NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Rozanolixizumab for treating antibody-positive generalised myasthenia gravis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using rozanolixizumab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation 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 recommendations sound and a suitable basis for guidance to the NHS?
- 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?

Issue date: September 2024

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using rozanolixizumab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 4 October 2024
- Second evaluation committee meeting: 12 December 2024
- Details of the evaluation committee are given in section 4

Issue date: September 2024

1 Recommendations

1.1 Rozanolixizumab is not recommended, within its marketing authorisation, as an add-on to standard treatment for generalised myasthenia gravis in adults who test positive for:

- anti-acetylcholine receptor antibodies or
- anti-muscle-specific tyrosine kinase antibodies.

1.2 This recommendation is not intended to affect treatment with rozanolixizumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Standard treatment for generalised myasthenia gravis in adults who test positive for anti-acetylcholine receptor or anti-muscle-specific tyrosine kinase antibodies includes surgery, acetylcholinesterase inhibitors, corticosteroids and immunosuppressants. For people whose condition does not improve with standard treatment, intravenous immunoglobulin or plasma exchange may be added. Rozanolixizumab would be used as an add-on to standard treatment.

Clinical trial evidence suggests that rozanolixizumab plus standard treatment improves symptoms and people's ability to carry out their normal activities compared with standard treatment alone. But its treatment effect in the longer term is uncertain. Rozanolixizumab has not been compared with plasma exchange, and the results of an indirect comparison of rozanolixizumab with intravenous immunoglobulin are uncertain. So, it is unclear how well it works compared with these treatments.

There are also uncertainties in the economic model and the cost-effectiveness estimates for rozanolixizumab. The most likely estimates are substantially above

what NICE considers an acceptable use of NHS resources. So, rozanolixizumab is not recommended.

2 Information about rozanolixizumab

Marketing authorisation indication

2.1 Rozanolixizumab (Rystiggo, UCB) is indicated 'as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for rozanolixizumab.

Price

2.3 £8,941.59 per 140 mg/1 ml vial of solution for injection (excluding VAT; BNF online accessed August 2024).

2.4 The company has a commercial arrangement, which would have applied if rozanolixizumab had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by UCB, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Myasthenia gravis is an autoimmune condition that can affect multiple muscle groups, and causes muscle weakness and fatigue. At first, it usually affects only the eye muscles. But in around 80% of people it will affect other muscle groups and become generalised myasthenia gravis (gMG). Most people with gMG have anti-acetylcholine receptor (anti-

AChR) antibodies, but a small proportion have anti-muscle-specific tyrosine kinase (anti-MuSK) antibodies. The patient experts explained that the condition can have substantial physical, emotional and financial impacts on both the person with gMG and their carers and family. They noted that the condition is highly variable and unpredictable, with symptoms typically including fatigue and problems with breathing, speaking, seeing and concentrating. It substantially affects daily activities and the person's ability to work. The symptoms have a high impact on quality of life and many people regularly need a high level of care. All current treatments for gMG aim to suppress the condition to reduce symptoms, and there is no cure. The patient experts noted that treatments for gMG are associated with side effects, and it is particularly difficult to manage the side effects of multiple treatments simultaneously. Many people with gMG take corticosteroids, but it can be difficult to optimise the lowest effective dose (to minimise side effects) without increasing the risk of exacerbations (an acute worsening of symptoms) or myasthenic crisis. A myasthenic crisis is a life-threatening complication of gMG in which the muscles that are used for breathing are affected and hospitalisation is required. The patient experts explained that there are limited options available for people whose condition does not improve with standard treatment (refractory gMG). Typically, people with refractory gMG will have intravenous immunoglobulin (IVIg) or plasma exchange (PLEX), or will try a different type of immunosuppressant. IVIg and PLEX both require regular hospital visits or stays. These can be difficult to fit around work and family commitments, and place a substantial burden on carers. One patient expert explained that, although PLEX had been effective, the permanent catheter line required had caused a blood clot, so this treatment had to be stopped. The patient experts highlighted the high burden of side effects associated with some current treatments, and the unmet need for treatments for refractory gMG. The committee concluded that gMG is a debilitating condition with a high treatment burden.

Clinical management

Treatment options and the use of rituximab in the treatment pathway

Current treatment options for gMG

3.2 gMG is a long-term condition and most people need lifelong treatment. The clinical experts explained that people would usually have treatments outlined in the Association of British Neurologists (ABN) guidelines. But, at the time of this evaluation, the ABN guidelines are being updated. The ABN (2015) guidelines recommend that people are first offered pyridostigmine at the lowest effective dose and that surgery to remove the thymus gland (thymectomy) can be considered for people under 45. The clinical experts noted that, after publication of the ABN guidelines, thymectomy is offered to people under 65, although it is not suitable for people who test positive for anti-MuSK antibodies. If symptoms continue, people are offered prednisolone. The clinical experts explained that corticosteroids such as prednisolone are associated with notable side effects, and they aim to use minimal effective doses to reduce these. The ABN guidelines recommend non-steroidal immunosuppressants, such as azathioprine, if remission is not achieved on corticosteroids alone. If there is insufficient response to immunosuppressants or people experience notable side effects on increasing corticosteroid doses, expert advice should be sought on the use of IVIg or PLEX. The NHS England commissioning criteria policy for the use of therapeutic immunoglobulin recommends IVIg should be used:

- when urgent inpatient treatment is needed and PLEX is not available
- in rare circumstances as a maintenance treatment when all standard treatments have failed, and the person is having treatment in a specialist neuromuscular service.

Rescue treatments for a myasthenic exacerbation or crisis include IVIg or PLEX. The clinical experts explained that rozanolixizumab would be used as an alternative to long-term maintenance IVIg or PLEX, but would not

replace rescue use. They highlighted that IVIg and PLEX are time-consuming and resource-intensive treatments, and that access to PLEX is highly variable across the NHS.

Company's proposed positioning for rozanolixizumab

3.3 The EAG noted that rozanolixizumab could be used in 2 places in the company's proposed positioning in the treatment pathway: as an alternative to IVIg or PLEX for refractory gMG, or when non-steroidal immunosuppressants are contraindicated. The EAG commented that it is uncertain whether rituximab is a relevant comparator for rozanolixizumab in people with refractory MuSK antibody-positive or in some people with AChR antibody-positive gMG. The clinical experts explained that the evidence for rituximab in refractory gMG is limited, and it takes a long time to start working. They advised that ideally rituximab should be used earlier in the treatment pathway and in the same position as non-steroidal immunosuppressants, and it is less widely used for treating refractory gMG. The clinical experts also explained that there is a lack of formal guidance from the NHS on the use of rituximab.

The use of rituximab in the treatment pathway

3.4 The committee understood that the treatment pathway and treatment options for gMG were recently discussed in the NICE evaluation of zilucoplan for treating antibody-positive gMG, where it was noted that rituximab is used earlier in the treatment pathway and is less widely used for refractory gMG. But, the committee noted that the population in the appraisal for zilucoplan is people with gMG who test positive for anti-AChR antibodies only, whereas rozanolixizumab is indicated for those who test positive for anti-AChR or anti-MuSK antibodies. The committee noted that there are some minor differences in the way that people with MuSK antibody-positive gMG are treated. For the MuSK antibody-positive gMG group, the clinical experts explained that rituximab can be offered after steroids and non-steroidal immunosuppressants have been tried, but there is variation in practice. Clinicians prefer to use it earlier for people

who test positive for anti-MuSK antibodies, before they become refractory, because it is more effective in this smaller subpopulation than in the majority of people who test positive for anti-AChR antibodies. The clinical experts also explained that if rituximab is not used earlier and is considered for use in people with refractory gMG, it is more likely to be offered as an option (in the same position as IVIg and PLEX) to those with MuSK antibody-positive gMG. But, the company added that it believed rituximab would be used after the targeted therapies (IVIg, PLEX and rozanolixizumab).

The committee noted that the company's proposed positioning for rozanolixizumab is largely appropriate, but there are uncertainties about where rituximab is used in the treatment pathway, particularly in relation to those with MuSK antibody-positive gMG. It understood that rituximab might be most commonly used earlier in the treatment pathway, in the same position as non-steroidal immunosuppressants. It noted that rituximab, if not used earlier, could be used as a targeted treatment for people with refractory MuSK antibody-positive gMG, but it was uncertain how many of them would have had rituximab earlier, and whether it is also offered as a subsequent treatment. It concluded that there is uncertainty about the use of rituximab in the treatment pathway for the population indicated for rozanolixizumab. It requested that the company do expert elicitation to fully understand the use of rituximab in NHS practice. This should include, but is not limited to, the following:

- Whether rituximab is currently used as a treatment option for people with refractory MuSK antibody-positive gMG, people with refractory AChR antibody-positive gMG, or everyone with refractory gMG in the NHS. If so, what the proportions are of each.
- Whether rituximab is offered as a targeted treatment option, as an alternative to IVIg and PLEX, to people with refractory MuSK antibody-positive gMG, people with refractory AChR antibody-positive gMG, or everyone with refractory gMG. If so, what the proportions are of each.

- Whether rituximab is offered as a subsequent treatment for refractory gMG after targeted treatments are stopped. If so, whether this is for people with refractory MuSK antibody-positive gMG, people with refractory AChR antibody-positive gMG, or everyone with refractory gMG, and what the proportions are of each.
- Whether there is variation in rituximab's use in practice. If so, what the variabilities are and the reasons for these.

Target population

3.5 The marketing authorisation for rozanolixizumab is for an add-on to standard treatment for AChR or MuSK antibody-positive gMG. In its submission, the company positioned rozanolixizumab for a narrower population – people with refractory AChR or MuSK antibody-positive gMG – based on the following criteria:

- the disease is classified as Myasthenia Gravis Foundation of America (MGFA) class II to IVa
- the disease is uncontrolled after 2 or more previous therapies, excluding anticholinesterase inhibitors
- an additional therapy, such as IVIg or PLEX, is being administered or considered.

The clinical experts agreed that these criteria broadly describe the refractory population that rozanolixizumab would be used for in the NHS. The EAG commented that it might expect the definition of refractory gMG to include reference to a disease severity threshold score, such as the myasthenia gravis activities of daily living (MG-ADL) score. The clinical experts explained that MG-ADL was routinely used, but it does not always reflect the level of disease severity. They also explained that a person's disease severity would likely be captured by their MGFA class, and that the use of other scores would not be expected to materially change the group of people defined as eligible for rozanolixizumab in the NHS. The committee agreed with the clinical experts that the population defined in

the company submission was similar to the population that would have rozanolixizumab in the NHS.

Comparators

3.6 The final scope issued by NICE listed the following comparators:

- efgartigimod (subject to NICE evaluation)
- zilucoplan (subject to NICE evaluation)
- ravulizumab (now terminated)
- standard of care without rozanolixizumab (including immunosuppressive therapies [including rituximab] with or without IVIg or PLEX).

The company proposed the following comparators:

- efgartigimod
- zilucoplan
- IVIg and PLEX, excluding corticosteroids and non-steroidal immunosuppressants.

At the time of the first committee meeting (14 August 2024), the NICE evaluation of efgartigimod for treating gMG and the NICE evaluation of zilucoplan for treating antibody-positive gMG were both ongoing, so efgartigimod and zilucoplan could not be considered established NHS practice. The committee noted that the company did not include rituximab as a comparator in its submission. It recalled the uncertainty about the use of rituximab in the treatment pathway (see section 3.4). The clinical experts explained that rituximab is offered to people with refractory gMG, after steroids and in the same position as immunosuppressive therapies (see section 3.4), where it is intended to prevent a person from developing refractory disease. They also explained that they would like to use rituximab earlier in the treatment pathway, but this was not commissioned by the NHS except for people with MuSK antibody-positive gMG. But they emphasised that gMG is a very heterogeneous disease, and that people

can respond very differently to different treatments. Because of this, it is possible that some people may be offered rituximab once they have become refractory to other standard treatments for gMG, particularly if they experience a rapid onset of disease or repeated myasthenic crises. They also explained that the evidence suggests that rituximab is more effective in the smaller subgroup of people with MuSK antibody-positive gMG, so people with AChR antibody-positive gMG are less likely to be offered rituximab (see section 3.4).

The committee noted that rozanolixizumab is intended to be used as an add-on treatment to corticosteroids and immunosuppressants. So, corticosteroids and immunosuppressants should be included in both arms of the model. The clinical experts commented on the substantial variation in access to IVIg and PLEX across the NHS. Some centres may exclusively use IVIg, some may use a mixture of IVIg and PLEX, and some may not have access to either. So, some people would try another type of immunosuppressant instead of IVIg or PLEX. To reflect this, the EAG preferred to use a 'basket' of standard care as the comparator. Within this blended comparator, some people have:

- IVIg (plus corticosteroids and immunosuppressants)
- PLEX (plus corticosteroids and immunosuppressants), or
- corticosteroids and immunosuppressants only.

The EAG explained that the company's consideration of IVIg and PLEX as standalone comparators did not reflect how refractory gMG is currently treated in the NHS. The EAG also explained that data on the proportion of people having each treatment from the efgartigimod Early Access to Medicines Scheme (EAMS) would be relevant for this evaluation. The EAG noted that, although 'refractory' was defined slightly differently, people in the efgartigimod EAMS were comparable to the population who would have rozanolixizumab in the NHS. The EAMS cohort included 48 people with refractory gMG in the NHS. At the time of starting efgartigimod:

- 43.8% were having long-term IVIg (plus corticosteroids and immunosuppressants)
- 14.6% were having long-term PLEX (plus corticosteroids and immunosuppressants)
- 41.6% were having only corticosteroids and immunosuppressants.

The committee recalled the uncertainties about the use of rituximab in the treatment pathway and in relation to MuSK antibody-positive gMG (see section 3.4). With the information available and in anticipation of clarification on the use of rituximab from the company, the committee considered that a 'basket' of standard care is consistent with the NICE scope, more reflective of NHS practice and the relevant comparator. The committee agreed with the EAG that corticosteroids and immunosuppressants should be included in both arms. The committee also agreed that the efgartigimod EAMS population was sufficiently similar to the rozanolixizumab target population, and that the proportion of people having each treatment could be taken from the EAMS population. The committee also concluded that it is not currently possible to determine whether rituximab is a relevant comparator, but it would welcome expert elicitation on this from the company (see section 3.4).

Clinical effectiveness

MycarinG

3.7 MycarinG was a phase 3, randomised, multicentre, double-blind, placebo-controlled trial. It recruited adults with gMG with positive serology for anti-AChR or anti-MuSK antibodies, with an MGFA class of II to IVa, an MG-ADL score of 3 or more and a Quantitative Myasthenia Gravis (QMG) score of 11 or more, and who were being considered for additional treatment (such as IVIg or PLEX). Of the 200 people included in the 3 trial arms, 66 were randomised to the licensed weight-based dose of around 7 mg/kg and 67 to the placebo arm (the 67 people who were randomised to the higher unlicensed dose of around 10 mg/kg are not relevant to this

evaluation). People in both arms also continued to have standard treatment with corticosteroids and immunosuppressants. MycarinG consisted of a 6-week treatment phase, followed by an 8-week observation period in which people did not have rozanolixizumab. In the treatment phase, people had either 6 once-weekly subcutaneous infusions of either rozanolixizumab or placebo as an add-on to standard care, which comprised 1 treatment cycle. The post-hoc refractory subgroup of relevance to this evaluation was defined as uncontrolled disease despite standard of care treatment, specifically 2 or more previous gMG therapies, excluding acetylcholinesterase inhibitors. The primary outcome was change in MG-ADL score (a higher MG-ADL score shows more severe symptoms) from baseline to day 43. From baseline to day 43 rozanolixizumab was associated with a statistically significant greater reduction in MG-ADL score than placebo in the overall trial population (−3.370 compared with −0.784, least squares mean difference −2.586 [95% confidence interval −4.091 to −1.249; p<0.001]). MycarinG also reported the number of people who had an MG-ADL response, defined as a 2-point or more improvement in MG-ADL score, as a secondary outcome. At day 43 and among the whole-trial population, more people who had rozanolixizumab had an MG-ADL response than those who had placebo (68.2% compared with 28.4% [odds ratio 5.77; 95% confidence interval 2.10 to 14.88; p<0.001]), and this was statistically significant. The treatment effect of rozanolixizumab on these outcomes is largely in the same direction for the post-hoc refractory subgroup, but this is considered confidential by the company so cannot be reported here. The anti-AChR and anti-MuSK antibody-positive subgroups were prespecified. The EAG noted that the results for change in MG-ADL in these 2 prespecified subgroups were also generally consistent with those of the overall study population. The committee noted that evidence showed that rozanolixizumab was associated with a reduction in mean MG-ADL scores in people with gMG from baseline to day 43 within 1 treatment cycle. But the treatment effect may be overestimated because

the chosen timing of outcomes assessment in MycarinG may have been the optimal time to assess the best response. Also, people in MycarinG only had 6 weeks' treatment, so the treatment effect of rozanolixizumab in the longer term is uncertain. The committee concluded that rozanolixizumab as an add-on to standard treatment is more effective at improving MG-ADL score than standard treatment alone, but the treatment effect may be overestimated and is uncertain in the longer term.

MG0007

3.8 MG0007 was an open-label extension trial that included people who had participated in other rozanolixizumab trials. People could enter MG0007 if they had:

- entered or completed the observation period of MycarinG
- required rescue therapy (limited to IVIg or PLEX) during the observation period of MycarinG, or
- completed at least 6 visits in MG0004 (a discontinued extension study of MycarinG).

MG007 had no placebo arm, so participants were randomised to a dose of either around 7 mg/kg or around 10 mg/kg (see section 3.7 about 10 mg/kg dosing not licensed) of rozanolixizumab. There was a consistent and clinically meaningful reduction (more than 2.0) in MG-ADL score from baseline to day 43 in both arms within treatment cycles assessed. The proportion of MG-ADL responders at day 43 of each treatment cycle was also consistent in both rozanolixizumab trial arms within the treatment cycles reported. The exact results of this trial are considered confidential by the company so cannot be reported here. The EAG noted that MG0007 was designed to evaluate multiple 6-weekly treatment cycles of rozanolixizumab (the number of cycles in the trial are considered confidential by the company so cannot be reported here). But dose switching between the doses of around 7 mg/kg and around 10 mg/kg was allowed in MG0007, so the evidence on the treatment effect of

rozanolixizumab cycles was still uncertain. The committee noted the uncertainty about the confounding of dosing, and concluded that MG0007 provided some supporting evidence for the effectiveness of rozanolixizumab.

Generalisability

3.9 In its submission, the company positioned rozanolixizumab for people with refractory gMG who tested positive for either anti-AChR or anti-MuSK antibodies. The EAG noted that people with refractory gMG were only a subgroup of the MycarinG population. It was concerned that the outcomes observed in the whole MycarinG population may not be generalisable to the refractory population that would have rozanolixizumab in the NHS. But clinical advice to the EAG suggested that the baseline characteristics of the whole MycarinG population approximated the baseline characteristics of the refractory population in the NHS that would be considered for IVIg or PLEX. This is because the MycarinG eligibility criteria included having or being considered for IVIg or PLEX, meaning that the overall trial population is likely to reflect a refractory population. The clinical experts also considered that refractory gMG is expected to respond as well as non-refractory gMG. This is because treatments like rozanolixizumab have a novel mechanism of action, which people with refractory gMG will not have previously tried and their gMG may respond to. The EAG explained that MycarinG primarily included people who tested positive for anti-AChR antibodies, with only a minority who tested positive for anti-MuSK antibodies (placebo, n=8, 11.9%; rozanolixizumab around 7 mg/kg, n=5, 7.6%). The EAG also explained that while the overall trial population approximates the relative proportions of people who test positive for anti-AChR antibodies or anti-MuSK antibodies in the NHS, there is uncertainty about the efficacy outcomes for people who test positive for anti-MuSK antibodies because of the very small number of people in this subgroup. The clinical experts explained that there are some differences in the way that AChR antibody-positive and MuSK antibody-positive gMG respond to treatments. In particular, MuSK antibody-positive gMG responds better to

treatment with PLEX. The clinical experts also explained that it is reasonable to assume that people with MuSK antibody-positive gMG might respond slightly better to rozanolixizumab, but this was uncertain because of the very small number of people who test positive for anti-MuSK antibodies. The committee concluded that the outcomes of the whole-trial population in MycarinG could be representative of the refractory gMG population in the NHS. It also concluded that the outcomes of the whole-trial populations in MycarinG could be generalised to those with MuSK antibody-positive gMG, because it is reasonable to assume that rozanolixizumab is at least as effective as in people with AChR antibody-positive gMG.

Indirect treatment comparisons

3.10 The company did network meta-analyses (NMAs) and matching-adjusted indirect comparisons (MAICs) to estimate the comparative effectiveness of rozanolixizumab with the comparators. NMAs were done for the outcomes of change from baseline to day 43 in MG-ADL score (defined as 2 or more in MG-ADL score), and MG-ADL response, but only for the comparisons with zilucoplan and efgartigimod. For the comparison with efgartigimod, the company also did an anchored MAIC on the outcomes of MG-ADL score and MG-ADL response. Neither zilucoplan nor efgartigimod was a relevant comparator at the time of evaluation (see section 3.6). The company also did an unanchored MAIC for the comparison between rozanolixizumab and IVIg. But this was limited because it did not analyse the outcomes of change from baseline to day 43 in MG-ADL score or MG-ADL response because data were not available. The results of the indirect treatment comparisons are considered confidential by the company so cannot be reported here. The EAG explained that for this unanchored MAIC the company matched the rozanolixizumab arm of the MycarinG trial to the IVIg arm of the trial reported by Barth et al. (2011). But this study did not report on MG-ADL outcomes. The company instead reported QMG response and QMG change from baseline for this unanchored MAIC analysis. The EAG also

explained that QMG outcomes do not inform the economic model, and the company had not reported QMG outcomes for any other NMA or MAIC analyses. So, this unanchored MAIC was not informative. No indirect comparisons were provided for PLEX. The EAG explained that it had requested that the company provide a systematic literature review to investigate whether any single-arm studies or phase 2 trials on IVIg or PLEX could be included in the unanchored MAIC to enable the comparisons between rozanolixizumab and IVIg or PLEX for the MG-ADL or any other relevant outcomes. But the company did not provide this. The clinical experts noted that there may be very few randomised controlled trials on IVIg or PLEX that could be used to inform the networks for indirect treatment comparisons, but agreed with the EAG that it might be useful to include phase 2 trials or single-arm studies. The EAG suggested that it may also be possible to explore real-world evidence sources and cohort studies reporting outcomes for IVIg or PLEX. The EAG also noted that imputation techniques could be used to map the results from different reported outcomes to the MG-ADL outcomes relevant to this evaluation. The committee concluded that the company's indirect treatment comparisons did not adjust for heterogeneity or baseline risk of populations across studies, so were not appropriate for decision making. The committee requested that the company:

- do a systematic literature review(s) that includes single-arm trials, phase 2 studies and real-world evidence, including observational studies and registries that assess the treatment effect of IVIg or PLEX on MG-ADL or other relevant outcomes
- explore the feasibility of other indirect treatment comparison methods, such as multivariate NMAs to borrow strength across different outcomes reported in the studies or NMAs adjusted for baseline risks with an informative prior on the between-study variability. This approach may provide more information on the relative treatment effects between relevant comparators and may adjust for potential placebo effects observed in some studies.

Economic model

Company's modelling approach

3.11 The company used a cohort state transition model to estimate the cost effectiveness of rozanolixizumab against the comparators. The model included 7 health states. People start in the 'uncontrolled' health state and transition to the 'response' health state if they meet the treatment response criteria (a decrease of 2 or more in MG-ADL score) at the response assessment timepoint. Responders are further divided into 3 health substates:

- 'stable response' (MGADL score remains stable after time of response assessment)
- 'loss of response'
- 'continued response' (MG-ADL score continues to improve after time of response assessment).

The exact proportion of people who transition into each state is considered confidential by the company so cannot be reported here. Within each health state (except death), people in the model can transition to the 'exacerbation', 'myasthenic crisis' or 'death' state. The model has a cycle length of 2 weeks and a time horizon of 52.5 years. The committee concluded that the model could be appropriate for decision making if it accounted for subsequent treatment use (see section 3.12).

Subsequent treatments

3.12 Over time, people in the model return to the 'uncontrolled' health state and have only corticosteroids and immunosuppressants. The company's model does not account for any future use of IVIg or PLEX for people who stop either rozanolixizumab or the comparator treatments. The EAG considered it likely that if gMG does not respond or loses response to a targeted treatment, people with the condition would change to an alternative treatment. The committee noted statements from the patient experts and clinical experts that gMG requires lifelong management. It

also recalled the discussion about whether rituximab might be used as a subsequent treatment for refractory gMG or only for people with refractory MuSK antibody-positive gMG (see section 3.4). The committee agreed that it was implausible that someone with refractory gMG would stop rozanolixizumab and never have another treatment except corticosteroids and immunosuppressants. The clinical experts noted that they would consider IVIg or PLEX for people who stop rozanolixizumab. They explained that if someone's refractory gMG did not previously respond to a particular treatment they would not use it again. So, there may be differences in the choice and proportion of subsequent treatments in the rozanolixizumab and comparator arms. The committee concluded that it would like to see the company include subsequent treatments in the economic model.

Treatment response rates

3.13 The company used the NMA results to estimate the MG-ADL response rates for rozanolixizumab, zilucoplan and efgartigimod. There were differences in placebo responses across the trials included in the company's NMAs. To adjust for differences in placebo response, the company converted the odds ratios of each of these treatments from the NMAs compared with placebo into relative risks. Then, the relative risks were applied to a referent response rate. The referent response rate was calculated by running a baseline random effects model using all the placebo response rates from studies identified in the NMA. The company considers the response rates for rozanolixizumab, zilucoplan and efgartigimod, and the referent response rate, confidential so they cannot be reported here. The EAG noted the uncertainties with the company's NMAs. It also considered the company's referent response rate implausible because the placebo response rates in MycarinG, RAISE and ADAPT were much higher or lower. IVIg or PLEX response rates in the company model were based on data from Barth et al. (2011), a Canadian randomised controlled trial of 84 people with gMG who had either IVIg or

PLEX. The calculated response rates were 51% (IVIg) and 57% (PLEX). The EAG noted the following limitations with using data from Barth et al.:

- the population was not explicitly defined as refractory
- MGADL data was not available, so the response was defined as a 3-point or more improvement in QMG
- no confidence intervals or standard errors were provided with the response rates.

Because of these uncertainties, the EAG instead used the individual trial arm data of 72%, 73% and 68% response from MycarinG, RAISE and ADAPT for rozanolixizumab, zilucoplan and efgartigimod, respectively. For IVIg and PLEX, the EAG received clinical advice that the expected response was much higher than estimated using Barth et al., with about 70% of people with gMG in clinical practice responding. So, the EAG preferred to use the 70% MG-ADL response rate for both IVIg and PLEX. The clinical experts noted that they would expect about two-thirds of people with gMG who have IVIg or PLEX to have an MG-ADL response, so considered a response rate of 70% plausible. The committee noted that the estimates of the comparative effectiveness of rozanolixizumab were uncertain. It also noted that the company's approach used results from the uncertain NMA and estimated IVIg and PLEX response from a study with several limitations. The committee also noted that the EAG's approach did not adjust for the placebo response observed in both RAISE for zilucoplan and ADAPT for efgartigimod. It noted that it would prefer response rates to be based on clinical data where possible, and would like the company to search for evidence using a systematic approach. The committee concluded that it had not been presented with accurate estimates of treatment response for any of the treatments. It asked the company to systematically identify evidence on IVIg and PLEX, and provide additional analyses to clarify this (see section 3.10).

Response assessment timepoint

3.14 The company selected the response assessment timepoints from the zilucoplan, efgartigimod and rozanolixizumab trials (12, 10 and 6 weeks, respectively) and used an assumption for IVIg and PLEX (6 weeks). The EAG noted that clinical advice suggested it would be reasonable to assess all interventions at 6 weeks, so it chose to use the response assessment timepoint of 6 weeks for all treatments in its analysis. The clinical experts explained that assessment of treatment response for IVIg and PLEX is typically done much earlier than 6 weeks, usually at 2 or 3 weeks, and that 3 weeks would be more appropriate to assess for a response. The committee noted that there appeared to be inconsistencies in clinical opinion on the most appropriate timepoint for the response assessment of IVIg and PLEX. It concluded that a response assessment timepoint of 3 weeks reflected NHS practice for IVIg and PLEX, but an assessment timepoint of 6 weeks was appropriate for rozanolixizumab.

Utility values

3.15 Health-related quality of life data was captured in MycarinG through the EQ-5D-5L. EQ-5D-5L scores were mapped to the EQ-5D-3L in line with the NICE reference case. Utility values based on EQ-5D scores from MycarinG were used in a regression model and fitted for everyone in the trial. Changes in utility depended on the person's baseline EQ-5D score, MG-ADL score and body mass index. The model applied disutilities for exacerbations and myasthenic crises, sourced from REGAIN for eculizumab. The committee noted that the company's model did not apply disutilities for adverse events, because the company noted that there were no serious adverse events with an incidence of 5% or more in MycarinG. The model also did not apply disutilities for caregivers. The EAG noted that the company's approach to modelling utilities was appropriate. The committee thought that there may be uncaptured benefits on adverse events associated with rozanolixizumab, and asked the company to provide scenarios that consider these (see section 3.21).

Costs

Resource use

3.16 The company's model applied treatment costs for IVIg every 3 weeks and for PLEX every 4 weeks. The EAG received clinical advice that, in the NHS, IVIg and PLEX are typically given every 4 to 8 weeks, with the interval between treatments sometimes extended to 12 weeks or, rarely, 16 weeks. The clinical experts at the committee meeting noted that treatment intervals of 8 weeks or longer are not common and that 4 weeks is more typical. The committee noted that IVIg and PLEX might be expected to be given every 6 weeks in the NHS and this is included in the EAG's base case. But it concluded that IVIg and PLEX costs should be applied every 4 weeks for consistency with the evaluation of zilucoplan.

Uncertainties and preferred assumptions

3.17 The committee noted the high level of uncertainty in the evidence and modelling, specifically that:

- the treatment effect of rozanolixizumab may be overestimated and its treatment effect in the longer term is uncertain (see section 3.7)
- the model does not account for subsequent treatments (see section 3.12)
- the comparative effectiveness of rozanolixizumab against IVIg and PLEX is highly uncertain, but this is not reflected in the model (see sections 3.10 and 3.13)
- there may be uncaptured benefits of rozanolixizumab that the committee would like the company to try to account for (see sections 3.15 and 3.21).

3.18 The committee's preferred assumptions included:

- The comparators should be modelled as a 'basket' of standard care, with some people having IVIg, some having PLEX, and some having neither. Everyone should have corticosteroids and

immunosuppressants. Zilucoplan and efgartigimod should not be included as comparators (see section 3.6).

- The results of the whole-trial populations of MycarinG can be generalised to those with refractory gMG in the NHS (see sections 3.7 to 3.9).
- The committee would prefer an indirect comparison that incorporates data from all available studies, includes IVIg and PLEX, and adjusts for the placebo response. Also, any uncertainty from indirect comparisons should be incorporated in the model (see sections 3.10 and 3.13).
- The response assessment timepoint should be 3 weeks for IVIg and PLEX, but 6 weeks is more appropriate for rozanolixizumab (see section 3.14).
- The costs of IVIg and PLEX should be applied every 4 weeks, and the NHS reference cost should be used for PLEX administration (see section 3.16).
- There may be uncaptured benefits of rozanolixizumab that may affect the utility of people who have it. The committee would prefer the company to present scenario analyses that incorporate some of these uncaptured benefits in the modelling (see sections 3.15 and 3.22).

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.19 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects, including uncaptured health benefits. Because of confidential commercial arrangements for rozanolixizumab and some of the comparators, the exact cost-effectiveness results are confidential and cannot be reported here. Although some of the

company's base-case incremental cost-effectiveness ratios (ICERs) were within the range NICE normally considers to be a cost-effective use of NHS resources, they did not include the committee's preferred assumptions. The EAG's base-case ICER was substantially above this range.

Other factors

Equality

3.20 The committee noted the variation in access to IVIg and PLEX across the NHS. Some centres may exclusively use IVIg, some may use a mixture of IVIg and PLEX, and some may not have access to either. The committee also considered that gMG may have a different burden on women than men. gMG is more prevalent in women, women are typically younger at disease onset, and women typically have higher mortality. Also, pregnancy may contraindicate some types of treatment. Sex is a protected characteristic under the Equality Act 2010. But, because its recommendation does not restrict access to treatment for some people over others, the committee agreed this was not a potential equality issue.

Uncaptured benefits

3.21 The committee considered whether rozanolixizumab was innovative. The patient experts clearly noted that treatment with IVIg or PLEX was time-consuming and required regular hospital stays. They thought that rozanolixizumab, as a short-duration subcutaneous infusion, would be more convenient and could improve adherence. The clinical experts noted how resource intensive IVIg and PLEX are to administer. They also explained that people who have rozanolixizumab may be able to reduce their corticosteroid dose. This could lead to fewer corticosteroid-related adverse effects. Both the patient and clinical experts considered rozanolixizumab to have advantages for patients, carers and healthcare professionals. But the committee noted that similar QALYs were generated by each treatment in the model. So, the committee concluded

that some benefits of rozanolixizumab may not be captured in the modelling. The committee asked the company to present scenario analyses that account for some of these benefits.

Additional evidence and analyses

3.22 The committee would like the company to provide the following:

- Expert elicitation on the use of rituximab in the NHS (see section 3.4).
- A systematic literature review that includes phase 2 and single-arm trials, and real-world evidence on IVLG and PLEX for the outcome of MG-ADL or other relevant outcomes for the indirect comparison of rozanolixizumab with IVIg and PLEX (see section 3.10).
- An improved indirect treatment comparison (see section 3.10) that:
  - uses data from more of the identified studies
  - includes IVIg and PLEX
  - considers outcomes other than MG-ADL response rate to produce estimates of relative effectiveness
  - accounts and adjusts for the differential placebo response observed in the trials or adjusts for baseline risks with an informative prior
  - maintains randomisation
  - 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 (see section 3.12).
- Scenario analyses that incorporate some of the potentially uncaptured benefits of rozanolixizumab (see section 3.21).

Conclusion

Rozanolixizumab is not recommended

3.23 The committee considered that the cost-effectiveness estimates presented by the company and EAG were highly uncertain. Given the uncertainty, it would like to see additional analyses. But the committee considered that, given its preferred assumptions and based on the

analysis it had seen, the cost-effectiveness estimates were highly likely to be above the range that NICE considers a cost-effective use of NHS resources. The committee concluded that rozanolixizumab could not be recommended for treating refractory gMG in adults who test positive for anti-AChR or anti-MuSK antibodies.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Dr Charles Crawley

Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Luke Cowie

Technical lead

Yelan Guo

Technical adviser

Jeremy Powell

Project manager

Emily Crowe

Associate director

ISBN: [to be added at publication]