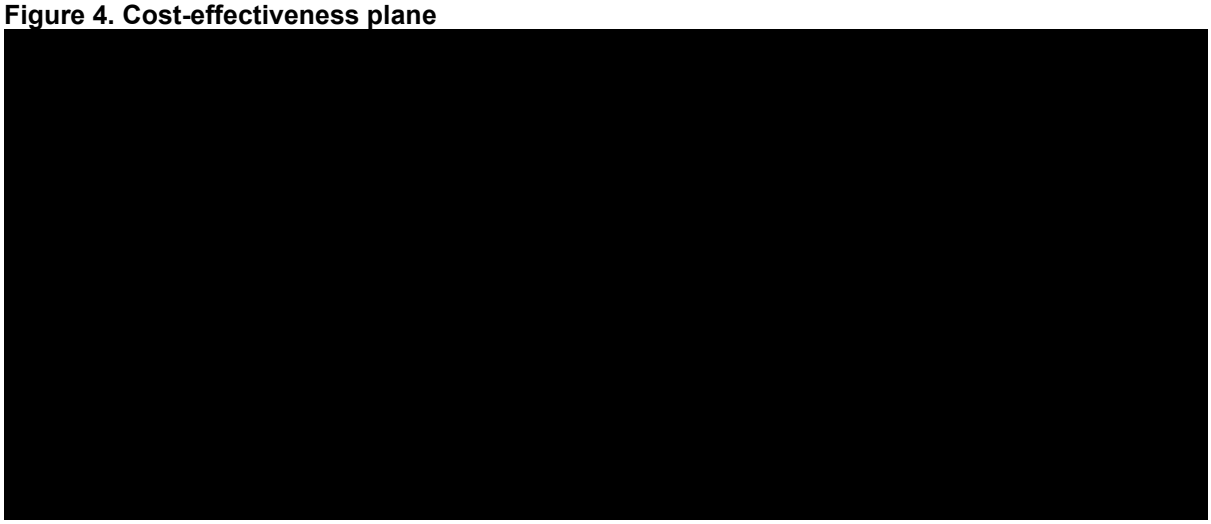
Abbreviations: bvNMA, bivariate network meta-analysis; ICER: incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year.

Figure 3. Cost-effectiveness acceptability curve



Abbreviations: IVIg, intravenous immunoglobulin.

Figure 4. Cost-effectiveness plane



Abbreviations: IVIg, intravenous immunoglobulin; QALY, quality-adjusted life years.

Figure 5: Congruence test results versus IVIg

Abbreviations: IVIg, intravenous immunoglobulin; QALY, quality-adjusted life year.

Figure 6: Congruence test results versus PLEX

Abbreviations: PLEX, plasma exchange; QALY, quality-adjusted life year.

2.1.5. Scenario analyses

2.1.5.1. Scenarios to understand the appropriateness of the blended SoC basket comparator

Table 4: Scenario A results: Comparison vs blended IVIg/PLEX arm (75:25)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.4151			
Blended IVIg/PLEX arm (75:25)	[redacted]	8.2612	[redacted]	0.1539	[redacted]

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

Table 5: Scenario B results

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.4151			
SoC (CSs and NSISTs only)	[redacted]	8.1540			
Rozanolixizumab arm using proportion on SoC from refractory EAMS cohort (75.6% rozanolixizumab, 24.4% SoC) vs basket of care using proportions from revised EAMS cohort (56.7% IVIg, 18.9% PLEX, 24.4% SoC)					
Rozanolixizumab	[redacted]	8.3514			
Basket of care	[redacted]	8.2567	[redacted]	0.0947	[redacted]

Abbreviations: CS, corticosteroids; EAMS, Early Access to Medicines Scheme; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant therapy; PLEX, plasma exchange; QALY, quality-adjusted life years; SoC, standard of care.

Table 6: Scenario C results: 10% cheaper and 10% more effective IVIg and PLEX vs revised EAMS basket of care

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Blended SoC basket using revised EAMS proportions†	[redacted]	8.2567			
10% cheaper and 10% more effective IVIg	[redacted]	8.2752	[redacted]	0.0185	[redacted]
10% cheaper and 10% more effective PLEX	[redacted]	8.3457	[redacted]	0.0890	[redacted]

Abbreviations: EAMS, Early Access to Medicines Scheme; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant therapy; PLEX, plasma exchange; QALY, quality-adjusted life years; SoC, standard of care.

† Comparison with basket of care based on the revised EAMS cohort proportions (56.7% IVIg, 18.9% PLEX, 24.4% SoC).

2.1.5.2. Blended SoC basket comparator

Basket using revised EAMS proportions

Table 7: Scenario analysis results: Rozanolixizumab versus revised EAMS basket

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.4151			
Revised EAMS SoC basket	[redacted]	8.2567	[redacted]	0.1584	[redacted]

Abbreviations: EAMS, Early Access to Medicines Scheme; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

Basket using revised EAMS proportions including rituximab

Table 8: Scenario analysis results: Rozanolixizumab versus revised EAMS basket including rituximab

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.4174			
Revised EAMS SoC basket incl. Rituximab	[redacted]	8.2624	[redacted]	0.1551	[redacted]

Abbreviations: EAMS, Early Access to Medicines Scheme; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

2.1.5.3. Subsequent treatment excluded

Table 9: Scenario analysis results: Subsequent treatment excluded

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	7.9042			
IVIg + SoC	[redacted]	7.7057	[redacted]	0.1984	[redacted]
PLEX + SoC	[redacted]	7.7504	[redacted]	0.1538	[redacted]

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

2.1.5.4. Subsequent treatment proportions

Table 10: Scenario analysis results: Subsequent treatment proportions

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Weighted Delphi proportions					
Rozanolixizumab + SoC	[redacted]	8.4100			
IVIg + SoC	[redacted]	8.2463	[redacted]	0.1637	[redacted]
PLEX + SoC	[redacted]	8.2840	[redacted]	0.1259	[redacted]
Delphi proportions including rituximab					
Rozanolixizumab + SoC	[redacted]	8.4426			
IVIg + SoC	[redacted]	8.2811	[redacted]	0.1614	[redacted]
PLEX + SoC	[redacted]	8.3184	[redacted]	0.1242	[redacted]
Expert elicitation					
Rozanolixizumab + SoC	[redacted]	8.4428			
IVIg + SoC	[redacted]	8.2814	[redacted]	0.1614	[redacted]
PLEX + SoC	[redacted]	8.3187	[redacted]	0.1241	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life year; SoC, standard of care

2.1.5.5. Response assessment timepoint

Table 11: Scenario analysis results: Response assessment timepoint of 3 weeks for all treatments

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	8.3786			
IVIg + SoC	[redacted]	8.2518	[redacted]	0.1268	[redacted]
PLEX + SoC	[redacted]	8.2894	[redacted]	0.0891	[redacted]

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

2.1.5.6. Steroid costs from Lee et al

Table 12: Scenario analysis results: Steroid costs from Lee et al

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	8.4151			
IVIg + SoC	[redacted]	8.2518	[redacted]	0.1633	[redacted]
PLEX + SoC	[redacted]	8.2894	[redacted]	0.1257	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange QALY, quality-adjusted life years; SoC, standard of care.

2.1.5.7. Excluding steroid disutility

Table 13: Scenario analysis results: Steroid disutility excluded

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	8.6005			
IVIg + SoC	[redacted]	8.4473	[redacted]	0.1533	[redacted]
PLEX + SoC	[redacted]	8.4832	[redacted]	0.1174	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange QALY, quality-adjusted life years; SoC, standard of care.

2.1.5.8. Annualised number of cycles for rozanolixizumab

Table 14: Scenario analysis results: Annualised number of cycles

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	8.4151			
IVIg + SoC	[redacted]	8.2518	[redacted]	0.1633	[redacted]
PLEX + SoC	[redacted]	8.2894	[redacted]	0.1257	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange QALY, quality-adjusted life years; SoC, standard of care.

2.1.5.9. Using IVIg change from baseline in MG-ADL score from the bvNMA

Table 15: Scenario analysis results – using IVIg change from baseline in MG-ADL score from the bvNMA†

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab + SoC	[redacted]	8.3988			
IVIg + SoC	[redacted]	8.2137	[redacted]	0.1850	[redacted]
PLEX + SoC	[redacted]	8.2722	[redacted]	0.1266	[redacted]

Abbreviations: bvNMA, bivariate NMA; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; PLEX, plasma exchange; QALY, quality-adjusted life years; SoC, standard of care.

† The QALYs for Rozanolixizumab+SOC and IVIg+SOC previously submitted for this scenario were incorrect. The issue arose because cell F43 in the SubsTx sheet had its formula overwritten with a hardcoded value during the PSA run. This has now been corrected, and the cell has been restored to use the appropriate formula.

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 04 October 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	ABN Neuromuscular Advisory Group

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	[redacted] - None [redacted] – Already submitted to NICE as a clinical expert
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None None
Name of commentator person completing form:	[redacted] and [redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Has all of the relevant evidence been taken into account?** Generally, yes. It would be ideal that the EAG preferred response rate for IVIG/PLEX at 70% had more robust supporting evidence, but it seems reasonable.

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

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	Adding evidence from the use of other treatments such as rituximab, which given late has poor efficacy (40-50% max) and patients at that stage have significant and likely life-long side effects (e.g. hypogammaglobulinemia), would be valuable.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We note that the company would like IVIG/PLEX costs applied every 3-4 weeks, whereas the EAG felt this should be every 6 weeks. In clinical practice, an average interval would be 4 weeks (with some patients receiving treatment more of less frequently). We support the committee's preferred assumption of applying the costs of IVIg and PLEX every 4 weeks. We welcome the committee's acknowledgement in the draft guidance (para 3.15) that there may be benefits of treatment that are not captured in the model. We think these are substantial, including avoiding the side effects of steroids/oral immunosuppression, and avoiding the adverse social consequences of regular hospital visits.
3	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We are aware of the extent of unmet need for new treatments for refractory MG, and hope NICE and the company will be able to work together to reach a positive for recommendation for rozanolixizumab. There is particular unmet need for patients do not respond to, or are unable to be treated with, current therapies. If rozanolixizumab is not judged to be cost-effective in the whole population, we would ask NICE to consider whether there is a subgroup of patients in whom it might be more cost-effective.
4	**Could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology?** Although not directly impacted by equality legislation, we are concerned that patients who are socially and economically disadvantaged may be less likely to receive IVIg/PLEX (because they live further from a neuroscience centre, can't afford to travel, or have caring responsibilities). These groups would particularly benefit from having access to a subcutaneous FcRn inhibitor.
5	**Could have any adverse impact on people with a particular disability or disabilities?** Patients with poor mobility may be not able to attend a centre for PLEX/IVIG, and SCig (Eg VTE disease) or Rituximab (Eg hypogammaglobulinaemia) may not be suitable. For such disabilities, a FcRn inhibitor may be a particularly useful option.
6	We are confident that a careful approach to implementation would make sure FcRN inhibitors are used appropriately and only when they are likely to have the greatest benefit. For instance, commissioners could ask for all cases considered for rozanolixizumab to be discussed in a regional MDT. For instance, in our MDT only around 50% of the patients discussed will require escalation of treatment; others require improvement of their diagnosis, optimisation of their comorbidities, and better use of standard therapy.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 04 October 2024. Please submit via NICE Docs.

second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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.

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Joint submission by myaware and Muscular Dystrophy UK (MDUK).

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	• 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. • Myaware has received funding from Merck totalling £19,641.93 to cover the cost of projects relating to awareness and literature library refresh. • **Muscular Dystrophy UK has received funding the following funding from UCB Pharma in the past 12 months.** • £600 for corporate attendance to the UK Neuromuscular Translational Research Conference in March 2024. • **Muscular Dystrophy UK has received the following funding from comparator treatment company Argenx in the past 12 months** • £2,610 fee for support provided in May 2023 for the gathering of carer insight into the carer disutility caused by generalised myasthenia gravis on July 2024. • **Muscular Dystrophy UK has received the following funding from comparator treatment company Alexion in the past 12 months** • £2,750 for sponsorship of the myasthenia gravis session of its 2023/24 virtual seminar series in February 2024 • **Muscular Dystrophy UK have received the following funding from comparator treatment company Roche in the past 12 months.** • £2,750 for sponsorship of MDUK Virtual Seminar Series - Spinal Muscular Atrophy seminar in October 2023 • £190 payment in kind for Director of Care, Campaigns and Support accommodation costs at Conservative Party Conference in October 2023 • £600 for participation by Director of Care, Campaigns and Support in co-creation exercise on health inequity in November 2023 • £1,050 for the participation of the Director of Research and Innovation in an advisory board in April 2024 • £25,000 to support the work of the UK SMA Newborn Screening Alliance, to which Muscular Dystrophy UK provided the co-secretariat, in October 2023 • £318.00 for a Labour Party Conference pass for the Director of Care, Campaigns and Support in August 2024

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 04 October 2024. Please submit via NICE Docs.

	• **Muscular Dystrophy UK has received the following funding from comparator treatment company Pfizer in the past 12 months** • £8,750 for sponsorship of the UK Neuromuscular Translational Research Conference in March 2024
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No such links exist between either patient organisation.
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the committee may not appreciate the inequality that exists for patients in terms of IVIg treatment. As has been reported, not all NHS trusts are able to offer IVIg treatment as a potential maintenance therapy to refractory patients. IVIg is another example of the existing geographical inequality that exists for MG patients across the UK and therefore this needs to be kept in mind when considering its place in the MG treatment algorithm. In addition, there are several risks associated with IVIg treatment, such as increased risk of thrombosis and infection.
2	We are concerned that the recommendation may imply that the committee has not been able to consider all uncaptured benefits of rozanolixizumab treatment. For example, rozanolixizumab is available as a subcutaneous injection, and patients have the option to be treated at home through this mode of administration. This is a contrast to the lengthy and disruptive IVIg/PLEX treatments that may require hospital stays. At-home treatment also directly benefits families and carers and reduces the emotional, financial, and physical burden of myasthenia gravis.
3	Another benefit is the potential for reducing steroid burden. We are concerned that this recommendation may imply that the committee hasn't quite acknowledged the significant impact long-term steroid reliance has on MG patients. Rozanolixizumab can offer a quicker, more controlled approach to reducing steroid dosage that may never have been possible on standard treatment.
4	A final benefit is that rozanolixizumab has been reported to improve symptom management in MuSK-antibody positive patients as well as AChR-antibody positive patients. This is a significant benefit as there are currently not many other targeted therapeutics that offer relief to this portion of MG patients.
5	Finally, we are concerned that once again, the testimony of patients isn't having the impact it should have when they deliver their experience of living with MG. MG is a lifechanging disease that brings tremendous burden on patients and their families. MG is also a disease that has been treated with blanket approaches, rather than targeted therapy, for a significantly long time. There

NICE National Institute for Health and Care Excellence

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

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	needs to be a period of reflection on the standard treatment pathways and how these impact patients both refractory and otherwise. Generally, patients report they are surviving with what's available, not thriving. For those who do not experience symptom management with standard therapy, there is very little available in terms of alternative treatments. Targeted therapeutics such as rozanolixizumab provide hope and choice for patients who have had neither due to the nature of their disease.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?
Myasthenia gravis is a rare disease with a heterogenous course and therefore having sufficient good quality evidence to support decision making will be difficult.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The burden of morbidity from standard care is not captured well with current evidence.

Are the recommendations sound and a suitable basis for guidance to the NHS?
There is a definite need for additional therapies in myasthenia as current options leave many young patients disabled and unable to achieve their full potential.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?
MG differs in severity with age of onset and therefore gender. It is a milder disease in older men and a more severe disease in younger women. This recommendation is potentially discriminating for women.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?
Rituximab as add on therapy RCT Beat-MG was negative.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Has costing included the likely reduction in hospital / critical care admissions? There are often capacity issues in providing IVIG/PLEX to outpatients, resulting in worsening of clinical condition whilst waiting for this and subsequent admissions, with associated high healthcare burden.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No, there is desparate need in certain individuals for additional treatment options. PLEX availability is patchy and for some IV access is an issue. IVIG is contraindicated in risk in many due to thrombosis risk. Immunosuppressants are frequently not tolerated or high risk (e.g. those who have lymphopenia and hypogammaglobulinaemia). In these circumstances additional immunogloublin modulating therapy with low side effect profile could provide significant benefits to QoL.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?
Women of childbearing potential (or women who often are the primary carer for small children or the elderly) are particularly disadvantaged by this decision. They suffer higher incidence of side effects of current therapies, and many are contraindicated due to pregnancy/breastfeeding considerations. Though Rosi cannot be given during pregnancy, it may allow early stabilisation of the condition to allow these individuals to return to work, or to caring for their families.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?
There is little information about the cost of treatment side effects with steroids and / or other immunosuppressants.

1.2 Recommendations – "Rozanolixizumab"
While this is true, the mode of action is very similar so the benefits are likely to be similar. however rozanolixizumab administration doesn't require central lines etc and would be much less disruptive for the patient

3.2 Current treatment options for gMG – "The ABN guidelines recommend non-steroidal immunosuppressants, such as azathioprine, if remission is not achieved on corticosteroids alone."
It is worth noting that there is very little empirical data to demonstrate that these are effective. They are quite burdensome for the patient as they require regular blood tests, take a long time to work and can cause

significant side effects that would be costly to the patient and the health service.

3.16 Resource use – "The company's model applied treatment costs for IVIg every 3 weeks"
I agree that this frequency of infusion would be very unusual and the gap between infusions is generally much longer

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

1.1 - Recommendations
There is great need for additional drugs for the treatment of patients with MG who have not responded to standard treatment +/- are IVIG or plasma exchange dependent - as an MG neurologist I would like to be able use this drug (in addition to other novel drugs including zilucoplan and efgartigimod) for patients who have noe been adequately controlled with steroids + rituximab

3.2 - Current treatment options for gMG
rozanolixizumab would not replace rescue use because there is currently no evidence for this - this would be a good question for a clinical trial

3.4 - The use of rituximab in the treatment pathway
rituximab is used for treatment refractory MG see commissioning guidelines for rituximab in MG (although they are outdated and limit the use of rituximab)

rituximab is increasingly used early in the MG treatment pathway ie when steroids cannot be weaned to a low dose without causing relapse of symptoms

It is worth noting that MUSK+ patients constitute a minority of MG cases (<5%)

rituximab is being used early in MUSK+ MG - treatment refractory MUSK + MG would be patients who have not responded to rituximab

rituximab is not being used instead of IVIG or PLEX - these treatments are used to keep patients out of hospital (emergency admissions) we would give rituximab and while we wait for its effect would continue to treat patients with IVIG or PLEX to improve their symptoms enough to avoid emergency admissions.

University of Southampton

SHTAC

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Rozanolixizumab for treating generalised myasthenia gravis (ID 5092)

External Assessment Group's critique of the company's response to the Draft Guidance following the first (August 2024) Advisory Committee Meeting

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Fay Chinnery, Research Fellow, Health Economics Lois Woods, Senior Research Assistant, Evidence Synthesis and Information Specialist Joanne Lord, Professorial Research Fellow, Health Economics David Alexander Scott, Professor, 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 Faculty of Medicine University of Southampton G.K.Frampton@southampton.ac.uk
Date completed	21st October 2025

[redacted]

Table of Contents

LIST OF TABLES

LIST OF ABBREVIATIONS

ABN	Association of British Neurologists
ACD	Appraisal committee Decision
AChR	Acetylcholine receptor
ACM	Appraisal Committee Meeting
ACM1	First ACM of this technology appraisal (14th August 2024)
BLRA	Baseline risk-adjusted
BvNMA	Bivariate network meta-analysis
CEM	Cost-effectiveness model
CFB	Change from baseline
CrI	Credible interval
CS	Corticosteroid
DGD1	Draft Guidance Document after the first Advisory Committee Meeting
DGD2	Draft Guidance Document after the second Advisory Committee Meeting
EAG	External Assessment Group
EAMS	Early Access to Medicines Scheme
FcRn	Neonatal fragment crystallizable receptor
FDG	Final Draft Guidance
gMG	Generalised myasthenia gravis
HCRU	Healthcare resource use
ICER	Incremental cost-effectiveness ratio
ISTs	Immunosuppressant therapies
ITC	Indirect treatment comparison
IVIg	Intravenous immunoglobulin
IVIg-C	Caprylate/chromatography purified intravenous immunoglobulin
LPE	Lymphoplasmpheresis
MAIC	Matching-adjusted indirect comparison
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living scale
MPSC	Medicines Procurement and Supply Chain
MSE	Minimal symptom expression
MuSK	Muscle-specific tyrosine kinase
NHSE	NHS England
NMA	Network meta-analysis

nRCTs	Non-randomised controlled trials
NSIST	Non-steroidal immunosuppressant
PAIA	Protein A immunoadsorption
PLEX	Plasma exchange
QALYs	Quality adjusted life years
QMG	Quantitative Myasthenia Gravis scale
RCT	Randomised controlled trial
SCIg	Subcutaneous immunoglobulin
SoC	Standard of care
SLR	Systematic literature review
Tx	Treatment

1 INTRODUCTION

This document is the External Assessment Group (EAG)'s critique of the response by the company, UCB, to the NICE Draft Guidance Document (DGD1), issued 13th September 2024, following the first NICE Advisory Committee Meeting (August 2024) for the technology appraisal of rozanolixizumab for treating antibody-positive generalised myasthenia gravis (ID5092). The EAG received the company's response documents and the revised economic model on 24th September 2025. Updated company economic models and an addendum to the supporting information document were received by the EAG on 8th October 2025.

The documents provided by the company that we refer to in this report, and the names we have used for these documents for brevity, are listed in Table 1 below.

Table 1 Documents provided by the company referred to in this report

Company document name	Document name used in this report
[ID5092] Rozanolixizumab – Draft guidance stakeholder comments form_FINAL_23Sep2025[CON]	Company Response Form
[ID5092] Rozanolixizumab DG response_supporting information_FINAL_23_Sep2025[CON]	Company Supporting Document
ID5092 Rozanolixizumab DG response_supporting information_addendum_v.2.0_06_Oct2025[CON]	Company Supporting Document addendum
[ID5092] rozanolixizumab – MG0007-tables	MG0007 Results Document
[ID5092] rozanolixizumab – 11181_Rituximab expert elicitation survey_FINAL_23Sep2025	Company Rituximab Expert Elicitation Report
[ID5092] rozanolixizumab – 11177_SLR in MG_Clinical update_17Dec2024	Company SLR Report
[ID5092] rozanolixizumab – 11511_Delphi survey report_FINAL_23Sep2025	Company Delphi Survey Report
[ID5092] rozanolixizumab – Bivariate and Baseline Risk Adjusted NMA_Short Report_RLZ	Company NMA Report
ID5092_gMG CEM rozanolixizumab v12_23.09.2025_CON	Company revised model (23-09-2025)
gMG CEM rozanolixizumab v12_06.10.2025_addendum [CON]	Company revised model (06-10-2025)
[ID5092] rozanolixizumab – gMG CEM (rozanolixizumab) – Technical report v2.0_30-07-24_clean	Company Model Report
ID5092_gMG CMA rozanolixizumab v12_23.09.2025_CON	Company CMA model

Company document name	Document name used in this report
gMG CMA rozanolixizumab v12_06.10.2025_addendum [CON]	Company revised CMA model

CEM, cost-effectiveness model; CMA, cost minimisation analysis; DG, draft guidance; NMA, network meta-analysis; SLR, systematic literature review

NICE's first Draft Guidance (DGD1)[1] provided a series of NICE appraisal committee requests and preferences which are listed, with a summary of the company response and EAG comment, in Table 2 below.

In their response, the company provide additional evidence and analysis: a rationale for unmet need, the latest and final results for the MG0007 extension study for rozanolixizumab, and a cost minimisation analysis. These are summarised, with EAG comment, in Table 3 below.

In this report we present the following:

- A summary overview of the company's response to committee requests and preferences and key points of the EAG critique (Table 2)
- A summary overview of the additional evidence provided by the company (Table 3)
- The EAG's critique of the company's response and new evidence (section 2)
- Validation of the results of the company's updated cost-effectiveness analysis (section 3).
- The EAG's preferred assumptions and analyses (section 4)

Table 2 Summary of the NICE appraisal committee's preferred assumptions and recommendations and the company's responses to these

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
1. Expert elicitation on the use of rituximab in the NHS (DGD1 section 3.4)	Not applicable	The company conducted a survey of clinical MG experts at all the specialist MG centres in the UK. They conclude that rituximab is not an alternative to maintenance IVIg and PLEX and that there is much variation in practice when considering use of rituximab as a subsequent treatment (Company response form section 3; Company supporting document section 2.2; Company Rituximab Expert Elicitation Report).	The survey shows consensus among the UK MG specialists consulted that rituximab is not considered an alternative to maintenance IVIg or PLEX. However, the methods of the elicitation are poorly reported, with some aspects unclear. The Association of British Neurologists (ABN) guidelines (2025 update) now incorporate rituximab into the treatment pathway as an option in several places. However, the escalation management flow diagram clearly positions rituximab before IVIg and PLEX. Discussed in sections 2.1 and 2.12.1.1 below.

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
2. A systematic literature review that includes phase 2 and single-arm trials, and real-world evidence on IVIg and PLEX for the outcome of MG-ADL or other relevant outcomes for the indirect comparison of rozanolixizumab with IVIg and PLEX (DGD1 section 3.10)	ID4008 FDG: the September 2024 update of the company SLR was considered by the EAG to have identified all relevant evidence for IVIg and PLEX for the same gMG indication that is currently being appraised for rozanolixizumab.	The company updated their SLR in September 2024 to identify further evidence for IVIg and PLEX not limited to RCTs. Additional studies included from the updated searches were: Leng 2024, Duan 2023 and Barnett 2017. Additionally, NCT02473952 was published and identified after the searches were run. Two studies previously identified were also included in the SLR (Zinman 2007 and Barth 2011). Company SLR Report; Section 7 pages 18-19 of the company response form.	The updated SLR is the same as that conducted for ID4008. It has identified all the relevant evidence. No relevant single-arm studies were identified that might enable a matching adjusted indirect comparison (MAIC). See section 2.2.1 below.
3. An improved indirect treatment comparison (DGD1 sections 3.10, 3.12) An indirect treatment comparison that addresses points (a) to (f) listed below:	See each point (a) to (f) below	See each point (a) to (f) below	The company carried out two sets of NMAs, one using bivariate methods and one using baseline risk-adjusted methods. The NMAs report both response and CFB outcomes; only the response outcomes are used in the economic model. See each point (a) to (f) below.

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
(a) uses data from more of the identified studies	Bivariate NMAs were conducted in ID4008 that included studies which reported both MG-ADL and QMG outcomes as well as those reporting only QMG, to enable MG-ADL estimates to be obtained from a larger number of studies.	Bivariate NMAs were provided in this response which include the same additional RCTs from the original SLR and the September 2024 update SLR as were included in the ID4008 bivariate NMAs. This maximises the number of studies in the NMAs from which the MG-ADL outcome can be estimated.	We agree the committee recommendation has been carried out.
(b) includes IVIg and PLEX	The bivariate NMAs in ID4008 included additional studies for which MG-ADL could be estimated, enabling additional evidence for IVIg and PLEX to be explored. The EAG suggested that none of the new PLEX studies were appropriate to add to the networks although including them was likely inconsequential for the NMA results.	The updated NMAs in this response include the same additional studies on IVIg and PLEX as included in ID4008.	We agree the committee recommendation has been carried out, and introducing PLEX studies has been explored. The EAG maintains that none of the new PLEX studies were appropriate to add to the network but their inclusion by the company is does not affect existing conclusions. See section 2.2 below.

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
(c) considers outcomes other than MG-ADL response rate to produce estimates of relative effectiveness	ID4008: As noted above, bivariate NMA methods were used to include studies that assessed QMG. The bivariate NMAs were accepted by the ID4008 NICE committee as appropriate for decision making while acknowledging the associated uncertainties (ID4008 FDG section 3.11).	As in ID4008, bivariate NMA methods were used to include studies that assessed QMG.	We agree the committee recommendation has been carried out. Results from the bivariate NMAs inform the cost-effectiveness model base case (which also aligns with the committee preferences in ID4008). See section 2.2.6 below.
(d) accounts and adjusts for the differential placebo response or adjusts for baseline risks with an informative prior	ID4008: Baseline risk-adjusted NMA methods were used to adjust for the differential placebo response across studies. A 2-step approach to combine this with the bivariate NMA method was also explored but could not be verified by the EAG.	As in ID4008, the company conducted baseline risk-adjusted NMAs to adjust for placebo response heterogeneity across the studies. A 2-step approach to combine the baseline risk-adjusted NMAs with the bivariate NMAs was not carried out.	We agree the committee recommendation has been carried out. However, it was not possible to carry out both committee recommendations in one set of NMAs. Both bivariate and baseline risk-adjusted NMAs have associated uncertainties. See section 2.2 below.

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
(e) maintains randomisation	ID4008: In the company's updated (i.e. latest) NMAs randomisation was maintained by using the response probabilities (i.e. response rates) for each treatment directly from the NMA results.	The conversion of the NMA results' odds ratios to relative risks with adjustment via a referent placebo response calculation, which was done in the original submission has been superseded by obtaining response rates directly from the NMA results.	We agree the committee recommendation has been carried out.

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
(f) includes subsequent treatment with IVIg and PLEX (and potentially rituximab, if relevant) in the modelling, and the effect of this on the cost-effectiveness estimates.	ID4008 zilucoplan FDG section 3.16: The Committee concluded that the appropriate approach to model subsequent treatment should use the overall EAMS cohort to inform the proportions of people on initial IVIg, PLEX, and NSISTs and/ or corticosteroids only in the 'basket' of standard care arm. The 'basket' of SoC should be applied consistently in both arms (this is also consistent with the approach in the efgartigimod appraisal, TA1069 FDG section 3.15). The EAG considered that the proportion of people switching from IVIg to PLEX and vice versa in the 'basket' of the SoC arm was reasonable albeit with uncertainties.	The company model includes subsequent treatment in the base case by using a standard of care basket; results of a company Delphi panel survey support company proportions for people receiving index treatment and subsequent treatment; a scenario analysis explored incorporating rituximab in the subsequent treatment basket (Company Response Form section 4, page 17, and section 9, pages 20 to 21; Company Supporting Document section 3.1.6).	We agree the ID5092 committee recommendation has been carried out. However, the company base case does not align with committee preferences from the ID4008 appraisal because the company use a revised EAMS cohort instead of the overall EAMS cohort to inform proportions of people receiving initial treatments. The EAG base case uses the overall EAMS cohort. Modelling subsequent treatments is challenging and the uncertainties are discussed in section 2.12.1 below.

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
4. Scenario analyses that incorporate some of the potentially uncaptured benefits of rozanolixizumab (DGD1 sections 3.15, 3.21 and 3.22)	In the ID4008 appraisal, the company explored scenarios where the model included: 1. A utility decrement associated with corticosteroid use 2. The disutility associated with IVIg and or PLEX use 3. Carer disutility The committee preferred to consider 1 and 3 qualitatively and that 2 was included in the model (ID4008 FDG section 3.27). ID4008 DG1 section 3.12: the committee's preferred carer disutilities were not included in the model; the qualitative benefits of efgartigimod on carers was considered (TA1069 section 3.18).	Company Supporting Document 3.1.7 describes the benefit of at-home subcutaneous administration of rozanolixizumab, in terms of NHS staff and patient hours saved per year. Company Supporting Document 3.1.10 states that the updated model incorporates the parameters for caregiver disutilities.	The revised company model includes the disutility associated with corticosteroid use. The company conducted a scenario analysis excluding this disutility (Company Supporting Document 3.3.5.7). We prefer to exclude this disutility in our base case, in line with the committee preferences given in ID4008 FDG 3.27. The company base case does not include a disutility for IVIg/PLEX administration. Carer disutilities are not included in the company base case and we prefer to also exclude them from the EAG base case. Discussed in section 2.4 below.

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
The comparators should be modelled as a 'basket' of standard care, with some people having IVIg, some having PLEX, and some having neither. (DGD1 section 3.6)	ID4008 FDG section 3.27: A 'basket' of standard care is the appropriate comparator, with some people having IVIg, some having PLEX, and some having neither; everyone should have corticosteroids and NSISTs; the unrevised EAMS cohort [i.e. 14.6% of patients receive PLEX, 43.8% IVIg, and 41.6% receive SoC (corticosteroids/immunosuppressants)(Moniz Dionisio 2024)[2] should be used to inform the proportion of people on treatment in the 'basket' of standard care.	Company Supporting Document 3.3.5.2: The company does not agree that a basket of standard care is a relevant comparator and excludes it from their base case. The company provided scenario analyses of rozanolixizumab versus: 1) a basket using revised EAMS proportions ([redacted] of patients receive PLEX, [redacted] IVIg, [redacted] receive SoC 2) a basket using revised EAMS proportions incorporating rituximab ([redacted] of patients receive PLEX, [redacted] IVIg, 10.5% rituximab, and [redacted] receive SoC).	We prefer to use the standard of care basket in our base case, comprising treatment proportions informed by the original EAMS cohort. We present a scenario analysis using a standard basket that includes rituximab. See section 4 below.

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
Everyone should have corticosteroids and immunosuppressants (DGD1 section 3.6)	ID4008 FDG section 3.27: A 'basket' of standard care is the appropriate comparator, with some people having IVIg, some having PLEX, and some having neither; everyone should have corticosteroids and immunosuppressants.	Not specifically addressed in the Company Supporting Document.	Costs for corticosteroids and immunosuppressants (azathioprine, mycophenolate, cyclosporine, tacrolimus, methotrexate and pyridostigmine) are included for all modelled treatments.
Zilucoplan and efgartigimod should not be included as comparators (DGD1 section 3.6)	Not applicable	Not applicable	Zilucoplan and efgartigimod are not included in the company's revised model. The committee preference remains relevant due to both treatments receiving negative recommendations and therefore not being established clinical management.

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
The results of the whole-trial populations of MycarinG can be generalised to those with refractory gMG in the NHS (DGD1 sections 3.7 to 3.9)	The committee has preferred that whole trial populations be used in this disease area in previous appraisals. For example, ID4008 FDG section 3.27: Results of the whole trial populations of RAISE and RAISE-XT can be generalised to those who would have zilucoplan in the NHS.	Not specifically addressed in the Company Supporting Document.	The participant characteristics given in Company Supporting Document section 3.2.1 are for the overall population from MycarinG and are used in the economic model. See section 2.8 below.

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
Any uncertainty from indirect comparisons should be incorporated in the model (DGD1 sections 3.10 and 3.13)	ID4008 FDG section 3.10: The committee were concerned that the uncertainty in the NMAs was not carried through into the modelling because the response rate estimates were included as point estimates, without credible intervals.	Not specifically addressed in the Company Supporting Document.	The revised model uses point estimate response rates from the bivariate NMA (Company Supporting Document section 3.1.4). These values are included in the deterministic and probabilistic sensitivity analyses and are varied using an assumed standard error of 10%. We believe the company should instead have provided credible intervals for the response rates obtained from the NMA and used these in the economic model to more accurately reflect the uncertainty. See section 2.9 below. We note that the odds ratios produced in the NMA have wide credible intervals, suggesting that credible intervals of the response rates would also be wide. See section 2.2.6 below

NICE appraisal committee's preferred assumptions and recommendations in ID5092 DGD1	How issue was addressed in previous NICE evaluation and committee's preferred assumptions	Summary of the company's response	EAG comments
The response assessment timepoint should be 3 weeks for IVIg and PLEX, but 6 weeks is more appropriate for rozanolixizumab (DGD1 section 3.14)	ID4008 FDG section 3.17: The committee concluded that a response assessment timepoint of 3 weeks (for IVIg and PLEX) reflected NHS practice.	The response assessment timepoint used in the company's base case is 6 weeks for rozanolixizumab and 3 weeks for IVIg and PLEX (Company Supporting Document 3.1.2)	The response assessment timepoint is 6 weeks for rozanolixizumab and 12 weeks for the SoC basket in the company's base case. We prefer to use a response assessment timepoint of 3 weeks for the standard of care basket in our base case, given that it includes IVIg and PLEX. See section 2.10 below.
The costs of IVIg and PLEX should be applied every 4 weeks, and the NHS reference cost should be used for PLEX administration (DGD1 section 3.16)	ID4008 FDG section 3.23: The committee concluded that IVIg and PLEX costs should be applied every 4 weeks and that the NHS reference cost for PLEX [SA44A – Single Plasma Exchange (£910)] should be used.	The dosing frequency for IVIg and PLEX is every 4 weeks in the updated model (Company Supporting Document 3.1.3)	We agree the dosing frequency change is applied correctly. However, we note the PLEX administration cost is set to £0 within the model; we prefer this is £993 (SA44A – Single Plasma Exchange; National Schedule of NHS Costs 2023/24) applied 5 times every 4 weeks. See section 2.11 below.

Abbreviations: ACM1, First Appraisal Committee Meeting; CFB, change from baseline; DGD1, Draft Guidance Document in response to the first Advisory Committee Meeting; EAMS, efgartigimod Early Access to Medicines Scheme; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis Activities of Daily Living score; MSE, minimal symptom expression; NMA, network meta-analysis; NSIST, non-steroidal immunosuppressant therapy; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis score.

Table 3 Additional evidence provided by the company

Evidence	Summary of the company's response	EAG comments
A summary of the evidence-base for unmet need in the refractory gMG population	Section 1 of the Company Supporting Document provides a review of the literature.	Not requested by the committee. Unmet need for this population is already acknowledged by the committee in DGD1 section 3.1. The EAG has therefore not considered this evidence further in this critique.
Final results from the extension phase of MG0007 for rozanolixizumab.	The company report results from the final data cut of MG0007, including patient disposition, efficacy outcomes, use of rescue therapy, and safety results (Company Supporting Document section 2.1). A supportive statement on dose switching and treatment effect in MG0007 (Company Response Form section 6).	It is appropriate to report the latest, and final, results from the MG0007 extension study. In addition, the latest MSE results are used to inform the economic analysis. See section 2.3 below.
A cost-minimisation analysis (CMA) for rozanolixizumab versus IVIg and PLEX.	Carried out to show that if the efficacy of rozanolixizumab is assumed to be equal to that of IVIg and PLEX it would still be cost-saving compared to both IVIg and PLEX (Company Response Form page 9; Company Supporting Document section 3.1.1). A separate CMA model was provided, and results that demonstrate cost-saving are reported in the Company Supporting Document section 3.3.2. These were superseded by the updated CMA model and supporting information addendum provided on 8th October.	We prioritised the CEM in our critique because a CMA analysis was not requested by the NICE committee. Rozanolixizumab is being assessed via the standard technology appraisal pathway, not the cost-comparison route. Consequently, assessing a CMA is not necessary.

Abbreviations: CEM, cost-effectiveness model; CMA, cost minimisation analysis; DGD1, Draft Guidance Document in response to the first Advisory Committee Meeting; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living score; MGC, Myasthenia Gravis Composite score; MSE, minimal symptom expression; NMA, network meta-analysis; PLEX, plasma exchange.

2 EAG CRITIQUE OF THE COMPANY'S RESPONSE TO THE APPRAISAL CONSULTATION DOCUMENT

2.1 Expert elicitation on the use of rituximab in NHS practice

The NICE appraisal committee requested an expert elicitation of how rituximab is currently used in NHS practice (DGD1 section 3.4), to understand:

- whether rituximab is used as a treatment option, and if so whether it is a targeted treatment option as an alternative to IVIg and PLEX, or a subsequent treatment option after targeted treatment is stopped,
- whether the rituximab treatment options differ for patients with refractory AChR antibody-positive gMG, refractory MuSK antibody-positive gMG, or everyone with refractory gMG and,
- whether there is variation in the use of rituximab in practice.

The company carried out an expert elicitation of 11 specialist MG clinicians across the UK (Company Response Form section 3; Company Supporting Document section 2.2; Company Rituximab Expert Elicitation Report). An anonymous online survey link was sent to all specialist MG centres in the UK (N=11; one in Scotland, the remainder in England) and there was a 100% response rate so the results should be comprehensively representative of specialist MG treatment in the UK. Rituximab use is not limited to use in specialist MG centres, but as rozanolixizumab is likely to be limited to use in specialist MG centres, it is appropriate to focus the survey on this population. The list of centres is not reported and cannot be verified, but comprehensive regional coverage is claimed.

The survey consisted of 13 questions which are not listed in the report, nor was a copy of the survey provided to the EAG. The company report notes that two of the respondents stated that some of the questions could have been more flexible or improved to obtain clearer answers. However, the EAG cannot comment on the survey structure or the questions as these were not provided in the company response.

Figure 4 in the Company Supporting Document shows a treatment pathway with categories A to I alongside each treatment stage which was presented to the survey respondents. Category H, "as an alternative option to IVIg/PLEX" is the intended position of rozanolixizumab (Company Supporting Document section 2.2.7), so if any respondents positioned rituximab here it could be considered a relevant comparator. No respondents

selected category H for using rituximab as an alternative option to IVIg/PLEX for either AChR antibody-positive patients or for MuSK antibody-positive patients.

The expert elicitation results generally align with the treatment pathway diagram in the recently updated ABN guidelines[3] which positions rituximab as a treatment option at several timepoints, and the simplified myasthenia management escalation diagram in the guidelines' supplemental information shows that rituximab is considered much earlier in the treatment pathway than novel therapies such as complement or FcRn inhibitors for both AChR and MuSK antibody-positive gMG.[3] Therefore, we do not consider rituximab as a direct comparator with rozanolixizumab but as a part of the basket of standard of care (SoC), for which the company provide a scenario analysis in the cost-effectiveness model (section 3.2 below).

The survey shows variability in the use of rituximab as a subsequent treatment (see also section 2.12.1).

EAG conclusion on rituximab relevance

Rituximab is not a direct comparator with rozanolixizumab as found by the expert elicitation survey and supported by the recently updated ABN guidelines. The current relevant comparator is SoC, i.e. the group of immunosuppressant therapies (ISTs), IVIg and PLEX treatments, which should also include consideration of a proportion of patients receiving rituximab. This is the same SoC that the EAG represent as a 'basket' of treatments in the economic analyses.

2.2 Clinical effectiveness: Updated indirect treatment comparison

As outlined in Table 2 above, the company updated their original NMAs by including additional studies on IVIg and PLEX identified from their updated systematic literature review (SLR). They carried out two sets of NMAs. One NMA used bivariate methods to allow for the inclusion of studies assessing QMG as well as MG-ADL, and the other used baseline risk-adjusted methods to adjust for the differential placebo response that was observed across the included studies. No one method was identified that addressed both objectives of including data from more of the identified studies and to include PLEX, and to deal with the differential placebo response.

2.2.1 Study selection for NMAs

The company updated their SLR in September 2024, and this informs the new NMA networks for this response which required inclusion of studies that reported the Quantitative

Myasthenia Gravis scale (QMG) outcome and the inclusion of further studies, e.g. non-randomised studies (nRCTs), for IVIg and PLEX. A copy of the Company SLR Report (version 2.0 from October 2024) was provided with the response.

The September 2024 update searches identified three new publications of RCTs on patients with moderate to severe MG with relevant comparator arms (Company SLR Report Table 4), of which one is the NCT02473952 trial[4] and the other two being additional publications for RCTs already identified in earlier searches. The SLR also identified eight new observational studies (Company SLR Report Table 5). We note that Tables 4 and 5 in the Company SLR Report show the same RCTs and observational studies that had been identified by the company in the appraisal of zilucoplan for MG (ID4008) (as listed in Tables 1 and 2 of the ID4008 company "SLR in MG Clinical update 17 Dec 2024"). Thus, the company's SLR update for rozanolixizumab does not include any new clinical evidence beyond that already identified in the company's response to the latest (DGD2) stage of the zilucoplan appraisal ID4008. We checked the company's search methods and review methods generally, and we believe that all relevant evidence, both RCT and non-RCT (including single-arm cohort studies that might inform a matching-adjusted indirect comparison, MAIC), for PLEX and IVIg has likely been identified.

2.2.2 Updated evidence networks

Based on their SLR update, the company have added six new studies to their NMAs, as shown in Table 4 below. As the rozanolixizumab SLR is the same as the latest zilucoplan SLR, the evidence networks in both appraisals are also the same and hence the EAG's critique of the latest NMAs in the zilucoplan appraisal ID4008 also applies to the present appraisal of rozanolixizumab.

To recap, the revised inclusion criteria for the NMAs (to include studies reporting the QMG outcome to enable bivariate NMAs) meant that three further studies which had been previously identified are now included in the networks (Zinman 2007[5], Barth 2011[6], and the NCT02473952 RCT[4]), one of which had previously informed a company MAIC for rozanolixizumab versus IVIg (Barth 2011[6]). The remaining studies are three of the eight newly identified observational studies (Barnett 2017[7], Duan 2023[8] and Leng 2024[9]) which included IVIg and/or PLEX (Table 4).

Table 4 Characteristics of the newly included studies listed by the company

Study	Outcomes	Comparators	NMAs study assigned to
Barth 2011 [6] (RCT, Canada)	● QMG response ● QMG CFB	● IVIg (N=41) ● PLEX (N=43)	● Bivariate (study included previously) [a]
Zinman 2007 [5] (RCT, Canada)	● QMG CFB	● IVIg (N=24) ● Placebo (N=27)	● Bivariate (study included previously)
NCT02473952 [4] (RCT, international) [b]	● MG-ADL response [c] ● QMG response ● QMG CFB	● IVIg-C (N=30) ● Placebo (N=32)	● Bivariate ● Baseline risk (study included previously)
Barnett 2017 [7] (Prospective non-RCT, Canada)	● MG-ADL CFB ● QMG CFB	● IVIg/PLEX (N=55) [d] ● Prednisone (N=50) ● Control (N=54) [e]	● Bivariate ● Baseline risk (new study)
Duan 2023 [8] (Retrospective non-RCT, China)	● QMG response ● QMG CFB	● PLEX (N=62) [f] ● LPE (N=62)	● Bivariate (new study)
Leng 2024 [9] (Retrospective non-RCT, China)	● QMG CFB	● PLEX (N=3) [f] ● PAIA (N=4)	● Bivariate (new study)

CFB, change from baseline; IVIg, intravenous immunoglobulin; IVIg-C, caprylate/chromatography purified intravenous immunoglobulin; LPE, lymphoplasmapheresis, MG-ADL, Myasthenia Gravis Activities of Daily Living scale; PAIA, Protein A immunoadsorption; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis scale; RCT, randomised controlled trial.
[a] Barth 2011 informed a company MAIC previously but was not previously included in any NMAs.
[b] 25 centres across Europe, Canada and the United States, none in UK.
[c] Response determined by improvement in MG-ADL score of $\geq$2 points; other studies used improvement in MG-ADL score $\geq$3 points.
[d] Treatments not separable but the company assigned this group to the IVIg node of the evidence network (Clarification Response A14 of ID4008).
[e] The control arm was not used because relevant outcome data was not reported for this group (Clarification Response A14 of ID4008).
[f] Duan 2023 and Leng 2024 do not contribute PLEX as a comparator but instead contribute LPE and PAIA respectively as comparators in the network.

The company have not reported an NMA feasibility assessment for the identified studies, and do not discuss whether the studies are sufficiently homogeneous in their characteristics to permit their inclusion in the NMAs, so the appropriateness of including several of the studies in the NMAs is unclear. The EAG disagree with including the studies by Barnett 2017, Duan 2023, and Leng 2024 in the NMA networks (Company NMA Report Figures 1 and 2) for the following methodological and generalisability reasons:

- Barnett 2017[7] was a Canadian prospective study which recruited patients at one centre between June 2014 and June 2016. The company have not explained their interpretation of this study in their Company Response Form, Company SLR Report, or Company NMA Report. However, according to Clarification Response A14 for ID4008 the company did not use the control group in the NMA because the study does not report outcome data for this group. Instead, the company regard the prednisone group as a placebo group in the evidence network, but the appropriateness of this is uncertain because the study publication does not report the background standard of care treatments received by each of the study groups. Furthermore, in this study outcomes for IVIg and PLEX are not separable. The company considered the IVIg/PLEX group as an IVIg node in the evidence network due to similar IVIg/PLEX efficacy and the ease of administration, lower risk profile, and widespread use of IVIg (Clarification Response A14 for ID4008). The EAG disagree with these criteria for interpreting IVIg/PLEX as being an IVIg group rather than a PLEX group and we note that including this study adds uncertainty to the NMA interpretation.
- Duan 2023[8] was a retrospective study of patients who were treated at three hospitals in China between November 2016 and June 2022. The company do not discuss how the PLEX and comparator group were selected and whether this might have been subject to bias. Furthermore, while the Duan study includes a PLEX arm, it lacks a common comparator arm to link PLEX to the network. So, instead of adding PLEX to the network the Duan study adds lymphoplasmapheresis (LPE) (Table 4) which is not a relevant comparator in this appraisal.
- Leng 2024[9] was a retrospective study of patients who were treated at one hospital in China between January 2021 and January 2023. This study had only three patients with generalised myasthenia gravis in the PLEX group. In Clarification Response A13 for ID4008, the company clarified both that they expected this study to have negligible effect in the network and that they believed sample size should not be a reason to exclude studies given the limited available data for IVIg and PLEX. It is unclear whether there was any overlap of the Duan and Leng studies, as these appear to have included the same hospital. Furthermore, while the Leng study includes a PLEX arm, it lacks a common comparator arm to link PLEX to the network. So, instead of adding PLEX to the network the Leng study adds Protein A immunoadsorption (PAIA) (Table 4) as a comparator which is not relevant in this appraisal.

The company's response does not acknowledge the geographical locations of the included studies and the company do not consider whether the studies conducted in China and Canada would be generalisable to the UK. The company also do not justify the rationale for including retrospective observational studies (Duan and Leng) in an NMA that is based on RCTs or consider whether this would violate any of the assumptions of NMA.

Without the additional observational studies there is only limited PLEX evidence, from the Barth 2011 study.

EAG conclusion

The EAG believe that the company have identified all relevant studies of IVIg and PLEX. However, several studies on PLEX have been inappropriately included in the evidence networks and do not reduce uncertainty. Consequently, the updated NMAs include the same limited PLEX evidence that was available prior to DG1 but they do include more evidence for IVIg.

2.2.3 Risk of bias of studies included in the NMAs

The company provided summary assessments of the RCTs included in the NMAs, using the NICE checklist framework, but without any justification of the judgements made (Table 11 of the Company SLR Report). However, the table does not include an assessment of the newly included NCT02473952 RCT, therefore the extent of bias that this study introduces into the networks has not been discussed and is uncertain. The EAG briefly looked at potential key sources of bias in this trial and we note that patients in the IVIg arm were around six years older, around 5kg heavier, and had a 3-year shorter time since diagnosis, than those in the placebo arm and therefore there is a high risk of selection bias. The company had provided a summary of risk of bias for NCT02473952 in Table 11 of their updated SLR Report for ID4008, where they implied there were also issues with randomisation and/or allocation concealment and with withdrawals but did not discuss these, and did not mention the imbalance in patient characteristics. Barth 2011 was assessed by the company to have some concerns of risk of bias associated with randomisation and allocation concealment and to be at low risk of bias in all other domains; Zinman 2007 was assessed to be at low risk of bias in all domains (Table 11 of Company SLR Report), and the EAG agree. The company do not discuss the impacts of these risks of bias on interpretation of the NMA results.

The company used the Effective Public Health Practice Project (EPHPP) checklist to assess the quality of the newly identified observational studies and present their assessment as an overall summary of seven of the eight studies (Company SLR Report Figure 5). The company do not report which study was not assessed, and it is impossible to distinguish individual assessments for the Barnett 2017, Duan 2023, and Leng 2024 studies that were included in the NMAs. Therefore, the extent of bias that these studies introduce into the networks has not been discussed and is uncertain.

The company have not discussed the implications of the risk of bias assessments, or lack thereof, for the new NMA networks.

EAG conclusion on the risk of bias

Risk of bias has not been reported for any of the newly included studies in the NMAs, and the implication of introducing uncertain risk of bias into the networks has been overlooked. The EAG considers the NCT02473952 RCT to have a high risk of selection bias due to unbalanced characteristics of the trial arms; and the observational studies (Barnett 2017, Duan 2023 and Leng 2024) as being at high risks of bias due to Duan and Leng being retrospective and Barnett conflating the IVIg and PLEX therapies. This increases uncertainty in the NMA results.

2.2.4 NMA heterogeneity assessment

The Company NMA Report does not consider the heterogeneity of the studies included in the evidence networks, nor is consideration given to the impact on heterogeneity of adding the newly identified studies to the networks. Statistical heterogeneity, e.g. I^2 and Chi^2 statistics, are not reported. The Company SLR Report tabulates the study characteristics and patient characteristics of all the studies included in the SLRs (Tables 6, 7, 9 and 10 of the Company SLR Report), and there is some textual summary, but it is not specific for the subset of the studies included in the NMAs.

EAG conclusion on study heterogeneity

The company have not assessed the impact of including new studies on the between-study heterogeneity in their updated NMAs. This adds uncertainty to the NMA results.

2.2.5 NMA statistical approach and validation

The original submission for rozanolixizumab used a standard Bayesian NMA approach which the company refer to as their "conventional NMA". In their response to DGD1, the company have provided bivariate NMAs (to make best use of all available outcome measures) and baseline risk-adjusted NMAs (to adjust for placebo response heterogeneity across studies). They used a Bayesian framework based on a random-effects model for both sets of NMAs which the EAG agree is appropriate. The WinBUGS code for both NMAs (bivariate and baseline risk-adjusted) is provided in the appendix of the Company NMA Report; the EAG was able to validate the code and we have not identified any concerns.

In the original rozanolixizumab company submission, the odds ratios from the NMAs reporting the differences between each treatment and placebo were converted to relative risks and adjusted using a referent placebo response calculation for use in the economic model (EAG Report section 4.2.6.1) which did not respect the randomisation of the trials included in the NMAs. Section 3.1.4 of the Company Supporting Document for this response states that the response rates of [redacted] for rozanolixizumab, [redacted] for IVIg and [redacted] for PLEX are from the bivariate NMA. These response rates are the same no matter whether the observational studies (nRCTs) are included in the network or not (Company NMA Report Appendix: MGADL absolute response rates and treatment effect, page 25), therefore we believe the newly added observational studies do not impact the results. No referent response rate calculation has been applied, as the response rates for each therapy have been obtained directly from the NMA response probabilities. We therefore judge that randomisation has been respected.

Both NMAs (bivariate and baseline risk-adjusted) compare each treatment versus placebo; there are no results reported for rozanolixizumab versus IVIg or PLEX individually. This aligns with the inputs required for the company cost-effectiveness model, but the EAG would have preferred also to see results for the comparison between PLEX and IVIg for comparison of clinical effectiveness, similar to the tabulated pairwise results reported in the original submission's NMAs.

EAG conclusion on the NMA statistical approach

The overall statistical approach to the NMA methods is appropriate and the committee request for maintaining randomisation has been met.

2.2.6 NMA results

The NMA results in the Company Supporting Document (section 2.4) are provided for each intervention (rozanolixizumab, IVIg and PLEX) compared against placebo. The NMAs in the original company submission reported results for each intervention (rozanolixizumab, efgartigimod and zilucoplan) versus placebo, and for rozanolixizumab versus efgartigimod and zilucoplan; but not any NMA results for IVIg or PLEX. The current company response also does not report results for rozanolixizumab versus IVIg or PLEX. Therefore, these results are not wholly comparable with the results from the original submission.

Note that although the NMA methods and evidence networks are the same as for the company's response to DG2 in the zilucoplan appraisal ID4008, the NMA results differ for two reasons. Firstly, the MG-ADL response is measured as a ≥2-point improvement (the minimum clinically important difference) whereas the NMAs in the zilucoplan appraisal ID4008 evaluated response as a ≥3-point improvement (slightly more stringent). Secondly, the correlation coefficients in the bivariate NMAs are derived from the different respective pivotal trials for rozanolixizumab and zilucoplan: here the correlation coefficients are derived from the MycarinG trial (Company NMA Report Table 5).

The bivariate NMA results inform the cost-effectiveness model which is appropriate because this NMA method was preferred by the NICE appraisal committee for decision making in the previous ID4008 zilucoplan appraisal.

2.2.6.1 Bivariate NMA results

The bivariate NMAs included six studies which reported both MG-ADL and QMG response (Company NMA Report Table 2), and 13 studies which reported both MG-ADL and QMG change from baseline (Company NMA Report Table 1).

The company report the probability of MG-ADL response ≥2 points as [redacted]% for rozanolixizumab, [redacted]% for IVIg and [redacted]% for PLEX (Company Supporting Document section 2.4.1; Company NMA Report appendix). These results are similar whether using the network that includes the observational studies or not, and this shows that adding the two observational studies on PLEX does not impact the NMA conclusions. As noted in section 2.2.2 above, this is because the design of the Duan and Leng studies adds LPE and PAIA as comparators to the networks instead of adding PLEX.

No credible intervals are provided by the company for the reported response rates. Therefore, we cannot assess the extent of certainty in these results, nor can we verify whether the correct associated uncertainty has been implemented to inform the cost-

effectiveness model (section 2.9 below). The company applied a 10% standard error to their deterministic and probabilistic scenario analyses and we believe this likely underestimates the uncertainty that would be captured by credible intervals of the response rates. However, in a scenario analysis we demonstrate that the response rates are not a key driver in the economic model (section 4.2 below).

The odds ratios for MG-ADL response provided by the bivariate NMAs, showing the difference between each treatment and placebo, are shown in Table 5 below. Rozanolixizumab performs better when compared against placebo than either IVIg or PLEX versus placebo. The credible intervals are wide and show uncertainty, especially for the IVIg and PLEX results. However, the rozanolixizumab versus placebo comparison is the only statistically significant comparison because the credible intervals are all greater than 1.0. Note that, as discussed above, there are further uncertainties in the NMA results that are not captured by the credible intervals (e.g. uncertainties around risks of bias).

Three models were run for the BLRA NMA: common, exchangeable, and independent. The estimates for the independent model did not converge, but the common and exchangeable models both indicated that placebo response is not statistically significantly different between the eight studies included in the network (Company Supporting Document pages 21 to 23; Company NMA Report Figures 7 and 8). Due to the absence of relevant studies in the networks (hence the bivariate NMAs above), there are no results for IVIg or PLEX for MG-ADL response, and no results for PLEX for MG-ADL change from baseline in the baseline risk-adjusted NMAs.

Table 5 NMA results for MG-ADL response

Analysis	**MG-ADL response ≥2 points, odds ratio versus placebo (95% CrI)**		
	Rozanolixizumab 7 mg	**IVIg**	**PLEX**
Original NMA [a]	[redacted]	Not done	Not done
Conventional NMA (RCTs)	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs)	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs + nRCTs)	[redacted]	[redacted]	[redacted]

Analysis	MG-ADL response ≥2 points, odds ratio versus placebo (95% CrI)		
	Rozanolixizumab 7 mg	IVIg	PLEX
BLRA NMA (common covariate model)	[redacted]	NA (NA, NA)	NA (NA, NA)
BLRA NMA (exchangeable covariate model)	[redacted]	NA (NA, NA)	NA (NA, NA)

BLRA, baseline risk-adjusted; CrI, credible interval; DGD1, NICE's first Draft Guidance Document; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; NA, not applicable; NMA, network meta-analysis; nRCTs, non-randomised studies; PLEX, plasma exchange; RCTs, randomised controlled trials.
[a] Comparison used in the company's economic model in the original submission.
Sources: Figure 3 in the corrected NMA report of the original submission; Figure 4 of Company NMA Report.

The mean differences in change from baseline in MG-ADL score for intervention versus placebo are summarised in Table 6 below. The credible intervals for IVIg and for PLEX comparisons with placebo include zero in all the NMAs and so results for IVIg and PLEX are uncertain.

Table 6 NMA results for MG-ADL change from baseline

Analysis	MG-ADL change from baseline, difference versus placebo (95% CrI)		
	Rozanolixizumab 7 mg	IVIg	PLEX
Original NMA [a]	[redacted]	Not done	Not done
Conventional NMA (RCTs)	[redacted]	[redacted]	[redacted]
Conventional NMA (RCTs + nRCTs)	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs)	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs + nRCTs)	[redacted]	[redacted]	[redacted]

Analysis	MG-ADL change from baseline, difference versus placebo (95% CrI)		
	Rozanolixizumab 7 mg	IVIg	PLEX
BLRA NMA (common covariate model)	[redacted]	[redacted]	[redacted]
BLRA NMA (exchangeable covariate model)	[redacted]	[redacted]	[redacted]

BLRA, baseline risk-adjusted; CrI, credible interval; DGD1, NICE's first Draft Guidance Document; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living; NA, not applicable; NMA, network meta-analysis; nRCTs, non-randomised controlled trials i.e. the observational studies; PLEX, plasma exchange; RCTs, randomised controlled trials.
[a] Comparison used in the company's economic model in the original submission.
Sources: Figure 6 in the corrected NMA Report of the original submission; Figure 5 of Company NMA Report.

2.2.6.2 Baseline risk-adjusted (BLRA) NMA results

The baseline risk adjusted NMA results are also reported because they were designed to account for the differential placebo rates. The BLRA NMA results indicate that placebo response heterogeneity was not statistically significant, although, as noted above, all the NMAs have inherent uncertainties (e.g. relating to risks of bias and lack of heterogeneity assessment) meaning that firm conclusions about the extent of placebo response heterogeneity remain difficult.

Unlike ID4008, the company have not combined the BLRA NMA and bivariate NMA into a two-stage NMA. We note that in ID4008 the two-stage NMA had very wide credible intervals that were not informative for decision-making. As such, we believe that the company's provision of the bivariate and BLRA NMA results is appropriate.

EAG conclusion on the NMA results

The bivariate NMA results for the MG-ADL response outcome show rozanolixizumab, but not IVIg, to be statistically significantly superior to placebo, but these NMAs do not account for heterogeneity of placebo responses. Too few data are available to draw firm conclusions relating to PLEX. Results of baseline risk-adjusted NMAs which do account for placebo response heterogeneity are not statistically significant. As in the zilucoplan appraisal ID4008, there therefore remains some uncertainty around the importance of the placebo response heterogeneity although we believe the company have

investigated this as thoroughly as possible. All results are associated with additional uncertainty due to lack of clarity around the extent of heterogeneity of the study characteristics and risks of bias in the included studies.

Credible intervals are not reported for the response rate probabilities, nor taken forward to the cost-effectiveness model, therefore uncertainty in the response rate probabilities has not been accounted for in the economic analysis.

2.3 Clinical effectiveness: MG0007 results: final data cut

The company provided results from the final data cut of the MG0007 extension study of the MycarinG (MG0003) trial which evaluated rozanolixizumab in 7 mg (licensed) and 10 mg (non-licensed) doses. This data cut provides an extra nine 6-week cycles of efficacy data (a total of [redacted] 6-week cycles) since the original submission. Data is reported for each cycle, rather than cumulatively, which means that although a small proportion of participants switched arms, i.e. switched doses, the treatment effect was based on the dose participants received for each cycle (Company Response Form section 6).

Consistent improvements (reduction in scores) were observed for each treatment cycle for change from baseline in MG-ADL, QMG, MGC, and MGSPRO (muscle weakness fatiguability, physical fatigue, and bulbar muscle weakness) scores, and the reductions were clinically meaningful for change from baseline in MG-ADL, QMG and MGC scores (Company Supporting Document section 2.1.2). MG-ADL responder (≥2-point improvement) rates in the 7 mg arm were high, ranging between [redacted] and [redacted] (Company Supporting Document section 2.1.2.7).

Minimal symptom expression (MSE; an MG-ADL score of 0 or 1 at any time during the treatment and observation period up to 16 weeks) was achieved by [redacted] of participants across all cycles, range [redacted] to [redacted] (Company Supporting Document section 2.1.2.10).

Data from MG0007 is the only longer term MSE data for rozanolixizumab in gMG and the company show that the results are similar to MSE results for other targeted gMG treatments (Company Supporting Document section 3.1.5). The MG0007 MSE results inform the proportion of people with continued response, i.e. [redacted], for rozanolixizumab in the cost-effectiveness model. The company have reported MSE for patients who achieved MSE in any (i.e. at least one) treatment cycle. The EAG are uncertain whether this is the most appropriate way to present MSE, as it would not distinguish patients who achieved MSE in one treatment cycle from those who had prolonged MSE across several cycles and does not

clarify whether MSE was more likely in earlier than later cycles or vice versa. Whilst the EAG agree that the MSE outcome is clinically relevant and appropriate to include, we believe the company could have provided more details about the distribution of MSE events among patients and treatment cycles, to assist interpretation of this outcome.

The company argue the importance of using MSE data in the model (Company Supporting Document section 3.1.5). The committee acknowledged in ID4008 FDG that MSE may be clinically relevant, and the updated ABN MG guidelines state that an MG-ADL score of 0-1 is considered a desirable goal in managing MG.[3]

[redacted] participants in the rozanolixizumab 7 mg arm completed the study (Company Supporting Document Table 1), and yet by the final ([redacted]) cycle there were [redacted] participants providing data for this arm for the MSE outcome (Company Supporting Document Table 8). This suggests either missing data or that [redacted] participants received the 10 mg dose for this cycle. Overall, [redacted] participants completed the study and the main reason for discontinuation was 'other' for [redacted]% of participants (Company Supporting Document Table 1). The sample size reduces steadily to [redacted] throughout the study. This suggests that understanding subsequent treatments is important in the overall treatment pathway because gMG is a chronic condition and current treatments, including rozanolixizumab, are not a cure. We do not find the 'other' category for discontinuation informative.

The final safety results from MG0007 do not raise any new concerns.

EAG conclusion on the MG0007 study data and minimal symptom expression (MSE)

It is appropriate to report the latest, and final, results of the MG0007 extension study. The results continue to show efficacy of treatment with rozanolixizumab, and no new safety concerns were raised. MSE is a clinically relevant outcome which informs the economic analysis although uncertainty in this measure (e.g. the proportions who achieved transient or more sustained MSE) has not been fully reported.

2.4 Economic analysis: Scenario analyses that incorporate some of the potentially uncaptured benefits of rozanolixizumab

In previous gMG appraisals, companies have explored scenarios where the economic model included:

1. A utility decrement associated with corticosteroid use
2. The disutility associated with IVIg and or PLEX use
3. Carer disutility

Previously, the committee have preferred to consider the utility decrement associated with corticosteroid use qualitatively (ID4008 FDG 3.27) and carer disutilities qualitatively (ID4008 FDG 3.27; TA1069 3.18), but to include the disutility associated with IVIg and or PLEX use (ID4008 FDG 3.27).

The revised company model includes the disutility associated with corticosteroid use. The company conducted a scenario excluding this disutility (Company Supporting Document 3.3.5.7). We prefer to exclude this disutility in our base case, in line with the committee's preference.

The utility decrement associated with IVIg and PLEX use that the committee discussed in ID4008 (FDG 3.21) reflected the detrimental effect of in-hospital treatment administration on patients' quality of life, compared with a treatment that could be administered at home. Under the heading 'Benefit of at-home subcutaneous administration', Company Supporting Document 3.1.7 describes the benefit of administration of rozanolixizumab in terms of NHS staff and patient hours saved per year:

- [redacted] hours of NHS staff time and [redacted] hours of patient time compared with IVIg
- [redacted] hours of NHS staff time and [redacted] hours of patient time compared with PLEX

We note that the administration cost for rozanolixizumab used in the economic model is for a subcutaneous infusion, and the EAG understands that this is currently administered in an outpatient centre or hospital setting (ID5092 CS Table 2).

Company Supporting Document 3.1.10 states that the revised model incorporates the parameters for caregiver disutilities. We note that these are not included in the company's base case, and we also prefer to exclude them from the EAG base case as per the committee's preferences (ID4008 FDG, TA1069).

EAG conclusion

We consider that the utility decrement for corticosteroid use and caregiver disutilities should be excluded from the model, because the committee have preferred to assess

these qualitatively previously. If it is possible for rozanolixizumab to be administered at home, it may be appropriate to include a utility decrement for use of IVIg and PLEX.

2.5 Economic analysis: The comparators should be modelled as a 'basket' of standard care, with some people having IVIg, some having PLEX, and some having neither.

The company do not agree that a 'basket' of standard care (called the 'standard basket' hereafter) is a relevant comparator to rozanolixizumab (Company Supporting Document 3.3.5.2) and present their base case as pairwise comparisons of rozanolixizumab versus IVIg and versus PLEX. We note that in the company's revised model, no patients receive subcutaneous immunoglobulin (SCIg), all patients receive intravenous immunoglobulin (IVIg), as per the committee's preferences in ID4008 Final Draft Guidance.

The company conducted a scenario analysis comparing rozanolixizumab with a standard basket, informed by a revised EAMS population, consisting of: [redacted]% of patients receiving PLEX, [redacted] receiving IVIg, and the remainder ([redacted]) receiving SoC (CSs/NSISTs). Company Supporting Document 3.3.5.2 describes how the proportions of patients on each of the treatments in the company's standard basket was calculated. Company Supporting Document Table 36 presents the results of this scenario analysis; rozanolixizumab [redacted].

The rozanolixizumab NICE Draft Guidance Document states the committee preferred that the comparators should be modelled as a 'basket' of standard care, with some people having IVIg, some having PLEX, and some having neither, and that the proportion of people having each treatment could be taken from the EAMS population (ID5092 DGD1 3.6). The EAG note that this is consistent with the ID4008 appraisal, where the committee preferred using the unrevised EAMS cohort (14.6% of patients receive PLEX, 43.8% IVIg, 41.6% receive SoC (CSs/NSISTs))[2] to inform the proportion of people on treatment in the standard basket (ID4008 FDG 3.27).

We note that the composition of the standard basket affects the basket response rate, the proportion achieving MSE/continued response, the change from baseline in MG-ADL score, treatment and administration costs and resource use costs associated with clinical events, because these parameters are calculated as weighted averages based on the treatment composition of the basket (Company Supporting Document 3.3.5.2).

2.5.1 Including rituximab in the standard basket

Expert clinical advice to the company was that rituximab should not be considered as a direct comparator to rozanolixizumab but could be included in the standard basket for patients with MuSK antibody-positive gMG (Company Supporting Document 3.3.5.2). The company conducted a scenario analysis where 10.5% of patients in the standard basket arm received rituximab.

The proportion of patients receiving rituximab was taken from MycarinG where 10.5% of patients had MuSK antibody-positive gMG; the company assumed that all of these patients would receive rituximab as part of the standard basket (Company Supporting Document 3.3.5.2). Company Supporting Document Table 40 presents the results of this scenario, rozanolixizumab [redacted].

We note that the original NICE Scope states about 3% to 7% of patients with gMG have autoantibodies that bind to MuSK. Clinical advice to the EAG was that the proportion of MG patients with MuSK autoantibodies in the UK is 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 (ID5092 EAG report section 2.2.1.1). Consequently, we consider that the company's scenario analysis is including a higher proportion of patients with MuSK autoantibodies compared with the population of patients with refractory gMG in the UK.

EAG conclusion

We prefer to use the standard basket, where the proportion of patients receiving the different treatments is informed by the unrevised EAMS cohort,[2] as the comparator in our base case, as per the committee's preferences.

We agree with the company and also exclude rituximab from the standard basket in our base case, but we conduct a scenario where 2% of patients in the standard basket (unrevised EAMS cohort) receive rituximab.

2.6 Economic analysis: Everyone should have corticosteroids and immunosuppressants

We note that costs for corticosteroids and immunosuppressants (azathioprine, mycophenolate, cyclosporine, tacrolimus, methotrexate and pyridostigmine) are included for all modelled treatments.

EAG conclusion

The model has been updated as per the committee's request. We agree with the company's approach.

2.7 Economic analysis: Zilucoplan and efgartigimod should not be included as comparators

Zilucoplan and efgartigimod are not included in the company's revised model.

EAG conclusion

The model has been updated as per the committee's request.

2.8 Economic analysis: The results of the whole-trial populations of MycarinG can be generalised to those with refractory gMG in the NHS

The participant characteristics given in Company Supporting Document 3.2.1 are for the overall population from MycarinG and are used in the model.

EAG conclusion

The model remains unchanged from that seen at ACM1 and meets the committee's request.

2.9 Economic analysis: Any uncertainty from indirect comparisons should be incorporated in the model

The revised model uses response rates that are direct outputs from the bivariate NMA: [redacted] for rozanolixizumab, [redacted] for IVIg and [redacted] for PLEX (Company Supporting Document 3.1.4). The company did not provide any credible intervals for these response rates. The response rates are included in both the deterministic sensitivity analysis and probabilistic sensitivity analyses (PSA) and are varied using an assumed standard error of 10%.

EAG conclusion

We consider that using a standard 10% variation for the NMA parameters in the PSA does not give a meaningful estimate of the uncertainty. If credible intervals for the response rates are available, the company could have tested these in scenario analyses. We test setting the rozanolixizumab response rate to be the same as the standard basket ([redacted]) in a scenario analysis (section 4.2). Note that there are uncaptured uncertainties on the NMA results relating to uncertainties and bias in the NMAs which are not reflected in the response rate standard errors or credible intervals.

2.10 Economic analysis: The response assessment timepoint should be three weeks for IVIg and PLEX, but six weeks is more appropriate for rozanolixizumab

The response assessment timepoint used in the company's base case is six weeks for rozanolixizumab and three weeks for IVIg and PLEX (Company Supporting Document 3.1.2).

EAG conclusion

We agree that the model has been updated in line with the committee's preferences, but we note that the response assessment time point for the standard basket is 12 weeks in the company's base case. We prefer to use a response assessment timepoint of three weeks for the standard basket in our base case, given that it includes IVIg and PLEX.

2.11 Economic analysis: The costs of IVIg and PLEX should be applied every four weeks, and the NHS reference cost should be used for PLEX administration

Company Supporting Document 3.1.3 states that the dosing frequency for IVIg and PLEX is every four weeks in the revised model.

We note that patients receive five sessions of PLEX per four-week treatment cycle in the company's base case, but the PLEX administration cost is set to £0 within the revised model. We set this to £2,482.50 per model cycle (i.e. every two weeks) in our base case, using the NHS reference cost of £993 (SA44A – Single Plasma Exchange, Clinical Immunology Service; National Schedule of NHS Costs 2023/24) applied five times every four weeks.

The EAG note there is an entry for 'SA44A – Single Plasma Exchange, General Internal Medicine' in the National Schedule 2023/24, associated with a national average unit cost of £544. But, we consider that patients with gMG would be managed via specialist clinical teams, not in general medicine.

We explore reducing the number of PLEX sessions per treatment cycle in a scenario analysis to reflect that frequency may vary, based on individual patients' needs and response to treatment (section 4.2).

EAG conclusion

We agree that the IVIg and PLEX dosing frequency change is applied as per the committee's preferences in the revised model, and we apply PLEX administration costs in our base case.

2.12 Economic analysis: Other key issues considered by the EAG

2.12.1 Subsequent treatment

Company Supporting Document 3.1.6 highlights the challenging nature of modelling subsequent treatment for patients with gMG, and that attempting to do so is associated with considerable uncertainty. However, the company has included subsequent treatment in their base case, modelled as a basket of treatment containing IVIg, PLEX and SoC (corticosteroids/NSISTs only). Company Supporting Document 3.1.6 explains that this basket represents a 'snapshot in time' i.e. the proportion of patients receiving each treatment remains constant but actually represents patients moving between the treatments over time.

Company Supporting Document 3.1.6 states that the composition of the subsequent treatment basket should be the same for all index treatments, because the basket is applied to patients over their remaining lifetime in the model (the model time horizon is 48.2 years). Over this length of time, the company consider it likely that the mix of subsequent treatments patients receive will ultimately be the same, regardless of their initial treatment. Company Supporting Document 3.1.6 highlights that the company's approach is consistent with that described in section 3.15 (Modelling of treatment pathway) of the final draft guidance for TA1069:

> "*the committee agreed the most reasonable approach would model the same proportions of people having plasma exchange and IVIg in both arms. That would mean that people who stop efgartigimod would have the same sequence of IVIg and plasma exchange as the comparator arm*".

The company conducted a Delphi panel (across two rounds), involving nine clinical experts in gMG from across England and Scotland, to obtain estimates of subsequent treatments following treatment with IVIg and PLEX (Table 7). Company Supporting Document 3.1.6 states that consensus was achieved for nearly all estimates.

These estimates were applied to the company's revised EAMS cohort standard basket ([redacted] of patients receiving PLEX, [redacted] receiving IVIg, and the remainder ([redacted]) receiving SoC (CSs/NSISTs)) to estimate the proportion of patients receiving each subsequent treatment, this subsequent treatment basket is applied in all treatment arms.

The EAG are unclear which data from the Delphi panel were used to calculate the subsequent treatment proportions in the company's revised base case, because multiplying the proportions of treatments in the company's revised standard of care basket by the mean

results shown in Table 7 does not produce the estimates of subsequent treatment proportions used in the model (Table 8):

- [redacted] (on IVIg initially) x [redacted] (swap to PLEX) = [redacted] on PLEX in subsequent treatment
- [redacted] (on PLEX initially) x [redacted] (swap to IVIg) = [redacted] on IVIg in subsequent treatment

The EAG note that if using the unrevised EAMS cohort to inform treatment proportions in the standard care basket, using the company's subsequent treatment proportions means that about 75% of patients receiving IVIg initially (48.3%) would go on to receive PLEX in subsequent treatment ([redacted]), and nearly all patients receiving PLEX initially (14.6%) would go on to receive IVIg in subsequent treatment ([redacted]) (Table 8). This disagrees with the expert estimates derived from the Delphi panel (Table 7). We prefer to recalculate the proportions in the subsequent treatment basket using the unrevised EAMS cohort proportions and clinical expert estimates (Table 8) and use these results in our base case.

However, we note that this calculation means the proportions of patients receiving IVIg and PLEX as subsequent treatment following rozanolixizumab do not match the clinical expert estimates (Table 7). Consequently, we prefer to use the treatment proportions of the unrevised EAMS cohort[2] to inform subsequent treatment in the rozanolixizumab arm so that the treatment proportions match those of the initial standard of care basket.

We note the wide range in clinical expert estimates (Table 7), suggesting there is a wide variation in clinical practice in the UK. In addition, subsequent treatment proportions are not included in the deterministic or probabilistic sensitivity analyses, so we conducted scenario analyses on subsequent treatment proportions on our base case (section 4.2).

Table 7 Subsequent treatment proportions

Treatment	Expert									Mean
	1	2	3	4	5	6	7	8	9	
Following failure on IVIg + SoC										
%PLEX + SoC	25%	0%	100%	33%	84%	43%	89%	80%	100%	**62%**
Following failure on PLEX + SoC										
%IVIg + SoC	14%	50%	90%	33%	83%	74%	0%	60%	100%	**56%**
Following failure on rozanolixizumab										
% IVIg + SoC	13%	53%	80%	33%	44%	63%	11%	0%	100%	**44%**
% PLEX +SoC	13%	0%	10%	11%	44%	13%	89%	80%	0%	**29%**
% SoC only	75%	47%	10%	28%	11%	25%	0%	20%	0%	**24%**

Source: Adapted from Delphi Survey Report Table 15

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

Table 8 EAMS cohort and modelled subsequent treatment proportions

Treatment	Proportion of patients			
	Company revised EAMS cohort	Unrevised EAMS cohort	Company subsequent treatment basket	EAG subsequent treatment basket
IVIg	56.7%	48.3%	14.05%	8.2%
PLEX	18.9%	14.6%	35.73%	29.9%
SoC (CSs/NSISTs)	24.4%	41.6%	50.22%	61.9%

Source: Adapted from Company Supporting Document Table 14

Abbreviations: CS, corticosteroid; EAMS, Early Access to Medicines Scheme; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant; PLEX, plasma exchange.

2.12.1.1 Including rituximab in subsequent treatment

We do not include rituximab in the subsequent treatment basket in our base case, because we consider that rituximab would be used as early as possible for patients with MuSK antibody-positive gMG, as per current ABN guidelines.[3]

EAG conclusion

We agree with the company that there is considerable uncertainty in attempting to model subsequent treatment accurately in either arm. We consider that the company have taken a pragmatic approach to modelling subsequent treatment, and that the Delphi survey involved a good number of clinical experts from a wide geographical spread across the UK.

However, we note that the Delphi survey (Delphi survey report_FINAL_23Sep2025) discusses zilucoplan, not rozanolixizumab. The company confirmed that the document is correct, and that relevant data from the Delphi survey were used to inform the company's response to the rozanolixizumab Draft Guidance.

We do not consider the company's calculated proportions of patients on subsequent treatment are appropriate for the comparator arm when using the unrevised EAMS population to inform the treatment proportions in the standard basket. We recalculated the subsequent treatment proportions using the company's experts' estimates (Table 8) and prefer to use these in our base case for the comparator arm.

The EAG prefer to use the unrevised EAMS cohort treatment proportions to inform subsequent therapy following treatment with rozanolixizumab, because this is consistent with the proportions used in the standard basket (i.e. the world without rozanolixizumab).

2.12.2 Source of corticosteroid management costs

Company Supporting Document 3.2.3.1 explains that the costs of managing steroid use were calculated from Stirnadel-Farrant et al. (2023).[10] The EAG prefer to use the costs from Lee et al. (2018)[11] in our base case, because the Lee at al. data is for people with gMG, whereas Stirnadel-Farrant et al. report costs for people with systemic lupus erythematosus. The committee have previously accepted using Lee et al. to inform corticosteroid management costs in gMG submissions (ID4008 Final Draft Guidance 3.27; TA1069 committee discussion 3.20).

We note that, in the company's base case, the MSE/continued response health state for IVIg and PLEX is associated with costs of managing corticosteroid use ([redacted] per year), whereas

the same health state for patients receiving rozanolixizumab is [redacted] (Table 9). We consider that patients in the same health state would accrue the same resource use costs and so set the costs for patients achieving MSE/continued response to be the same in both arms in our base case.

Table 9 Annual costs of managing corticosteroid use

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

Source: Company model

IVIg, intravenous immunoglobulin; MSE; minimal symptom expression; PLEX, plasma exchange

3 EAG VALIDATION OF THE COMPANY'S REVISED COST-EFFECTIVENESS RESULTS

3.1 Company's revised base case cost-effectiveness results

The company provided a revised model dated 23-09-2025, which includes a revised Patient Access Scheme (PAS) discount for rozanolixizumab of [redacted]. All results presented in this report include the PAS discount for rozanolixizumab. Analyses including appropriate Medicines Procurement and Supply Chain (MPSC) costs are presented in a separate confidential addendum.

The revised model included an 'Updatelog' tab that summarised the changes between the revised model and the model seen at Appraisal Committee Meeting 1 (ACM1). However, without tabulated results showing the impact of each change on the model results, we are unable to validate the company's revised economic model.

Post-submission, the company and EAG identified some errors in the model, summarised in Company Supporting Document addendum (section 1). The Company submitted a second model on 7th October 2025, dated 06-10-2025, which included:

- Corrections to ensure the PSA and DSA run correctly
- A revised calculation of rozanolixizumab treatment costs so that the annualised number of infusions ([redacted]) are used in the company's base case, not the annualised number of cycles ([redacted]).

The EAG successfully validated the new model by applying the updates in model version 06-10-2025 to the older model (version 23-09-2025); we were able to reproduce the results of model version 06-10-2025.

All results in this report refer to the company's revised model dated 06-10-2025.

The company's revised base case is a pairwise comparison of rozanolixizumab with IVIg and PLEX; Company Supporting Document addendum Table 7 presents scenario results for rozanolixizumab versus the company's revised EAMS population ([redacted] of patients receiving PLEX, [redacted] receiving IVIg, and the remainder ([redacted]) receiving SoC (CSs/NSISTs)), reproduced in Table 10. Rozanolixizumab [redacted].

Table 10 Base case results, company revised model

Treatment	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.415			
Revised standard basket	[redacted]	8.257	[redacted]	0.158	[redacted]

Source: Reproduced from Company Supporting Document addendum Table 7
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

The company present the results of their deterministic sensitivity analysis (DSA) as tornado diagrams in Company Supporting Document addendum 2.1.3, and results of their probabilistic sensitivity analysis (PSA) in Company Supporting Document addendum 2.1.4. However, the company did not present results for rozanolixizumab versus their revised standard basket.

3.2 Scenario analyses on the company's revised base case

The company present the results of their scenario analyses in Company Supporting Document addendum 2.1.5 for:

1. Exploring the appropriateness of the blended SoC basket comparator
2. Comparing rozanolixizumab with the company's revised standard basket (results shown in Table 11).
    a. Including rituximab in the revised standard basket

And for rozanolixizumab versus IVIg and PLEX for:

3. Excluding subsequent treatment
4. Adjusted subsequent treatment proportions
    a. Using weighted means of the responses from the Delphi panel
    b. Including rituximab as a subsequent treatment
    c. Using expert elicitation data to inform subsequent treatment proportions
5. Setting the response assessment timepoint to three weeks for all treatments
6. Using costs for corticosteroid management from Lee et al.[11]
7. Excluding the disutility associated with corticosteroid use
8. Using the annualised number of cycles for rozanolixizumab treatment ([redacted]), assuming six infusions per cycle, rather than the annualised number of infusions ([redacted])
9. Using IVIg change from baseline in MG-ADL score from the bvNMA (i.e. [redacted])

We have reproduced scenarios 2.a – 9 using the company's revised standard basket as the comparator and also conducted our scenario analyses on the company's revised base case (Table 11).

We note that altering the composition of the standard basket changes the total QALYs accrued in the rozanolixizumab arm (**Error! Reference source not found.**, scenario 1 and scenario 11; Company Supporting Document addendum Table 8). This is because the average MG-ADL score for the 'Uncontrolled off initial treatment' health state is used to inform the utilities for 'Uncontrolled off initial treatment' and thus the QALYs for 'Uncontrolled off initial treatment' in the economic model.

The average MG-ADL score is a weighted average change from baseline (CFB) in MG-ADL score calculated from the proportions of patients experiencing MSE, loss of response and stable response for IVIg, rituximab, PLEX and the standard basket. The proportion experiencing loss of response remains fixed at [redacted], but the proportions achieving MSE in the standard basket change with the proportions of patients receiving IVIg and PLEX in the standard basket. The proportion achieving MSE also affects the proportion experiencing stable response.

The EAG are unsure why the standard basket would be used to inform the proportion of patients achieving MSE in subsequent treatment for the 'Uncontrolled off initial treatment' health state, because it itself is not a treatment. We consider that this should be the proportion achieving MSE on SoC (CSs and NSISTs only; [redacted]) and adjusted the model accordingly (Table 11, scenario 17).

Using the original EAMS cohort to inform the treatment proportions in the standard basket (scenario 11) has the most influence on the ICER, increasing it to [redacted] per QALY. The model is also sensitive to excluding subsequent treatment (scenario 2) and to using the annualised number of cycles to calculate rozanolixizumab treatment costs (scenario 9). The EAG note that the annualised number of cycles equates to [redacted] infusions of rozanolixizumab per year, compared with the company's base case of [redacted] infusions per year.

Table 11 Company and EAG scenario analyses for rozanolixizumab compared with the revised standard basket, conducted on the company's revised base case

No	Scenario description	Treatment	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
Company revised base case		Rozanolixizumab	[redacted]	8.383	[redacted]	0.127	[redacted]
		Standard basket	[redacted]	8.257			
1	Include rituximab (10.5% of patients) in the revised standard basket	Rozanolixizumab	[redacted]	8.385	[redacted]	0.123	[redacted]
		Standard basket	[redacted]	8.262			
2	Subsq Tx: Exclude subsequent treatment	Rozanolixizumab	[redacted]	7.904	[redacted]	0.179	[redacted]
		Standard basket	[redacted]	7.726			
3	Subsq Tx: Use weighted means of the responses from the Delphi panel	Rozanolixizumab	[redacted]	8.383	[redacted]	0.132	[redacted]
		Standard basket	[redacted]	8.251			
4	Subsq Tx: Include rituximab as a subsequent treatment	Rozanolixizumab	[redacted]	8.586	[redacted]	0.301	[redacted]
		Standard basket	[redacted]	8.285			
5	Subsq Tx: Use expert elicitation data to inform proportions	Rozanolixizumab	[redacted]	8.384	[redacted]	0.098	[redacted]
		Standard basket	[redacted]	8.285			
6	Response assessment timepoint = 3 weeks for all treatments (rozanolixizumab and the standard basket)	Rozanolixizumab	[redacted]	8.346	[redacted]	0.098	[redacted]
		Standard basket	[redacted]	8.248			
7	Costs for corticosteroid management from Lee et al.	Rozanolixizumab	[redacted]	8.383	[redacted]	0.127	[redacted]
		Standard basket	[redacted]	8.257			
8	Exclude the disutility associated with corticosteroid use	Rozanolixizumab	[redacted]	8.569	[redacted]	0.119	[redacted]
		Standard basket	[redacted]	8.450			
9	Use the annualised number of cycles for rozanolixizumab treatment	Rozanolixizumab	[redacted]	8.383	[redacted]	0.127	[redacted]
		Standard basket	[redacted]	8.257			
10	Use IVIg change from baseline in MG-ADL score from the bvNMA	Rozanolixizumab	[redacted]	8.333	[redacted]	0.094	[redacted]
		Standard basket	[redacted]	8.240			
EAG scenarios							

No	Scenario description	Treatment	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
11	Use the original/unrevised EAMS cohort to inform the standard basket treatment proportions	Rozanolixizumab	[redacted]	8.371	[redacted]	0.139	[redacted]
		Standard basket	[redacted]	8.233			
12	Use a response assessment time point of 3 weeks for the standard basket; 6 weeks for rozanolixizumab	Rozanolixizumab	[redacted]	8.383	[redacted]	0.136	[redacted]
		Standard basket	[redacted]	8.248			
13	Apply treatment and admin costs for 5 PLEX sessions every 4 weeks	Rozanolixizumab	[redacted]	8.383	[redacted]	0.127	[redacted]
		Standard basket	[redacted]	8.257			
14	Subsq Tx: unrevised EAMS cohort post-rozanolixizumab	Rozanolixizumab	[redacted]	8.383	[redacted]	0.127	[redacted]
		Standard basket	[redacted]	8.257			
15	Subsq Tx: EAG calculated proportions for the standard basket	Rozanolixizumab	[redacted]	8.383	[redacted]	0.155	[redacted]
		Standard basket	[redacted]	8.228			
16	Use the same corticosteroid resource use costs for MSE in both arms	Rozanolixizumab	[redacted]	8.383	[redacted]	0.127	[redacted]
		Standard basket	[redacted]	8.257			
17	Use SoC MSE proportion to inform the 'Uncontrolled off initial treatment' health state	Rozanolixizumab	[redacted]	8.330	[redacted]	0.139	[redacted]
		Standard basket	[redacted]	8.191			

Source: EAG created table
Abbreviations: bvNMA; bivariate network meta-analysis; EAMS, Early access to medicines scheme; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life-year; SoC, standard care (corticosteroids and non-steroidal immunosuppressants); Subsq Tx, subsequent treatment

4 EAG ANALYSES

4.1 EAG preferred assumptions

Based on the EAG's critique of the company's revised model, we have identified several aspects of the company's base case with which we disagree. Our preferred model assumptions are to:

1. Remove the disutility associated with corticosteroid use (discussed in section 2.4)
2. Use a standard basket as the comparator, and to use the unrevised EAMS cohort[2] to inform the proportions of patients on each treatment in the standard basket (43.8% receive IVIg, 14.6% receive PLEX, 41.6% receive standard care; discussed in section 2.5)
3. Use a response assessment time point of three weeks for the standard basket (discussed in section 2.10)
4. Apply PLEX admin costs for five PLEX sessions every four weeks (£2,482.50 per model cycle; discussed in section 2.11)
5. Use the treatment proportions from the unrevised EAMS cohort to inform subsequent treatment following rozanolixizumab (discussed in section 2.12.1)
6. Use the EAG-calculated treatment proportions for subsequent treatment following the standard basket (8.2% receive IVIg, 29.9% receive PLEX, 61.9% receive standard care (corticosteroids/NSISTs)) (discussed in section 2.12.1)
7. Use the costs from Lee et al.[11] to inform the resource use costs of corticosteroid management (discussed in section 2.12.2)
8. Use the same corticosteroid management resource use costs for MSE in both arms (discussed in section 2.12.2)
9. Use SoC (CSs and NSISTs only) MSE proportion to inform the '

10. off initial treatment' health state (discussed in section 3.2)

The cumulative effect of these changes results rozanolixizumab [redacted] (Table 12).

Table 12 Cumulative effect of the EAG's preferred assumptions, rozanolixizumab compared with the standard basket

Assumption	Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	Cumulative ICER (£/QALY)
Company revised base case	Rozanolixizumab	[redacted]	8.383	[redacted]	0.127	[redacted]
	Standard basket	[redacted]	8.257			
1 Exclude the disutility associated with corticosteroid use	Rozanolixizumab	[redacted]	8.569	[redacted]	0.119	[redacted]
	Standard basket	[redacted]	8.450			
2 Use the original EAMS cohort for the standard basket (43.8% IVIg, 14.6% PLEX, 41.6% SoC)	Rozanolixizumab	[redacted]	8.557	[redacted]	0.130	[redacted]
	Standard basket	[redacted]	8.427			
3 Use a response assessment time point of 3 weeks for the standard basket; 6 weeks for rozanolixizumab	Rozanolixizumab	[redacted]	8.557	[redacted]	0.136	[redacted]
	Standard basket	[redacted]	8.421			
4 Apply PLEX admin costs for 5 PLEX sessions every 4 weeks	Rozanolixizumab	[redacted]	8.586	[redacted]	0.136	[redacted]
	Standard basket	[redacted]	8.421			
5 Subsq Tx: unrevised EAMS cohort post-rozanolixizumab	Rozanolixizumab	[redacted]	8.557	[redacted]	0.136	[redacted]
	Standard basket	[redacted]	8.421			
6 Subsq Tx: EAG calculated proportions for the standard basket	Rozanolixizumab	[redacted]	8.557	[redacted]	0.168	[redacted]
	Standard basket	[redacted]	8.389			
7 Costs for corticosteroid management from Lee et al.	Rozanolixizumab	[redacted]	8.557	[redacted]	0.168	[redacted]
	Standard basket	[redacted]	8.389			
8 Use the same corticosteroid resource use costs for MSE in both arms	Rozanolixizumab	[redacted]	8.557	[redacted]	0.168	[redacted]
	Standard basket	[redacted]	8.389			
9 Use SoC MSE proportion to inform the 'Uncontrolled off initial treatment' health state	Rozanolixizumab	[redacted]	8.515	[redacted]	0.190	[redacted]
	Standard basket	[redacted]	8.325			
EAG base case	Rozanolixizumab	[redacted]	8.515	[redacted]	0.190	[redacted]
	Standard basket	[redacted]	8.325			

Source: EAG created table
Abbreviations: EAMS, Early access to medicines scheme; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MSE, minimal symptom expression; NMA, network meta-analysis; PLEX, plasma exchange; QALY, quality-adjusted life-year; SoC: standard care (corticosteroids and non-steroidal immunosuppressants); Subsq Tx, subsequent treatment

4.2 Scenario analyses on the EAG's preferred assumptions

The EAG ran scenario analyses on our base case assumptions (Table 13). The model is sensitive to the number of PLEX sessions patients receive every four weeks (scenario 4) and to the proportions of patients receiving IVIg and PLEX in subsequent treatment (scenarios 5-7).

Table 13 Scenario analyses for rozanolixizumab compared with the standard basket, EAG base case

No	Scenario description	Treatment	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
EAG base case		Rozanolixizumab	[redacted]	8.515	[redacted]	0.190	[redacted]
		Standard basket	[redacted]	8.325			
1	Company's revised EAMS cohort as the standard basket in the comparator arm	Rozanolixizumab	[redacted]	8.515	[redacted]	0.182	[redacted]
		Standard basket	[redacted]	8.333			
2	Include rituximab (2% of patients) in the EAG standard basket	Rozanolixizumab	[redacted]	8.515	[redacted]	0.189	[redacted]
		Standard basket	[redacted]	8.326			
3	Response assessment timepoint for the standard basket = 12 weeks	Rozanolixizumab	[redacted]	8.515	[redacted]	0.181	[redacted]
		Standard basket	[redacted]	8.334			
4	Apply PLEX admin costs for 4.6 PLEX sessions every 4 weeks	Rozanolixizumab	[redacted]	8.515	[redacted]	0.190	[redacted]
		Standard basket	[redacted]	8.323			
5	Subsq Tx: Company's base case proportions, for both arms	Rozanolixizumab	[redacted]	8.515	[redacted]	0.147	[redacted]
		Standard basket	[redacted]	8.369			
6	SubsqTx: Increase proportion on IVIg and PLEX in the rozanolixizumab subsq Tx basket by 1%: 44.8% on IVIg, 15.6% on PLEX	Rozanolixizumab	[redacted]	8.522	[redacted]	0.197	[redacted]
		Standard basket	[redacted]	8.325			
7	SubsqTx: Decrease proportion on IVIg and PLEX in the standard basket subsq Tx basket by 1%: 7.2% on IVIg, 28.9% on PLEX	Rozanolixizumab	[redacted]	8.515	[redacted]	0.197	[redacted]
		Standard basket	[redacted]	8.318			
8	Use the annualised number of cycles for rozanolixizumab treatment	Rozanolixizumab	[redacted]	8.515	[redacted]	0.190	[redacted]
		Standard basket	[redacted]	8.325			
9	Use IVIg change from baseline in MG-ADL score from the bvNMA	Rozanolixizumab	[redacted]	8.461	[redacted]	0.147	[redacted]
		Standard basket	[redacted]	8.314			
10		Rozanolixizumab	[redacted]	8.430	[redacted]	0.104	[redacted]

No	Scenario description	Treatment	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Set rozanolixizumab response rate to the same as standard care (CS and NSISTs): [redacted]	Standard basket	[redacted]	8.325			

Source: EAG created table
Abbreviations: bvNMA, bivariate network meta-analysis; CS, corticosteroids; EAMS, Early access to medicines scheme; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living score; NSISTs, non-steroidal immunosuppressants; PLEX, plasma exchange; QALY, quality-adjusted life-year; Subsq Tx, subsequent treatment

4.3 Economic analysis summary

The company presented the results of their revised base case as pairwise comparisons of rozanolixizumab versus IVIg and versus PLEX. A company scenario analysis compared rozanolixizumab with the company's revised standard basket (Table 10). We reviewed the company's revised model and section 4.1 summarises our preferred assumptions. Applying the EAG's preferred assumptions results in rozanolixizumab [redacted].

We conducted scenarios on our base case to explore the remaining uncertainty when comparing the cost-effectiveness of rozanolixizumab with the standard basket. The model is most sensitive to PLEX administration costs and to the proportions of patients receiving IVIg and PLEX in subsequent treatment in both arms (Table 13**Table**).

5 REFERENCES

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NICE National Institute for Health and Care Excellence

Requests for analyses post ACM2: rozanolixizumab for generalised myasthenia gravis [ID5092]

The company must amend its economic model to ensure that it is fully executable and transparent. This includes, but is not limited to, the following issues:

- Unhide all sheets and tables, for example cells informing health state occupancy that affect model calculations are in a table on the tab SeverityScore!E31:I39, which was hidden in the model
- Ensure all text and values are visible. For example, values in G31:G39 are white text on a white background.

MSE

1. Provide more details about the distribution of MSE events among patients and treatment cycles, to assist interpretation of MSE. Please provide a table of proportion achieving MG-ADL of 0-1 (MSE), proportion achieving MG-ADL 0-2, proportion achieving MG-ADL 0-3, and proportion achieving MG-ADL 0-4.

2. Does the company consider that the proportion of 'MSE responders' is greater for patients receiving rozanolixizumab than other treatments? If so, please justify this and provide evidence.

3. There is no data (other than expert elicitation) for the proportion achieving MSE on the basket comparator. For estimating the proportion reaching MSE for the comparator basket, please use the mean and range of patients receiving rozanolixizumab who achieved MSE in MycarinG. Note that we do not want to assume that the final proportion of people achieving MSE is the same for rozanolixizumab as for the basket of care; but that of the responders, the same proportion achieve MSE. So we are assuming that the quality of

response, if you respond, is the same distribution. Specifically, please run the following scenarios:

- MSE based on expert elicitation as in ACM2.

- Scenario A: [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket
- Scenario B: [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket
- Scenario C: [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket

Time on treatment

4. Exacerbation (and to a lesser extent myasthenic crisis) is what allows people to leave response health states. Please explore a higher probability of exacerbation for people in stable response than for people in the MSE/continued response state. Please explore a range of probabilities of exacerbation rates and report the time on treatment for each scenario.

Exacerbations

5. The length of hospital stay for an exacerbation in the rozanolixizumab model is 2.04 days (ResourceUse! L17 and L31). This was 7.5 days in the model seen at ACM1. **Please explain why this change was made. T**he length of hospital stay for an exacerbation in the zilucoplan model is different: 28 days (ResourceUse! L17 and L31).

6. UCB's DG response section 3.19 states "The duration of crisis and exacerbation were amended to 28 days each following expert clinical opinion received (and discussions at ACMs for various gMG appraisals)." The model update log (Updatelog! row 22) states that the duration of the disutility from clinical events was set to 28 days, but it does not mention costs. The clinical event disutility is set to 28 days in the rozanolixizumab model (Utilities! D25 and D26). Exacerbation costs are [redacted] higher for the standard basket compared with rozanolixizumab. **The company is requested to**

justify and provide evidence if different costs are appropriate for people having an exacerbation after different treatments.

Myasthenic crisis

The length of a hospital stay for a myasthenic crisis event is 1.62 days in the rozanolixizumab model seen at ACM2 (ResourceUse! N17 and N31). It was 15 days in the model seen at rozanolixizumab ACM1 and is 28 days in the zilucoplan model seen at ACM3. **Please explain why this change was made.**

7. UCB is requested to provide analyses incorporating the following assumptions:

    - Length of hospital stay for an exacerbation set to 28 days for rozanolixizumab and the standard care basket arms.
    - Costs of an exacerbation set to the same amount for rozanolixizumab and standard care basket arms.
    - Length of hospital stay for a myasthenic crisis set to the same duration for rozanolixizumab and standard care basket arms.
    - Costs of a myasthenic crisis set to the same amount for rozanolixizumab and standard care basket arms.

8. If the company believes that costs and length of hospital stay should differ between the rozanolixizumab and standard care basket arms, UCB should provide evidence or clinical expert advice on why and how they should differ.

9. For all scenarios requested in this document, provide a change log for the model, specifying the cells where the change has been made. Please provide a table showing the total and incremental costs and QALYs and the ICER for the current base case and the cumulative effect each change has on the results.

Please submit your responses and updated model via NICE Docs by 2 January 2026 close of business. The link is here:

https://appraisals.nice.org.uk/request/226948

NICE National Institute for Health and Care Excellence

Company response: ID5092 rozanolixizumab in myasthenia gravis requests for analyses post-ACM2 v0.3

Updates to the model for transparency and executability

The company must amend its economic model to ensure that it is fully executable and transparent. This includes, but is not limited to, the following issues:

- **Unhide all sheets and tables, for example cells informing health state occupancy that affect model calculations are in a table on the tab SeverityScore!E31:I39, which was hidden in the model.**
- **Ensure all text and values is visible – for example values in G31:G39 are white text on a white background.**

Company response

The company can confirm that all sheets, tables and cells in the model are unhidden, and that all text and values are visible in the model.

The company would like to emphasise that the models provided to NICE and the EAG have always been fully executable and it was never the company's intention to be anything other than completely transparent in its modelling.

The cells referred to (E31:I39) in the question were previously hidden in the model because they functioned as *helper* or intermediary cells only. Based on the selection made in the response distribution dropdown (cells E29:G29), they retrieved the appropriate response distribution values from either the KOL opinion (cells E44:I52) or the MSE data (cells E55:I63).

The *SeverityScore* sheet has now been updated. The table in cells E39:I39 has been removed and an additional user specified option has been added to the response distribution dropdown (in cells E25:I25) for the user to manually input response distribution values for rozanolixizumab and all comparators.

Upon selection of the desired response distribution, the values are displayed in cells E27:I31 and are then passed into the sheet *TransitionsProbs* to calculate the transition probabilities. These transition probabilities are subsequently used in sheets *EngineT0* through *EngineT7* to estimate the distribution of patients across the health states. The screenshot below illustrates the described ranges along with their respective cell references (columns and rows).

MSE

1. **Provide more details about the distribution of MSE events among patients and treatment cycles, to assist interpretation of MSE. Please provide a table of proportion achieving MG-ADL of 0-1 (MSE), proportion achieving MG-ADL 0-2, proportion achieving MG-ADL 0-3, and proportion achieving MG-ADL 0-4.**

Company response

The information requested is provided for Cycle 1 (Day 43) responders only and for the overall population (all participants, Safety Set) in Table 1 and Table 2, respectively.

Table 1. MG-ADL MSE Rate by Cycle - Subsequent MSE Rates Among Responders at Day 43 of Cycle 1 (Safety Set)

Symptom-driven cycle number	RLZ ~7mg/kg n/ Nsub (%) MG-ADL MSE (0-1)	RLZ ~7mg/kg n/ Nsub (%) MG-ADL (0-2)	RLZ ~7mg/kg n/ Nsub (%) MG-ADL (0-3)	RLZ ~7mg/kg n/ Nsub (%) MG-ADL (0-4)
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ~=equivalent dose' RLZ, Rozanolixizumab; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MSE, minimal symptom expression.
Notes: MG-ADL responder is defined as a participant with a 2.0-point improvement in MG-ADL Score from Baseline at Day 43 of Cycle 1. MSE is MG-ADL score of 0 or 1 achieved at any time during treatment and observation period of cycle. MG-ADL is total score achieved at any time during treatment and observation period of cycle. Nsub is the number of participants who have completed a post-baseline MG-ADL assessment. Percentages are based on Nsub.

Table 2. MG-ADL MSE Rate by Cycle – All participants (Safety Set)

Symptom-driven cycle number	RLZ ~7mg/kg n/ Nsub (%) MG-ADL MSE (0-1)	RLZ ~7mg/kg n/ Nsub (%) MG-ADL (0-2)	RLZ ~7mg/kg n/ Nsub (%) MG-ADL (0-3)	RLZ ~7mg/kg n/ Nsub (%) MG-ADL (0-4)
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]

Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ~=equivalent dose' RLZ, Rozanolixizumab; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MSE, minimal symptom expression.
Notes: MSE is MG-ADL score of 0 or 1 achieved at any time during treatment and observation period of cycle. MG-ADL is total score achieved at any time during treatment and observation period of cycle. Nsub is the number of participants who have completed a post-baseline MG-ADL assessment. Percentages are based on Nsub.

2. Does the company consider that the proportion of 'MSE responders' is greater for patients receiving rozanolixizumab than other treatments? If so, please justify this and provide evidence.

Yes, the company considers that the proportion of MSE responders is greater for patients receiving rozanolixizumab than other treatments. The company's expert elicitation responses and clinical opinion indicated that the MSE response rates of targeted treatments are expected to be greater than for either IVIg, PLEX or SoC (CSs and NSISTs) alone.

Due to the paucity of data on the proportion of patients who achieve MSE on comparator treatments, the company conducted a structured clinical expert elicitation to obtain estimates from UK clinicians specialised in treating refractory gMG. The estimates the clinicians provided for IVIg, PLEX and SoC (CSs and NSISTs) were lower compared to the rozanolixizumab MSE rates observed in the MycarinG trials. For SoC (CSs and NSISTs) specifically, all the clinicians stated that they expected 0% to achieve MSE since, by definition, if patients are refractory to standard therapy then they are not responding to SoC (CSs and NSISTs) and therefore will not achieve MSE with that regimen (CSs and NSISTs).

In general, some clinicians questioned whether it is even possible to achieve MSE in a refractory gMG patient at all if they were being treated with IVIg, PLEX or SoC (CSs and NSISTs) as those patients would be very symptomatic and treatment-resistant.

Secondly, the change from baseline in MG-ADL scores, which signifies the depth of improvement in gMG symptoms, was statistically significant for rozanolixizumab compared to placebo (representing SoC alone) and numerically higher for rozanolixizumab than either IVIg or PLEX in both the bivariate NMA (bvNMA) and the two stage-stage baseline risk adjusted NMA (BLRA NMA). In particular, for IVIg, the NMA results showed that gMG patients were actually getting worse on IVIg treatment, not better. This suggests that it is highly probable that patients treated with rozanolixizumab are more likely to achieve an MG-ADL score of 0 or 1 (MSE) compared to IVIg, PLEX and SoC alone.

Thirdly, in the MycarinG clinical trial, the response rate for participants treated with rozanolixizumab was statistically significantly higher than that for placebo [25% vs. 3%]. Approximately 41% of patients in the EAMS cohort (unrevised proportions) were receiving SoC (CSs and NSISTs) only. It is therefore reasonable to assume that the proportion of MSE responders in the population of interest is likely to be higher for patients receiving rozanolixizumab than for other treatments. This is also clinically plausible and aligns with rozanolixizumab's mechanism of action as a targeted therapy licensed specifically to treat gMG.

Taken together, these points clearly demonstrate that it is implausible to assume that patients receiving treatment with rozanolixizumab would not achieve a higher MSE response than those receiving IVIg, PLEX or SoC only.

3. **There is no data (other than expert elicitation) for the proportion achieving MSE on the basket comparator. For estimating the proportion reaching MSE for the comparator basket, please use the mean and range of patients receiving rozanolixizumab who achieved MSE in MycarinG. Note that we do not want to assume that the final**

proportion of people achieving MSE is the same for rozanolixizumab as for the basket of care; but that of the responders, the same proportion achieve MSE. So we are assuming that the quality of response, if you respond, is the same distribution. Specifically, please run the following scenarios:

- **MSE based on expert elicitation as in ACM2.**
- **Scenario A: [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket**
- **Scenario B: [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket**
- **Scenario C: [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket**

Company response

For clarity, the model base case was revised to include a 28-day length of hospital stay (LoS) for both exacerbation and crisis for all treatments following ACM2. The proportion of patients in the continued health state (MSE) who are treated with SoC only as subsequent treatment has also been amended to 3% to reflect the MSE rate for SoC only and not the previously used proportion ([redacted]%), which represents the entirety of the SoC comparator basket.

The results from the scenarios requested in Question 3 are presented in Tables 3-6 for all patients (Safety Set) and in Tables 7-10 for cycle 1 responders only. All scenarios were run using the revised base case.

Table 3: MSE based on expert elicitation proportions as in ACM2 (all patients, revised base case: LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]

Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]

Table 4: Scenario A. [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket (all patients, revised base case: LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.6038			
IVIg	[redacted]	8.4876	[redacted]	0.1163	[redacted]
Standard care basket comparator	[redacted]	8.5001	[redacted]	0.1038	[redacted]
Plasma exchange	[redacted]	8.5190	[redacted]	0.0848	[redacted]

Table 5: Scenario B. [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket (all patients, revised base case: LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.4245			
IVIg	[redacted]	8.3033	[redacted]	0.1212	[redacted]
Standard care basket comparator	[redacted]	8.3159	[redacted]	0.1086	[redacted]
Plasma exchange	[redacted]	8.3372	[redacted]	0.0873	[redacted]

Table 6: Scenario C. [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket (all patients, revised base case: LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.7477			
IVIg	[redacted]	8.6354	[redacted]	0.1123	[redacted]
Standard care basket comparator	[redacted]	8.6477	[redacted]	0.0999	[redacted]

Plasma exchange	[redacted]	8.6648	[redacted]	0.0828	[redacted]

The company has replicated the scenarios in Tables 3-6 for all patients (Safety Set) using the MSE results for patients who responded to rozanolixizumab (i.e. who achieved an MG-ADL score of at least a 2-point improvement) after the first treatment cycle at day 43 in the MycarinG trial only. Among cycle 1 treatment responders, the average MSE response rate at any given cycle (from cycle 2-13) was [redacted] % (Table 7 and Table 8), ranging from [redacted] % (Table 9) to [redacted] % (Table 10).

Table 7: MSE based on expert elicitation proportions as in ACM2 (responders only [redacted]: LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.3561			
IVIg	[redacted]	8.1841	[redacted]	0.1720	[redacted]
Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1653	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1335	[redacted]

Table 8: Scenario A. [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket (responders only, revised base case: LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.6272			
IVIg	[redacted]	8.5115	[redacted]	0.1156	[redacted]
Standard care basket comparator	[redacted]	8.5240	[redacted]	0.1031	[redacted]
Plasma exchange	[redacted]	8.5427	[redacted]	0.0845	[redacted]

Table 9: Scenario B. [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket (responders only, revised base case: LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.5031			
IVIg	[redacted]	8.3840	[redacted]	0.1190	[redacted]
Standard care basket comparator	[redacted]	8.3966	[redacted]	0.1065	[redacted]
Plasma exchange	[redacted]	8.4169	[redacted]	0.0862	[redacted]

Table 10: Scenario C. [redacted] of responders achieve MSE for both the rozanolixizumab and comparator basket (responders only, revised base case: LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.7921			
IVIg	[redacted]	8.6810	[redacted]	0.1111	[redacted]
Standard care basket comparator	[redacted]	8.6933	[redacted]	0.0987	[redacted]
Plasma exchange	[redacted]	8.7098	[redacted]	0.0822	[redacted]

These scenarios demonstrate that the ICERs do not change using different proportions of responders reaching MSE, when the proportion of responders is the same in both the rozanolixizumab and comparator basket. In summary, the ICERs are not sensitive to MSE response rates. Rozanolixizumab remains [redacted] in all scenarios.

The company reiterates, however, that these scenarios are not clinically plausible and so are not relevant for decision-making. It is not clinically plausible to expect the same MSE rate for rozanolixizumab, IVIg and PLEX for the reasons given in response to Question 2 above.

Time on treatment

4. **Exacerbation (and to a lesser extent myasthenic crisis) is what allows people to leave response health states. Please explore a higher probability of exacerbation for people in stable response than for people in the MSE/continued response state. Please explore a range of probabilities of exacerbation rates and report the time on treatment for each scenario.**

Company response

The company has explored a higher probability of exacerbation for people in stable response by increasing the risk of exacerbation in 10% increments. The time on treatment (ToT) associated with higher probabilities of exacerbation for patients in stable response are provided in Table 11.

Table 11. Higher probability of exacerbation for people in stable response and impact on time on treatment

Increase exacerbation risk (for stable response only) by n%	Time on Treatment (months)			
	Rozanolixizumab	IVIg	PLEX	SoC basket[a]
Base case	[redacted]	[redacted]	[redacted]	[redacted]
10%	[redacted]	[redacted]	[redacted]	[redacted]
20%	[redacted]	[redacted]	[redacted]	[redacted]
30%	[redacted]	[redacted]	[redacted]	[redacted]
40%	[redacted]	[redacted]	[redacted]	[redacted]
50%	[redacted]	[redacted]	[redacted]	[redacted]
60%	[redacted]	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]	[redacted]
90%	[redacted]	[redacted]	[redacted]	[redacted]
100%	[redacted]	[redacted]	[redacted]	[redacted]

[a] The SoC basket is based on the revised EAMS proportions submitted by the company.

When the probability of exacerbation in the stable-response health state was increased in 10% increments, the ToT decreased across all treatments. The greatest relative reduction occurred at the first increment, with subsequent decreases becoming progressively smaller as exacerbation risk rose,

indicating a diminishing marginal impact. Sensitivity to exacerbation risk varied by treatment.

The longer ToT for the SoC basket compared to IVIg and PLEX was primarily driven by a longer time to treatment response assessment (12 weeks versus 3 weeks).

As for the impact on the ICER, rozanolixizumab [redacted] over all comparators across every scenario of increased exacerbation risk in the stable-response health state.

Exacerbations

5. **The length of hospital stay for an exacerbation in the rozanolixizumab model is 2.04 days (ResourceUse! L17 and L31). This was 7.5 days in the model seen at ACM1. Please explain why this change was made. The length of hospital stay for an exacerbation in the zilucoplan model is different: 28 days (ResourceUse! L17 and L31).**

Company response

The length of hospital stay (LoS) for exacerbation should be 28 days, in line with the zilucoplan model and the committee's preferred assumptions for appraisal ID4008. This was a human error oversight that occurred when the global version of the model was updated during the period when this appraisal (ID5092) was paused.

The global version of the model used a LoS value of 2.04 days for exacerbation in all arms. This was revised to 7.5 days for the NICE submission (ACM1) for all treatment arms based on expert elicitation. Following ACM1 and during the period the appraisal was paused, the model was updated again in response to the DG consultation, but the length of stay values was reset to 2.04 days for exacerbation. It should, instead, have been further updated to 28 days for all treatment arms, to match the committee's preferred assumptions for ID4008, which came to light following ACM1 for this

appraisal (ID5092). This has now been updated in the model, and results are shown in Table 12.

Table 12: Length of hospital stay of 28 days for exacerbation and crisis in all arms of the model; continued response rate for SoC-only subsequent treatment: 3%

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]
Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]

6. **UCB's DG response section 3.19 states "The duration of crisis and exacerbation were amended to 28 days each following expert clinical opinion received (and discussions at ACMs for various gMG appraisals)." The model update log (Updatelog! row 22) states that the duration of the disutility from clinical events was set to 28 days, but it does not mention costs. The clinical event disutility is set to 28 days in the rozanolixizumab model (Utilities! D25 and D26). Exacerbation costs are ~£20,000 higher for the standard basket compared with rozanolixizumab. The company is requested to justify and evidence if different costs are appropriate for people having an exacerbation after different treatments.**

Company response

As clarified above, the length of hospital stay for exacerbation was always applied equally across all treatment arms; it was just the value that was inputted in error. The difference in costs per event of exacerbation between rozanolixizumab and the standard of care basket (and indeed, versus IVIg and PLEX also) stems from the acute 'rescue' treatment of IVIg/PLEX to treat the exacerbation or crisis. For rozanolixizumab, both IVIg and PLEX can be used as an acute rescue treatment for exacerbation, in the proportions 73% IVIg and 27% PLEX, as reported in Phillips et al, 2022[1]. However, it was

clinical opinion that, if patients were receiving maintenance IVIg as their index treatment and experienced an exacerbation, they would receive acute rescue PLEX to treat the exacerbation and vice versa. This is because, if they have experienced an exacerbation while receiving maintenance IVIg, they would not be given it again as rescue treatment. Therefore, 100% of patients receiving maintenance IVIg as index treatment would receive PLEX as acute rescue treatment in the case of exacerbation, and 100% of patients receiving maintenance PLEX as index treatment would receive IVIg as acute rescue treatment. All other costs and resource use values per event for exacerbation remain consistent between treatment arms (Table 13).

Table 13: Healthcare resource use for exacerbation

	Unit costs (£)	Length of stay (days)	Frequency of resource use
Patients receiving rozanolixizumab and SoC only (CSs and NSISTs) as index treatment			
IVIg	6,352.00		0.73
PLEX	12,937.25		0.27
GP visit	33.00		0.82
Visit to other healthcare professionals	52.00		0.58
Outpatient hospital visits	485.85		0.75
Presenting at emergency room	278.10		0.38
Hospital stay (with ICU, cost per critical care period)	11,737.70		0.03
Hospital stay (no ICU, cost per day)	595.42	28.00	0.33
Total cost (£)			**14,539.83**
Patients receiving IVIg as index treatment			
IVIg	6,352.00		0.00
PLEX	12,937.25		1.00
GP visit	33.00		0.82
Visit to other healthcare professionals	52.00		0.58
Outpatient hospital visits	485.85		0.75
Presenting at emergency room	278.10		0.38
Hospital stay (with ICU, cost per critical care period)	11,737.70		0.03
Hospital stay (no ICU, cost per day)	595.42	28.00	0.33
Total cost (£)			**19,316.11**
Patients receiving PLEX as index treatment			
IVIg	6,352.00		1.00
PLEX	12,937.25		0.00

GP visit	33.00		0.82
Visit to other healthcare professionals	52.00		0.58
Outpatient hospital visits	485.85		0.75
Presenting at emergency room	278.10		0.38
Hospital stay (with ICU, cost per critical care period)	11,737.70		0.03
Hospital stay (no ICU, cost per day)	595.42	28.00	0.33
Total cost (£)			**12,730.86**

The cost per exacerbation event for the standard of care basket was calculated using the weighted average of those receiving maintenance IVIg, PLEX, and SoC only, based on the revised EAMS proportions. The estimated cost for the SoC basket is presented in Table 14.

Table 14: Estimated cost per exacerbation event for the standard of care basket

Treatment	Revised EAMS proportion	Cost per exacerbation event (£)	Weighted contribution (£)
IVIg	56.70%	19,316.11	10,952.23
PLEX	18.90%	12,730.86	2,406.13
SoC only	24.40%	14,539.83	3,547.72
Total cost per exacerbation event for SoC basket			
SoC basket	**100%**	**-**	**16,906.09**

The consequence of this is that the cost per event for exacerbation differs between rozanolixizumab and the SoC basket comparator, as well as differing if alternative proportions of patients are assigned IVIg and PLEX in the index basket SoC comparator (e.g. choosing unrevised EAMS treatment proportions versus revised EAMS proportions).

Myasthenic crisis

7. **The length of a hospital stay for a myasthenic crisis event is 1.62 days in the rozanolixizumab model seen at ACM2 (ResourceUse! N17 and N31). It was 15 days in the model seen at rozanolixizumab ACM1 and is 28 days in the zilucoplan model seen at ACM3. Please explain why this change was made.**

Company response

The length-of-stay for myasthenic crisis should be 28 days, in line with the zilucoplan model and the committee's preferred assumptions for appraisal ID4008. This was a human error oversight that occurred when the global version of the model was updated during the period that this appraisal (ID5092) was paused.

The global version of the model used a length-of-stay value of 1.62 days for myasthenic crisis in all arms. This was edited to 7.5 days for the NICE submission (ACM1) for all treatment arms based on expert elicitation. Following ACM1 and during the period the appraisal was paused, the model was updated again in response to the DG consultation, but the length of stay values was reset to 1.62 days for myasthenic crisis. It should, instead, have been further updated to 28 days for all treatment arms, to match the committee's preferred assumptions for ID4008, which came to light following ACM1 for this appraisal (ID5092). This has now been updated in the model, and the results are shown in Table 13.

8. **UCB is requested to provide analyses incorporating the following assumptions:**

    - **Length of hospital stay for an exacerbation set to 28 days for rozanolixizumab and the standard care basket arms.**
    - **Costs of an exacerbation set to the same amount for rozanolixizumab and standard care basket arms.**
    - **Length of hospital stay for a myasthenic crisis set to the same duration for rozanolixizumab and standard care basket arms.**
    - **Costs of a myasthenic crisis set to the same amount for rozanolixizumab and standard care basket arms.**

Company response

The results showing the length of stay for exacerbation and crisis set to 28 days across all treatments are shown in Table 15.

Table 15: LoS for exacerbation and crisis is 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]
Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]

Results from a scenario showing the same cost of an exacerbation for rozanolixizumab and other treatments ([redacted] per event) are shown in Table 16.

Table 16: Cost of exacerbation event same across all arms [redacted], LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]
Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]

Results from a scenario showing the same cost of a myasthenic crisis for rozanolixizumab and other treatments ([redacted] per event) are shown in Table 17.

Table 17: Cost of crisis event same across all arms[redacted]), LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]

Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]

Results from a scenario showing the same cost of an exacerbation *and* myasthenic crisis for rozanolixizumab and other treatments are shown in Table 18.

Table 18: Cost of exacerbation and crisis events same across all arms [redacted] and [redacted], respectively), LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]
Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]

As noted in the response to Question 3 above, the base case was revised to include a 28-day length of stay for both exacerbation and crisis for all treatments following ACM2. The proportion of patients in the continued health state (MSE) who are treated with SoC only as subsequent treatment has also been amended to 3% to reflect the MSE rate for SoC only and not the previously used proportion ([redacted]), which represents the SoC comparator basket. In spite of these changes to the base case, the ICERs remain largely unchanged; rozanolixizumab [redacted] for all scenarios explored, except those where equal exacerbation costs are applied to all arms/comparators. When equal exacerbation costs are applied to all arms/interventions, the ICERs increase to a range between [redacted] and [redacted].

However, as described in the company's responses to Questions 6 and 9, the company does not believe that it is plausible to assume that the costs of exacerbation or crisis would be equal for all treatments and in both arms of the model, nor is it representative of UK clinical practice. Expert clinical

opinion has confirmed that patients receiving maintenance IVIg as index treatment who then go on to experience an exacerbation or myasthenic crisis would receive acute rescue PLEX to treat the event, and vice versa. As such, the scenarios reflected above are unrealistic in practice and irrelevant to the present decision problem.

9. **If the company believes that costs and length of hospital stay should differ between the rozanolixizumab and standard care basket arms, UCB should provide evidence or clinical expert advice on why and how they should differ.**

Company response

As clarified above, the length of hospital stay for myasthenic crisis (and exacerbation, and all other healthcare resource use) was always applied equally across all treatment arms; it was just the value that was inputted in error. The difference in costs per event of myasthenic crisis between rozanolixizumab and the standard of care basket (and indeed, versus IVIg and PLEX also) stems from the use of IVIg/PLEX as an acute 'rescue' treatment to treat the myasthenic crisis or exacerbation. For patients treated with rozanolixizumab who go onto experience an exacerbation or myasthenic crisis, either or both IVIg and PLEX can be used as an acute rescue treatment, in the proportions of 73% IVIg and 23% PLEX for exacerbation, and 5% IVIg and 95% PLEX for crisis, as reported in Phillips et al, 2022[1].

However, UK clinical opinion advised that, if patients were receiving maintenance IVIg as their index treatment and experienced a myasthenic crisis, they would receive acute rescue PLEX to treat the myasthenic crisis and vice versa. This is because, if a patient has experienced a myasthenic crisis while receiving maintenance IVIg, they would not be given it again as rescue treatment. Therefore, 100% of patients receiving maintenance IVIg as index treatment would receive PLEX as acute rescue treatment in the case of myasthenic crisis, and 100% of patients receiving maintenance PLEX as index treatment would receive IVIg as acute rescue treatment. All other costs

and resource use values per event for myasthenic crisis remain consistent between treatment arms.

The differences in healthcare resource use for myasthenic crisis are presented in Table 19 and Table 20, by index treatment.

Table 19: Healthcare resource use for myasthenic crisis

	Unit costs (£)	Length of stay (days)	Frequency of resource use
Patients receiving rozanolixizumab and SoC only (CSs and NSISTs) as index treatment			
IVIg	6,352.00		0.05
PLEX	12,937.25		0.95
GP visit	33.00		0.06
Visit to other healthcare professionals	52.00		0.32
Outpatient hospital visits	485.85		0.50
Presenting at emergency room	278.10		1.00
Hospital stay (with ICU, cost per critical care period)	11,737.70		1.00
Hospital stay (no ICU, cost per day)	595.42	28.00	1.00
Total cost (£)			**41,549.59**
Patients receiving IVIg as index treatment			
IVIg	6,352.00		0.00
PLEX	12,937.25		1.00
GP visit	33.00		0.06
Visit to other healthcare professionals	52.00		0.32
Outpatient hospital visits	485.85		0.50
Presenting at emergency room	278.10		1.00
Hospital stay (with ICU, cost per critical care period)	11,737.70		1.00
Hospital stay (no ICU, cost per day)	595.42	28.00	1.00
Total cost (£)			**41,887.41**
Patients receiving PLEX as index treatment			
IVIg	6,352.00		1.00
PLEX	12,937.25		0.00
GP visit	33.00		0.06
Visit to other healthcare professionals	52.00		0.32
Outpatient hospital visits	485.85		0.50
Presenting at emergency room	278.10		1.00
Hospital stay (with ICU, cost per critical care period)	11,737.70		1.00
Hospital stay (no ICU, cost per day)	595.42	28.00	1.00

Total cost (£)			**35,302.16**

The cost per myasthenic crisis event for the SoC basket was calculated using the weighted average of those receiving maintenance IVIg, PLEX, and SoC only, based on the revised EAMS proportions. The estimated cost for the SoC basket is presented in Table 20.

Table 20: Estimated cost per myasthenic crisis event for the standard of care blended basket

Treatment	Revised EAMS proportion	Cost per myasthenic crisis event (£)	Weighted contribution (£)
IVIg	[redacted]	41,887.41	23,750.16
PLEX	[redacted]	35,302.16	6,672.11
SoC only	[redacted]	41,549.59	10,138.10
Total cost per myasthenic crisis for SoC basket			
SoC basket	***100%***	**-**	**40,560.37**

The consequence of this is that the cost per event for myasthenic crisis differs between rozanolixizumab and the SoC basket comparator, as well as differing if alternative proportions of patients are assigned IVIg and PLEX in the index basket SoC comparator (e.g. choosing unrevised EAMS proportions versus revised EAMS proportions), as the resultant cost per event is a weighted average of the proportions of patients receiving each treatment within the index SoC basket.

10. **For all scenarios requested in this document, provide a change log for the model, specifying the cells where the change has been made. Please provide a table showing the total and incremental costs and QALYs and the ICER for the current base case and the cumulative effect each change has on the results.**

Company response

A complete change log is provided as part of the Excel model.

The cumulative effect of each change on the total and incremental costs and QALYs, as well as the ICERs, is presented in Table 21.

Table 21. Current base case and cumulative effect of each change

Base case (ACM2 model): MSE based on expert elicitation, LoS for exacerbation and crisis: 2.04 and 1.62 days for all arms; continued response rate for SoC-only subsequent treatment: 15.5%					
Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	
Rozanolixizumab	[redacted]	8.4151			
IVIg	[redacted]	8.2518	[redacted]	0.1633	[redacted]
Standard care basket comparator	[redacted]	8.2567	[redacted]	0.1584	[redacted]
Plasma exchange	[redacted]	8.2894	[redacted]	0.1257	[redacted]
Base case: MSE based on expert elicitation, LoS for exacerbation and crisis: 2.04 and 1.62 days for all arms; continued response rate for SoC-only subsequent treatment: 3%					
Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]
Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]
Base case + LoS for exacerbation and crisis 28 days for all arms; continued response rate for SoC-only subsequent treatment: 3%					
Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]
Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]

Base case + LoS for exacerbation and crisis 28 days for all arms + Cost of exacerbation event same across all arms [redacted]; continued response rate for SoC-only subsequent treatment: 3%					
Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]
Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]
Base case + LoS for exacerbation and crisis 28 days for all arms + Cost of crisis event same across all arms ([redacted]); continued response rate for SoC-only subsequent treatment: 3%					
Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]
Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]
Base case + LoS for exacerbation and crisis 28 days for all arms + Cost of exacerbation event same across all arms ([redacted]) + Cost of crisis event same across all arms ([redacted]); continued response rate for SoC-only subsequent treatment: 3%					
Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	
Rozanolixizumab	[redacted]	8.3518			
IVIg	[redacted]	8.1841	[redacted]	0.1677	[redacted]
Standard care basket comparator	[redacted]	8.1909	[redacted]	0.1609	[redacted]
Plasma exchange	[redacted]	8.2227	[redacted]	0.1291	[redacted]

Reference:

1. Phillips G, Abreu C, Goyal A, Li Y, Whangbo A, Gelinas D, Brauer E and Bhattacharya S (2022) Real-World Healthcare Resource Utilization and Cost Burden Assessment for Adults With Generalized Myasthenia Gravis in the United States. Front. Neurol. 12:809999. doi: 10.3389/fneur.2021.809999

Please submit your responses and updated model via NICE Docs by **2 January 2026** close of business. The link is here:

https://appraisals.nice.org.uk/request/226948

University of Southampton

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Rozanolixizumab for treating generalised myasthenia gravis (ID5092)

External Assessment Group's critique of the company's response to the Committee's requests post-Advisory Committee Meeting 2 (ACM2)

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Fay Chinnery, Research Fellow, Health Economics Lois Woods, Senior Research Assistant, Evidence Synthesis and Information Specialist Joanne Lord, Professorial Research Fellow, Health Economics Geoff Frampton, Principal Research Fellow, Evidence Synthesis
Correspondence to	Lois Woods Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation Faculty of Medicine University of Southampton l.e.woods@southampton.ac.uk
Date completed	6th February 2026

[redacted]

Table of Contents

LIST OF TABLES

1 INTRODUCTION

This document is the External Assessment Group (EAG)'s critique of the response by the company, UCB, to the Committee's request for further analyses post-Advisory Committee Meeting 2 (ACM 2, held November 2025) for the technology appraisal of rozanolixizumab for treating antibody-positive generalised myasthenia gravis (ID5092).

The EAG received the company's revised economic model and draft response document on 5th January 2026, and the final response document containing additional information concerning minimum symptom expression (MSE) analyses on 12th January. The EAG received an updated model to correctly run the MSE scenarios and an updated response document on 23rd January 2026. Hereafter, we refer to these as the company revised model and the company response.

2 EAG CRITIQUE OF THE COMPANY'S RESPONSE TO THE COMMITTEE'S REQUESTS

2.1 Model updates

The company were asked to:

- Unhide sheets, tables and cells for transparency
- Ensure 'loss of response' for all treatments is no longer hard-coded

We confirm that there are no hidden rows or columns in the sheets of the company's revised model. We note that the *MycarinG_time_on_tx* and *KMdata* sheets were still hidden, but these were not required for our critique. The company have made the changes requested by the committee.

2.2 Minimum symptom expression (MSE)

2.2.1 Distribution of MSE events among patients and treatment cycles

The company provide data from the MG0007 extension study for participants receiving the licensed 7 mg/kg dose that show,

- Between [redacted] of participants who had responded in their first cycle (i.e. achieved an MG-ADL score improvement ≥2 in cycle 1) [redacted] in subsequent cycles (i.e. cycles 2-13) (Table 1 of the Company Response).
- Of those who had responded in cycle 1, across the following cycles (i.e. cycles 2 to 13), [redacted] achieved an MG-ADL score of 0-2, [redacted] achieved an MG-ADL score of 0-3, and [redacted] achieved an MG-ADL score of 0-4 (Table 1 of the Company Response).
- The ranges appear broad, likely due to small sample sizes ([redacted] sample sizes appear from [redacted] onwards), but response rates increase consistently across the incremental MG-ADL response thresholds.

The company have not explained why the denominators and in some cases also the numerators in Table 2 are larger, for each cycle and MG-ADL score category, than those in Table 1. We assume that Table 2 is based on the full 7 mg/kg dose population of MG0007 which includes patients originally recruited from MG0004 as well as from MG0003 (total N=88; CS Figure 7). The sample sizes in Table 2 indicate that the denominator incudes both responders and non-responders. The company have not

explained the relevance of the data in Table 2 and these data have not been used in the economic analysis.

2.2.2 Company rationale for the proportion of 'MSE responders' being greater for patients receiving rozanolixizumab than other treatments

The company argue three main points for the proportion of MSE responders being greater for patients who receive rozanolixizumab compared to those receiving intravenous immunoglobulin (IVIg), plasma exchange (PLEX) or standard of care (SoC) (company response pages 4 to 5):

1. Estimates from a structured clinical expert elicitation for MSE rates in patients receiving IVIg, PLEX or SoC were lower than MSE rates observed for rozanolixizumab in the MycarinG trial.

   EAG comment: The company expert elicitation consisted of three clinical experts who answered the MSE questions (company expert elicitation report supplied with the response to DG1). The estimated MSE rate of 0% for SoC is indeed lower than the MSE rates for rozanolixizumab. The upper end of the estimated range of 10% to 25% for both IVIg and PLEX (reported in the company expert elicitation report supplied with the response to Draft Guidance 1) meets the lower end of the range of proportions for rozanolixizumab.

2. Statistically significant results in favour of rozanolixizumab for the change from baseline in MG-ADL scores in the bivariate network meta-analysis (bvNMA) and the baseline risk-adjusted network meta-analysis (BLRA NMA) suggest high probability that patients treated with rozanolixizumab are more likely to achieve MSE than those receiving other treatments.

   EAG comment: The link between change from baseline in MG-ADL score and achievement of MSE in the indirect treatment comparisons (bvNMA and BLRA NMA is not clear. We note that change from baseline can be clinically meaningful without achieving MSE. A baseline MG-ADL score as low as 4 (maximum score is 24) could achieve clinically meaningful change (MCID of 2 points)[1, 2] and not reach MSE.

3. Statistically significant results for response rates in favour of rozanolixizumab compared to placebo in the MycarinG trial make it reasonable to assume that the proportion of MSE responders is higher for patients receiving rozanolixizumab than those receiving other treatments.

EAG comment: This is not a logical inference, and placebo is not a comparator of interest. For reference, the MycarinG response rate outcome cited in this point is for MSE at any time during treatment and observation periods (CS Table 28, CS section B.2.6.1.3).

2.2.3 Scenario analyses concerning the proportion of patients reaching MSE for the comparator basket

The committee requested the company run scenarios altering the proportions of patients achieving MSE (Company Response Document p.6). The company conducted these scenarios using their revised base case for all patients (Company Response Document Tables 3-6). The Company Response Document also presents results for the patients who only responded to treatment in cycle 1 (Company Response Document Tables 7-10). Rozanolixizumab [redacted].

The company explained via email (received 22-Jan-2026 by the EAG) that it is necessary to set the MSE distribution to be identical across all comparators for these scenarios, because the MSE response rates for the individual treatments are used to calculate the weighted distribution for the subsequent treatment basket. If the MSE values for IVIg and PLEX are not updated, the model generates incorrect results for rozanolixizumab compared with the standard basket.

The company provided an updated model (dated 22-Jan-2026) correcting a minor error in the MSE response distribution for standard of care (i.e. corticosteroids and non-steroidal immunosuppressive therapy (NSISTs), hereafter referred to as 'SoC only') in the subsequent treatment setting, which was leading to an inaccurate estimation of the weighted distribution used for MSE in the standard basket when running the MSE scenario analyses. This update had a negligible effect on results, rozanolixizumab [redacted].

EAG conclusion

Further data provided from the MG0007 study shows the extent to which patients who had responded in cycle 1 achieved MG-ADL scores of 0-1 (i.e. MSE), 0-2, 0-3, and 0-4 in subsequent cycles. Response rates were [redacted] whether response ($\geq$2 points improvement from baseline to Day 43) was achieved during the first cycle or not.

The rationale for the proportion of MSE responders being greater in patients receiving rozanolixizumab relies on expert elicitation and assumptions around clinical

plausibility. The EAG cannot identify any stronger evidence; further expert opinion may validate the clinical plausibility of the company's rationales.

The EAG notes that the ICER results are not sensitive to changing MSE response rates in the company's revised model. We ran selected scenario analyses, using our preferred assumptions (section 4.2).

2.3 Time on treatment

2.3.1 Exploration of a higher probability of exacerbation for people in stable response than for people in the MSE/continued response state and a range of probabilities of exacerbation rates; time on treatment reported for each scenario

The company conducted scenario analyses where the risk of exacerbation was increased in 10% increments (up to 100%) for people in stable response and reported the effect on time on treatment in Company Response Document Table 11. The Company Response Document highlights that increasing the probability of exacerbation decreases time on treatment for all treatments and that rozanolixizumab [redacted] in all scenarios.

EAG conclusion

The EAG are uncertain if the scenarios increasing exacerbation risk in patients with a stable response represents a reasonable range, and we consider that clinical expert advice regarding the increased risk of an exacerbation for patients in stable response compared with MSE would be beneficial.

The EAG validated the *Exac_Scenario* results by manually entering the appropriate stable response exacerbation rate into the *ClinicalEvents* sheet (cell C11) and checking the effect on time on treatment in the *Engine* sheets (cells AD32). We reproduce the results of these scenarios (for rozanolixizumab versus the standard basket) using our base case in section 4.2.

2.4 Exacerbations

2.4.1 Length of hospital stay for an exacerbation

The company have updated the length of hospital stay to 28 days for an exacerbation for all treatments, in line with the committee's preferred assumptions for ID4008, and in ID5092 ACM1. The results of using a length of hospital stay of 28 days for exacerbation and crisis in

all arms of the economic model are presented in Company Response Document Table 12. Rozanolixizumab [redacted].

2.4.2 Exacerbation costs

The Company Response Document (p.12-13) explains that the difference in exacerbation costs between rozanolixizumab and the standard basket is caused by the dissimilar use of IVIg and PLEX in acute rescue treatment in the two groups. Clinical expert advice to the company was that if patients receive maintenance IVIg treatment and experience an exacerbation, they will receive PLEX rescue treatment and vice versa.

The healthcare resource use per exacerbation for each index treatment is presented in Company Response Document Table 13:

- 100% of patients receiving maintenance IVIg receive PLEX as rescue treatment
- 100% of patients receiving maintenance PLEX receive IVIg as rescue treatment
- Of patients receiving rozanolixizumab as index treatment, 73% receive IVIg as rescue treatment and 27% receive PLEX (Phillips et al. 2022)[3]

The EAG are uncertain how the proportions of patients receiving IVIg and PLEX rescue therapy following rozanolixizumab or SoC only therapy have been calculated from the cited reference (Phillips et al (2022) [(1)]) and we note that the evidence informing these proportions is from a US source.

However, the proportions of patients receiving IVIg and PLEX rescue therapy following rozanolixizumab treatment used in the company revised model are the same as used in the economic model seen at ACM1 and ACM2. When reviewing the economic model seen at ACM1, our clinical experts did not highlight any concerns with the proportions of patients receiving IVIg or PLEX rescue therapy for an exacerbation.

We note that the company assumes the cost for managing an exacerbation is the same for patients receiving rozanolixizumab and SoC only. To estimate the cost per exacerbation for the standard basket, the company use a weighted average of people receiving maintenance IVIg, PLEX, and SoC only, based on the revised EAMS proportions (£16,906; Company Response Document Table 14). This cost is £16,368 in the EAG base case because we prefer to use the unrevised EAMS cohort data, in which patients receive different treatment proportions.

We use the exacerbation costs from the company revised base case in our base case and conducted a scenario analysis setting the costs of an exacerbation to be the same in both arms. Results are presented in section 4.2.

EAG conclusion

The length of hospital stay for an exacerbation in the company revised model has been updated as per the committee's preference.

We consider that the company's justification for 100% of people on maintenance IVIg receiving PLEX rescue treatment for an exacerbation, and vice versa, is appropriate. We also consider their weighted-average method for calculating the rescue treatment cost per exacerbation for the standard basket to be reasonable.

2.5 Myasthenic crisis

2.5.1 Length of hospital stay for myasthenic crisis

The length of hospital stay for a myasthenic crisis has been updated to 28 days, to match the committee's preferred assumptions for ID4008 and ID5092 following ACM1.

2.5.2 Costs of a crisis event

The costs for treating a myasthenic crisis varies by index treatment in the company revised base case. Clinical expert advice to the company was that, if patients were receiving IVIg as a maintenance treatment, they would not receive it as an acute rescue therapy and would receive PLEX instead. Similarly, patients receiving PLEX maintenance therapy would not receive PLEX as rescue therapy in the event of a crisis (Company Response Document (p.17).

The healthcare resource use per myasthenic crisis event for each index treatment is presented in Company Response Document Table 19:

- 100% of patients receiving maintenance IVIg receive PLEX as rescue treatment
- 100% of patients receiving maintenance PLEX receive IVIg as rescue treatment
- Of patients receiving rozanolixizumab as index treatment, 5% receive IVIg as rescue treatment and 95% receive PLEX (Phillips et al. 2022).[3]

We are unsure how the company have calculated the proportions of patients receiving IVIg and PLEX rescue therapy following rozanolixizumab or SoC only therapy using Phillips et al. (2022).[3] However, the proportions of patients receiving IVIg and PLEX crisis rescue therapy following rozanolixizumab treatment used in the company revised model are unchanged from the economic model seen at previous ID5092 committee meetings. Our clinical experts did not highlight any concerns with the proportions of patients receiving IVIg or PLEX rescue therapy for a myasthenic crisis when reviewing the company's original economic model.

The EAG notes that the company assumes the costs for managing a myasthenic crisis is the same for patients receiving rozanolixizumab and SoC only. The cost per myasthenic crisis for the standard basket is estimated using a weighted average of people receiving maintenance IVIg, PLEX, and SoC only, based on the revised EAMS proportions (£40,560; Company Response Document Table 20). Using the unrevised EAMS cohort in the EAG base case produces a cost of £40,785 per crisis event.

We use the costs for a myasthenic crisis from the company revised base case in our base case and conducted a scenario analysis setting the costs of a crisis event to be the same in both arms. Results are presented in section 4.2.

EAG conclusion

The length of hospital stay for a myasthenic crisis in the company revised model has been updated as per the committee's preference. We agree with the company's reasoning for using different costs for a myasthenic crisis in each treatment group, and with the method used for calculating the cost per crisis event for the standard basket.

2.6 Committee's scenario analyses requests

The committee requested the company run scenario analyses altering the length of hospital stay and costs for an exacerbation and a myasthenic crisis. Scenario results are presented in Company Response Document (p.15-17) for:

1. Length of hospital stay for an exacerbation and crisis event both set to 28 days for all treatments (Table 15); the EAG notes that this is the ICER result of company's revised base case
2. Costs of an exacerbation set to the same amount ([redacted]) for all treatments (Table 16)
3. Costs of a myasthenic crisis set to the same amount ([redacted]) for all treatments (Table 17)
4. Costs of an exacerbation and a myasthenic crisis set to the same amount ([redacted] and [redacted], respectively) for all treatments (Table 18)

Rozanolixizumab [redacted], except in scenarios 2 and 4, where the ICER is [redacted] for rozanolixizumab compared with the standard basket.

The company has run all of the scenarios requested by the committee.

3 EAG VALIDATION OF THE COMPANY'S REVISED COST-EFFECTIVENESS RESULTS

3.1 Company's revised base case cost-effectiveness results

The company provided a revised economic model (dated 02-01-2026), which the EAG successfully validated (Table 2).

Table 1 Cumulative changes to the company base case seen at ACM2, and base case results of the company's revised model

Description	Treatment	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
Company base case seen at ACM 2	Rozanolixizumab	[redacted]	8.415	[redacted]	0.158	[redacted]
	Standard basket	[redacted]	8.257			
Length of hospital stay of 28 days for exacerbation and crisis in all arms	Rozanolixizumab	[redacted]	8.415	[redacted]	0.158	[redacted]
	Standard basket	[redacted]	8.257			
Continued response rate of 3% for SoC-only Subsq Tx	Rozanolixizumab	[redacted]	8.352	[redacted]	0.161	[redacted]
	Standard basket	[redacted]	8.191			
Company revised base case (dated 02-01-2026)	Rozanolixizumab	[redacted]	8.352	[redacted]	0.161	[redacted]
	Standard basket	[redacted]	8.191			

Source: EAG created table
Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life-year; SoC, standard care (corticosteroids and non-steroidal immunosuppressants); Subsq Tx, subsequent treatment

In response to clarification questions from the EAG, the company provided an updated version of the economic model (dated 22-Jan-2026) that corrected a minor error (discussed in section 2.2.3) and implemented a VBA macro to automate running the MSE scenarios. We thank the company for the updated model and MSE scenario macro but owing to time constraints we did not programme our preferences into this updated model.

Consequently, **all results in this report refer to the company's revised model dated 02-01-2026** and include the PAS discount for rozanolixizumab. Analyses including appropriate Medicines Procurement and Supply Chain (MPSC) costs are presented in a separate confidential addendum.

In the company's revised base case of rozanolixizumab versus the standard basket, using the company's revised EAMS population ([redacted] of patients receiving PLEX, [redacted] receiving IVIg, and the remainder ([redacted]) receiving SoC (CSs/NSISTs)), rozanolixizumab [redacted] (Table *1*).

4 EAG ANALYSES

4.1 EAG preferred assumptions

As per the 'EAG critique of company response to Draft Guidance Document 1' (EAG critique of DGD1 response), we disagree with some aspects of the company's revised base case. Our preferred model assumptions are to:

1. Remove the disutility associated with corticosteroid use (discussed in EAG critique of DGD1 response section 2.4)
2. Use a standard basket as the comparator, and to use the unrevised EAMS cohort[4] to inform the proportions of patients on each treatment in the standard basket (43.8% receive IVIg, 14.6% receive PLEX, 41.6% receive standard care; discussed in EAG critique of DGD1 response section 2.5)
3. Use a response assessment time point of three weeks for the standard basket (discussed in EAG critique of DGD1 response section 2.10)
4. Apply PLEX admin costs for five PLEX sessions every four weeks (£2,482.50 per model cycle; discussed EAG critique of DGD1 response section 2.11)
5. Use the treatment proportions from the unrevised EAMS cohort to inform subsequent treatment following rozanolixizumab (discussed in EAG critique of DGD1 response section 2.12.1)
6. Use the EAG-calculated treatment proportions for subsequent treatment following the standard basket (8.20% receive IVIg, 27.16% receive PLEX, 64.64% receive standard care (corticosteroids/NSISTs)) (discussed in EAG critique of DGD1 response section 2.12.1)[a]
7. Use the costs from Lee et al.[5] to inform the resource use costs of corticosteroid management (discussed in EAG critique of DGD1 response section 2.12.2)
8. Use the same corticosteroid management resource use costs for MSE in both arms (discussed in EAG critique of DGD1 response section 2.12.2)

The cumulative effect of these changes results in an ICER of [redacted] per QALY for rozanolixizumab compared with the standard basket (Table 2).

[a]**Please note:** There was a factual error in the EAG calculation of the proportion of patients receiving PLEX subsequent treatment (following IVIg treatment in the standard basket arm) in the EAG base case seen at ACM2. The correct proportion is **27.16%** (43.8% of patients on IVIg multiplied by 62% [company clinical expert estimate of the proportion who switch to PLEX; Delphi Survey Report Table 15]). This was previously miscalculated and reported as 29.9% in the 'EAG critique of company response to DGD1'.

Table 2 Cumulative effect of the EAG's preferred assumptions, rozanolixizumab compared with the standard basket

Assumption		Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	Cumulative ICER (£/QALY)
Company revised base case (02-01-2026)		Rozanolixizumab	[redacted]	8.352	[redacted]	0.161	[redacted]
		Standard basket	[redacted]	8.191			
1	Exclude the disutility associated with corticosteroid use	Rozanolixizumab	[redacted]	8.537	[redacted]	0.153	[redacted]
		Standard basket	[redacted]	8.384			
2	Use the original EAMS cohort for the standard basket (43.8% IVIg, 14.6% PLEX, 41.6% SoC)	Rozanolixizumab	[redacted]	8.537	[redacted]	0.161	[redacted]
		Standard basket	[redacted]	8.376			
3	Use a response assessment time point of 3 weeks for the standard basket; 6 weeks for rozanolixizumab	Rozanolixizumab	[redacted]	8.537	[redacted]	0.169	[redacted]
		Standard basket	[redacted]	8.369			
4	Apply PLEX admin ad treatment costs for 5 PLEX sessions every 4 weeks	Rozanolixizumab	[redacted]	8.537	[redacted]	0.169	[redacted]
		Standard basket	[redacted]	8.369			
5	Subsq Tx: unrevised EAMS cohort post-rozanolixizumab	Rozanolixizumab	[redacted]	8.515	[redacted]	0.147	[redacted]
		Standard basket	[redacted]	8.369			
6	Subsq Tx: EAG calculated proportions for the standard basket	Rozanolixizumab	[redacted]	8.515	[redacted]	0.203	[redacted]
		Standard basket	[redacted]	8.312			
7	Costs for corticosteroid management from Lee et al.	Rozanolixizumab	[redacted]	8.515	[redacted]	0.203	[redacted]
		Standard basket	[redacted]	8.312			
8	Use the same corticosteroid resource use costs for MSE in both arms	Rozanolixizumab	[redacted]	8.515	[redacted]	0.203	[redacted]
		Standard basket	[redacted]	8.312			
EAG base case		Rozanolixizumab	[redacted]	8.515	[redacted]	0.203	[redacted]
		Standard basket	[redacted]	8.312			

Source: EAG created table
Abbreviations: EAMS, Early access to medicines scheme; ICER, incremental cost-effectiveness ratio; Incr., incremental; IVIg, intravenous immunoglobulin; MSE, minimal symptom expression; PLEX, plasma exchange; QALY, quality-adjusted life-year; SoC: standard care (corticosteroids and non-steroidal immunosuppressants); Subsq Tx, subsequent treatment

4.2 Scenario analyses on the EAG's preferred assumptions

The EAG ran scenario analyses on our base case assumptions (Table 3). We reproduced the company's time on treatment scenarios, exploring a higher probability of exacerbation for people in stable response, in Table 4.

Table 3 Scenario analyses for rozanolixizumab compared with the standard basket, EAG base case

No	Scenario description	Treatment	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
EAG base case		Rozanolixizumab	[redacted]	8.515	[redacted]	0.203	[redacted]
		Standard basket	[redacted]	8.312			
EAG scenarios							
1	Company's revised EAMS cohort as the standard basket in the comparator arm	Rozanolixizumab	[redacted]	8.515	[redacted]	0.195	[redacted]
		Standard basket	[redacted]	8.320			
2	Response assessment timepoint for the standard basket = 12 weeks	Rozanolixizumab	[redacted]	8.515	[redacted]	0.194	[redacted]
		Standard basket	[redacted]	8.321			
3	Subsq Tx: Company's base case proportions, for both arms	Rozanolixizumab	[redacted]	8.537	[redacted]	0.169	[redacted]
		Standard basket	[redacted]	8.369			
4	Use the annualised number of cycles for rozanolixizumab treatment	Rozanolixizumab	[redacted]	8.515	[redacted]	0.203	[redacted]
		Standard basket	[redacted]	8.312			
5	Set rozanolixizumab response rate to the same as standard care (CS and NSISTs): [redacted]	Rozanolixizumab	[redacted]	8.430	[redacted]	0.117	[redacted]
		Standard basket	[redacted]	8.312			
MSE scenarios							
6	All patients: [redacted] of responders achieve MSE for all treatments (lowest proportion achieving MSE in the scenarios)	Rozanolixizumab	[redacted]	8.579	[redacted]	0.115	[redacted]
		Standard basket	[redacted]	8.463			
7	Cycle 1 Tx responders[a]: [redacted] of responders achieve MSE for all treatments (highest proportion achieving MSE in the scenarios)	Rozanolixizumab	[redacted]	8.952	[redacted]	0.121	[redacted]
		Standard basket	[redacted]	8.830			
Costs of exacerbations and myasthenic crises scenarios							
8	Costs of an exacerbation set the same in both arms ([redacted])	Rozanolixizumab	[redacted]	8.515	[redacted]	0.203	[redacted]
		Standard basket	[redacted]	8.312			

No	Scenario description	Treatment	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
9	Costs of a myasthenic crisis set the same in both arms ([redacted])	Rozanolixizumab	[redacted]	8.515	[redacted]	0.203	[redacted]
		Standard basket	[redacted]	8.312			
10	Costs of an exacerbation and a myasthenic crisis set the same in both arms ([redacted] and [redacted])	Rozanolixizumab	[redacted]	8.515	[redacted]	0.203	[redacted]
		Standard basket	[redacted]	8.312			

Source: EAG created table

[a] The same patient characteristics are used for both 'cycle 1 responders' and the 'all patients' group (company email, received via NICE 22-Jan-2026)

Abbreviations: bvNMA, bivariate network meta-analysis; CS, corticosteroids; EAMS, Early access to medicines scheme; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living score; NSISTs, non-steroidal immunosuppressants; PLEX, plasma exchange; QALY, quality-adjusted life-year; Subsq Tx, subsequent treatment; Tx, treatment

Table 4 Higher probability of exacerbation for people in stable response and impact on time on treatment, EAG base case

Increase in exacerbation risk (%)	Treatment	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Time on treatment (months)
Base case	Rozanolixizumab	[redacted]	0.203	[redacted]	[redacted]
	Standard basket				[redacted]
10%	Rozanolixizumab	[redacted]	0.1983	[redacted]	[redacted]
	Standard basket				[redacted]
20%	Rozanolixizumab	[redacted]	0.1945	[redacted]	[redacted]
	Standard basket				[redacted]
30%	Rozanolixizumab	[redacted]	0.1911	[redacted]	[redacted]
	Standard basket				[redacted]
40%	Rozanolixizumab	[redacted]	0.1882	[redacted]	[redacted]
	Standard basket				[redacted]
50%	Rozanolixizumab	[redacted]	0.1856	[redacted]	[redacted]
	Standard basket				[redacted]
60%	Rozanolixizumab	[redacted]	0.1832	[redacted]	[redacted]
	Standard basket				[redacted]
70%	Rozanolixizumab	[redacted]	0.1812	[redacted]	[redacted]
	Standard basket				[redacted]
80%	Rozanolixizumab	[redacted]	0.1793	[redacted]	[redacted]
	Standard basket				[redacted]
90%	Rozanolixizumab	[redacted]	0.1775	[redacted]	[redacted]
	Standard basket				[redacted]
100%	Rozanolixizumab	[redacted]	0.1760	[redacted]	[redacted]
	Standard basket				[redacted]

Source: Adapted from Company Response Document Table 1
Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; QALY, quality-adjusted life-year

4.3 Sensitivity analyses on the EAG's preferred assumptions

4.3.1 Probabilistic sensitivity analysis (PSA)

The EAG conducted a PSA for the EAG base case analysis with 1000 simulations (Table 5). Rozanolixizumab [redacted] The EAG are uncertain why there is such a discrepancy between the deterministic and probabilistic EAG base cases and consider that the PSA is not running correctly when set to the EAG base case.

Furthermore, we note that running the PSA macro strips out some of the EAG programming, meaning that the model no longer represents the EAG base case.

Table 5 Probabilistic results for the EAG base case

Treatment	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
Rozanolixizumab	[redacted]	8.515	[redacted]	0.190	[redacted]
Standard basket	[redacted]	8.325			

4.4 Economic analysis summary

The company revised economic model (dated 02-01-2026) presents the results of the company's base case as pairwise comparisons of rozanolixizumab versus IVIg, versus the standard basket and versus PLEX. Rozanolixizumab [redacted]

We reviewed and successfully validated the company's revised model (Table 1). Section 4.1 summarises our preferred assumptions, which are consistent with those applied to the company's economic model seen at ACM2, apart from correcting the proportion of patients receiving PLEX subsequent treatment in the standard basket arm (following IVIg treatment) from [redacted] to [redacted]. Using the EAG's preferred assumptions results in an ICER of [redacted] per QALY for rozanolixizumab compared with the standard basket.

We conducted scenario analyses on our base case to explore the remaining uncertainty when comparing the cost-effectiveness of rozanolixizumab with the standard basket (section 4.2). The model is most sensitive to using the company's revised EAMS cohort as the standard basket in the comparator arm (scenario 1), [redacted] of responders achieving MSE for all treatments (scenario 6), and using the company's base case subsequent treatment proportions for both arms (scenario 3).

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Company response

ID5092 rozanolixizumab in myasthenia gravis: number of exacerbation events

Based on the company's base case, the average estimated number of exacerbation events per patient over the model time horizon is [redacted] for rozanolixizumab, [redacted] for IVIg/SCIg, [redacted] for standard care basket comparator and [redacted] for plasma exchange.

Estimated number of exacerbations over model time horizon by treatment

Treatment	Number of exacerbation events over model time horizon
Rozanolixizumab	[redacted]
IVIg/SCIg	[redacted]
Standard care basket comparator	[redacted]
Plasma exchange	[redacted]