Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]
Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Contents:

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UCB Pharma Limited (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	Company holding marketing authorisation and submitting the appraisal for zilucoplan.

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mentioned in the stakeholder list • whether it is ongoing or has ceased.	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	
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.

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The company has provided the following as listed in Section 3.32 ('Additional analyses') of the draft guidance:	
Clarification on the target population for zilucoplan (Section 3.3 and 3.6 in the draft guidance)	The definition of refractory generalised myasthenia gravis (gMG) on page 7 of the Draft Guidance document is the definition from the RAISE trial, **not** the definition from the company submission in the decision problem. To clarify, the target population for zilucoplan, as stated in the company submission, is: • patients with anti-acetylcholine receptor antibody-positive generalised myasthenia gravis whose condition is uncontrolled despite receiving standard of care (SoC) treatment, and • who are being considered for, or treated with, intravenous immunoglobulin (IVIg) or plasma exchange (PLEX). Feedback from several UK clinicians also indicates that refractory gMG patients who have exhausted standard treatment, including corticosteroids and non-steroidal immunosuppressants, and are being treated with or considered for IVIg or PLEX, are those with the most urgent unmet need who will benefit the most from zilucoplan (1).
Indirect treatment comparison (Section 3.11 in the draft guidance), including revised treatment response	**SLR** 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:

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rates (Section 3.15 in the draft guidance)	• 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. **NMAs** NICE committee B noted that the indirect treatment comparison for zilucoplan should include both IVIg and PLEX studies, to account for differential placebo effects across studies and respect randomisation. In response to these issues, the company has conducted three separate network meta-analyses (NMAs) in

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	addition to the conventional NMA, to establish the comparative efficacy of zilucoplan versus IVIg and PLEX. The new NMAs are: 1. Bivariate NMA (bvNMA) – used within the model base case. 2. Two-stage baseline risk-adjusted NMA (BLRA NMA) and bvNMA – used for a scenario analysis. 3. Baseline risk-adjusted NMA – this has not been included in the economic analysis because it does not include PLEX in the network The outcomes for the bivariate NMA were MG-ADL and QMG (change from baseline and responders [≥3 point improvement]). The bvNMA allowed for QMG data to be used to predict MG-ADL outcome, thereby allowing PLEX studies that reported QMG outcomes (including Barth et al) to be included in the network. Correlation coefficients between change from baseline and responder outcomes for both MG-ADL and QMG score were calculated using individual patient data from the RAISE trial. The bivariate NMA was conducted under two scenarios: one using only RCTs, and another combining RCTs with non-randomised controlled trials. In the RCT-only analysis, the bivariate NMA retained six studies that would have been discarded in a conventional NMA due to incomplete reporting of either MG-ADL or QMG responder data. The combined RCT and non-RCT scenario incorporated an additional non-RCT study reporting only QMG responder data.

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	The two-stage analysis combined both a BLRA NMA and bivariate NMA to produce a relative treatment effect that accounted for differences in the placebo effects across the studies, and allowed studies that did not report MG-ADL outcomes to be included by using QMG data. The NMA report, with full methods and results, is provided as a supporting reference along with this document. **Results for bvNMA: Responders** In the bivariate NMA, the odds ratio for response for zilucoplan was [redacted] (95% CrI: [redacted]) for the analysis with RCTs, compared with [redacted] (95% CrI: [redacted]) for IVIg and [redacted] (95% CrI: [redacted]) for PLEX. For the analysis including RCTs and non-RCTs, the odds ratios for response were [redacted] (95% CrI: [redacted]) for zilucoplan, [redacted] (95% CrI: [redacted]) for IVIg, and [redacted] (95% CrI: [redacted]) for PLEX. The placebo response rate from the bvNMA was the same as that from the Bayesian NMA ([redacted]). The odds ratios for response are largely similar to the conventional NMA results for zilucoplan and IVIg (it was not possible to include PLEX in the conventional NMA for responders), but the credible intervals are slightly narrower in the bivariate NMA compared with the conventional NMA (please see the supporting reference, Figure 4, for a comparison between the bvNMA and conventional NMA results). The wider credible intervals for IVIg and PLEX are a consequence of small sample sizes in the studies for these treatments. In addition, the responder results for IVIg from Bril et al 2024 is based on a 2-point improvement in MG-ADL, so

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	the results are conservative in comparison with zilucoplan, where responders are assessed as a 3-point improvement. **Results for bvNMA: Change from baseline in MG-ADL score** In the bivariate NMA, the change from baseline in MG-ADL score for zilucoplan was [redacted] (95% CrI: [redacted]) for the analysis with RCTs, compared with [redacted] (95% CrI: [redacted]) for IVIg and [redacted] (95% CrI: [redacted]) for PLEX. For the analysis including RCTs and non-RCTs, the changes from baseline in MG-ADL score were [redacted] (95% CrI: [redacted]) for zilucoplan, [redacted] (95% CrI: [redacted]) for IVIg, and [redacted] (95% CrI: [redacted]) for PLEX. Again, the credible intervals are wider for IVIg and PLEX than for zilucoplan, and the results actually show a worsening in MG-ADL score for IVIg, and the credible interval for PLEX crosses zero. **Results for two-stage BLRA NMA and bvNMA: Responders** In the two-stage bivariate NMA, the odds ratio for response for zilucoplan was [redacted] (95% CrI: [redacted]) for the analysis with RCTs, compared with [redacted] (95% CrI: [redacted]) for IVIg and [redacted] (95% CrI: [redacted]) for PLEX. For the analysis including RCTs and non-RCTs, the odds ratios for response were [redacted] (95% CrI: [redacted]) for zilucoplan, [redacted] (95% CrI: [redacted]) for IVIg, and [redacted] (95% CrI: [redacted]) for PLEX. The placebo response rate from the two-stage bvNMA was slightly [redacted] than that from the Bayesian NMA ([redacted] vs [redacted], respectively).

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	As can be seen in the results, the credible intervals are extremely wide, which is why these data should be treated with caution and are used in scenario analysis only. In the baseline risk-adjusted part of the two-stage NMA, there are relatively sparse MGADL responder data and change from baseline (CFB) MG-ADL information in studies involving placebo and IVIg treatments, which introduces an inherent level of variability in the estimation of the mean placebo effect. This is more prominent because most of these studies report QMG responder and CFB QMG data. This variability in the placebo effect calculation subsequently influences the overall adjusted effect size for all treatments under consideration. The lack of consistent data across studies creates challenges in accurately determining the true impact of placebo, which in turn affects the comparative assessment of treatment efficacies. **Results for two-stage bivariate NMA: Change from baseline in MG-ADL score** In the bivariate NMA, the change from baseline in MG-ADL score for zilucoplan was [redacted] (95% CrI: [redacted]) for the analysis with RCTs, compared with [redacted] (95% CrI: [redacted]) for IVIg and [redacted] (95% CrI: [redacted]) for PLEX. For the analysis including RCTs and non-RCTs, the changes from baseline in MG-ADL score were [redacted] (95% CrI: [redacted]) for zilucoplan, [redacted] (95% CrI: [redacted]) for IVIg, and [redacted] (95% CrI: [redacted]) for PLEX. Again, the results actually show a worsening in MG-ADL score for IVIg, and the credible interval for PLEX crosses zero. **Conclusions** The results are generally consistent with the conventional NMA, although the bivariate NMA tends to reduce the uncertainty to some extent by predicting slightly narrower credible intervals. The credible intervals in the

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	two-stage bvNMA for responders are very wide. The results of all analyses show a consistently and significantly higher odds of response and change from baseline in MG-ADL score with zilucoplan than placebo. To fulfil the NICE committee's request to include all available IVIg and PLEX studies, the results from RCTs and nRCTs were used in the economic analysis. These scenarios also somewhat reduced the uncertainty by producing narrower credible intervals compared to the RCTs scenarios. As stated in ACM2, the uncertainties from the NMA were included in the model. The CODA for the response rates from the bvNMA and the two-stage BLRA NMA and bvNMA is used to inform the probabilistic sensitivity analysis by pulling random values from the CODA for primary response rate.
Statistical codes for any NMAs conducted	The statistical code from the NMA is included in the NMA report provided along with this document.
Information and justification to support the use of a revised EAMS cohort to inform the preferred refractory standard care treatments	The company revised the efgartigimod Early Access to Medicines scheme (EAMS) proportions to make them relevant to the population of zilucoplan that reimbursement is being sought for in this appraisal. As stated above, the target population for zilucoplan is patients with refractory AChR+ gMG whose condition is uncontrolled despite receiving SoC treatment, and who are being considered for, or treated with, IVIg or PLEX. These patients would have exhausted standard treatments before being considered for targeted therapies. This is different from the patients included in the EAMS cohort, some of whom did not have refractory gMG and were not receiving any MG treatment. As zilucoplan is licensed as an add-on to standard

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(Section 3.6 in the draft guidance)	therapy, patients who are not receiving MG treatments (such as those in the EAMS data set) would not be eligible for zilucoplan and therefore are not an appropriate population for decision making in this appraisal. In agreement with this, feedback from UK clinicians (n=4) in November 2024 indicates that if a patient was receiving no treatment (such as some patients in the EAMS cohort), they would not be considered to be refractory, and if a patient was taking only corticosteroids and had not yet tried one or more NISISTs, they could not be considered to be refractory either (because they had not yet exhausted the SoC options) (1). In addition, it was deemed to be very rare (<5% of refractory patients) for a patient to be unable to take any non-steroidal immunosuppressant treatments (NSIST) due to adverse effects or side effects, contraindications, comorbidities, or other reasons. Further details of the expert elicitation are provided in the report provided along with this document. The **modified basket** (using a revised version of the EAMS cohort) (Table 1) is more appropriate for decision making than the EAMS cohort for several reasons: 1. All patients in the modified basket can be considered refractory (unlike the EAMS cohort, of whom only 77% [n=37] were refractory) 2. In the EAMS cohort, three patients received no treatment (therefore would not be eligible for zilucoplan) and 10 patients were on corticosteroids only (therefore would likely be considered for an NSIST prior to

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<table>
<tr><td></td><td>initiation of zilucoplan). Removing these patients from the cohort, as confirmed by UK clinical experts is a reasonable assumption, results in a total of 35 patients.

To match the number of patients designated as refractory in the efgartigimod EAMS dataset (n=37), UCB have included two of the CS-only patients to reflect those who might have previously trialled NSISTs. This leaves a remaining 76% (n=28/37) of patients using IVIg/PLEX in the refractory subgroup (Table 1).

Table 1. Patients receiving subsequent treatments in the reweighted (modified) EAMS basket
<table>
<tr><th>Treatment</th><th>n</th><th>N</th><th>%</th></tr>
<tr><td>CS only</td><td>2</td><td>37</td><td>5.4</td></tr>
<tr><td>CS and NSISTs</td><td>27</td><td>37</td><td>73.0</td></tr>
<tr><td>NSIST only</td><td>5</td><td>37</td><td>13.5</td></tr>
<tr><td>Regular IVIg w CS/NSIST</td><td>18</td><td>37</td><td>48.6</td></tr>
<tr><td>IVIg only</td><td>3</td><td>37</td><td>8.1</td></tr>
<tr><td>PLEX</td><td>7</td><td>37</td><td>18.9</td></tr>
</table>
Abbreviations: CS, corticosteroids; EAMS, Early Access to Medicines scheme; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant treatment; PLEX, plasma exchange.</td></tr>
<tr><td>The use of blended standard of care basket (Section 3.27)</td><td>UCB maintains that zilucoplan, if recommended, will displace chronic IVIg and PLEX in clinical practice in refractory gMG patients who have failed SoC alone, and therefore IVIg and PLEX are the only relevant</td></tr>
</table>

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	comparators to zilucoplan (Figure 2). It is these patients that UK clinicians have confirmed have the greatest need for a novel, targeted treatment and for whom they expect to use zilucoplan. However, following requests from the EAG and NICE committee B, UCB have provided an alternative base case for transparency and to support the decision-making process towards a positive recommendation for zilucoplan and enabling access to zilucoplan for those in most need. In the alternative base case comparing against the revised refractory SoC basket, zilucoplan [redacted]. Model results are provided in the supporting document.

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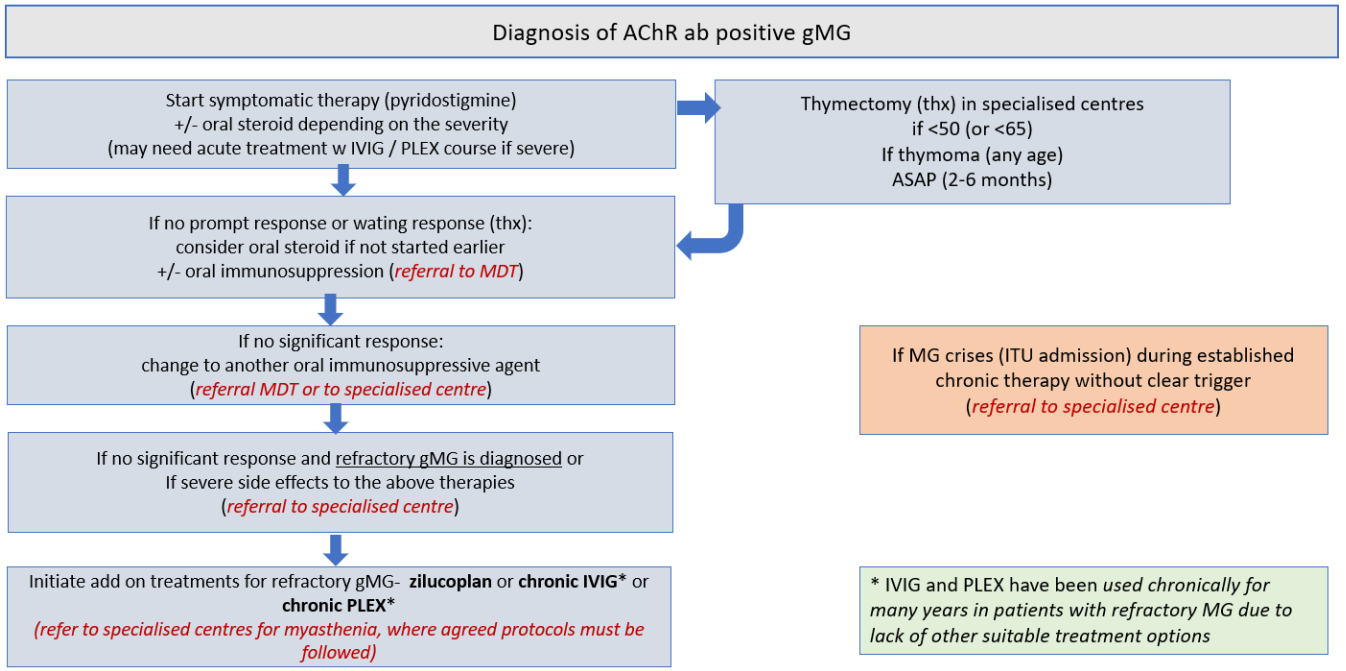
Figure 1. Treatment algorithm for patients with acetylcholine receptor positive gMG



Abbreviations: FcRn, neonatal Fc receptor; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; NHSE, National Health Service England; PLEX, plasma exchange.
Source: Adapted from a diagram provided by Professor Leite.

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Information and justification for MSE (Section 3.13 in the draft guidance)	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 (2-4). 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 zilucoplan 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 (2-4). The clinical expert at the second committee meeting agreed and explained that MSE is a clinically relevant and important outcome to consider (along with a reduction of ≥3 points in MG-ADL score), as reported in the Draft Guidance document (page 19). 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 may 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 (2). In an analysis of MSE in patients receiving zilucoplan in the RAISE-XT trial, of responders at Week 12 (≥3-point improvement in MG-ADL score), [redacted] had MSE. This is an average of all observations at all time points from Week 12 to Week E108.

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	Therefore, of patients responding to zilucoplan, [redacted] become free or virtually free of MG symptoms. The proportion of responders who reached MSE showed a trend to increase over time to [redacted] at Week E48; therefore, [redacted] is considered a conservative assumption. In addition, patients receiving zilucoplan in RAISE-XT spent a mean of [redacted] of their total study time in MSE. In the overall zilucoplan pooled arm, the rate of MSE among patients who did not achieve MSE at Week 12 tends to increase throughout the open label extension visits. MSE data from the zilucoplan clinical trial is in line with that from other targeted treatments, such as efgartigimod (45.5% of patients achieving MSE) (5) and eculizumab (21.4% of patients achieving MSE) (3). UCB sought expert clinical opinion (n=5 clinical experts) on the estimated proportion of refractory gMG patients receiving IVIg or PLEX that achieve MSE. This expert opinion informed the [redacted] rate that was used in the model base case. No refractory gMG patients on SoC are assumed to achieve MSE in the base case, but a scenario with [redacted] has been tested, as per the placebo arm in RAISE who had [redacted] MSE at week 12. Recent (November 2024) expert clinical opinion (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 2) (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

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unknown reasons). According to the interviewed experts, patients who achieve MSE are expected to remain in MSE whilst on treatment.

Table 2. The proportion of patients expected to achieve MSE with treatment, as estimated by clinical experts

Questions	Expert 1	Expert 2	Expert 3	Expert 4
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]
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
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.

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	MSE with zilucoplan				
	For patients that reach MSE with zilucoplan, is it reasonable to assume that they will remain at MSE if they continue with zilucoplan treatment?	Yes		Yes	Yes

Abbreviations: gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; MSE, minimal symptom expression; PLEX, plasma exchange; SoC, standard of care.

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 10.2 in the continued response health state, which achieves a 0.5 score from the baseline MG-ADL score in the model of 10.7.

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. For zilucoplan, [redacted]% of patients respond to treatment. Therefore, per-cycle, [redacted]% of patients transition from Uncontrolled to one of the three response health states on the zilucoplan arm. [redacted]% of patients initiated with zilucoplan achieve MSE on

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	responding to treatment. Therefore, of the [redacted]% of patients who transition from Uncontrolled to a Response health state, 38% achieve "Continued response" (ie [redacted]% x [redacted]% = [redacted]% achieving continued response per-cycle). Similarly, [redacted]% of responders have a stable response and 5% have a loss of response, meaning [redacted]% x [redacted]% transition from Uncontrolled to Stable response per-cycle, and 5% 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 zilucoplan and moved to a subsequent treatment.
Additional modelling and information on subsequent treatments (Section 3.14 in the draft guidance)	In response to the second draft guidance, health benefits (as well as costs) of the subsequent treatments have been incorporated in the model, as well as the proportion of people with refractory gMG receiving the following subsequent treatments: • IVIg after IVIg • PLEX after IVIg • IVIg after PLEX • PLEX after PLEX • corticosteroids and or NSISTs only after IVIg

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	• corticosteroids and or NSISTs only after PLEX. The “uncontrolled off initial treatment” health state captures patients who discontinue their initial treatment, because they do not achieve response, defined by a minimum 3-point reduction in MG-ADL score. In the previous model, a percentage of patients in the uncontrolled health state would incur the treatment and administration costs of IVIg and PLEX, as these were included as healthcare resources to manage uncontrolled patients. However, the efficacy of IVIg and PLEX were not accounted for in this health state. The model has been adapted to reflect subsequent treatments by applying a weighted basket of subsequent treatments, including IVIg, PLEX and SOC, to patients in the “uncontrolled off initial treatment” health state. Due to limited published data on the subsequent treatment pathway and variability of treatment sequencing in refractory gMG, the company believes it is plausible to assume a steady-state basket of subsequent treatments to avoid multiple treatment lines and manage the uncertainty. Each first-line treatment is assigned an individual subsequent treatment basket. The percentage of patients receiving each subsequent treatment was informed by the expert elicitation undertaken in November 2024 (n=4 clinician interviews) and are shown below for zilucoplan (Table 3), IVIg (Table 4), PLEX (Table 5) and SoC blended basket (Table 6). For the SoC blended basket, the total proportion of patients on IVIg, PLEX and SoC only (without IVIg and PLEX) as subsequent treatments for first-line IVIg and PLEX were weighted to estimate the percentages for the basket.

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It is possible that lack of response may influence the response rate of subsequent treatments, therefore the updated model incorporates a response rate adjustment factor which can be used to adjust the response of rates of subsequent treatments, which was included in scenario analysis (please see the supporting document for full details). These data for the scenario were derived from the clinical opinion of one clinician during the interview (the other three felt that the response would not be influenced by prior treatments). Where a range was provided, the midpoint was used, and if the approximation was 'less than' or 'greater than', then the exact value was used.

Table 3. First line treatment with zilucoplan

Subsequent treatments	Expert 1	Expert 2	Expert 3	Expert 4	Average
IVIg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**100%**	**100%**	**100%**	**100%**	**100%**
Response rate reduction (IVIg)					[redacted]
Response rate reduction (PLEX)					[redacted]

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

Table 4. First line treatment with IVIg

Subsequent treatments	Expert 1	Expert 2	Expert 3	Expert 4	Average
IVIg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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SoC only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**100%**	**100%**	**100%**	**100%**	**100%**
Response rate reduction (IVIg)					[redacted]
Response rate reduction (PLEX)					[redacted]

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

Table 5. First line treatment with PLEX

Subsequent treatments	Expert 1	Expert 2	Expert 3	Expert 4	Average
IVIg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**100%**	**100%**	**100%**	**100%**	**100%**
Response rate reduction (IVIg)					[redacted]
Response rate reduction (PLEX)					[redacted]

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

Table 6. First line treatment with SoC blended basket

Subsequent treatments	Average
IVIg	[redacted]
PLEX	[redacted]
SoC only	[redacted]
Total	**100%**

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	Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SoC, standard of care. The treatment response rates for IVIg, PLEX, and SoC only are applied to the subsequent treatment bundles to determine an overall response rate to subsequent treatments. To estimate the per-cycle cost of the subsequent treatment basket, the bundle composition is applied to the treatment and administration cost per cycle of each individual treatment in the basket. These are applied to the percentage of patients who respond to their subsequent treatment; remaining non-responder patients are assigned the cost of the add-on SoC basket. To estimate the efficacy of the subsequent treatment basket, the mean change from baseline MG-ADL score was calculated and used to estimate health state utilities for patients in the "uncontrolled off initial treatment health state". The mean change from baseline for continued, loss of response and stable response was weighted by the bundle composition and multiplied by the percentage of patients who respond to subsequent treatment, to estimate a weighted mean change from baseline for each level of response. These were then further weighted by the proportion of patients who achieve each level of response, to determine a total mean change from baseline, accounting for the percentage of patients that responded and achieved continued, loss of, or stable response across the treatments in the bundle.

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	The calculated average mean CFB is taken away from the baseline "uncontrolled on initial treatment" MG-ADL score to determine the total MG-ADL score for the "uncontrolled off initial treatment" health state. This score is then used to calculate health state utility values using the ITT regression equation, as with all other health states. Therefore, the "uncontrolled off initial treatment" health state reflects the efficacy of subsequent treatments by estimating the average change from baseline MG-ADL score given the bundle of subsequent treatments and is reflected in a health state utility value that is slightly higher than patients in the "uncontrolled on initial treatment" health state.
Analysis for utility decrement associated with IVIg and PLEX (Section 3.21 in the draft guidance)	As requested in the draft guidance and to support decision making, parameters have been added for the per-infusion/administration disutility of IVIg and PLEX administrations and an administration utility benefit for zilucoplan has been removed. These are weighted by the number of IVIg/PLEX infusions per model cycle to calculate a per-model cycle disutility of IVIg and PLEX administrations. The utility was derived from a study that assessed the utility impact of intravenous infusion in haemophilia A (6), due to a lack of available data in gMG, and the need to capture the utility outcomes associated with burdensome treatment administration, which is important to patients. Due to the absence of data for PLEX, the same disutility was applied to PLEX. These disutilities are applied to the following:

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	• disutility of IVIg and PLEX for subsequent treatments, for the proportion of patients who receive each treatment as part of their subsequent treatment bundle, if subsequent treatments are included in the model • disutility of IVIg and PLEX for the proportion of patients who require these treatments to manage an exacerbation • disutility of IVIg and PLEX for the proportion of patients who require these treatments to manage a myasthenic crisis • disutility of IVIg for patients who receive this as their first-line treatment, while they are on treatment • disutility of PLEX for patients who receive this as their first-line treatment, while they are on treatment • disutility of IVIg and PLEX for patients who receive these as a part of the comparator basket bundle, while they are on treatment These changes have very little impact to the economic modelling, but were included to represent the negative impact (disutility) of PLEX and IVIg on the lives of gMG patients and their support network.
Analysis that explores corticosteroid costs from the Lee et al. study (Section	Costs for corticosteroid use were incorporated into the model following data becoming available showing a steroid-sparing effect of zilucoplan, an important and relevant benefit. A study by Stirnadel-Farrant et al (2023) presented the overall costs of corticosteroid use by dose range and therefore provided the opportunity

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3.24 in the draft guidance)	to incorporate this steroid-sparing benefit of zilucoplan into the modelling by differentiating costs by dose range on different treatments and by health state (7). The original company submission used the same paper to apply corticosteroid costs to different health states, but the updated model for ACM2 applied slightly different values to different health states based on updated data and information on the steroid-sparing effect of zilucoplan. In response to the committee's request for additional analysis in the DG2, including the EAG's recommendation to use data from the Lee et al for adverse events (AEs) (which was accepted as part of GID-TA10986 [the NICE efgartigimod appraisal in gMG]), the model was updated to incorporate the costs based on data from Lee et al as a scenario analysis.. However, 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. 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

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	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 company maintains that the most appropriate evidence source is the Stirnadel-Farrant et al (2023) but has provided this additional analysis at the committee's request and to support decision making.
Scenario analyses that explore a range of time on treatment **Assumptions** (Section 3.18 in the draft guidance)	As explained at ACM2, the treatment stopping rule was included in error and was rectified before ACM2 but not in time for the EAG to review. The treatment rule is not included in the model as it does not reflect clinical practice.
Corticosteroid disutility (Section 3.20 in the draft guidance)	The company maintains that it is unlikely that the utility decrement associated with corticosteroid use is captured in the EQ-5D scores. 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. (8) and Brexelius et al (9)

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	from systemic lupus in the UK have been used as a proxy to quantitatively estimate the utility impact of steroid use in this appraisal. As per the NICE appraisal of efgartigimod (ID4003), UCB believes that the disutility should be included quantitatively (due to the reasons we have cited above). However, if NICE still believes that it should only be considered qualitatively then please could a clear description be provided of how this is being taken into account in the decision making for this appraisal. In addition, the utilities from the regression analysis come from the RAISE trial, before the full steroid-sparing effect of zilucoplan has been captured. Applying these utilities will not be reflecting the benefit of reducing the dose/discontinuing at any timepoint so the disutility bridges this gap.

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Insert extra rows as needed

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References

1. UCB. Data on file. Interviews with clinical experts on topics highlighted in the second NICE draft guidance document for the appraisal of zilucoplan. November 2024. 2024.
2. Uzawa A, Ozawa Y, Yasuda M, Onishi Y, Akamine H, Kuwabara S. Minimal symptom expression achievement over time in generalized myasthenia gravis. Acta Neurologica Belgica. 2023 2023/06/01;123(3):979-82.
3. Vissing J, Jacob S, Fujita KP, O'Brien F, Howard JF. 'Minimal symptom expression' in patients with acetylcholine receptor antibody-positive refractory generalized myasthenia gravis treated with eculizumab. J Neurol. 2020 Jul;267(7):1991-2001.
4. Watanabe K, Ohashi S, Watanabe T, Kakinuma Y, Kinno R. Case report: Recovery from refractory myasthenic crisis to minimal symptom expression after add-on treatment with efgartigimod. Front Neurol. 2024;15:1321058.
5. Bril V, Muppidi S, Howard JF, Murai H, Phillips G, Qi C, et al. P.057 Achievement of minimal symptom expression in acetylcholine receptor antibody-positive participants treated with efgartigimod in ADAPT/ADAPT+. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques. 2024;51(s1):S31-S.
6. Johnston K, Stoffman JM, Mickle AT, Klaassen RJ, Diles D, Olatunde S, et al. Preferences and Health-Related Quality-of-Life Related to Disease and Treatment Features for Patients with Hemophilia A in a Canadian General Population Sample. Patient Prefer Adherence. 2021;15:1407-17.
7. Stirnadel-Farrant HA, Golam SM, Naisbett-Groet B, Gibson D, Langham J, Langham S, Samnaliev M. Adverse Outcomes, Healthcare Resource Utilization, and Costs Associated with Systemic Corticosteroid use Among Adults with Systemic Lupus Erythematosus in the UK. Rheumatol Ther. 2023 Oct;10(5):1167-82.
8. Sullivan PW, Ghushchyan VH, Globe G, Sucher B. Health-related quality of life associated with systemic corticosteroids. Qual Life Res. 2017 Apr;26(4):1037-58.
9. Bexelius C, Wachtmeister K, Skare P, Jonsson L, Vollenhoven R. Drivers of cost and health-related quality of life in patients with systemic lupus erythematosus (SLE): a Swedish nationwide study based on patient reports. Lupus. 2013 Jul;22(8):793-801.

Overview of new evidence and modelling updates and results

1.1. 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.

1.1.1. Decision problem definitions

<table>
<tr><td>Population</td><td>Refractory gMG population
Table 1. Cohort baseline characteristics
<table>
<tr><th>Patient characteristic</th><th>Mean value</th><th>Lower range</th><th>Upper range</th><th>Source</th></tr>
<tr><td>The average age of the population at baseline (years)</td><td>51.8</td><td>43.</td><td>53.0</td><td>UCB data on file, 2022 (1)</td></tr>
<tr><td>Males, %</td><td>35.2%</td><td>31.68</td><td>38.7</td><td>UCB data on file, 2022 (1)</td></tr>
<tr><td>Average MG-ADL score at the start</td><td>10.7</td><td>6.00</td><td>19.0</td><td>UCB data on file, 2022 (1)</td></tr>
<tr><td>Average weight (kg)</td><td>85.7</td><td>44.00</td><td>166.0</td><td>UCB data on file, 2022 (1)</td></tr>
<tr><td>Average BSA (m^2)</td><td>2.01</td><td>1.81</td><td>2.2</td><td>Mosteller, 1987 (2); UCB data on file, 2022 (1)</td></tr>
<tr><td>Baseline BMI (kg/m^2)</td><td>29.8</td><td>16.0</td><td>54.0</td><td>UCB data on file, 2022 (1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Zilucoplan</td></tr>
<tr><td>Comparators</td><td>• IVIg/SCIg
• PLEX
• Standard of care blended comparator (for scenario analysis)</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 (MSE)
• 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)</td></tr>
<tr><td>Currency</td><td>GBP 2023</td></tr>
<tr><td>Decision rule</td><td>WTP £30,000 per QALY</td></tr>
</table>

Abbreviations: BSA, body surface area; BMI, body mass index; GBP, British pound sterling; gMG, generalized Myasthenia Gravis; IST, immunosuppressive therapies; IVIg, intravenous immunoglobulin; MG-ADL; Myasthenia

Gravis Activities of Daily Living; MSE, minimal symptom expression; NHS, National Health Service; PLEX, plasma exchange; QALY, quality-adjusted life year; SCIg, subcutaneous immunoglobulin; WTP, willingness to pay.

1.1.2. Standard of care blended comparator

Table 2. Standard of care blended comparator composition, response rates and costs

Medication	Bundle composition	Response rate	Average treatment cost per model cycle (£)	Admin costs per model cycle (£)
IVIg	56.7%	[redacted]	2,322.00	757.00
PLEX	18.9%	[redacted]	6,468.63	1,137.50
SOC	24.4%	[redacted]	27.72	0
Weighted average		[redacted]	2,545.91	644.21

Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SCIg, subcutaneous immunoglobulin; SOC, standard of care..

1.1.3. Efficacy assumptions and inputs

Table 3. Primary response rate and response assessment timepoint

Treatment	Response rate used in the model	Response assessment timepoint used in the model (weeks)	Source
Zilucoplan	[redacted]	3	bvNMA
IVIg/SCIg	[redacted]	3	bvNMA
Standard of care blended comparator	[redacted]	3	bvNMA
PLEX	[redacted]	3	bvNMA

Abbreviations: bvNMA, Bivariate Network Meta-Analysis; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SCIg, subcutaneous immunoglobulin.

Table 4. Treatment-specific MG-ADL score CFB

Treatment	Continued Response	Loss of response	Stable response
Zilucoplan	10.2	4.1	4.1
IVIg/SCIg	10.2	3.0	3.0
Refractory standard of care	10.2	3.0	3.0
PLEX	10.2	3.0	3.0

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

The time of the last response assessment was 3 weeks for zilucoplan and all comparators.

Table 5. Response distribution

	Continued response	Loss of response	Stable response	Source
Zilucoplan	[redacted]	5.0%	[redacted]	RAISE and RAISE-XT

IVIg/SCIg	19.2%	5.0%	76%	Expert elicitation
Refractory standard of care	1.25%	5.0%	74%	Expert elicitation
Plasma exchange	20.83%	5.0%	94%	Expert elicitation

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

Table 6. Clinical event rates

Health state	Event	Mean	Lower range	Upper range	Source
Annual event rate					
Uncontrolled	Exacerbation	0.65	0.59	0.72	Abuzinadah et al 2021 (3)
Response	Exacerbation	0.24	0.19	0.31	Abuzinadah et al 2021 (3)
Uncontrolled	Myasthenic crisis	0.06	0.06	0.07	Abuzinadah et al 2021 (3)
Response	Myasthenic crisis	0.02	0.01	0.05	Abuzinadah et al 2021 (3)
2-week event rate					
Exacerbation	Myasthenic crisis	0.18	0.17	0.20	Gajdos, 2005 (4)

Table 7. Mortality parameters

Health state/event	Mean	Lower range	Upper range	Source
Uncontrolled/response/exacerbation	1.0	0.9	1.1	
Myasthenic crisis	4.5%	4.0%	4.9%	Alshekhlee et al, 2009 (5)

1.1.4. Cost assumptions and inputs

Table 8. Administration costs per treatment

	Mean	Lower	Upper	Source
Intravenous				
Initial (£)	195.74	£176.17	£215.32	NHS collection of costs WF01B (6)
Subsequent (£)	184.23	£165.81	£202.65	NHS collection of costs WF01A (6)
IG-specific (£)	504.67	454.20	555.13	NHS collection of costs WF10B, WF01A and DOF (7-9)
PLEX-specific (£)	455	409.50	500.50	NHS reference cost SA44A – Single Plasma Exchange (£910†)
Subcutaneous				
Initial (£)	41.00	£36.90	£45.10	Nurse time: 60 minutes, Band 5 hospital-based nurse (10)
Oral	0.00	£0.00	£0.00	Assumption

Abbreviations: DOF, data on file; IG, immunoglobulin; NHS, National Health Service; PLEX, plasma exchange.
† PLEX is assumed to be given every 4 weeks; therefore, the cost is halved for the 2-week cycle.

Table 9. Average costs per cycle (calculations in Table 16)

	Weighted cost per mg (£)	Cost per cycle (£)	Annual drug cost (£)	Annual admin. cost (£)	Total annual cost (£)
Zilucoplan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVIg/SCIg	0.06	2,322.00	60,372.00	19,682.00	80,054.00
Standard of care blended comparator		2,545.91	66,193.60	644.21	66,837.81
Plasma exchange	2,587.45	6,468.63	168,184.25	29,575.00	197,759.25

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

Table 10. 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	6,158.00	0.00	0	0.00	0	0.00	0
PLEX	12,937.25	0.00	0	0.00	0	0.00	0
GP visit	33.00 (29.70-36.30)	13.62	13.29–13.97†	9.53	9.45–9.61†	9.53	9.45–9.61†

Visit to other healthcare professionals	52.00 (46.80-57.20)	11.47	11.16–11.78†	6.89	6.82–6.96†	6.89	6.82–6.96†
Outpatient hospital visits	485.85 (437.26-534.43)	7.10	6.86–7.35†	4.77	4.71–4.83†	4.77	4.71–4.83†
Presenting at an emergency room	278.10 (250.29-305.91)	0.44	0.38–0.51†	0.33	0.31–0.34†	0.33	0.31–0.34†
Hospital stay (with ICU, cost per critical care period)	11,737.70 (10,563.93-12,911.47)	0.13	0.12–0.14	0.07	0.06–0.08	0.07	
Hospital stay (no ICU, cost per day) (1.19 days per stay)	595.42 (535.88-654.97)	1.40	1.26–1.54	0.75	0.67–0.82	0.75	
Cost of managing steroid use		10,087.00		4,670.50		4,670.50 (for IVIg and PLEX only)	
Total cost for ZLP and refractory SoC (£)		17,240.09		9,111.33		4,440.83	
Total cost for IVIg and PLEX		17,240.09		9,111.33		9,111.33	

Abbreviations: GP, general practitioner; ICU, intensive care unit; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SoC, standard of care; ZLP, zilucoplan.
†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 11. HCRU per event (as detailed in the Section 2.4.4.1 of Global CEM technical report)

	Unit cost (£)	**Frequency of resource use per event**					
		Exacerbation			**Myasthenic crisis**		
		ZLP/SoC	**IVIg**	**PLEX**	**ZLP/SoC**	**IVIg**	**PLEX**
IVIg	6,158.00	0.73	0	1	0.05	0	1
PLEX	12,937.25	0.27	1	0	0.95	1	0
GP visit	33.00	0.82			0.06		

Visit to other healthcare professionals	52.00	0.58			0.32		
Outpatient hospital visits	485.85	0.75			0.50		
Presenting at emergency room	278.10	0.38			1.00		
Hospital stay (with ICU, cost per critical care period)	11,737.70	0.03			1.00		
Hospital stay (no ICU, cost per day) (28 days per stay)	595.42	0.33			1.00		
Total cost (£)		14,399.12	19,316.11	12,536.86	41,539.64	41,887.41	35,108.16

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

A unit cost of £48.00 was associated with the meningococcal vaccine, with 4.00% of patients requiring the vaccine. One-off costs associated with end-of-life care per affected patient were £3,785.00.

1.1.5. Utilities inputs and assumptions

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

$$Utility\ Change = \beta_0 + \beta_1 \times EQ\text{-}5D_{baseline} + \beta_2 \times BMI_{baseline} + \beta_3 \times MG\text{-}ADL$$

The change in utility depended on the patient's baseline EuroQOL-5 Dimension (EQ-5D) score, MG-ADL score, and body mass index (BMI).

Table 12. MG0010 outcomes

	Mean	Lower	Upper	Source
Baseline EQ-5D	[redacted]	[redacted]	[redacted]	UCB data on file (1, 11)
Baseline BMI (kg/m^2)	[redacted]	[redacted]	[redacted]	UCB data on file (1, 11)
Intercept	[redacted]	[redacted]	[redacted]	UCB data on file (11, 12)
Coefficient of baseline EQ-5D (Beta 1)	[redacted]	[redacted]	[redacted]	UCB data on file (11, 12)

Coefficient of MG-ADL score	[redacted]	[redacted]	[redacted]	UCB data on file (11, 12)
Coefficient of BMI	[redacted]	[redacted]	[redacted]	UCB data on file (11, 12)

Abbreviations: BMI, body mass index; EQ-5D, EuroQol- 5 Dimension; MG-ADL, myasthenia gravis activities of daily living profile.

Table 13. Variance covariance matrix

Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Coefficient of baseline EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]
Coefficient of MG-ADL score	[redacted]	[redacted]	[redacted]	[redacted]
Coefficient of BMI	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; EQ-5D, EuroQol- 5 Dimension; MG-ADL, myasthenia gravis activities of daily living profile.

Table 14. Clinical event disutility

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

Table 15. Annual disutility of steroid use (excluded for base case)

	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

Table 16. Per-cycle disutility for IVIg/PLEX

	Disutility	Disutility per infusion)	Infusions per model cycle	Source
IVIg	0.0005	0.0003	1.5	Johston et al 2021 (13)
PLEX	0.0008	0.0003	2.5	Johston et al 2021 (13)

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

1.1.6. Subsequent treatments

Table 17.Proportion of patients on each subsequent treatment, stratified by first-line treatment, based on expert clinical opinion

	Subsequent treatment bundles by first-line treatment			
Subsequent treatment	**Zilucoplan**	**IVIg/SCIg**	**Plasma exchange**	**Standard of care blended comparator**
IVIg	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]
	100%	100%	100%	100%
Assumed reduction in response rate for subsequent treatments versus first-line treatments, stratified by first-line treatment, based on expert clinical opinion				
Response rate reduction (IVIg)	0%	0%	0%	0%
Response rate reduction (PLEX)	0%	0%	0%	0%

Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SCIg, subcutaneous immunoglobulin; SOC, standard of care.

Table 18. Response rates, change from baseline MG-ADL scores and costs for subsequent treatments based on first-line model inputs defined earlier in the model

Subsequent treatment	**Response rate**	**Change from Uncontrolled MG-ADL**			**Costs**	
		Continued response	**Loss of response**	**Stable response**	**Treatment cost per cycle(£)**	**Admin costs per cycle(£)**
IVIg	[redacted]	10.2	3.0	3.0	2,322.00	757.00
PLEX	[redacted]	10.2	3.0	3.0	6,468.63	1,137.50
Rituximab	[redacted]	10.2	3.0	3.0	3230.60	379.97
SOC	[redacted]	10.2	3.0	3.0	27.72	0

Abbreviations: IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living profile; PLEX, plasma exchange; SOC, standard of care.

Table 19. Proportion of patients achieving each level of response based on model inputs defined earlier in the model

	Percentage achieving Continued response, Loss of response or Stable response from Uncontrolled MG-ADL		
	1%	5%	94%
	Weighted change from Uncontrolled: Continued response	**Weighted change from Uncontrolled: Loss of response**	**Weighted change from Uncontrolled: Stable response**
First-line = Zilucoplan	10.2	3.0	3.0
First-line = IVIg	10.2	3.0	3.0
First-line = PLEX	10.2	3.0	3.0
First-line = SOC	10.2	3.0	3.0

Abbreviations: IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis activities of daily living profile; PLEX, plasma exchange; SOC, standard of care.

Table 20. Final calculated weighted average change from baseline (based on stratified level of response) and costs (based on overall response rate and subsequent treatment bundles) used in the model engine, for each first line treatment

	Weighted average change from Uncontrolled	Treatment cost per cycle (£)	Admin cost per cycle (£)
First-line = Zilucoplan	1.59	1,580.30	331.73
First-line = IVIg	1.70	2,703.40	474.96
First-line = PLEX	1.66	1,130.04	345.09
First-line = SOC	1.68	1,908.16	409.33

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

1.2. Model results and scenario analyses

1.2.1. Base case results (discounted)

The base-case cost-utility analysis results are based on the data, assumptions and structure described in Section 1.1 and within the global CEM technical report.

Table 21 presents the estimated total costs and QALYs for zilucoplan and its comparators as well as the pairwise comparison in terms of incremental costs, QALYs, and ICER (£/QALYs) assuming the £30,000 WTP threshold. Zilucoplan [redacted]. The standard-of-care basket is included as a comparator to address the committee's specific request.

Table 21: Base case results (discounted)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.4417			
IVIg/SCIg	[redacted]	10.3426	[redacted]	0.0991	[redacted]
Standard of care basket	[redacted]	10.3222	[redacted]	0.1195	[redacted]
Plasma exchange	[redacted]	10.4189	[redacted]	0.0229	[redacted]

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

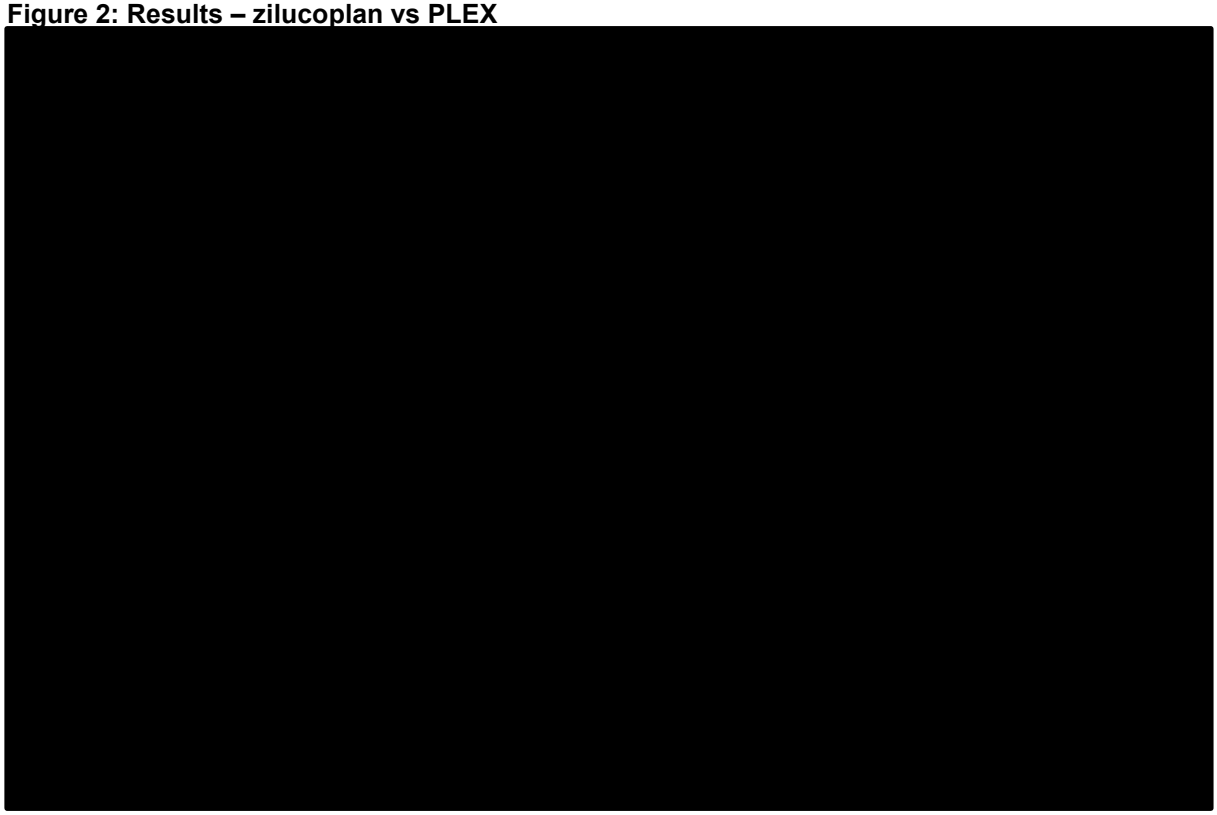
1.2.2. Deterministic sensitivity analysis results

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 1 and Figure 2. The pairwise ICER results are consistent with deterministic mean results except when IVIg and PLEX resource use parameters for uncontrolled health state are set to maximum extreme value when zilucoplan is compared to IVIg.

Figure 1: Results – zilucoplan vs IVIg

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

Figure 2: Results – zilucoplan vs PLEX



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

1.2.3. 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. For the PSA, all parameters utilised literature-derived confidence intervals or standard deviations when available. When such data were unavailable, parameters were varied by 10% around the mean. Response rates, informed by the CODA analysis, were included in the model and applied as part of the PSA.

Results are shown in Table 22 and Figure 3. The ICER scatterplot (Figure 4) 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.

For the pairwise comparison of zilucoplan 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 22. Probabilistic sensitivity results (all parameters varied 10% around the mean, except parameters informed by CODA and bvNMA)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.4160			

IVIg/SCIg	[redacted]	10.3068	[redacted]	0.11	[redacted]
Plasma exchange	[redacted]	10.3892	[redacted]	0.03	[redacted]

Abbreviations: bvNMA, Bivariate Network Meta-Analysis; CODA, Convergence Diagnostic and Output Analysis; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; QALYs, quality-adjusted life years; SCIg, subcutaneous immunoglobulin.

Figure 3. Cost-effectiveness acceptability curve

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

Figure 4. Cost-effectiveness plane

Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALY, quality-adjusted life years; SCIg, subcutaneous immunoglobulin.

1.2.4. Scenario analyses

1.2.4.1. Overall gMG population

This scenario illustrates the summary of model results for the overall gMG population.

Table 23: Scenario analysis results – overall gMG population

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.7702			
IVIg/SCIg	[redacted]	9.6419	[redacted]	0.1283	[redacted]
Plasma exchange	[redacted]	9.7286	[redacted]	0.0416	[redacted]

Abbreviations: gMG, generalized Myasthenia Gravis; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; QALY, quality-adjusted life years; SCIg, subcutaneous immunoglobulin.

1.2.4.2. Societal perspective (both societal costs and carer disutilities)

This scenario provides estimates of when societal costs and utilities are integrated in the model. The results of this scenario show higher total costs and lower total QALYs across all interventions compared with the base case.

Table 24 Scenario analysis results - societal perspective

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.2699			
IVIg/SCIg	[redacted]	9.1626	[redacted]	0.1073	[redacted]
Plasma exchange	[redacted]	9.2459	[redacted]	0.0240	[redacted]

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

1.2.4.3. SoC basket proportions from EFG EAMS

This scenario uses SoC basket informed by unrevised EFG EAMS proportions: IVI (43.8%), PLEX (14.6%), SoC only (41.6%).

Table 25: Scenario analysis results - SoC basket proportions from EFG EAMS

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.4417			
Standard of care basket	[redacted]	10.3163	[redacted]	0.1255	[redacted]

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

1.2.4.4. Include disutility of corticosteroids

In this scenario, QALYs are lower across all comparators in comparison with the base case.

Table 26: Scenario analysis results – Steroid disutility included

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	7.7207			
IVIg/SCIg	[redacted]	7.5955	[redacted]	0.1252	[redacted]
Plasma exchange	[redacted]	7.6868	[redacted]	0.0339	[redacted]

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

1.2.4.5. Two-stage BLRA NMA + bivariate NMA (RCTs + nRCTs)

This scenario uses the primary response rates from two-stage BLRA NMA and bivariate NMA (RCT+nbRCTs): Zilucoplan ([redacted]%); IVI ([redacted] %), PLEX ([redacted] %), SoC ([redacted] %). The pairwise ICER in this scenario is consistent with base-case results.

Table 27: Scenario analysis results - Two-stage BLRA NMA + bivariate NMA (RCTs + nRCTs

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.6335			
IVIg/SCIg	[redacted]	10.5762	[redacted]	0.0573	[redacted]
Plasma exchange	[redacted]	10.5865	[redacted]	0.0470	[redacted]

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

1.2.4.6. Subsequent treatment removed

The pairwise ICER in this scenario show that assuming the £30,000 WTP threshold. Zilucoplan [redacted].

Table 28: Scenario analysis results – subsequent treatment removed

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.0106			
IVIg/SCIg	[redacted]	9.9286	[redacted]	0.0820	[redacted]
Plasma exchange	[redacted]	9.9492	[redacted]	0.0614	[redacted]

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

1.2.4.7. Same subsequent treatment proportions

This scenario uses the same subsequent treatment proportions for comparators as for zilucoplan: IVIg ([redacted]%), PLEX ([redacted] %), SoC ([redacted] %).

Table 29: Scenario analysis results – subsequent treatment same proportions

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.4417			
IVIg/SCIg	[redacted]	10.3613	[redacted]	0.0805	[redacted]
Plasma exchange	[redacted]	10.3787	[redacted]	0.0630	[redacted]

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

1.2.4.8. Reduced response rate for subsequent treatments

This scenario uses a reduced response rate of subsequent treatments as indicated in Table 29.

Table 30. Assumed reduction in response rate for subsequent treatments versus first-line treatments, stratified by first-line treatment, based on expert clinical opinion

	Zilucoplan	IVIg/SCIg	Plasma exchange	Standard of care blended comparator
Response rate reduction (IVIg)	[redacted]	[redacted]	[redacted]	[redacted]
Response rate reduction (PLEX)	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 31: Scenario analysis results – reduced response rate for subsequent treatments

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.3034			
IVIg/SCIg	[redacted]	10.0200	[redacted]	0.2834	[redacted]
Plasma exchange	[redacted]	10.3078	[redacted]	-0.0045	[redacted]

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

1.2.4.9. Lee et.al. source for costs for corticosteroid management

This scenario uses the costs for corticosteroid management from EAG of TA10986, inflated to 2022/23 (£342.84 for low dose, £2,448.29 for high dose).

Table 32: Scenario analysis results – reduced response rate for subsequent treatments

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.7122			
IVIg/SCIg	[redacted]	10.3426	[redacted]	0.0991	[redacted]
Plasma exchange	[redacted]	10.4189	[redacted]	0.0229	[redacted]

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

1.3. References

1. UCB data on file. Zilucoplan - MG0010 (RAISE) Clinical Study Report. 30 Jun 2022.
2. Mosteller RD. Simplified calculation of body-surface area. The New England journal of medicine. 1987;317(17):1098.
3. Abuzinadah AR, Alanazy MH, Butt NS, Barohn RJ, Dimachkie MM. Exacerbation Rate in Generalized Myasthenia Gravis and Its Predictors. Eur Neurol. 2021;84(1):43-8.
4. Gajdos P, Tranchant C, Clair B, Bolgert F, Eymard B, Stojkovic T, et al. Treatment of Myasthenia Gravis Exacerbation With Intravenous Immunoglobulin: A Randomized Double-blind Clinical Trial. Archives of Neurology. 2005;62(11):1689-93.
5. Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. Neurology. 2009 May 5;72(18):1548-54.
6. NHS England. National Cost Collection: National Schedule of NHS costs - Year 2020-21 - NHS trust and NHS foundation trusts. Available from: https://www.england.nhs.uk/national-cost-collection/. Accessed on: 24th January 2023. 2022.
7. Outpatient care. Non consultant led. Neurology Service. WF01B - Non-Admitted Face-to-Face Attendance, First. NHS England. National Cost Collection: National Schedule of NHS costs - Year 2021-22 - NHS trust and NHS foundation trusts. Available from: https://www.england.nhs.uk/national-cost-collection/. Accessed on: 9th May 2023.
8. Outpatient care. Non consultant led. Neurology Service. WF01A - Non-Admitted Face-to-Face Attendance, Follow-up. NHS England. National Cost Collection: National Schedule of NHS costs - Year 2021-22 - NHS trust and NHS foundation trusts. Available from: https://www.england.nhs.uk/national-cost-collection/. Accessed on: 9th May 2023.
9. UCB Data on File. A retrospective observational study on characteristics, treatment patterns and healthcare resource use of patients with Myasthenia Gravis in England. January 2024.
10. Curtis LA, Burns A. Unit costs of health and social care 2020. Personal Social Services Research Unit; 2021.
11. UCB data on file. Zilucoplan - MG0011 (RAISE-XT) Interim Clinical Study Report. March 2024. 2024.
12. UCB data on file. MG0010 utility vs disease activity. Descriptive analysis & formal modelling.
13. Johnston K, Stoffman JM, Mickle AT, Klaassen RJ, Diles D, Olatunde S, et al. Preferences and Health-Related Quality-of-Life Related to Disease and Treatment Features for Patients with Hemophilia A in a Canadian General Population Sample. Patient Prefer Adherence. 2021;15:1407-17.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Clarification questions on the company's response to the second Draft Guidance Document

December 2024

File name	Version	Contains confidential information	Date
ID4008 EAG clarification questions for company response to DGD2 to PM [CON]	**1.0**	**Yes**	**23/12/2024**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on company's target population and Early Access to Medicines Scheme (EAMS cohort)

Company's target population

A1. PRIORITY QUESTION: For what reason has the definition of the target population, on page 5 of the company DG comments form, omitted people for whom systemic treatments are contraindicated or not tolerated (who are included in the decision problem population in CS Table 1 of the original submission)? If these people remained in the decision problem this would include people in the EAMS cohort who were categorised as starting efgartigimod due to 'burden of treatment' and 'side-effects'.

UCB maintains that the target population is as described in the draft guidance (which is reiterated in the response to question A2 below). It wasn't the company's intention to omit patients for whom systemic treatments are contraindicated or not tolerated from the definition of the target population included in the DG comments form. In the company DG comments form, the company was focusing the response on describing the definition of refractory in the DG comment form therefore this was omitted in error. Patients would not be eligible for zilucoplan unless they meet all

three criteria outlined in the decision problem and further clarified in the response to question A2.

UCB would like to provide further clarification of the target population for zilucoplan by stating that patients who cannot tolerate standard-of-care treatments, but are not being considered for IVIg/PLEX, are not the target population for zilucoplan. Please see the response to A2 for the full definition of the target population for this appraisal, which remains as it was in the decision problem of the original company submission but with further clarification for the first bullet point.

A2. PRIORITY QUESTION: Please could the company clarify its target population while explaining the above.

This submission is for zilucoplan as an add-on to standard therapy for the treatment of adult patients with refractory AChR antibody-positive gMG, if:

- the disease has not responded to adequate treatment with steroids and at least 2 non-steroidal immunosuppressants or these options are contraindicated or not tolerated, and
- the disease is uncontrolled, as defined by a MG-ADL score of ≥6 or a QMG score of ≥12, and
- an additional therapy such as IVIg or PLEX is being considered, or patients are being treated chronically with IVIg/PLEX

The first bullet point has been re-worded to clarify the definition of prior treatments to reflect insights from UK clinicians that they are more likely to try at least two non-steroidal immunosuppressants before considering targeted therapies, including zilucoplan. This is confirmed by the clinical consensus achieved before the introduction of the efgartigimod EAMS scheme, which stated that “it would be reserved for patients with refractory disease who had not responded to ≥ 2 non steroids immunosuppressant agents who were intolerant or ineligible for such therapies and those who were dependent on IVIg and TPE” {Moniz Dionisio, 2024 #589}. The re-wording is not a change to the target population but to make it more specific and align with UK clinical practice since patients are likely to have tried at least 2 NSISTs, unless contraindicated or not tolerated, before being treated with or considered for regular IVIg or PLEX. Also, the company believe that this population

represents those patients who would most benefit from treatment with zilucoplan in clinical practice.

Early Access to Medicines Scheme (EAMS cohort)

A3. PRIORITY QUESTION: As reported in the EAMs cohort publication (Dionisio et al. 2024), 29.2% (14/48) of patients in the EAMS cohort (n=48) started treatment because they were 'dependent on IVIg/TPE (PLEX)'. Please clarify how you reconcile this proportion of the population which fits the definition of the target population for zilucoplan ('treated with intravenous immunoglobulin or plasma exchange') with the 77.1% (37/48) of EAMs cohort categorised as refractory given that: i) these categories are not exclusive because more than one reason could be selected, and ii) they may not have been selected as refractory because they may have responded to the intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) , which may increase the number of patients with refractory gMG in the revised EAMS cohort to more than 77.1%?

A challenge to determining which patients from the efgartigimod EAMS scheme would meet the eligibility criteria for treatment with zilucoplan is that there is no formal or consistently used definition of refractory gMG. Even in the EAMS publication, there are differing definitions of patients, including refractory, severe, active disease despite treatment with at least two trials of immunosuppressive agents, and dependency on IVIg and PLEX. The paper also states that it is a heterogenous group of patients, that the cohort was mainly composed of patients with refractory long-term MG and the study did not answer the question of where efgartigimod should fit in the treatment pathway.

The reasons for starting efgartigimod listed in Table 1 are not mutually exclusive and the number of patients who are 'dependent on IVIg/PLEX' is different to that listed as receiving 'regular' IVIg/PLEX in Table 2, for reasons which are unclear. In addition, the options for reasons for starting efgartigimod were listed by the participant and are therefore subjective (and not definitely consistent with a definition of refractory, for example). Therefore, UCB preferred to use the number of patients receiving regular IVIg and PLEX from Table 2.

It is reported in the EAMS publication that 77.1% (37/48) of patients were classed as refractory; therefore, UCB tried to approximate this cohort to accurately reflect the refractory patients who would be treated with zilucoplan since the proportion of patients who received regular IVIg and PLEX is for the overall population and not the 77% who were considered refractory.

Therefore, there are 11 patients who are not classified as refractory in the publication. UCB tried to estimate the proportions of the refractory patients who were receiving regular IVIg or PLEX to inform the subsequent treatment in the model to better reflect the target population of zilucoplan. As per recent expert elicitation, clinicians confirmed that patients on no treatment and patients on corticosteroids alone would not be considered to be refractory. Therefore, the three patients on no treatment were excluded from the analysis, and eight of the 10 patients on prednisolone only were excluded to make 11 patients removed altogether, which corresponds with the 11 patients who were not selected as refractory in the EAMS cohort. It appears from Table 2 of the publication that the 27 patients listed as receiving prednisolone and NSIST also includes the 18 patients receiving regular IVIg with additional NSIST/prednisolone and the seven patients receiving regular PLEX. With the addition of three patients who were receiving IVIg only, this means that 21/37 refractory patients were receiving IVIg and 7/37 refractory patients were receiving PLEX. The remaining 9 patients consisted of 5 patients receiving NSIST only, 2 patients receiving NSISTs with prednisolone, and 2 patients receiving prednisolone only.

UCB believe that the scenario described in part ii of the question is unlikely since, while there are many varying definitions of refractory and no formal consensus on the criteria, the most used definitions are being refractory to standard of care treatment, including corticosteroids and non-steroidal immunosuppressants (NSISTs), not including IVIg and PLEX.

A4. PRIORITY QUESTION: Table 1 in the EAMS cohort publication (Dionisio et al. 2024) shows that all patients in the EAMS cohort had at least 1 prior non-steroidal immunosuppressant therapy (NSIST), (and 36 had at least 2 prior NSISTs), which therefore includes the 10 patients in receipt of corticosteroids only at the start of efgartigimod treatment. Please clarify for what reasons

these 10 patients would need to be considered for another prior NSIST (pages 11-12 of the company DG comments form) if they had already had one?

As stated in the response to A3, a challenge to determining which patients from the efgartigimod EAMS scheme would meet the eligibility criteria for treatment with zilucoplan is that there is no formal or consistently used definition of refractory gMG. Excluding 8 of the 10 patients on corticosteroids only (as well as the patients on no treatment) was the company's way of trying to emulate the refractory cohort of 37 patients, as reported in Table 1 of the publication. This is supported by recent expert elicitation, where all clinicians who responded agreed that patients only taking corticosteroids are unlikely to be termed as refractory, and that the proportion of patients unable to tolerate any NSIST is small (0 to <5%). In addition, it is stated in the publication that "the consensus achieved before the introduction of the scheme with UK MG clinicians was that it would be reserved for patients with refractory disease who had not responded to ≥ 2 NSISTs who were intolerant or ineligible for such therapies and those patients who were dependent on IVIg and PLEX"; however, there are 12 patients who only received 1 previous NSIST. Since the proportion of patients expected to be intolerant or contraindicated to all NSISTs is 0 to <5%, the company assumed that the majority, if not all, of these 12 patients would receive/trial another NSIST before being eligible for zilucoplan. This also aligns with the wording clarification change in the target population as explained in the response to question A2. It is worth noting that the data in the publication, which is not yet peer-reviewed, are sparse and it is impossible to know whether the patients receiving prednisolone only are also part of the 12 patients who have only received 1 previous NSIST.

However, as zilucoplan is only expected to displace IVIg and PLEX in clinical practice, UCB maintains that a pairwise comparison with these treatments is the most appropriate approach to evaluative the cost-effectiveness of zilucoplan. The EAMS basket should only be used to estimate the proportions of IVIg:PLEX, which is in a 75:25 ratio in this cohort.

In current practice, as the committee has stated, not all patients receive IVIg or PLEX in the refractory cohort and thus we are now using limited data to estimate proportions. UCB reiterates that for the same reason that IVIg and PLEX are not

currently used in the whole refractory group (under the care of a specialist centres, strict prescribing controls) zilucoplan will also only be reserved for the patients who are most in need, as determined by expert HCPs; and the proposed critieria in the target population of “an additional therapy such as IVIg or PLEX is being considered” should limit prescribing in the same way as IVIg and PLEX are limited today.

A5: PRIORITY QUESTION: Please could the company explain its interpretation of how “refractory” was defined in the original EAMs cohort (n=48) in relation to its target population for zilucoplan. For the company’s target population as currently stated in the Draft Guidance and company’s submission before the first committee meeting, the Draft Guidance stated that the committee was aware that the criteria were based on the pre-planned refractory subgroup of the RAISE trial.

Patients eligible for zilucoplan would have exhausted standard treatments before being considered for targeted therapies; this is different from the patients included in the EAMS cohort, some of whom did not have refractory gMG and were not receiving any MG treatment. As zilucoplan is licensed as an add-on to standard therapy, patients who are not receiving MG treatments (such as 3 patients in the EAMS data set) would not be eligible. UCB have explained the approximation of the 37 refractory patients in the EAMS cohort to the target population for zilucoplan in responses to questions A3 and A4.

As mentioned in question A4, there is no consistent formal definition of refractory gMG in treatment guidelines or even within the EAMS publication itself or amongst gMG clinicians. In addition, there were no definite criteria for inclusion in the study other than AChR-antibody-positive gMG that was not adequately controlled on standard therapies. Therefore, depending on access to clinical trials, clinical experience, and access to infusion centre facilities, individual sites may have had different thresholds for patient inclusion.

In addition, the study mentioned that there is potential for use of efgartigimod in situations other than refractory disease, but it was not stated what these situations are to know if they are consistent with the population that would be eligible for zilucoplan. In addition, the profile of the group of patients that are more likely to

benefit from efgartigimod, as well as its exact timing in refractory MG remains to be determined.

The target population for zilucoplan is as described in the company submission (apart from 'an alternative option to efgartigimod' which has since been removed as efgartigimod is not part of clinical practice, and refinement to the wording for prior treatments) and in response to question A2. The definition of refractory used in RAISE differs from the draft guidance (and target population for zilucoplan) as it states that patients would need to have been treated with and failed to respond to standard of care treatments for ≥1 year, whereas no such timeframe is stipulated in the draft guidance or company submission. Interviewed clinicians during the committee meeting were in support of this as they would not wait a specific period of time before defining a patient as refractory and switching treatment.

Clarification on effectiveness data

Systematic literature review

A6. Please tabulate the participant baseline characteristics of the newly included studies (i.e. those not included in the original CS) and consider the comparability of the baseline characteristics of these studies between all relevant study arms that they link to in the network meta-analyses (NMAs).

In total one additional RCTs (Barth 2011) and three observational studies (Barnett 2017, Leng 2024, Duann 2023) were identified in the SLR update and used in the NMA. The sample size ranged from 7 (Leng 2024) to 124 (Duan 2023) across the observational studies and 83 in the RCT (Barth 2011). Duration of studies ranged from 3-4 weeks (Barnett 2017) to 3 months (Leng 2024).

The baseline characteristics of participants in these studies is provided in Table 4. In summary, studies included participants of both sexes with a mean age ranging between 47 years (Duan 2023) to about 58 years (Barth 2011) and disease duration ranging from about 52 months (Duan 2023) to 141 months (Barnett 2017). Participants' condition was described as general MG (Barth 2011, Barnett 2017, Leng 2024), or severe MG (Duan 2023). MGFA classification was reported in all but one

studies (Leng 2024). Studies included participants of various MG classes except for one study conducted on participants with MGFA class IV only (Duan 2023). Baseline MG-ADL was reported in one study (Barnett 2017), while baseline QMG scores was available in three studies (Duan 2023, Bernett 2017 and Barth 2011). Disease duration ranged from about 53 months (Suan 2023) to 93 months (Barnett 2017).

Table 1: Baseline characteristics from studies newly included in the SLR update that were included in the NMA

Study name	Treatment	Evaluable N	Disease severity	Age (Mean)	Male (%)	Disease duration (Months)	MGFA I (%)	MGFA II (%)	MGFA III (%)	MGFA IV (%)	MGFA V (%)	Baseline QMG Score (mean ± SD)	Baseline MG-ADL Score (mean ± SD)
Duan 2023	PLEX	62	MGFA IV	47.2	29.0	53.2	NR	NR	NR	82.3	NR	23.0 ± 4.0	NR
	LPE	62	MGFA IV	47.8	35.5	51.2	NR	NR	NR	80.6	NR	23.2 ± 4.1	NR
Leng 2024	PAIA	4	Moderate to severe	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	PLEX	3	Moderate to severe	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Barnett 2017	Placebo	50	MGFA I-IV	57.0	56.0	93.0	40	34	22	4.0	NR	9.1 ± 5.6	5.7 ± 3.7
	IVIg	45	MGFA I-IV	51.0	29.0	65.0	0	31	26	13.0	NR	13.6 ± 7.7	7.7 ± 3.8
Barth 2011	IVIg	41	MGFA II-V	57.0	42.0	71.0	NR	22	17	NR	0	14.3 ± 4.0	NR
	PLEX	43	MGFA II-V	58.0	45.0	64.0	NR	26	15	NR	1	14.4 ± 3.8	NR

Abbreviations: IV Ig: Intravenous immunoglobulin; MG: Myasthenia gravis; MG-ADL score: Myasthenia gravis Activities of Daily Living; MGFA: Myasthenia gravis foundation of America; NR: not reported; PLEX: Plasma exchange; SD: standard deviation; QMG score: Quantitative Myasthenia Gravis score.

A7. Please summarise the clinical heterogeneity of the studies included in each NMA and conduct sensitivity analyses where appropriate to examine the impact of the heterogeneity on the overall results.

Feasibility assessment was not carried out as a part of the current NMA update as the objective was to conduct a sensitivity analysis to support the robustness of previously conducted NMA (only RCTs). As such, clinical heterogeneity was not assessed for the current sensitivity analysis by including non-RCTs.

A8. Please explain the inconsistencies between Table 8 and Table 10 in the systematic literature review (SLR) report, where details like study sample size change between tables for the same study, and please correct the information if necessary.

Table 8 doesn't contain any column for sample size. There was some inconsistency in Table 6 and Table 9, and Table 7 and Table 10, which has been corrected via 'Track Changes' and re-submitted separately.

A9. It is not possible to open the list of 60 included publications embedded beneath Table 54 in A.5 of the SLR report. Please supply a copy separately.

Please see the Excel file submitted separately.

A10. Please supply the citation of the publication for the NCT02473952 RCT that was published after the date of the SLR searches and included in the NMA (company DG comments form, page 6).

Bril V, Nicolle M.W., Vaitkus A et al. Efficacy and safety of maintenance intravenous immunoglobulin in generalized myasthenia gravis patients with acetylcholine receptor antibodies: A multicenter, double-blind, placebo-controlled trial. Muscle & Nerve 2024;71:43–54 (https://doi.org/10.1002/mus.28289).

NMA report

A11. What were the feasibility criteria and what was the feasibility assessment process that led to the inclusion of just 3 of the 11 newly identified studies, from the September 2024 update, in the NMAs?

Formal feasibility assessment was not carried out since this was a sensitivity analysis to support the previously carried out NMA with RCTs. Two criteria were considered for the inclusion of non-RCTs:

1. The study should be able to be connected within the network
2. Outcomes of CFB in QMG/MG-ADL scores or responders using QMG/MG-ADL scores should be reported in the study

The inclusion of non-RCTs with RCTs itself may introduce bias due to differences in the study design The study count, after including Barth et al 2011 (this study was not included in the prior NMA as not a P3 RCT) is 11 and hence 4/11 studies are included in the presented NMA (Table 5).

Table 2: List of studies evaluated for NMA inclusion

Study Name	Intervention	Comparator	Inclusion in NMA	Reason
Quiroz 2023	NMD670 400mg and NMD670 1200mg	Placebo	No	CFB data for placebo arm is not available. Responder data also not available
Cutter 2019	IVIg	PLEX	No	Outcome data not available.
Ronager 2001	PLEX->IVIg	IVIg->PLEX	No	The paper evaluates efficacy of treatment sequence
Sheckley 2021	PLEX	-	No	Single arm study
Eienbroker 2014	IVIg	-	No	Single arm study
Seyhanli 2022	PLEX	-	No	Single arm study
Watanabe 2018	IVIg	Multiple treatments	No	Outcome data not available for the comparator arm

Duan 2023	LPE	PLEX	Yes	
Barnett 2017	IVIg	Placebo	Yes	
Leng 2024	PAIA	PLEX	Yes	
*Barth 2011	IVIg	PLEX	Yes	

Abbreviations: CFB, change from baseline; IVIg, intravenous immunoglobulin; LPE, lymphoplasmapheresis; NMA, network meta-analysis; nRCT, non-randomised controlled trial; PAIA, protein A immunoadsorption; PLEX, plasma exchange.
*Additionally, Barth 2011 was included in the analysis along with nRCTs as it was not included in previous NMA considering it was a phase IV study.

A12. Please explain how the Leng 2024 and Duan 2023 studies contribute to the network in Figure 1 of the NMA report, given that NMAs need a common treatment comparator to preserve relative effectiveness?

Studies by Leng 2024 and Duan 2023 have expanded the treatment comparison network in our analysis. Leng compared protein A immunoadsorption (PAIA) to PLEX, while Duan examined lymphoplasmapheresis (LPE) versus PLEX. Both Leng and Duan studies are connected in the network via Barth 2011 study which reported the comparison between IVIg and PLEX.

A13. Please justify the inclusion of Leng 2024 in the NMA, given that the study only has 3 participants in the PLEX arm. Did you consider a sensitivity analysis to explore the effect of excluding this study from the network?

The inclusion of studies in the NMA network was carried out after assessing distinct treatment arms that can be connected to the network via common treatment nodes and the availability of outcomes data. Due to the limited availability of studies, exclusion based on the sample size of the studies was not performed. Since Leng 2024 is a considerably small study based on sample size, the impact of eliminating this study would be negligible. In addition, the NICE committee stated that sample size should not be a reason to exclude studies given the limited data available for IVIg and PLEX.

A14. Barnett 2017: a) Please explain why the combined IVIg/PLEX arm in Barnett 2017 represents IVIg and not PLEX, given that by connecting it to PLEX in the network, it might draw the Leng and Duan studies properly into the network, and b) please confirm which of the other arms (prednisone and

control) in the Barnett 2017 study have been used to represent a placebo population for inclusion in the network and explain how this is appropriate.

IVIg and PLEX have similar efficacy as reported in Barnett et al 2013 (1) and Barth et al, 2011 (2). Furthermore, due to its ease of administration, lower risk profile, and widespread use as an alternative to PLEX, IVIg was considered as the treatment node. Leng and Duan studies are connected in the network via Barth 2011 which reports the comparison of IVIg and PLEX.

Although Barnett 2017 mentions the control arm (n= 54), it does not report any outcome data. To avoid exclusion of this study, the prednisone arm was considered a placebo arm.

Expert interviews

A15. What information was recorded for each expert's centre for how they accessed IVIg and how they accessed PLEX, i.e. what services and facilities are available at their centre? What was the experts' experience of administering zilucoplan or other novel generalised myasthenia gravis (gMG) therapy? Please assess how these aspects may influence their responses regarding choice of treatment.

Expert 2 and expert 4 were principal investigators in RAISE. In addition, expert 1 has 1 patient in zilucoplan's interim access programme and expert 4 has 5-6. All four experts have patients receiving efgartigimod as part of EAMS, and expert 3 was involved in ADAPT. It is important to assess any bias in the context of rare diseases, i.e. there are a limited number of experts from a limited number of expert centres from whom to gather information, therefore they are all likely to have some experience in either a clinical trial or managed access. Information on access to IVIg and PLEX was not recorded during the interviews.

As these experts were sampled from the specialist centres that will be among the restricted centres where zilucoplan will be available, UCB believes that these responses are the best estimation of treatment practices that are most relevant to zilucoplan.

A16. Please provide a tabulated set of questions and responses for the discussion of the definition of refractory gMG, as provided for the other discussion topics in the expert interviews report.

The requested information is provided in Table 6.

Table 3: Expert elicitation – definition of refractory gMG

Questions	Expert 1	Expert 2	Expert 3	Expert 4
Zilucoplan is positioned for use as an add-on treatment in patients with refractory AChR Ab+ gMG, where refractory is defined as those patients whose condition is uncontrolled despite receiving standard of care treatment (CSs and NSISTs), and who are being considered for or treated with IVIg or PLEX.				
Is it reasonable to assume that this group of patients would not include those receiving no treatment?	[redacted]	[redacted]	[redacted]	[redacted]
Is it reasonable to assume that this group of patients would not include those who are only taking CSs (since they would be expected to trial NSISTs before being given zilucoplan?	[redacted]	[redacted]	[redacted]	[redacted]

Section B: Clarification on cost-effectiveness data

B1. PRIORITY QUESTION: Please clarify which previous version of the company's model the current changes (submitted as response to DG2) have been applied to. Note: the EAG were unable to replicate the changes to the company's base case model from ACM1 to ACM2.

- For clarity and transparency, please provide a table outlining the cumulative effect of each of the changes made to the company base case model (for zilucoplan versus standard of care blended comparator results) used in ACM1 to produce the current base case results (Excel file: ID4008 Zilucoplan CEM 05.12.24_CON). Please follow the example shown in **Table 7**.

Table 4: Example of a table showing the impact of the changes made to the company's model post ACM1

		Total costs	Total QALYs	ICER
Company's base case in ACM1	Zilucoplan			
	Standard of care blended comparator			
Change 1	Zilucoplan			
	Standard of care blended comparator			
+Change 2	Zilucoplan			
	Standard of care blended comparator			
+ ---	Zilucoplan			
	Standard of care blended comparator			
+ Change n	Zilucoplan			
	Standard of care blended comparator			
Company's base case submitted as response to DG2	Zilucoplan			
	Standard of care blended comparator			

The updates following ACM2 (in the response to draft guidance) were applied to the model submitted for ACM2 (ID4008 Zilucoplan CEM 20.09.2024_final.xlsb). The model technical report and change logs for the adaptation to each subsequent version (ACM1 to ACM2 and ACM2 to current) have been submitted separately.

As explained in the clarification meeting, it is not feasible to update the ACM1 model again and conduct all the scenarios requested as this will require substantial structural changes and cannot be completed within the require timeframe.

- Please also provide a change log outlining all the changes made to the ACM1 company model.

As stated above, this has been provided separately.

Having had further discussion on the population for the basket of care comparator arm that is currently NICE's preferred assumption, and considering that zilucoplan 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:

1. 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 zilucoplan and would not be eligible for treatment with zilucoplan in clinical practice. In this case, the pairwise comparisons with IVIg and PLEX would seem to be the most appropriate. The results for these are shown in Table 1, and the company have also included a blended IVIg/PLEX arm (scenario 1c), 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). [redacted]
2. 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 zilucoplan 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 zilucoplan 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 2). [redacted]

3. Those on SoC only are patients who cannot access IVIg or PLEX due to geographical restrictions. In this case, the difference in the cost-effectiveness results (i.e. a high ICER) is due to IVIg not being cost-effective versus SoC, but it is still used in the NHS. This means that, whilst zilucoplan is dominant versus IVIg and the blended arm of patients receiving IVIg and PLEX in clinical practice (Table 1), UCB acknowledges that zilucoplan is not cost-effective versus SoC only. This can be further illustrated by comparing a theoretical version of IVIg that is 10% cheaper and 10% more effective than the currently used IVIg versus the standard of care basket according to the treatments being received at initiation of efgartigimod in EAMS (Table 3). Four scenarios were conducted with different baskets of care, and all ICER results are far above the willingness-to-pay threshold for reimbursement in the NHS, which would lead to a cheaper and more effective version of IVIg being not recommended by NICE, which is clearly a perverse outcome for patients, being denied an effective treatment in the NHS. In addition, if geographical location is the reason for patients not receiving IVIg or PLEX, then the introduction of zilucoplan would improve equity of treatment.

The results for scenario 1c (blended IVIg/PLEX) were calculated by comparing the zilucoplan 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 1). It is worth highlighting that the cost-effectiveness results versus PLEX are largely driven by the new proportions of subsequent treatments applied (as shown for zilucoplan in Figure 1 and for IVIg and PLEX in Figure 2); in the previous analysis (Table 24 of the supporting information submitted as part of the response to the draft guidance document following ACM1), [redacted] versus PLEX. In addition, in the scenario with subsequent treatment removed that was presented as part of the response to the draft guidance following ACM1 (Table 29 in the supporting document describing the CEM results), [redacted] versus PLEX.

Table 5: Scenario 1 results (discounted) – zilucoplan versus IVIg and PLEX

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.4417			
1a) Pairwise comparison vs IVIg					
IVIg	[redacted]	10.3426	[redacted]	0.0991	[redacted]
1b) Pairwise comparison vs PLEX					
PLEX	[redacted]	10.4189	[redacted]	0.0228	[redacted]
1c) Comparison vs blended IVIg/PLEX arm (75:25)					
Blended IVIg/PLEX	[redacted]	10.36168	[redacted]	0.0800	[redacted]

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

In scenario 2, patients in both the zilucoplan 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 zilucoplan in the current version of the model, for efficiency (due to time constraints), 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 zilucoplan 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 2. The costs and QALYs for the zilucoplan arm were then weighted to incorporate those patients who would be on SoC only based on both the refractory EAMS cohort (scenario 2a) and the overall EAMS cohort (scenario 2b). This means that the zilucoplan arm for scenario 2a (refractory EAMS cohort) includes 75.6% of patients on zilucoplan 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. For scenario 2b, the zilucoplan arm includes 58.3% of patients on zilucoplan and 41.7% on SoC compared with the standard of care basket of 43.8% IVIg, 14.6% PLEX, and 41.6% SoC (Table 2). 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 ~0.06), illustrating that IVIg and PLEX are not cost-effective but are currently used in the NHS.

Table 6: Scenario 2 results (discounted) – zilucoplan versus basket of care

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.4417			
SoC (CSs and NSISTs only)	[redacted]	10.2339			
2a) Zilucoplan arm using proportion on SoC from refractory EAMS cohort (75.6% zilucoplan, 24.4% SoC) vs basket of care using proportions from refractory EAMS cohort (56.7% IVIg, 18.9% PLEX, 24.4% SoC)					
Zilucoplan	[redacted]	10.3910			
Basket of care	[redacted]	10.2960	[redacted]	0.0950	[redacted]
2b) Zilucoplan arm using proportion on SoC from overall EAMS cohort (58.3% zilucoplan, 41.7% SoC) vs basket of care using proportions from refractory EAMS cohort (43.8% IVIg, 14.6% PLEX, 41.6% SoC)					
Zilucoplan	[redacted]	10.3551			
Basket of care	[redacted]	10.2898	[redacted]	0.0653	[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 3, in the comparison of the basket of care with a version of IVIg that is 10% cheaper and 10% more effective than currently available IVIg, the acquisition cost was reduced by 10% and the initial response rate and change 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 both the refractory EAMS cohort and the overall EAMS cohort (Table 3). Scenarios 3a and 3b show the new cheaper and more effective IVIg versus the basket of care and represent the refractory and overall EAMS proportions of treatments in the basket of care, respectively.

Table 7: Scenario 3 results (discounted) – 10% cheaper and 10% more effective IVIg vs basket of care

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
10% cheaper and 10% more effective IVIg	[redacted]	10.3577			
3a) Comparison with basket of care based on the refractory EAMS cohort proportions (56.7% IVIg, 18.9% PLEX, 24.4% SoC)					
Basket of care	[redacted]	10.2960	[redacted]	0.0617	[redacted]

3b) Comparison with basket of care based on the overall EAMS cohort proportions (43.8% IVIg, 14.6% PLEX, 41.6% SoC)					
Basket of care	[redacted]	10.2898	[redacted]	0.0679	[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.

B2. PRIORITY QUESTION: Please provide a flowchart showing patient flow through the model for the zilucoplan arm and for the standard of care blended comparator arm, including:

- First-line treatment: the mean time on treatment for zilucoplan, IVIg and PLEX, and the proportion of patients receiving each treatment

- Second-line treatment: the mean time on treatment for IVIg and PLEX, and the proportion of patients receiving each treatment

Please see Figure 1 for the flowchart showing patient flow through the model for the zilucoplan arm and Figure 2 for the flowchart for the standard of care blended comparator arm. It is worth noting that the proportions of subsequent treatment are based on the November 2024 clinical expert elicitation. A scenario was conducted where the proportions were set to be equal across arms using the proportions for zilucoplan. The results are showed in Table 30 of zilucoplan CEM DGD2. Another consideration is that there doesn't appear to be a set, linear pathway for refractory MG, and that treatment varies among clinicians, between geographical areas, and is highly individualised to the patient.

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Figure 1: Zilucoplan subsequent treatment pathway

Figure 2: SoC basket subsequent treatment

B3. PRIORITY QUESTION: Please conduct scenario analyses that explore a range of time on treatment assumptions, as requested by the committee in the Draft Guidance Consultation 2 document (pages 27 & 28 and discussed in section 3.18) and explain how to run these scenarios.

1. Clarification on the Stopping Rule:

The treatment-stopping rule was included in error in the ACM2 model. This was clarified by UCB during ACM2. UCB does not believe this omission has a major impact on the results, as both the EAG and clinicians have stated that the stopping rule assumption is unrealistic. Patients would not discontinue treatment after a fixed time if they were continuing to respond to that treatment. The stopping rule was subsequently removed from the ACM3 model, which the EAG could not review. As a result, this functionality is no longer available in the current version of the model.

The shorter overall time on treatment for zilucoplan is due to the lower response rate for zilucoplan's subsequent treatment basket. The time on initial treatment is higher for zilucoplan than IVIg and SoC, as its response rate is higher. However, the response rate for subsequent treatment bundles is lower for those initiated on zilucoplan than those initiated on IVIg. Therefore, the time on treatment with subsequent treatments is lower for zilucoplan, meaning the overall time on treatment in the zilucoplan arm is lower than the comparators (Table 9).

Table 8: Mean time on treatment including subsequent treatments

Treatment	Response rate	Time on treatment	Subsequent tx bundle response rate	Time on subsequent tx
Zilucoplan	[redacted]	[redacted]	[redacted]	[redacted]
IVIg	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]

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

2. Alternative Approach Using Loss of Response Scenarios:

In response to the committee's request and discussion in the clarification meeting, UCB has conducted scenario analyses exploring loss-of-response probabilities as a proxy for varying treatment duration assumptions (Table 9). These scenarios do not

directly model time-on-treatment but provide insights into the impact of treatment discontinuation through transitions to the "loss of response" health state.

To run these scenarios, the following steps should be followed in the model:

- Time on treatment assumptions should be adjusted for both zilucoplan and the comparators on the SeverityScore worksheet cells G26-G29 accordingly, as specified in the updated scenarios.

Table 9. Loss of response (treatment duration) scenarios (Zilucoplan)

Loss of response (%)	Transition probability from uncontrolled (initial treatment) to loss of response	Pairwise ICER (£/QALY)	
		vs IVIg	vs PLEX
5% (base case)	[redacted]	[redacted]	[redacted]
1%	[redacted]	[redacted]	[redacted]
3%	[redacted]	[redacted]	[redacted]
10%	[redacted]	[redacted]	[redacted]

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

B4. PRIORITY QUESTION: Please provide the calculations to show how the proportions of patients receiving IVIg and PLEX as subsequent treatment in the standard of care blended comparator arm (SubsTx!I9-I10) were determined.

Upon review of the calculations, the company has detected an error in the proportions of subsequent treatments for the standard of care blended comparator arm in the DG2 response. The percentages in the submission were the weighted proportions from the expert elicitation that did not take into account the proportion of patients on SoC only in the first line blended basket.

Please see the calculations below showing the correct and incorrect calculations. The correct proportions have been used to rerun the scenario for the blended comparator basket.

Standard of care blended comparator

- First-line treatment proportions (informed by revised EAMS cohort)
    - IVIg = 56.7%, PLEX = 18.9%, SoC only = 24.4%
- Subsequent treatments
    - IVIg pathway (informed by expert elicitation)

  Re-treat with IVIg = [redacted]%, Switch to PLEX = [redacted]%, Soc only = [redacted]%
    - PLEX pathway (informed by expert elicitation)

  Re-treat with PLEX = [redacted]%, Switch to IVIg = [redacted]%, SoC only = [redacted]%
- Overall subsequent treatment proportions for the blended basket
- Correct calculations
    - IVIg: (56.7% x [redacted]%) + (18.9% x [redacted]%) = [redacted]%
    - PLEX: (56.7% x [redacted]%) + (18.9% x [redacted]%) = [redacted]%
    - SoC only: (56.7% x [redacted]) + (18.9% x [redacted]%) + 24.4% = [redacted]%
- Incorrect calculations submitted in the DG2 response
    - IVIg: ([redacted]) / 200 = [redacted]%
    - PLEX: ([redacted]) / 200 = [redacted]%
    - SoC only: ([redacted]) / 200 = [redacted]%

These corrected calculations have been applied in the model and used to calculate the results presented in Table 1, Table 2 and Table 3.

B5. PRIORITY QUESTION: Please clarify how the benefit from subsequent treatments is accounted for in the model.

The full details of the approach for modelling the benefit of subsequent treatments is described in “Additional modelling and information on subsequent treatments“

starting on page 20 of the Consultation on the draft guidance document sent on 5th December. The key points are shown here:

- To estimate the efficacy of the subsequent treatment basket, the mean change from baseline MG-ADL score was calculated and used to estimate health state utilities for patients in the “uncontrolled off initial treatment health state”.
- The mean change from baseline for continued, loss of response and stable response was weighted by the bundle composition and multiplied by the percentage of patients who respond to subsequent treatment, to estimate a weighted mean change from baseline for each level of response.
- These were then further weighted by the proportion of patients who achieve each level of response, to determine a total mean change from baseline, accounting for the percentage of patients that responded and achieved continued, loss of, or stable response across the treatments in the bundle.
- The calculated average mean CFB is taken away from the baseline “uncontrolled on initial treatment” MG-ADL score to determine the total MG-ADL score for the “uncontrolled off initial treatment” health state. This score is then used to calculate health state utility values using the ITT regression equation, as with all other health states.
- Therefore, the “uncontrolled off initial treatment” health state reflects the efficacy of subsequent treatments by estimating the average change from baseline MG-ADL score given the bundle of subsequent treatments and is reflected in a health state utility value that is slightly higher than patients in the “uncontrolled on initial treatment” health state

The resulting weighted average change from uncontrolled ADL scores are shown in Table 20 in the “Overview of new evidence and modelling updates and results” document sent on 5th December and are also highlighted below.

Table 10. Final calculated weighted average change from baseline (based on stratified level of response) and costs (based on overall response rate and subsequent treatment bundles) used in the model engine, for each first line treatment

	Weighted average change from Uncontrolled	Treatment cost per cycle (£)	Admin cost per cycle (£)
First-line = Zilucoplan	[redacted]	[redacted]	[redacted]
First-line = IVIg	[redacted]	[redacted]	[redacted]
First-line = PLEX	[redacted]	[redacted]	[redacted]
First-line = SOC	[redacted]	[redacted]	[redacted]

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

B6. PRIORITY QUESTION: The 'Zilucoplan CEM DG2 results 051124' section 1.1 refers to a technical report that provides full details of the methodology used for the modelling updates and results. Please provide a copy of this technical document.

The technical report for the CEM and the change logs for the different versions has been submitted separately.

B7. Please provide further evidence for minimum symptom expression (MSE) enduring through the lifetime of the economic model.

UCB have included the MSE data from RAISE-XT in the response to the draft guidance following ACM1. There are no further data available apart from the recent expert interviews, where clinicians agreed that it was reasonable to assume that patients who reach MSE on IVIg, PLEX and zilucoplan would remain at MSE if they continue to receive treatment (please see Page 12 and Table 2 of the expert elicitation report). Overall, the clinicians felt that a patient was more likely to reach MSE with zilucoplan than with SoC, IVIg or PLEX.

We have described how MSE was implemented in the model in the response to draft guidance following ACM1, by applying a reduction in MG-ADL score to reach an absolute score of 0.5 points in the relevant proportions of patients reaching MSE. In addition, it is worth noting that MSE remains for the lifetime of the patient

independent of the treatment they received to reach it, i.e. there is no bias or advantage for zilucoplan compared with IVIg and PLEX.

B8. We attempted to reproduce the scenario results for the societal perspective analysis by ticking the box in SocietalCosts!E5. This gives the same Total Costs as reported, but different Total QALYs (Zilucoplan CEM DGD2 results 051124, Table 25). Please explain how to run this scenario to achieve the results presented.

In addition to ticking the box in SocietalCosts!E5, the societal perspective (caregiver disutility) also needs to be switched on in the Utilities worksheet to achieve the results presented.

Section C: Textual clarifications

C1. The footnote to Table 1 in the NMA report refers to an "identified outlier study", but there is no corresponding symbol within the table. Which study, or studies, are outliers and why?

The footnote was included in error, and no further feasibility assessment was carried out to identify outlier studies among those included in the presented NMA. Please ignore the footnote with apologies.

References

1. Barnett C, Wilson G, Barth D, Katzberg HD, Bril V. Changes in quality of life scores with intravenous immunoglobulin or plasmapheresis in patients with myasthenia gravis. Journal of Neurology, Neurosurgery & Psychiatry. 2013;84(1):94-7.
2. Barth D, Nabavi Nouri M, Ng E, Nwe P, Bril V. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology. 2011 Jun 7;76(23):2017-23.

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Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of British Neurologists

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Name of commentator person completing form:	[redacted] on behalf of the ABN Neuromuscular disorders advisoty board

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 very concerned that this recommendation will have a significant negative impact on the management of adult patients with AChR abs positive MG and subsequently on their quality of life.
2	Population to be treated with zilucoplan: the number of patients with severe refractory MG (i.e. not responsive, or seriously intolerant, to several long-term standard treatments escalated overtime, majority of which have been on regular IVIG or/and PLEX, is relatively small (10% of gMG with AChR abs); by restricting the refractory disease subgroup to those with such severe, either persistent or highly fluctuating clinical features, one can more accurately define the subgroup of patients requiring target therapies such as Zilucoplan.
3	Such group of patients are those with complex MG management issues (number of different treatment regimens needed and MG-associated complications requiring hospital admissions, including in ICU, ventilation requirements, other medical and surgical complications and subsequent impact in their life overall). This is the patient population that need new target therapy.
4	Cost-effectiveness analyses of zilucoplan vs standard of care in such group of patients with severe refractory disease is more likely to favour treatment with zilucoplan. Examples are those with intractable MG on long-term immunosuppressants, regular inpatient PLEX or IVIG for years, some still having MG crisis and needing hospital admissions (+/- ICU). There is evidence that by starting zilucoplan reduces and stops the need for those treatments, namely the PLEX and IVIG, and hospital admissions, allowing patients to become productive and independent.
5	There are no studies comparing directly zilucoplan efficacy to that of PLEX or IVIG. However, the Raise/Raise XT clinical trials show a significant reduction (or complete weaning off) of the use of such treatments following being on zilucoplan treatment. This is currently the best available evidence of the superiority of zilucoplan over IVIG or PLEX; i.e. zilucoplan replaces those treatments as well as allows weaning off standard therapy and subsequent complications.
6	Having criteria to stopping zilucoplan is essential. Firstly, when it shows no benefit: this may be assessed by the week 3 or 4 of treatment, although one could argue that some patients are slower to respond or there may be some uncertainty of the level and consistency of the improvement and thus the ability to wean off or reduce significantly other ongoing treatments (e.g. IVIG or PLEX), needing a longer period of assessments (up to 6-12 weeks maximum). Secondly, although not seen in the clinical trials, zilucoplan may be stopped if there is a sustained loss of effect, after excluding any other potential causes for exacerbation of the disease following successful treatment with zilucoplan (e.g. from infections to recurrence of thymic tissue). Thirdly, although zilucoplan is unlikely to have a disease modifying effect, it is possible that overtime, as it happens with other treatments, eventually the disease may get in remission; if so, zilucoplan may be

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	weaned successfully; note that there is no clear evidence of such possibility yet, but conceivable, and something to explore in prospective studies.
7	We are very concerned if patients with severe g MG with AChR abs have no new treatments to improve their disease and subsequent health problems and quality of life. If zilucoplan is not recommended to a particular group of patients, they will continue needing regular and frequent hospital admissions for IVIG or PLEX if available to them, with potential associated complications, and being admitted when they suffer life threatening MG crisis. Costs to the NHS to treat these patients,as it happens currently, will be well above zilucoplan treatment costs. Having seen the transformation that vulnerable and seriously affected patients (previously on long-term IVIG or PLEX and standard therapy) experienced following starting and continuing on zilucoplan it became clear that medically, socially and economically, there is a small group of patients that need and must be offered zilucoplan to treat their severe MG.

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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- 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.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Myaware and Muscular Dystrophy UK (MDUK)

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No such links exist for either stakeholder.
Name of commentator person completing form:	[redacted] ([redacted], myaware)

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Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation does not fully weigh the benefits of zilucoplan over existing therapies such as plasma exchange (PLEX) and IVIg. Both PLEX and IVIg require vascular access, with central line use an additional drawback of PLEX treatment. Central line complications are well-reported in the literature. (Kornbau et al, 2015) In comparison, zilucoplan can be taken subcutaneously and therefore minimises this risk.
2	We would like to bring attention to the evidence that shows zilucoplan treatment can contribute to minimal symptom expression (defined as an MG-ADL score of 0 or 1 without rescue therapy) in myasthenia gravis (MG) patients. The RAISE clinical trial reported this improvement in 14% of the treatment group, and myaware members who have taken part in the trial have provided their own testimony of this life-changing response. This is a benefit of zilucoplan that has been reported in these patients where standard therapy has failed – patients are able to reclaim independence and get their lives back through zilucoplan. We are concerned that this benefit wont be available to other MG patients who are in a similar situation based on the draft guidance recommendation.
3	We wish to raise the importance of zilucoplan and its ability to allow MG patients to reduce their steroid dosage. There must be a careful balance between symptom manifestation and side effect management in the treatment of MG, and unfortunately steroids have historically made this balance very difficult to obtain. The symptomatic expression of MG causes a loss of control over the patient's body. Steroids can offer some of this control back, however at the cost of significant side effects. These side effects are well reported, however a few that are significant for MG patients are weight gain, insomnia, and mood swings. These side effects again reduce the control a patient has over their body, making the balance in treatment more difficult to manage. Zilucoplan has reportedly allowed patients to reduce their dependence on steroids to manage their MG symptoms, and therefore offers an opportunity to reduce the significance of their side effects.
4	The draft guidance unfortunately further isolates a proportion of MG patients who face great uncertainty and few options in terms of managing their disease. The refractory population of MG patients, particularly those who do not respond to rescue therapies such as PLEX and IVIg, or those who are unable to provide vascular access due to previous therapeutic complications, are left without choice and at the mercy of their symptoms. We wish to emphasise that patients within this group can experience a significantly low quality of life and lack of independence. Refractory patients are dependent on the care of others and experience a disease burden that touches upon physical, social, financial, and mental aspects of life. With the negative guidance of zilucoplan, the few potential options for this group has become smaller.
5	Finally, we wish to state that the negative guidance of zilucoplan raises concerns that the difference in life quality for patients who have received treatment with this therapy compared to those who haven't is not being properly considered. We appreciate that NICE have welcomed the testimony of patient experts and representatives throughout this process, but we must implore the committee (and the company) to think strongly of the reality for patients, particularly in the target population, of coming so close to a targeted therapeutic for their disease and hearing the perspective of those who have had their life changed so positively, only for they themselves not to experience this. The MG patient population is a tenacious and resilient group of people who have lived with blanket approaches to their treatment for the longest time, and the significant unmet need in treatment must be addressed.
6	

Insert extra rows as needed

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NHSE responses to NICE queries

A colleague has discussed with clinicians and provided the following information:

- Further IVIg following IVIG

Only a small number of patients (c4% of eligible patients) receive regular maintenance treatment with IVIG.
More patients receive IVIG for frequent acute exacerbations and could be classed as emergency recurring patients. They receive IVIG 4 to 5 times per year. This is used in around 10-15% of eligible patients.

- PLEX following IVIg

Used fairly infrequently in maintenance treatment so numbers are small.

- IVIg after PLEX

This is very rare and would only be used in seriously ill patients.

- Further PLEX after PLEX

PLEX access is variable across the NHS. It is common for PLEX patients to receive more than one round of treatment.

- corticosteroids and or non-steroidal immunosuppressants only after IVIg.

Clinicians would look to review disease response after IVIG and optimise clinical management to ensure appropriate immunosuppression. This may be limited to corticosteroids and or non-steroidal immunosuppressants only but could include rituximab, early access programmes and clinical trials.

- corticosteroids and or non-steroidal immunosuppressants only after PLEX

Clinicians would look to review disease response after PLEX and optimise clinical management to ensure appropriate immunosuppression.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	On behalf of **UCB**

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have no past or present links to, or funding from, the tobacco industry
Name of commentator person completing form:	Dr Maria Isabel Leite – Consultant Neurologist and Associate Professor

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.
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1: Has all of the relevant evidence been taken into account?	Most of the evidence has been taken into account, but there are aspects that could have been explored further; The subgroup of patients with **severe refractory** disease should have been distinguished from refractory disease overall. This is because those with severe refractory disease will have no opportunity to be treated with zilucoplan and, thus, their severe disease status will continue to lead to very significant burden on health services /NHS and to cause a unbearably negative impact on personal, family, social and economic aspects of the patients and communities. There must be a way of stratifying the recommendations according to the different levels of refractory disease. There are no studies **comparing zilucoplan with IVIG or PLEX**. However, Raise & Raise XT results demonstrate that patients on zilucoplan are able to wean off IVIG or PLEX successfully which constitutes indirect evidence that zilucoplan is more effective than IVIG or PLEX. Costs of years of treatment with IVIG or PLEX (plus respective admissions) for several years should be compared with that of zilucoplan treatment.
2: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	The summaries of clinical effectiveness seem reasonably interpreted. However, cost effectiveness appears to take into account standard of care as comparator of zilucoplan, when indeed the care of patients with severe refractory MG has extremely high costs (this includes standard of care and its multiple complications, treatment related to such complications, inability to work or complete education, regular treatment with IVIG or PLEX, hospital admissions that can last weeks to months, including in the ICU, ventilation and prolonged rehabilitation. All of us neurology experts have patients with such problems and "their real costs" are extremely high (e.g. 3-day PLEX course weekly for 2.5 years, or 2-day course of IVIG every 4-6 weeks for more than a decade, frequent admissions to the hospital, DVTs). For clarification, patients who do not respond to IVIG will be treated instead with the other modality (PLEX) and vice versa; great majority of these treatments swich from one to the other treatment modality; only a very small proportion of patients will have no benefit of both treatments; these will be left on standard therapy – including high dose steroids, which will appear to be of low cost, but these patients will be unable to work, will be admitted to the hospital frequently because disease deterioration and possibly be in ICU; together this constitutes and a very expansive management of a very severe refractory MG on standard treatment. Even those coping with regular IVIG or PLEX, if there are delays in these elective treatments, usually because logistic issues (no bed availability, shortage of staff, recurrent problems with supplies, either IVIG or more recently albumin for PLEX), often require admission with significant exacerbation or even myasthenia crisis, requiring ICU admission and ventilation, more treatments, more complications, and use of resources. In addition, other uncosted consequences to patients and families, and society. This means that even when patients are on regular IVIG or PLEX, there is no guarantee that patients will be always free of complications and need for unplanned acute admissions, which have high costs. According to the Zilucoplan treatment publications in the context of the clinical trials (RAISE and RAISE XT), in addition to the rapid efficacy of the treatment, its stable and sustained benefit is remarkable (during the day, day to day, and over the months and years; there are patients on zilucoplan for nearly 5 years). In addition, the treatment benefit allowed great majority of patients to stop IVIG and PLEX treatments and to wean off standard of care medication, which was not the primary intention of the trial as such, but, one of the very positive outcomes of the zilucoplan treatment. Zilucoplan allowed to improve patient care overall, and subsequently patient general health, and all that follows

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Draft guidance comments form

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	– i.e. return to (nearly or) normal life. The difference in costs during pre- and on zilucoplan must be very different, favouring zilucoplan treatment. This needs, of course, to take into account several aspects; (i) clearly identify full responders, good responders and those where the benefit was less good, maintain standard of care by preventing admissions; (ii) the above exercise would help to build up a predictive model of response to zilucoplan; (iii) have a clear plan to stop zilucoplan in patients with no response to this treatment for weeks; (iv) build a predictive model of achievement of remission in those where MG could have become in remission during the course of a very successful zilucoplan treatment. Disease complete remission is well recognised in gMG with AChR abs after a variable time period (usually years) following diagnosis and treatments, based on some patient or disease characteristics: e.g. age at onset, time to diagnosis, time to treatment initiation, thymectomy if indicated, thymus histology, response to immunotherapy. Disease remission may also be achieved by zilucoplan +/- another immunotherapy). Remission needs to be considered and explored in gMG patients that respond well to zilucoplan, and could be included in models of cost-effectiveness.
3. Are the recommendations sound and a suitable basis for guidance to the NHS?	We are very concerned that the current recommendations (no-recommendation of the zilucoplan) will have a very negative, and even devastating, effect on a subgroup of patients with severe refractory gMG with AChR abs. The no recommendation of zilucoplan will expand the demands of NHS resources If zilucoplan was recommended, the experts' guidance is for zilucoplan to be accessible and to be prescribed by experts only following detailed referrals, and in person clinical review of such patients by MG experts, followed by MDT discussions with at least two expert consultants. Close monitoring of safety and efficacy will be mandatory to identify and differentiate good responders from non-responders and promptly be able to implement treatment plans going forward (if no response, stop zilucoplan and recommend best alternative treatment, or if there is clear benefit, to continue and monitor long-term) Other recommendations should address consideration of weaning zilucoplan treatment in good responder patients thought to be in remission, as per section above.
4. 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	The current recommendation will discriminate, first of all, patients with severe and refractory disease against those with less severe disease. Secondly, even when the zilucoplan is recommended, in addition to the examples listed, (highlighting older patients and women of child bearing age or during pregnancy), there is great concern that patients living away from centres with MG experts will not have access to zilucoplan. This will be even more concerning in patients of lower social or economic classes. Therefore, education of patients and doctors will be crucial to ensure we avoid unlawful discrimination against patients that are geographically away from large centres.

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Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

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reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?	
5	
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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- 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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Draft guidance comments form

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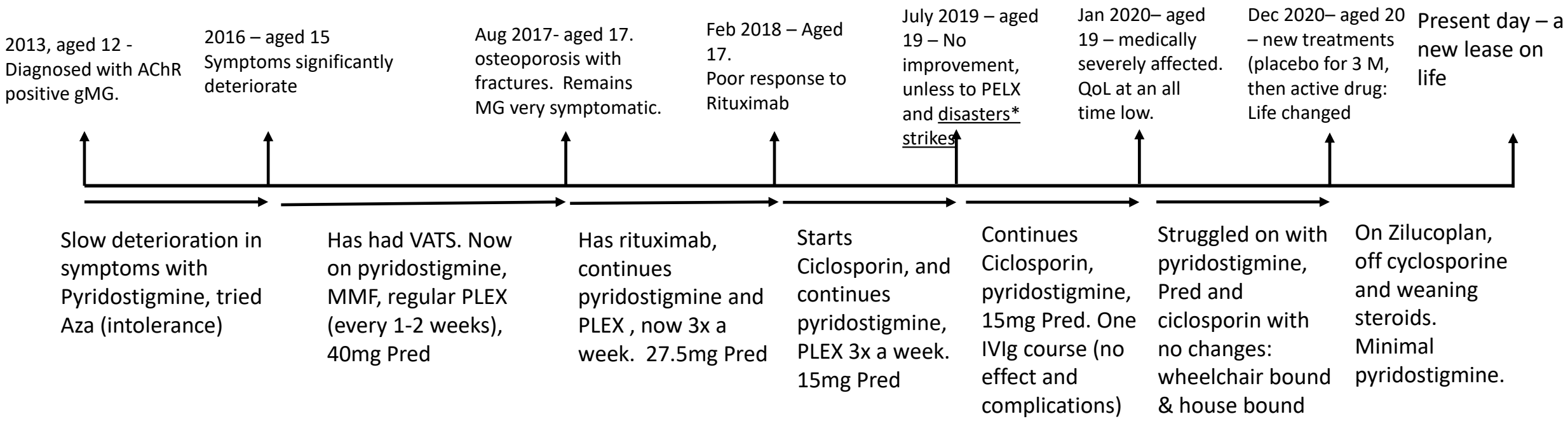
A clinical and chronological summary of a very severe refractory gMG with AChR abs



Disasters = 1. severe complication of long-term PLEX: suffered superior vena cava syndrome; 2. acute bleeding to Hb 4.0
(both events were life-threatening)

PLEX regularly (x3 a week) for 3 years, very effective. Stopped because of life-threatening complication; left anticoagulated, which led to a second life-threatening event. IVIG not effective and complicated with aseptic meningitis. Eventually left house bound and wheelchair bound; completely dependent on parents for basic ADL.

Complications of steroids included bone fractures aged 17. Complications of cyclosporine included high blood pressure and mild renal problems aged 20.

NICE National Institute for Health and Care Excellence

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments the end of 5 December 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):	

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Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments the end of 5 December 2024. Please submit via NICE Docs.

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.	Nothing to disclose.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose.
Name of commentator person completing form:	Gary Mahon (patient expert).

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	I am concerned that the committee is requiring an amount of detail for its analysis that just does not currently exist for gMG patients due to the rarity of the disease and the wide range of disease manifestations in individuals and the associated range of treatment options in use. This in part

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Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

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	may explain why none of zilucoplan, efgartigimod or rozanolixizumab have received NICE approval. Meanwhile there is an unmet patient need that is being delayed and/or denied.
2	The clinical experts highlighted that the treatments currently offered to refractory gMG patients needing IVIg or PLEX are highly variable across the NHS. Because Zilucoplan is self-administered it offers the possibility of all patients receiving an effective treatment option regardless of their local NHS constraints and/or proximity to appropriate centres. I don't think this patient perspective has been given sufficient prominence.
3	
4	
5	
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 funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- 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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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.

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Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments the end of 5 December 2024. Please submit via NICE Docs.

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Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Comments on the draft guidance received through the NICE website

Role	
Other role	
Organisation	
Location	
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

I think it's difficult for all of the evidence to be unearthed. Examples include emergency admissions for acute MG exacerbations, 'hidden maintenance IVIg' ie repeated doses of IVIg that appear to be given for emergencies but in fact are required so often that it may as well be regular and the real harm (and cost) caused by high dose steroids.

The MG guidelines are being written currently - it is the opinion of the MG specialists that drugs such as Zilucoplan should be only available in specialist centres in patients who are not responding to standard of care and who otherwise would need IVIg or PLEX. This patient group would otherwise be liable to unplanned admissions, repeated IVIg and PLEX treatments and potentially, ICU admission.
Moreover it is the opinion of the MG specialists that patients with active disease despite SoC should be discussed in an MDT.
This approach will limit the use of these drugs which should be reserved for a select group of patients.

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

As above I think that the cost of unplanned admissions and the cost of should be emphasised more.
Reducing the need for unplanned admissions due to better control of refractory MG would have knock on effects in terms of bed days, morbidities (eg nosocomial infections), IVIg cost etc. Furthermore the ability to self administer the drug would improve access - day care beds are costly and scarce

Are the recommendations sound and a suitable basis for guidance to the NHS?

I believe that not recommending targeted therapies such as Zilucoplan places NHS patients at a significant disadvantage to our European neighbours.

It would mean that the small minority of patients with active disease despite SoC treatment are more at risk of acute deteriorations with resultant morbidity and mortality.

It would mean that care is more likely to have to be delivered in hospital rather than the community.

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?

Patients with certain religious beliefs may not be able to access IVIg /PLEX due to contraindication to blood products but they would be able to access complement inhibitor treatment

Role	
Other role	
Organisation	Nottingham University Hospital NHS Trust
Location	
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

It would be useful to look at the real world data for efgartigimod from the UK or other countries and see how many people failed rituximab who would then potentially need to go on to IVIG or PLEX

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

Cost effectiveness needs to be measured against times/resources for equivalents eg PLEX and IVIG if the drug is to be positioned where standard care has failed eg NSIMs (up to rituximab) and steroids and pyridostigmine

Are the recommendations sound and a suitable basis for guidance to the NHS?

I think recognising the challenges faced by patients with treatable but rare diseases is key to the guidance

Role	
Other role	
Organisation	
Location	
Notes	
Comments on the DG:	
This has really helped one of our patients who was admitted on ITU and intubated due to myasthenic crisis. Now since she is on this drug, she has been able to go swimming exercises which she has never done before having treatment. *Has all of the relevant evidence been taken into account?* We always double check the eligibility criteria before we discuss this as a treatment option.	

University of Southampton

SHTAC

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

Zilucoplan for treating generalised myasthenia gravis (ID 4008)

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

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Fay Chinnery, Research Fellow, Health Economics Neelam Kalita, Senior Research Fellow, Health Economics Lois Woods, Senior Research Assistant, Evidence Synthesis and Information Specialist 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	20th January 2025

[redacted]

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LIST OF ABBREVIATIONS

ACD	Appraisal Committee Decision
ACM	Appraisal Committee Meeting
ACM1	First ACM of this technology appraisal (9th May 2024)
ACM2	Second ACM of this technology appraisal (9th October 2024)
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
gMG	Generalised myasthenia gravis
HCRU	Healthcare resource use
ICER	Incremental cost-effectiveness ratio
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	Minimum symptom expression
NMA	Network meta-analysis
NHSE	NHS England
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 (DGD2), issued 7th November 2024, following the second NICE Advisory Committee Meeting (October 2024) for the technology appraisal of zilucoplan for treating generalised myasthenia gravis (ID4008). The EAG received the company's response documents and the revised economic model on 6th December 2024.

We submitted our clarification questions for the company to NICE on 12th December 2024. NICE added questions A2 and A5. A partial response from the company was received on 30th December 2024; the remaining parts – the updated model and its accompanying technical report – were received on 6th January 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
ID4008 Zilucoplan CEM DGD2 results 051124	Company Results Document
ID4008 Zilucoplan expert interviews for ACM3_Q4_2024_report_v2_05Dec2024	Company Expert Interviews Report
ID4008 Zilucoplan – 11177_SLR in MG_Clinical update_25OCT2024	Company SLR Report
ID4008 Zilucoplan – Bivariate Bayesian Network Meta_Short Report for ZLP_v3.0_05Dec2024	Company NMA Report
ID4008 Zilucoplan – DG comments form_draft 6_5th December 24	Company Response Form
ID4008 Zilucoplan CEM 05.12.2024	Company revised model
NMA, network meta-analysis; SLR, systematic literature review	

NICE's second Draft Guidance provides a series of NICE Committee requests and recommendations, which can be divided into five issues relating to the decision problem and clinical effectiveness evidence and five issues relating to the economic analysis, as summarised in Table 2 below.

In this report we present the following:

- A summary overview of the company's response and key points of the EAG critique (Table 2)
- 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 Committee's preferred assumptions and recommendations in the Draft Guidance Document (DGD2) and the company's responses to these

NICE Committee's preferred assumptions and recommendations in DGD2		Summary of the company's response	EAG comments
1. Clarification on the target population for zilucoplan	The NICE Committee was concerned about restricting the refractory target population so that access to zilucoplan would only be possible if people with refractory gMG had exhausted all prior treatment options. It noted the very small sample size of the EAMS cohort. The Committee would like the company to clarify the target population for zilucoplan and provide further evidence and rationale to support its preference for a revised EAMS cohort to inform its preferred basket of refractory standard care (DGD2 sections 3.6, 3.32).	The company clarified on page 5 of their Response Form that the target population for zilucoplan is as stated in their CS Decision Problem. The company changed the wording of the first criterion of the target population to be more specific, requiring patients to have had 2 or more NSISTs and adequate corticosteroid treatment (Clarification Response A2). For the company's response about the EAMS cohort see also point (4) below.	The wording of the company's target population on page 5 of their Response Form differs from that in their CS Decision Problem (CS Table 1), as their current definition omits patients who are contraindicated to systemic therapies. However, the company clarified that this was not their intention (Clarification Response A1). They reiterated that patients contra-indicated to systemic treatments are included (Clarification Response 2). The wording around prior NSISTs and corticosteroid treatment has changed (Clarification Response A2) which is relevant to the interpretation refractory patients in the EAMS cohort. See section 2.1 below.
2. Updated indirect treatment comparison	The NICE Committee requested (DGD2 sections 3.10, 3.11, 3.32) that the company provide an indirect treatment comparison that: (a) uses data from more of the identified studies	The company conducted three sets of NMAs (baseline risk-adjusted, bivariate, two-stage) which use more data from existing studies and include new studies than had been considered in their response to the first NICE Draft Guidance (Company NMA Report; Company Response Form pages 6 to 11).	For specific details see points (b) to (f) below

NICE Committee's preferred assumptions and recommendations in DGD2		Summary of the company's response	EAG comments
		Further details of these NMAs are in points (b) to (f) below. The NMAs were supported by an updated systematic literature review (SLR) designed to identify further IVIg and PLEX evidence (Company SLR Report; Company Response Form page 5).	
	(b) includes IVIg and PLEX	The company provided bivariate NMAs that enabled missing MG-ADL outcomes to be predicted from QMG outcomes, thereby maximising the available relevant outcomes (and hence comparators) that could be included in the analysis. The bivariate NMAs were conducted under two scenarios, (i) based on RCTs, and (ii) based on RCTs plus non-randomised studies. The RCT-only bivariate NMAs included six RCTs that could not have been included in a conventional NMA due to incomplete reporting of MG-ADL or QMG response data. The RCT plus non-RCT NMAs included one such study.	The EAG have been unable to validate the company's bivariate NMAs (see section 2.2.4). These NMAs inform the base case of the company's economic analysis which is therefore uncertain. The company have included four studies in the NMAs which had not previously been included in the CS or the company's analyses following the first Advisory Committee Meeting. The EAG disagree with the inclusion of three of these studies but exclusion of these would likely be inconsequential (see section 2.2.5). The company have not reported all sensitivity analyses stated in the Methods section of their NMA Report (see section 2.2.6). The NMAs on MG-ADL response used a 3-point threshold except for one study which had a 2-point threshold but did not explore the implications of this (see section 2.2.6). Results of the bivariate NMAs have very wide credible intervals and none of the active treatment

NICE Committee's preferred assumptions and recommendations in DGD2		Summary of the company's response	EAG comments
			comparisons against placebo are statistically significant (see section 2.2.7).
	(c) considers outcomes other than MG-ADL response rate to produce estimates of relative effectiveness	The company's NMAs report results only for the MG-ADL response and MG-ADL change from baseline (the latter does not inform the economic model). QMG response and QMG change from baseline are included as inputs in the bivariate NMAs to enable estimation of MG-ADL response and change from baseline outcomes from studies that could not otherwise have been included in the analysis (Company NMA Report; Company Response Form pages 7 to 11).	Although the study selection process in the company's updated SLR is unclear in places we believe the SLR has identified all relevant studies that reported MG-ADL and/or QMG outcomes (section 2.2.1) and the company have included these in their bivariate NMAs where feasible. We therefore agree that the company have considered the relevant outcomes.
	(d) accounts and adjusts for the differential placebo response and baseline population heterogeneity observed in the trials	The company conducted baseline risk-adjusted NMAs to adjust for placebo response heterogeneity and baseline population heterogeneity in the studies. These NMAs do not directly inform the economic analysis but inform a two-stage NMA approach that combines both the baseline risk-adjusted NMAs and bivariate NMAs to (i) allow the placebo response heterogeneity to be adjusted for whilst (ii) maximising the clinical outcomes that can be included in the NMAs.	The company's two-stage NMA approach is new for this response to NICE's second Draft Guidance. This approach optimally addresses NICE's requests in DGD2 since both (i) placebo response heterogeneity is adjusted for and (ii) studies that report QMG outcomes but not MG-ADL outcomes have been included in the analysis to increase the available outcomes and hence comparators that can be analysed. However, note that as the EAG could not validate the bivariate NMAs and these have very wide credible intervals this renders the two-stage NMA approach results uncertain.

NICE Committee's preferred assumptions and recommendations in DGD2		Summary of the company's response	EAG comments
	(e) explores linking the networks by using IVIg as the common comparator to include PLEX	The company have included the Barth 2011 RCT (PLEX versus IVIg) in the bivariate NMA networks for the QMG response and QMG change from baseline outcomes to add PLEX as a comparator, linking to the network via the IVIg node. The company have also linked two further studies (Duan 2023 and Leng 2024) to the PLEX node of the Barth 2011 RCT (Company NMA Report Figures 1 and 2). The company connected a further study (Barnett 2027) to the placebo and IVIg nodes of the MG-ADL response and MG-ADL change from baseline networks which strengthens the existing IVIg versus placebo comparison in the networks but does not add any new comparators (Company NMA Report Figures 1 and 3).	We agree with the addition of the Barth 2011 RCT to the networks, which enables PLEX to be included as a comparator in the bivariate NMAs for the first time. However, the Duan 2023 and Leng 2024 studies do not form logical connections to the network and do not add any further relevant comparators (see section 2.2.5). We note that the Barnett study has key uncertainties and may not be appropriate for inclusion in the networks (see also section 2.2.5). Overall, given the limitations of the Duan, Leng, and Barnett studies, the main difference of the current analysis from the networks that were provided in response to NICE's first Draft Guidance lies in the addition of the PLEX comparator provided by the Barth 2011 RCT.
	(f) respects randomisation	For the clinical effectiveness inputs to economic analysis the company use response rates from the NMAs for each treatment instead of the odds ratios for each treatment versus placebo which had informed previous versions of the economic analysis.	As noted in section 2.2.4, response rates from the NMAs are used directly in the economic analysis instead of being adjusted via relative risks by a referent placebo response calculation. The EAG agrees that this appropriately respects randomisation (as the response rates are derived directly from the NMAs) and in the two-stage

NICE Committee's preferred assumptions and recommendations in DGD2		Summary of the company's response	EAG comments
			NMA (but not the bivariate NMA) heterogeneity of placebo responses is adjusted for.
3. Statistical code for the analyses conducted	The NICE Committee requested that the company provide statistical codes for the NMAs for verification (DGD2 section 3.32).	The company have provided WinBUGS code for their NMAs.	The EAG was able to validate the baseline risk-adjusted NMAs using the company's code but could not validate the bivariate NMAs (see section 2.2.4 below).
4. Justification of the revised EAMS cohort to inform the target population	The NICE Committee requested information and justification on the company's use of a revised EAMS cohort to inform its preferred refractory standard of care treatments (DGD2 section 3.32).	The company provided a summary justification and description of the revised EAMS cohort used in the economic analysis (Company Response Form pages 11 to 13). As part of the company's expert elicitation exercise, to help interpret the EAMs cohort they asked four clinical experts whether a definition of refractory should exclude (i) patients receiving no treatment and (ii) patients receiving corticosteroids but not non-steroidal immuno-suppressants (NSISTs). (Company Expert Interviews Report; Clarification Response A16). Further discussion of the EAMS cohort in relation to the target population is provided in Clarification Responses A3, A4 and A5.	The company's revised EAMS cohort subgroup (N=37) requires assumptions to be made about the characteristics of patients included in the EAMS cohort and implies that a refractory subgroup can be more precisely defined than the granularity of data reported from the EAMS appears to allow. The company's admission that there is no consistent and precise definition of refractory gMG available is at odds with their attempt to define one within the EAMS cohort. As explained in section 2.3 below, the EAG believe that the full EAMS cohort (N=48) is more likely to reflect the population of refractory gMG patients in clinical practice where guidance on the refractory definition is lacking. We note that the full EAMS cohort more closely aligns with the NICE Committee's interpretation of the refractory population in the first NICE Draft Guidance.

NICE Committee's preferred assumptions and recommendations in DGD2		Summary of the company's response	EAG comments
5. Justification for using minimum symptom expression (MSE)	The NICE Committee requested that the company provide the following (DGD2 section 3.32): (a) Information on sources of MSE data and how MSE was implemented in the model, particularly its effect on transition probabilities MSE on zilucoplan.	The company stated that the proportion of patients achieving MSE governed the distribution of patients responding to their initial treatment in the 'continued response' (i.e., MSE), 'loss of response' and 'stable response' health states in their model (Company Response Form (pages 19-20). These proportions inform the transition probabilities for each treatment, which apply until the response assessment timepoint. Furthermore, these health states are associated with utility values (discussed in section 2.5.2); those who respond to treatment and achieve MSE accrue more QALYs.	We view the company's explanation on how MSE is implemented within their model is reasonable.
	(b) Additional information on the estimation of the proportion of people on zilucoplan reaching MSE.	In the company's revised base case, the proportion of patients achieving MSE on zilucoplan is estimated from RAISE-XT; those on IVIg, PLEX and SoC (excluding IVIg and PLEX) were obtained as averages taken from their expert interviews. The company assumed [redacted] of patients in the comparator basket achieve MSE. No further details and justification are provided regarding the proportions of patients achieving minimum symptom	We are uncertain whether using the MSE proportions for estimating continued response is appropriate as the data are heavily reliant on clinical expert estimates for IVIg and PLEX. We disagree with the proportion of patients achieving MSE in the comparator basket, because the company's approach does not account for patients receiving IVIg and PLEX, and the associated benefit of these treatments. There is uncertainty regarding the source of utilities associated with the continued/stable/loss of response health states; the company do not
	(c) Further details and justification for the company's assumptions on the proportion of people reaching MSE on IVIg and PLEX.		
	(d) Further details and justification for the company's assumptions on the proportion of people on		

NICE Committee's preferred assumptions and recommendations in DGD2		Summary of the company's response	EAG comments
	refractory standard of care treatment reaching MSE in the model.	expression and how long minimum symptom expression persists once it is achieved. The company stated that this was due to lack of any further information beyond what they had already provided at ACM2.	describe the source of these utilities. Lastly, there is currently no further evidence available to show that minimum symptom expression endures over the lifetime of the economic model.
	(e) Evidence of the proportion of people in the RAISE trial placebo arm reaching MSE.		
	(f) Further details and justification for MSE enduring through the lifetime of the economic model.		
6. Additional information and modelling of subsequent treatments	The NICE Committee requested (DGD2 section 3.32): (a) Modelling of subsequent treatments that includes both the costs and benefits associated with subsequent treatment.	The company describe their approach to modelling subsequent treatment in Company Response Form pages 20-25.	We consider the company's modelling approach to be reasonable.
	(b) Information on the routine practice for subsequent treatment in the NHS.	The company provided information on subsequent treatment following each initial treatment based on four clinical experts' opinions (Company Response Form Table 3, Table 4 and Table 5). However, there was no consensus regarding the proportions of patients receiving subsequent treatment when they switch treatment e.g. IVIg to PLEX or vice versa, and that there is a wide range	For the comparator basket, we disagree with the company's estimates of the proportions of patients switching from IVIg to PLEX and vice versa in subsequent treatment. For our base case, we use the lowest company clinical expert estimate of these proportions: [redacted] from IVIg to
	(c) Analysis on the proportions of people with refractory gMG who have: • IVIg after IVIg • PLEX after IVIg		

NICE Committee's preferred assumptions and recommendations in DGD2		Summary of the company's response	EAG comments
	• IVIg after PLEX • PLEX after PLEX • Corticosteroids and NSISTSs only after IVIg • Corticosteroids and NSISTSs only after PLEX (DGD2 section 3.14)	in estimates when switching between IVIg and PLEX.	PLEX and [redacted] from PLEX to IVIg. The model is very sensitive to changing these estimates. For the zilucoplan arm, the EAG view that the proportions of patients receiving IVIg and PLEX as subsequent treatment following zilucoplan should be the same as the proportions of patients receiving IVIg and PLEX initially in the comparator basket, because the comparator basket is then applied consistently in both arms.
7. Revised treatment response rates for PLEX based on NMAs, accounting for heterogeneity of placebo responses and baseline characteristics	The NICE Committee would prefer response rates to be based on clinical data rather than expert opinion. The committee asked the company to provide more analyses to clarify this (DGD2 sections 3.15, 3.16, 3.32): (a) Revised response rates informed by NMAs that explore the inclusion of studies on PLEX (including Barth et al.)	As stated in point (2) above, the company conducted three sets of NMAs, in addition to their conventional NMA: a bivariate NMA, a baseline risk-adjusted NMA and a two-stage NMA approach (baseline risk-adjusted NMA plus bivariate NMA). For their base case, the company use the bivariate NMA and conduct scenario analysis using the two-stage NMA (Company Response Form pages 5–11).	Methodologically, the two-stage NMA aligns most closely with the NICE committee's request from ACM2. Therefore, the EAG use this in our base case, although there are uncertainties with both the bivariate and two-stage NMA approaches as noted above.
	(b) The revised NMAs should be adjusted for placebo response and baseline population heterogeneities across studies.		

NICE Committee's preferred assumptions and recommendations in DGD2		Summary of the company's response	EAG comments
8. Analysis of utility decrements for IVIg and PLEX	The NICE Committee concluded that, if appropriate to include, this uncaptured benefit should be incorporated as a utility decrement for IVIg and PLEX, rather than a utility increment for zilucoplan. (DGD2 section 3.21).	The company's revised base case applied a utility decrement associated with IVIg and PLEX based on a Canadian study (Johnston et al.) on haemophilia A (Company Response Form pages 25-26).	The company do not provide evidence showing that haemophilia A is an appropriate proxy for gMG and they do not explain how the disutilities in the revised model were calculated from Johnston et al. We exclude these decrements from the EAG base case.
9. Updated analysis of corticosteroid costs	The committee concluded that it would like to see the corticosteroid costs from the Lee et al. study (DGD2 section 3.24).	In their revised base case, the company used the study by Stirnadel-Farrant et al.[1] for the costs of corticosteroids (Company Response Form pages 26-27). They conducted a scenario analysis using the study by Lee et al.	In our revised EAG base case, we use the NICE committee's (efgartigimod submission) preferred source for corticosteroid costs (Lee et al.(2018) [2]) and add costs for corticosteroid management for patients achieving minimum symptom expression in the zilucoplan arm.
10. Scenario analysis of time on treatment assumptions	The committee concluded it would like the company to provide scenario analyses that explore a range of time on treatment assumptions for zilucoplan and treatments in the 'basket' of standard care (DGD2 sections 3.18, 3.32).	The company stated that the treatment stopping rule was included in error in the version of their model used at ACM2 (Company Response Form page 28). In their response to EAG Clarification Question B3, the company conducted scenarios using the transition probability to the 'loss of response' health state as a proxy to model zilucoplan time on treatment.	The EAG are uncertain if the company's estimated time on treatment of [redacted], [redacted] and [redacted] months for zilucoplan, IVIg and PLEX reflect clinical practice. While we consider their proxy approach (submitted as part of Clarification Response B3) to modelling time on treatment to be reasonable, further expert opinion concerning time to treatment discontinuation for each of the treatments is warranted.

NICE Committee's preferred assumptions and recommendations in DGD2	Summary of the company's response	EAG comments
ACM2, Second Appraisal Committee Meeting; CFB, change from baseline; DGD1, Draft Guidance Document in response to the first Advisory Committee Meeting; DGD2, Draft Guidance Document in response to the second Advisory Committee Meeting; EAMS, efgartigimod Early Access to Medicines Scheme; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; LPE, lymphoplasmapheresis; MG-ADL, myasthenia gravis Activities of Daily Living score; MSE, minimum symptom expression; NMA, network meta-analysis; NSIST, non-steroidal immunosuppressant therapy; PAIA, protein A immunoadsorption; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis score.		

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

2.1 Decision problem: Clarification of the target population for zilucoplan

NICE's second Draft Guidance concluded that the target population defined in the company submission was similar to the population that would have zilucoplan in the NHS, but the definition of refractory was uncertain (DGD2 section 3.3). The NICE Committee requested the company to clarify the target population for zilucoplan (DGD2 section 3.6).

The company state in their response to DGD2 that the target population is as stated in the company submission (Company response form page 5):

- patients with anti-acetylcholine receptor antibody-positive generalised myasthenia gravis whose condition is uncontrolled despite receiving standard of care (SoC) treatment, and
- who are being considered for, or treated with, intravenous immunoglobulin (IVIg) or plasma exchange (PLEX).

The company's statement in their response is different to the decision problem population in the original submission (CS section B.1.1) because it omitted people for whom systemic treatments (i.e. standard of care treatments) are contraindicated or not tolerated. However, the company clarified that omitting these people was an error (Clarification Response A1) and reinstated them in Clarification Response A2, so for this aspect the company's current definition of the target population is the same as in their original submission. The company confirmed in Clarification Response A2 that a patient needs to meet all three of the following decision problem criteria to be eligible for zilucoplan:

- the disease has not responded to adequate treatment with steroids and at least 2 non-steroidal immunosuppressants or these options are contraindicated or not tolerated, and
- the disease is uncontrolled, as defined by a MG-ADL score of ≥6 or a QMG score of ≥12, and
- an additional therapy such as IVIg or PLEX is being considered, or patients are being treated chronically with IVIg/PLEX

This target population matches the wording of the target population in the original submission (CS Table 1), except that the company have re-worded the first bullet point. For reference, both versions of the first bullet point are in **Table 3** below:

Table 3 First criterion for eligibility for treatment with zilucoplan

Clarification response A2 (DG2 response)	**CS Table 1 (original decision problem)**
• the disease has not responded to adequate treatment with steroids and at least 2 non-steroidal immunosuppressants or these options are contraindicated or not tolerated, and	• the disease has not responded to other systemic treatments, including pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate and ciclosporin, or these options are contraindicated or not tolerated, and

The company argue this is not a change to the target population but makes it more specific and aligns with UK practice since patients are likely to have tried at least two NSISTs, unless contraindicated or not tolerated, before being treated with or considered for regular IVIg or PLEX.

The EAG believe that since there is no established definition of refractory in any MG treatment guidelines, and that as definitions vary in the scientific literature (and varied across the studies included in the company's NMAs), either worded version describes refractory legitimately. However, the more recent change to the wording may be more specifically aligned with the company's interpretation of the efgartigimod Early Access to Medicines Scheme (EAMS) cohort study publication[3] to support use of a narrower EAMS cohort for the population in the company's economic model (see also section 2.3 below). We note that the nature of data collection and reporting in the EAMS cohort[3] is open to subjectivity of interpretation. The company have had to make assumptions about patients in the cohort and they acknowledge that it is challenging to determine which patients in the EAMS cohort would meet the eligibility criteria for treatment with zilucoplan (Clarification Responses A3 and A4). Despite the lack of consistency in how refractory is defined, the company attempt to identify a specific refractory subgroup within the EAMS cohort. The EAG accept that not all patients in the EAMS cohort would necessarily meet criteria for being refractory, but the company subgroup reduces the already small sample size to just 37 patients and we question whether applying a specific definition of refractory to this small cohort is reasonable. We suggest that the overall EAMS cohort (N=48) would approximate of the

heterogeneous population of patients who are classified as having refractory gMG in clinical practice. Given the uncertainty around which population group is most appropriate to reflect refractory gMG we use the overall EAMS cohort in our economic analysis base case (see section 4.1) and the more specific company-defined refractory subgroup in scenario analysis (see section 4.2).

2.2 Clinical effectiveness: Updated indirect treatment comparison

The company state that they conducted three sets of NMAs, each for MG-ADL response and MG-ADL change from baseline (CFB) outcomes (in addition to their 'conventional' NMA which they provided for comparison):

- Bivariate NMAs to enable more outcomes and studies, and hence treatments, to be included in the analysis. This method can impute missing data for a given outcome (i.e. MG-ADL response, or CFB) by using corresponding data from an alternative outcome (i.e. QMG response, or CFB) if the correlation between the two outcomes is known. For the company's bivariate NMA the MG-ADL / QMG correlation coefficients for the response and CFB outcomes were obtained using individual patient data from the RAISE trial. The company had already provided bivariate NMAs for these outcomes in their response to NICE's first Draft Guidance. The present bivariate NMAs include four additional studies on IVIg or PLEX identified in the company's updated systematic literature review (Barth et al. 2011,[4] Barnett et al. 2017,[5] Duan et al. 2023,[6] Leng et al. 2024 [7]). The bivariate NMAs inform the company's economic model base case.

- Baseline risk-adjusted NMAs to adjust for heterogeneity across the included studies, including any heterogeneity in placebo responses. The company state that this approach has not been included in their economic analysis because it did not include PLEX in the network.

- A two-stage analysis comprising a baseline-risk adjusted NMA followed by a bivariate NMA. In this analysis the placebo response rate and precision outputs from the baseline risk-adjusted NMA served as inputs to the bivariate NMA. This two-stage approach therefore addresses key recommendations of the NICE Committee in their second Draft Guidance (see Table 2 above), since both (i) placebo response heterogeneity and (ii) all relevant studies for the IVIg and PLEX comparators are considered. The two-stage NMA informs a scenario analysis in the company's economic model.

2.2.1 Study selection for NMAs: Company's updated SLR

The company state on page 5 of their Response Form that their September 2024 systematic literature review (SLR) update identified 11 studies of IVIg and PLEX, of which three were randomised controlled trials (RCTs) and eight were observational studies, but these studies are not listed in the Response Form. The company did provide a list of 11 studies in Clarification Response A11 but the observational studies within this do not fully match those listed in Table 5 of the company's SLR Report.

Instead, the company's Response Form lists six studies, comprising three randomised controlled trials (RCTs) and three observational studies (see Table 4 below) which were included in the updated NMA analyses (Company Response Form page 6), although we note that three of these studies had been identified and included in company analyses previously.

The company state that "feasibility assessment was not carried out since this was a sensitivity analysis to support the previously conducted RCT NMAs" (Clarification Response A11) and that "clinical heterogeneity was not assessed for the current sensitivity analysis" (Clarification Response A7). To be eligible for consideration non-RCTs only had to (1) be connectable to the network and (2) report relevant MG-ADL or QMG outcomes (Clarification Response A11). The EAG disagree with the company's rationale for not conducting a feasibility assessment, since an appropriate degree of homogeneity of the study characteristics is a requirement of any NMA. We also note that the company have not reported any critical appraisal of the newly-identified studies (see section 2.2.2 below).

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

Study	Outcomes	Comparators	NMAs study assigned to
Barth 2011 [4] (RCT, Canada)	● QMG response ● QMG CFB	● IVIg (N=41) ● PLEX (N=43)	● Bivariate (study included previously) [a]
Zinman 2007 [8] (RCT, Canada)	● QMG CFB	● IVIg (N=24) ● Placebo (N=27)	● Bivariate (study included previously)
NCT02473952 [9] (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 [5] (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 [6] (Retrospective non-RCT, China)	● QMG response ● QMG CFB	● PLEX (N=62) ● LPE (N=62)	● Bivariate (new study)
Leng 2024 [7] (Retrospective non-RCT, China)	● QMG CFB	● PLEX (N=3) ● 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 et al. 2011 [4] informed the company's economic analysis previously but was not previously included in any NMAs.
[b] 25 centres across Europe, Canada and the United States, none in UK.[9]
[c] Response determined by improvement in MG-ADL score of ≥2 points; other studies used improvement in MG-ADL score ≥3 points.
[d] Treatments not separable but the company assigned this group to the IVIg node of the evidence network (Clarification Response A14).
[e] The control arm was not used because relevant outcome data was not reported for this group (Clarification Response A14).

Although the selection process for excluding several of the 11 studies mentioned by the company is not clear and we disagree with the company's superficial eligibility screening process, we have checked the 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 matching-adjusted indirect comparison, MAIC), for PLEX and IVIg has likely been included.

In summary, the updated NMAs provided by the company include four new studies. One had been previously identified but had not been included in any NMAs (Barth et al. 2011 [4]) while three are newly-identified studies (Barnett et al. 2017,[5] Duan et al. 2023,[6] Leng et al. 2024[7]). The remaining two studies from the list of six had been included in previous company NMAs (NCT02473952, [9] Zinman et al. 2007 [8]). The NMAs that these studies inform are shown in Table 4 above.

As explained further below (section 2.2.5) the EAG disagree with the inclusion of the studies by Barnett et al. 2017,[5] Duan et al. 2023,[6] Leng et al. 2024[7]) for methodological reasons.

EAG conclusion

The company's process for selecting studies is not transparent but we checked the company's searches and overall review methods in their updated SLR and do not

believe any relevant studies (RCTs or observational studies) that could be included in NMAs have been missed. We did not identify any single-cohort studies of PLEX or IVIg within the company's SLR results that would be suitable for MAIC analysis.

2.2.2 Risk of bias and generalisability of studies included in the NMAs

The company SLR Report mentions that a mix of prospective and retrospective studies was included among the identified observational studies, but does not identify the design of each study. According to the study publications of the included observational studies (summarised in Table 4 above):

- Barnett et al. 2017 [5] was a Canadian prospective study which recruited patients at one centre between June 2014 and June 2016. The company did not use the control group in the NMA because the study does not report outcome data for this group (Clarification Response A14). The company regard the prednisone group as a placebo group in the evidence network (Clarification Response A14), 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). 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 et al. 2023 [6] 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.
- Leng et al. 2024 [7] 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 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.

The NMA Report 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 NHS (although the Canadian study by Barth et al. 2011 [4] previously informed the economic analysis in the absence of more relevant data).

The company state in Clarification Response A11 that "The inclusion of non-RCTs with RCTs itself may introduce bias due to differences in the study design". However, the company's Response Form and NMA Report do not discuss any potential sources of bias in the newly included studies and do not mention any risk of bias or quality assessments.

Section 4.3 in the company SLR Report does briefly mention that the Effective Public Health Practice Project (EPHPP) checklist (no reference provided) was used to assess the methodological quality of the observational studies. However, only summary results across all the included studies are provided, and it is unclear which studies were included in the assessment (SLR Report Figure 5). No risk of bias assessments have been provided for individual non-randomised studies in any of the company's documents.

Given the substantial limitations of the studies by Barnett 2017,[5] Duan 2023,[6] and Leng 2024 [7] already noted above, the EAG has not further investigated risks of bias in these studies. Risks of bias in the remaining studies, Barth 2011, [4] NCT02473952,[9] and Zinman 2007,[8] are reported in SLR Report Table 11 and have been discussed previously, alongside those of the other studies included in the NMAs (EAG Report sections 3.3.4, 4.2.6.1, and EAG Report Table 18).

EAG conclusion

The company have not reported any risk of bias or generalisability assessments for the studies included in their updated NMAs. We have noted a range of limitations of these studies.

2.2.3 NMA heterogeneity assessment

The company tabulated the characteristics of four of the six newly included studies – three observational studies and the Barth 2011 RCT [4] – in Clarification Response A6. The company have narratively summarised the baseline characteristics of the studies but do not mention whether any of the differences in baseline characteristics between studies would have implications for the between-study heterogeneity in the NMAs when these studies are added to the networks. Almost no baseline data is available for the Leng 2024 study

(Clarification Response Table 1) since the study covered several medical conditions and the MG population in the study was only a very small subgroup.

EAG conclusion

The company have not assessed the impact of including new studies on the between-study heterogeneity in their updated NMAs.

2.2.4 NMA statistical approach and validation

Each of the company's NMAs followed a Bayesian framework and was based on a random-effects model (NMA Report section 2) which the EAG agree is appropriate. The company provided the WinBUGS code and the EAG was able to validate the company's baseline risk-adjusted NMA, with some slight differences in the MG-ADL response rates between the EAG and company results which may reflect inherent uncertainty in the analysis (Table 5).

Table 5 MG-ADL response rates for the company baseline risk-adjusted NMA (RCTs plus non-RCTs)

Therapy	Response rate (95% CrI) (common covariate model)	
	Company [a]	EAG
Placebo	[redacted]	[redacted]
Zilucoplan	[redacted]	[redacted]
Rozanolixizumab 7mg [b]	[redacted]	[redacted]
Rozanolixizumab [b]	[redacted]	[redacted]
Efgartigimod [b]	[redacted]	[redacted]
Eculizumab [b]	[redacted]	[redacted]
Ravulizumab [b]	[redacted]	[redacted]
IVIg	[redacted]	[redacted]
PLEX	No data	No data

CrI, credible interval; IVIg, intravenous immunoglobulin; PLEX, plasma exchange.
[a] From EAG Report Table 6.
[b] Therapies not of current relevance to the technology appraisal are included here to illustrate validation of the overall NMA.

Although the company's statistical approach for the bivariate NMAs appears broadly appropriate, there are some differences in the company's statistical code from those recommended in the NICE Decision Support Unit Technical Support Document. The EAG was unable to validate the bivariate NMAs, and hence also the 2-stage NMAs which they inform, within the time available for this critique. This means that we are more confident in

the baseline risk-adjusted NMA results than we are in the results of the two-stage NMAs. This has implications for confidence in the company's economic analysis since the company's base case analysis utilises the bivariate NMA results whilst the two-stage NMA results, which also depend on the bivariate NMAs, inform a model scenario. Moreover, the credible intervals of the two-stage NMA results are very wide, with no statistically significant differences evident between each of the active comparators and placebo (see section 2.2.7 below).

Response rates from the NMAs are used directly in the economic analysis instead of being adjusted via relative risks by a referent placebo response calculation as they were in the company's previous response to the first NICE Draft Guidance. The EAG agrees that this appropriately respects randomisation (as the response rates are derived directly from the NMAs).

EAG conclusion

The EAG validated the company's baseline risk-adjusted NMA for the MG-ADL response outcome we were unable to validate the more complex bivariate NMA approach within the time available for this critique. Given that the bivariate NMAs inform the company's two-stage NMA approach there is uncertainty around the results of both the bivariate and two-stage NMAs.

2.2.5 Evidence networks

As shown in the evidence network diagrams (NMA Report Figures 1 and 2), two of the included observational studies, Leng et al. 2024[7] and Duan et al. 2024, [6] do not logically connect to the evidence networks because they do not share a common comparator (other than PLEX) with any of the other included studies (PLEX was compared against protein A immunoadsorption by Leng et al. 2024 whilst PLEX was compared against lymphoplasmapheresis by Duan et al. 2024). When the Duan study is included in the network it adds lymphoplasmapheresis, not PLEX, as a comparator. Similarly, when the Leng study is included in the network it adds protein A immunoadsorption, not PLEX, as a comparator. The EAG requested the company to explain how these studies contribute to the network but the company's response (Clarification Response A12) does not add any new information. Note that for the RAISE trial the whole trial population rather than the refractory subgroup was included in the evidence networks (NMA Report Tables 2 & 3).

The EAG do not believe the Duan 2023[6] and Leng 2024[7] studies should have been included in the evidence networks, due to each study lacking a relevant common comparator, as well as the Leng 2024 study having a tiny sample size and almost no information on baseline population characteristics. Furthermore, these Chinese studies have questionable generalisability to the UK NHS. However, as these studies do not connect properly to the evidence networks their exclusion would be inconsequential.

We also suggest that the Barnett 2017 study[5] may not be appropriate for inclusion in the evidence networks, or its influence should ideally have been tested in a sensitivity analysis, given the uncertainties with interpreting the results of this study noted in section 2.2.5 above. However, results of the bivariate NMAs were broadly similar between the post-DGD2 and post-DGD1 analyses, suggesting that the addition of this study had relatively little impact.

One of the studies included in the MG-ADL response NMAs, NCT02473952, [9] used a caprylate/chromatography-purified formulation of IVIg (IVIg-C). We assume this was the only study on IVIg that used this formulation. We are uncertain whether the choice of IVIg formulation would affect clinical efficacy.

EAG conclusion

The company have included four new studies in their NMAs in response to NICE's second Draft Guidance. The EAG does not agree with the inclusion of three of these studies, although we believe that excluding them would probably have negligible impact on NMA results. In comparison to the company's analyses following DGD1, the key difference in the company's current evidence networks has been the addition of PLEX as a comparator to the bivariate NMA.

2.2.6 Inconsistencies in reporting the NMA methods and results

The NMA methods, as briefly stated in the company's NMA Report, are not fully consistent with the results provided:

- For responder outcomes the NMA Report states that sensitivity analyses were conducted to assess alternative improvement thresholds (≥2 points for MG-ADL and ≥3 points for QMG) (NMA Report section 3.1). However, only one set of thresholds appears to have been reported in the results section, i.e. for NMAs which used ≥3 points for both MG-ADL and QMG, except for NCT02473952 [9] where NMA Report section 3.1 states that an MG-ADL response threshold of ≥2 points was included. The company have not explored the impact that including the outlier threshold in the

Bril et al. 2024 study has on the NMA results. This adds uncertainty to the odds ratios from the NMAs.

- Three covariate methods were employed in the NMA statistical analysis approach (common, exchangeable, and independent) (NMA Report section 2). This is consistent with the approach used in the company's response to NICE's first Draft Guidance and we agree is appropriate. However, results appear to be reported for only one of these methods but the NMA Report is not explicit about which one. The NMA Report states that the independent method failed to converge and "the exchangeable interaction model showed potential for estimation with limited data, offering a balance between the other two approaches". However, the reported response rates for the baseline risk-adjusted NMA (NMA Report Table 6) appear to be for the common covariate approach.
- The methods for responder analyses (NMA Report section 3.1) and for change from baseline analyses (NMA Report section 3.2) state that the NMA base case analysis focused on phase III studies, with sensitivity analyses conducted including both phase II and phase III studies. However, the reported results (NMA Report section 4 and Appendices) appear to be for analyses based on both phase II and phase III studies, with no results provided for an analysis on phase III studies alone.
- For the change from baseline outcome the NMA Report (section 3.2) states that an assessment of the impact of the measurement timepoint was conducted. Results of this have not been provided. However, as this would focus on relatively short timescales (<12 weeks) we do not consider it an essential analysis.

EAG conclusion

Although the company have broadly conducted the NMAs as stated in the Methods section of their NMA Report, several sensitivity analyses are missing. We believe these would be unlikely to substantively influence interpretation of the NMA results. A possible exception is that one study with an MG-ADL response cutoff of 2 points was included in the MG-ADL response NMA whereas all other studies had a cutoff of 3 points. The company should have investigated the sensitivity of the NMA results to inclusion of studies with different score cutoffs.

2.2.7 NMA results

Results of the company's conventional NMAs are broadly similar to those that were obtained in the company's analysis in response to the first NICE Draft Guidance, except that they have notably wider credible intervals. The EAG are uncertain why this is; the company have

not listed the studies included in the conventional NMAs so it is unclear whether or how the networks differ between the earlier and current analyses.

Results of the bivariate, baseline risk-adjusted and two-stage NMAs are shown below in Table 6 for MG-ADL response and in Table 7 for MG-ADL change from baseline.

2.2.7.1 Baseline risk-adjusted NMAs

The baseline risk-adjusted NMAs included eight studies which reported MG-ADL response (NMA Report Table 3) and 13 studies which reported MG-ADL change from baseline (NMA Report Table 4).

As noted in section 2.2.4 above, the EAG was able to validate the baseline risk-adjusted NMAs for MG-ADL response, although these have wide credible intervals and no statistically significant differences in the response rates for active comparators versus placebo are evident. The company have not reported odds ratios from these NMAs and the baseline risk adjusted NMAs do not inform the company's economic analysis since PLEX was not included in the evidence networks (Company Response Form page 7).

2.2.7.2 Bivariate NMAs

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

The company note in section 3.3 of their NMA Report that bivariate NMA was not strictly necessary for IVIg outcomes since sufficient studies on IVIg had been included in the company's NMAs following the NICE first Draft Guidance.

Table 6 NMA results for MG-ADL response

Analysis	MG-ADL response ≥3 points,[a] odds ratio versus placebo (95% CrI)		
	Zilucoplan	**IVIg**	**PLEX**
NMA results after DGD1 (August 2024)			
Conventional NMA (RCTs)	[redacted]	No IVIg studies in network	No PLEX studies in network
Bivariate NMA (RCTs)	[redacted]	[redacted]	No PLEX studies in network

Baseline risk-adjusted NMA (RCTs)	[redacted]	No IVIg studies in network	No PLEX studies in network
Two-stage NMA	Not conducted	Not conducted	Not conducted
NMA results after DGD2 (current, December 2024)			
Conventional NMA (RCTs)	[redacted]	[redacted]	No PLEX studies in network
Bivariate NMA (RCTs) [b]	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs + non-RCTs)	[redacted]	[redacted]	[redacted]
Baseline risk-adjusted NMA	Only response rate reported (NMA Report Table 6) [c]	Only response rate reported (NMA Report Table 6) [c]	Not reported [c] (no PLEX studies in network [d])
Two-stage NMA (RCTs) [b]	[redacted]	[redacted]	[redacted]
Two-stage NMA (RCTs + non-RCTs)	[redacted]	[redacted]	[redacted]

CrI, credible interval; DGD1, NICE's first Draft Guidance Document; DGD2, NICE's second Draft Guidance Document; IVIg, intravenous immunoglobulin; NMA, network meta-analysis; PLEX, plasma exchange; RCTs, randomised controlled trials.
[a] ≥3-point threshold for all studies except NCT02473952[9] (≥2-point).
[b] Except the Barth 2011 RCT which was included with the non-RCTs (Clarification Response Table 2 footnote).
[c] Odds ratios and credible intervals for the baseline risk-adjusted NMAs are not reported in the company NMA Report. We note that Figures 6 and 7 at this point in the report are missing.
[d] Confirmed in company Response Form page 7 as the reason that the baseline risk-adjusted NMA does not inform the economic analysis.

Sources: Table 4 in EAG Critique of company's response to DGD1 and Figures 4 and 8 in current company NMA Report

For MG-ADL response the current bivariate NMA odds ratios for zilucoplan versus placebo are broadly similar to those obtained by the company in their analyses following the first NICE Draft Guidance (Table 6), although the EAG were unable to validate those as the NMA code was not provided in the company's response to DGD1. As discussed above (section 2.2.4), the EAG were unable to validate that the bivariate NMAs had been conducted correctly and this adds uncertainty to the results shown in Table 6 and Table 7.

For MG-ADL response, which informs the company's economic analysis base case, the bivariate NMAs are the only ones to show a statistically significant difference between

zilucoplan and placebo (i.e. odds ratio >1 with credible intervals not including 1.0). Corresponding results from the two-stage NMAs have very wide credible intervals, with no differences statistically significant (Table 6).

2.2.7.3 Two-stage NMAs

The two-stage NMAs are the most relevant to the NICE Committee's recommendations as they both (i) adjust for heterogeneity in placebo response rates and (ii) enable inclusion of all available outcomes and therapies. These two-stage NMAs yielded higher odds ratios for all active treatment comparisons against placebo than the bivariate NMAs but with notably wide credible intervals (Table 7). Their results indicate that for zilucoplan, IVIg and PLEX the response rates did not differ significantly from placebo when baseline heterogeneity in the response rate was adjusted for. Aside from the very wide credible intervals, a major uncertainty in the results of the two-stage NMAs is that the EAG was not able to validate the results of the bivariate NMAs on which these two-stage analyses depend (section 2.2.4)

Table 7 NMA results for MG-ADL change from baseline

Analysis	MG-ADL change from baseline, difference versus placebo (95% CrI)		
	Zilucoplan	**IVIg**	**PLEX**
NMA results after DGD1 (August 2024)			
Conventional NMA (RCTs)	[redacted]	[redacted]	No PLEX studies in network
Bivariate NMA (RCTs)	[redacted]	[redacted]	No PLEX studies in network
Baseline risk-adjusted NMA – two covariate model assumptions [a] (RCTs)	Common [redacted] Exchangeable [redacted]	Common [redacted] Exchangeable [redacted]	No PLEX studies in network
Two-stage NMA	Not conducted	Not conducted	Not conducted
NMA results after DGD2 (current, December 2024)			
Conventional NMA (RCTs)	[redacted]	[redacted]	No PLEX studies in network
Conventional NMA (RCTs + non-RCTs)	[redacted]	[redacted]	No PLEX studies in network

Bivariate NMA (RCTs) [b]	[redacted]	[redacted]	[redacted]
Bivariate NMA (RCTs + non-RCTs)	[redacted]	[redacted]	[redacted]
Baseline risk-adjusted NMA	Not reported	Not reported	Not reported
Two-stage NMA (RCTs) [b]	[redacted]	[redacted]	[redacted]
Two-stage NMA (RCTs + non-RCTs)	[redacted]	[redacted]	[redacted]

CrI, credible interval; DGD1, NICE's first Draft Guidance Document; DGD2, NICE's second Draft Guidance Document; IVIg, intravenous immunoglobulin; NMA, network meta-analysis; PLEX, plasma exchange; RCTs, randomised controlled trials.
[a] Independent covariate assumption was also tested but the model results did not converge.
[b] Except the Barth 2011 RCT which was included with the non-RCTs (Clarification Response Table 2 footnote).

Sources: Figure 5 in company NMA Short Report provided in response to DGD1 and Figure 5 and Figure 9 in current company NMA Report.

EAG conclusion

The bivariate NMA results for the MG-ADL response outcome show zilucoplan to be statistically significantly superior to placebo, but these NMAs do not account for heterogeneity of placebo responses. Conversely, results of the two-stage NMAs which do account for placebo response heterogeneity have very wide credible intervals and no treatment differences are statistically significant. All results are associated with additional uncertainty as the EAG could not validate the results of the bivariate (and hence also the two-stage) NMAs.

2.3 Clinical effectiveness: Justification of the revised EAMS cohort to inform the target population

The second NICE Draft Guidance recommends that the company provide information and justification to support the use of a revised EAMS cohort to inform the preferred refractory standard care treatments (DGD2 section 3.6).

The company carried out expert elicitation, described in the Company Expert Interviews Report. The company asked four clinical experts whether a definition of refractory should exclude (i) patients receiving no treatment and (ii) patients receiving corticosteroids but not non-steroidal immuno-suppressants (NSISTs). The experts confirmed that patients on no treatment and those on corticosteroids alone would not be considered refractory. Based on

the experts' responses the company inferred that only 77% (37/48) of the EAMS cohort were refractory (company Response Form pages 11-13). As explained in Clarification Response A3 the company used this information to try to estimate proportions of the refractory patients who were receiving regular IVIg or PLEX to inform the subsequent treatment in the model to better reflect the target population of zilucoplan. However, this required assumptions to make the numbers balance, e.g. "eight of the 10 patients on prednisolone only were excluded to make 11 patients removed altogether, which corresponds with the 11 patients who were not selected as refractory in the EAMS cohort". This approach appears to have assigned eight patients who received prednisone only to be excluded as being non-refractory whilst two patients who received prednisone only were retained and assigned as being refractory.

We note that there is some uncertainty in the reporting of the EAMS cohort[3] which states both that three patients received no treatment and that all patients had received previous NSIST (the number of NSISTs received is not stated). We also note that the categories in Table 2 of the EAMS publication[3] for the reason for starting treatment are not exclusive since more than one reason could be selected; and it is unclear whether patients might have been reported as not refractory if they had responded to IVIg or PLEX (receipt of which contributes to eligibility to receive zilucoplan). We therefore believe that the company's attempts to identify a refractory subgroup within the EAMS cohort apply an inappropriate assumption of precision to a population which is described with some uncertainty in the EAMS study publication.[3] As the company agree there is "no formal or consistently used definition of refractory gMG" (Clarification Response A4), we believe there should be no reason to make a specific definition to narrow down the already small cohort that represents the only directly UK generalisable evidence.

In summary, the EAG believe that the overall EAMS cohort (i.e. N=48) is probably more generalisable to the refractory MG population in the NHS than the company's proposed subgroup, as it likely reflects clinical practice where there is no standard or mandatory definition of refractory gMG available in any guideline or scientific literature. The NICE Committee previously accepted that the whole trial populations in RAISE and RAISE-XT could be generalised to the refractory gMG population in the NHS (DGD1 section 3.7), so using the overall EAMS population would be consistent with that approach. We note that in DGD1 the NICE Committee considered the efgartigimod EAMS population to be sufficiently similar to the zilucoplan target population, and the proportions of people having each treatment could be inferred from the EAMS population (DGD1 section 3.4).

EAG conclusion

The company's justification for using a selected subgroup of the EAMS cohort to represent patients with refractory gMG has several limitations. The EAG believe that the full EAMS cohort is more likely to be reflective of how patients would be classified as having refractory gMG in clinical practice.

2.4 Clinical effectiveness: Justification for using minimum symptom expression (MSE)

2.4.1 Clinical effectiveness assessment of use of minimum symptom expression

Four clinicians consulted by the company agreed that minimum symptom expression (MG-ADL score ≤1) is a relevant clinical parameter (Company Expert Interviews Report). The EAG agree that MSE is intuitively clinically relevant as it reflects the patient state with minimal symptoms. However, as noted in the Company Expert Interviews Report, caveats are that MSE does not necessarily imply the absence of symptoms, and MG-ADL scores are not always reflective of the clinical definition of MSE (e.g. an MG-ADL score of 1 could be accompanied by symptoms which might be bothersome for certain people). The company say in their Expert Interviews Report that patients with MSE approach normal quality of life and activities of daily living but do not cite evidence sources for this and it is unclear whether this inference is from the expert elicitation.

2.4.2 Use of minimum symptom expression within the economic model

The Company Response Form (pages 19-20) explains that the proportion of patients achieving minimum symptom expression governs the distribution of patients that respond to their initial treatment in the 'continued response' (i.e. minimum symptom expression), 'loss of response' and 'stable response' health states. Table 8 shows the proportion of patients in each health state in the company's revised base case.

The proportions of patients achieving minimum symptom expression on IVIg, PLEX and standard of care (excluding IVIg and PLEX) are the averages taken from Company Expert Interviews Report Table 2; the proportion of patients achieving minimum symptom expression on zilucoplan is estimated from RAISE-XT. These proportions inform the transition probabilities for each treatment, which apply until the response assessment timepoint. After this time, patients not responding stop their initial treatment and move to a subsequent treatment.

The health states are associated with a utility value:

- Continued response (i.e. minimum symptom expression): [redacted]

- Stable response: [redacted]
- Uncontrolled: [redacted]

The patients who respond to treatment and achieve minimum symptom expression accrue more QALYs. Response rates and health state (continued/stable/loss of response) proportions differ by treatment, which is how the company are modelling the benefit of both initial and subsequent treatment. However, the company do not explain the source of these utilities, so we are uncertain how they have been calculated.

In their response to Clarification Question B7, the company explain that no further information is available, beyond what they have already provided (including the interviews with their experts), regarding the proportions of patients achieving minimum symptom expression and how long minimum symptom expression persists once it is achieved.

Table 8 Proportion of patients in the 'continued', 'loss of' and 'stable' response categories, company revised model

Treatment	Continued response / MSE		Loss of response		Stable response	
	Company base case	Clinical validation	Company base case	Clinical validation	Company base case	Clinical validation
Zilucoplan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVIg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparator basket[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company model
IVIg, intravenous immunoglobulin; MSE, minimum symptom expression; PLEX, plasma exchange
[a] Comparator basket: the standard of care blended comparator (a proportion of patients on IVIg, a proportion on PLEX, and a proportion on corticosteroids and/or NSISTs only)

In their revised base case, the company assume the proportion of patients receiving the standard of care blended comparator (a proportion of patients on IVIg, a proportion on PLEX, a proportion on corticosteroids and/or NSISTs only; hereafter referred to as the 'comparator basket') and achieving minimum symptom expression to be [redacted]%. We note that some patients receiving the comparator basket are receiving IVIg and others are receiving PLEX. Therefore, we consider that the appropriate proportion of patients receiving the comparator basket and achieving minimum symptom expression in the company's revised base case is [redacted]% (Table 9).

Table 9 Proportion of patients achieving minimum symptom expression in the comparator basket arm, company revised base case

Treatment	Proportion achieving MSE	Proportion in the comparator basket	Proportion achieving MSE in the comparator basket
IVIg	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]
		Total:	[redacted]

Source: EAG created table
IVIg, intravenous immunoglobulin; MSE, minimum symptom expression; PLEX, plasma exchange; SoC, standard of care (excluding IVIg and PLEX)

EAG conclusion

We are uncertain whether using the minimum symptom expression proportions for estimating continued response is appropriate, because the data rely on clinical expert estimates for IVIg and PLEX. However, we acknowledge that the previous 'clinical validation' proportions were also clinical experts' estimates. The company have provided the minimum symptom expression data for zilucoplan from RAISE-XT, but there is currently no further evidence available to show that minimum symptom expression endures over the lifetime of the economic model.

There is uncertainty regarding the source of utilities associated with the continued/stable/loss of response health states; the company do not describe the source of these utilities in the Company Response Form, but we use them in our base case, because there is no alternative.

Finally, we disagree with the proportion of patients achieving minimum symptom expression in the comparator basket, because the company's approach does not account for patients receiving IVIg and PLEX, and the associated benefit of these treatments.

2.5 Economic analysis: Additional modelling and information on subsequent treatments

The company describe their approach to modelling subsequent treatment in Company Response Form pages 20-25). The revised model applies a weighted basket of subsequent treatments, including IVIg, PLEX and SoC only (NSISTs and/or corticosteroids), to patients in the "uncontrolled off initial treatment" health state. The company assume a steady-state basket of subsequent treatments to avoid multiple treatment lines and minimise uncertainty.

Each first-line treatment is assigned an individual subsequent treatment basket (informed by interviews with the company's clinical experts). The treatment response rates for IVIg, PLEX,

and SoC only are applied to the subsequent treatment basket to determine an overall response rate to subsequent treatments. Costs are applied to the percentage of patients who respond to their subsequent treatment; non-responders are assigned the cost of the add-on SoC basket.

The "uncontrolled off initial treatment" health state also reflects the efficacy of subsequent treatments by estimating the average change from baseline MG-ADL score given to the bundle of subsequent treatments (Company Response Form pages 24-25).

2.5.1 Comparator basket

During their response to clarification questions, the company noticed an error in the proportions of patients receiving subsequent treatments in the comparator arm. The company discuss this error and describe their correction in their response to Clarification Question B4. The changes are summarised in Table 10 and the values used in the company revised base case 06-Jan-2025 are shown in Table 11.

Table 10 Subsequent treatment proportions for patients receiving the comparator basket first line

Subsequent treatment	Initial revised model	Revised model 06-Jan-2025
IVIg	[redacted]	[redacted]
PLEX	[redacted]	[redacted]
Standard of care excl. IVIg and PLEX	[redacted]	[redacted]
Source: EAG created table IVIg, intravenous immunoglobulin; PLEX, plasma exchange		

Table 11 Proportion of patients on each subsequent treatment, stratified by first-line treatment, company revised base case 06-Jan-2025

Subsequent treatment	First-line treatment			
	Zilucoplan	IVIg	PLEX	Comparator basket
IVIg	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]
Source: Company model IVIg, intravenous immunoglobulin; MSE; minimum symptom expression; PLEX, plasma exchange; SoC, standard of care (excluding IVIg and PLEX)				

Company Expert Interviews Report Table 1 shows the company's four clinical experts' opinions regarding subsequent treatment following each initial treatment, summarised in Table 12. We note that the clinicians generally agree that they would not re-treat with the same initial treatment; but that there is no consensus regarding the proportions of patients

receiving subsequent treatment when they switch treatment e.g. IVIg to PLEX or vice versa, and that there is a wide range in estimates when switching between IVIg and PLEX (Table 12, underlined). We also note that two company experts raised concerns that IVIg may not be available and that a third commented that NHS England commissioning restricts its use. When considering subsequent treatments after zilucoplan, one company clinical expert commented that PLEX *"was difficult to get and too cumbersome to arrange; hence, it was not a viable subsequent treatment option." (Footnote of Table 1 from the document titled "ID4008 Zilucoplan expert interviews for ACM3_Q4_2024_report _v2_05Dec2004_CLEAN")* However, the expert did provide an estimate for the proportions of patients receiving PLEX after IVIg.

The NICE technical team sought advice from clinical experts at NHS England concerning routine practice for subsequent treatment of refractory generalised MG in the NHS. The full response is available in the document 'ID4008 zilucoplan – NHSE responses – 091224'. Key responses for the economic model concern the proportions of patients switching from IVIg to PLEX, and vice versa, in subsequent treatment:

- PLEX following IVIg
  - NHS England response: "Used fairly infrequently in maintenance treatment so numbers are small."
- IVIg after PLEX
  - NHS England response: "This is very rare and would only be used in seriously ill patients."

Given the wide range in the company's clinical experts' estimates of the proportions of patients switching from IVIg to PLEX, and from PLEX to IVIg in the comparator arm, the uncertainty concerning the availability of these treatments, and the responses from the clinical experts at NHS England, we consider the company's modelled proportions of patients receiving IVIg after PLEX ([redacted]) and PLEX after IVIg ([redacted]) to be optimistic (Table 11). We prefer to use the lowest estimate from the company's clinical experts regarding the proportions of patients switching treatment in the comparator arm ([redacted] from IVIg to PLEX, and [redacted] from PLEX to IVIg; Table 12) in our base case. We conducted a scenario analysis around the proportion of patients switching treatments (Table 23).

Table 12 Company clinical experts' estimates of proportions of patients receiving each subsequent treatment

Subsequent treatment	First-line treatment		
	Zilucoplan	IVIg	PLEX
IVIg	[redacted] **Range:** [redacted]	[redacted] **Range:** [redacted]	[redacted] (if available); [redacted] (if available) **Range:** [redacted]
PLEX	[redacted] **Range:** [redacted]	[redacted] **Range** [redacted]	[redacted] **Range:** [redacted]
SoC	[redacted] **Range:** [redacted]	[redacted] **Range:** [redacted]	[redacted] **Range:** [redacted]

Source: Adapted from Company Expert Interviews Report Table 1
IVIg, intravenous immunoglobulin; MSE; minimum symptom expression; PLEX, plasma exchange; SoC, standard of care (excluding IVIg and PLEX).
[a] This clinician observed that PLEX was difficult to get and too cumbersome to arrange; hence, it was not a viable subsequent treatment option.
[b] This clinician said that there are restrictions on the use of IVIg due to NHSE commissioning and that PLEX isn't readily available, therefore patients would be forced to remain on SoC but that this is poor care and that they are going back to the "same miserable life". They also stated that they would fight for other options for these patients, for example entering a clinical trial.
[c] Clinicians would not revert to the exact same SoC as before, but would modify or 'enhance' the SoC options, such as trying a different CS or a different NSIST, or increasing the dose of one or more SoC components.

The company's response to Clarification Question B4 explains how they calculated the proportions of patients receiving IVIg and PLEX as subsequent treatment in the comparator basket in their revised base case 06-Jan-2025 (shown in Table 13). We disagree with the company's approach and we use our preferred company's clinical experts' suggestions ([redacted] from IVIg to PLEX, and [redacted] from PLEX to IVIg; Table 12) to calculate the proportions of patients on IVIg and PLEX subsequent treatment in the comparator arm (Table 13).

Table 13 Patient treatment proportions in the comparator basket

First-line treatment	Approach	First-line treatment	Proportion on subsequent treatment	Subsequent treatment
IVIg	Company	56.7%	[redacted] receive PLEX	[redacted] receive PLEX
	EAG	43.8%	[redacted] receive PLEX	[redacted] receive PLEX
PLEX	Company	18.9%	[redacted] receive IVIg	[redacted] receive IVIg
	EAG	14.6%	[redacted] receive IVIg	[redacted] receive IVIg
SoC	Company	24.4%	-	[redacted] receive SoC
	EAG	41.6%	-	[redacted] receive SoC

Source: Company model, EAG created table

First-line treatment	Approach	First-line treatment	Proportion on subsequent treatment	Subsequent treatment
IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SoC, standard of care (excluding IVIg and PLEX)				

2.5.2 Zilucoplan

We consider that the proportions of patients receiving IVIg and PLEX as subsequent treatment following zilucoplan should be the same as the proportions of patients receiving IVIg and PLEX initially in the comparator basket, because the comparator basket is then applied consistently in both arms. Consequently, we prefer to use treatment proportions from the original EAMS cohort to inform zilucoplan subsequent treatment, shown in Table 14.

Table 14 Proportion of patients on each subsequent treatment after receiving zilucoplan

Subsequent treatment	Company base case	Original EAMS cohort (EAG base case)	Modified EAMS cohort (EAG scenario)
IVIg	[redacted]	43.8%	56.7%
PLEX	[redacted]	14.6%	18.9%
SoC	[redacted]	41.6%	24.4%

Source: EAG created table
IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SoC, standard of care (excluding IVIg and PLEX)

EAG conclusion

We disagree with the company's estimates of the proportions of patients switching from IVIg to PLEX and vice versa in subsequent treatment in the comparator arm. We prefer to use the lowest company clinical expert estimate of these proportions: [redacted] from IVIg to PLEX and [redacted] from PLEX to IVIg in our base case. We note that the model is extremely sensitive to changing these estimates (Table 23).

We consider that the comparator basket should be applied consistently in each arm, and that proportions of patients receiving IVIg and PLEX as subsequent treatment following zilucoplan should be the same as the proportions of patients receiving IVIg and PLEX initially in the comparator basket.

2.6 Economic analysis: Revised treatment response rates informed by NMAs

The company conducted three network meta-analyses (NMAs), in addition to the conventional NMA, to establish the comparative efficacy of zilucoplan compared with IVIg and PLEX (see section 2.2 above):

1. Bivariate NMA - used in the company's revised base case
2. Two-stage baseline risk-adjusted NMA (baseline risk-adjusted NMA plus bivariate NMA) – used in a company scenario analysis
3. Baseline risk-adjusted NMA – the company did not include this in their economic analysis because it does not include PLEX in the network

Table 15 shows the treatment response rate results of the network meta-analyses. Note: The standard of care response rate excludes IVIg and PLEX, because this is considered later in the model where the comparator basket is constructed.

Table 15 Treatment response rates derived from the company's updated network meta-analyses

Treatment	Response rate		
	Bivariate NMA	Two-stage NMA	Conventional NMA
Zilucoplan	[redacted]	[redacted]	[redacted]
IVIg	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]

Source: Company model
IVIg, intravenous immunoglobulin; NMA, network meta-analysis; PLEX, plasma exchange; SoC, standard of care (excluding IVIg and PLEX)

EAG conclusion

We note that, methodologically, the two-stage baseline risk-adjusted NMA (baseline risk-adjusted NMA and bivariate NMA) aligns most closely with the NICE committee's request from ACM2 (discussed fully in section 2.2). Consequently, we use results from this NMA in our base case but acknowledge that there is substantial uncertainty associated with these results, as shown by the wide credible intervals, as well as the fact that we could not validate the NMA results (see section 2.2.4). We conducted a scenario analysis using response rates derived from the bivariate NMA on our base case (Table 23).

2.7 Economic analysis: Analysis for utility decrement associated with IVIg and PLEX

The revised company model has an option to include a utility decrement associated with IVIg treatment (0.0005 per model cycle i.e. every two weeks) and PLEX treatment (0.0008 every two weeks). The Company Response Form explains that owing to a lack of data for generalised MG, the company use a source for haemophilia A (Johnston et al. (2021)[10]) which presents results for intravenous prophylaxis (2-3 infusions per week and daily infusions). We note that:

- Data are derived from the Canadian general population
- Utilities were estimated via an online, interviewer-guided, vignette-based time trade-off exercise by Canadian adults, not from people with haemophilia
- The study had a small sample size (n = 82)

The company do not explain how the utility decrements used in their revised model were calculated from the results presented in Johnston et al.[10] nor do they provide evidence showing that haemophilia A is an appropriate proxy for gMG.

EAG conclusion

We do not consider haemophilia to be an appropriate proxy for generalised MG and the disutilities are not from patients with generalised MG in the UK. Consequently, we prefer to remove these disutilities in our base case.

2.8 Economic analysis: Analysis that explores corticosteroid costs from the Lee et al. study[2]

The company's revised base case uses estimates for the costs of corticosteroid management from Stirnadel-Farrant et al. (2023).[1] We note that the NICE Committee assessing the efgartigimod submission[11] accepted using data for intolerable side effects caused by corticosteroid use from Lee et al. (2018)[2] as the source of the costs of managing corticosteroids, because these data are from people with generalised MG, whereas Stirnadel-Farrant et al. report costs for people with systemic lupus erythematosus.

Table 16 shows the costs from these two sources, as applied in the company's revised base case. We use the costs from Lee et al. in the EAG base case to be consistent with previous NICE Committee preferences. We note that although the company briefly describe how these costs were calculated in Company Response Form (pages 27-28), they did not provide their working, so we were unable to check the calculations.

Table 16 Cost of corticosteroid management, company's revised model

Health state	Source of costs	All Tx except IVIg and PLEX (£)	IVIg and PLEX (£)
Uncontrolled	Stirnadel-Farrant et al.	10,087	10,087
	Lee at al.	2,448	2,448
Stable response	Stirnadel-Farrant et al.	4,671	4,671
	Lee et al.	343	343
Continued response / MSE	Stirnadel-Farrant et al.	0	4,671
	Lee et al	0	343

Source: Company model
IVIg, intravenous immunoglobulin; MSE; minimum symptom expression; PLEX, plasma exchange; Tx, treatment

In our previous EAG base case (submitted as part of our critique of the company's response to DGD1), we removed costs for corticosteroid management for the 'continued response/ minimum symptom expression' health state for IVIg and PLEX treatment. Thus, costs were the same for all treatments when achieving the same health state.

Company Expert Interviews Report Table 2 shows the experts' estimates about the proportion of patients who achieve minimum symptom expression who are able to stop or reduce their use of corticosteroids while receiving IVIg, PLEX, zilucoplan or standard of care (excluding IVIg and PLEX). The responses from the three experts who answered the question are summarised in Table 17.

We note there is no consensus regarding the proportion of patients who reduce corticosteroid use on each treatment. The clinical experts suggest that not all patients can stop corticosteroid treatment, even if achieving minimum symptom expression. We consider that all patients achieving minimum symptom expression would have the same corticosteroid use, regardless of treatment. Consequently, in the EAG base case, we add costs for corticosteroid management into the zilucoplan arm for patients achieving minimum symptom expression.

Table 17 Company expert estimates of the proportion of patients achieving minimum symptom expression who could reduce their corticosteroid use

Treatment	Expert 1	Expert 3	Expert 4
Zilucoplan	[redacted]	No estimate given	[redacted]
IVIg	[redacted]	[redacted]	No estimate given
PLEX	[redacted]	[redacted]	No estimate given
SoC	[redacted]	No estimate given[a]	No estimate given[a]

Source: EAG created table

Treatment	Expert 1	Expert 3	Expert 4
IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SoC (standard of care excluding IVIg and PLEX) [a] These experts commented that a small percentage of patients become asymptomatic / go into remission spontaneously, for reasons unknown.			

EAG conclusion

We use the NICE committee's preferred source for corticosteroid costs (Lee et al.(2018)) and add costs for corticosteroid management for patients achieving minimum symptom expression in the zilucoplan arm in our base case.

2.9 Economic analysis: Scenario analyses that explore a range of time on treatment assumptions

In the Company Response Form (page 28) the company explain that "the treatment stopping rule was included in error and was rectified before ACM2 but not in time for the EAG to review. The treatment rule is not included in the model as it does not reflect clinical practice."

In response to Clarification Question B2 the company provided flowcharts showing patient flow through the model for the zilucoplan arm for the comparator basket arm (reproduced in Figure 1 and Figure 2 below). The company highlighted that treatment varies among clinicians, between geographical areas, and is highly individualised to the patient.

Figure 1 Zilucoplan subsequent treatment pathway

Source: Company response to DGD2 clarification questions, Figure 1

Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SoC (standard of care excluding IVIg and PLEX)

Figure 2 Comparator basket subsequent treatment pathway

Source: Company response to DGD2 clarification questions, Figure 2
Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SoC (standard of care excluding IVIg and PLEX)

The EAG notes that mean time on treatment for zilucoplan is [redacted] months, and [redacted] months for the comparator basket initial treatment (Table 18). In their response to Clarification Question B3, the company explain that the initial time on treatment for zilucoplan is higher, because the patient response rate is higher.

Table 18 Mean time on treatment

Treatment	Response rate	Time on treatment
Zilucoplan	[redacted]	[redacted]
IVIg	[redacted]	[redacted]
PLEX	[redacted]	[redacted]
Comparator basket	[redacted]	[redacted]

Source: Adapted from Company response to DGD2 clarification questions, Table 9
IVIg, intravenous immunoglobulin; PLEX, plasma exchange

In response to Clarification Question B3, the company conducted scenarios using the transition probability to the 'loss of response' health state as a proxy to model zilucoplan time-on-treatment (Clarification Response B3, Table 10). Increasing the transition probability causes patients to discontinue zilucoplan treatment sooner, reducing time on treatment;

decreasing the transition probability results in patients remaining on zilucoplan for longer, increasing time on treatment. We reproduced these analyses comparing zilucoplan with the comparator basket as shown in Table 21, scenarios 10-12.

EAG conclusion

We are uncertain whether a mean time on treatment of [redacted] months for zilucoplan (for a well-tolerated and easy to administer therapy, aimed at treating a lifetime condition) and of [redacted] months for IVIg and [redacted] months for PLEX respectively, reflect clinical practice. Further information from clinical experts and patient experts concerning zilucoplan, IVIg and PLEX time to discontinuation would be beneficial.

We consider the company's proxy approach to modelling zilucoplan time on treatment to be reasonable and note that zilucoplan was not cost effective compared with the comparator basket in any of these time on treatment scenarios on the company's base case (Table 21).

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

3.1 Company's revised base case cost-effectiveness results

All results presented in this report include the PAS discount for zilucoplan. Analyses including appropriate Medicines Procurement and Supply Chain (MPSC) costs for all treatments are presented in a separate confidential addendum.

The company provided a revised model on 06-Jan-2025, which includes the revised subsequent treatment proportions shown in column 3 of Table 10. **All results in this critique use the company revised model provided on 06-Jan-2025**. Results are shown below in Table 19 for zilucoplan compared with the company's comparator basket, which uses the modified EAMS population. Zilucoplan provides an increase of 0.146 QALYs for a cost of [redacted], resulting in an ICER of [redacted] per QALY.

Table 19 Base case results, company revised model 06-Jan-2025

Treatment	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	10.44	-	-	[redacted]
Comparator basket	[redacted]	10.30	[redacted]	0.146	
Source: Company revised model 06-Jan-2025 ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year					

In Clarification Question B1, we asked the company to provide tabulated results showing the impact of the changes made to the company's model from the version seen at Committee Meeting 1 (ACM1 version) and the current company revised model. In their response, the company explain that they were unable to do this, because it would require substantial structural changes to the model and could not be completed within the required time. Consequently, we are unable to validate the company's revised economic model.

The company did submit change logs showing the model adaptations from the ACM1 model to the ACM2 version (seen at Committee Meeting 2), and from the ACM2 version to the revised model (dated 05-Dec-2024), which provide a narrative list of the changes made.

The company presents the results of their deterministic sensitivity analysis (DSA) as tornado diagrams in Company Results Document section 1.2.2, and results of their probabilistic sensitivity analysis (PSA) in company response section 1.2.3. However, the company did not present results for zilucoplan versus the comparator basket.

3.2 Company scenario analyses

The company present the results of their scenario analyses in Company Results Document section 1.2.4 for:

1. The overall generalised MG population
2. Societal perspective (both societal costs and carer disutilities)
3. Comparator basket proportions from the original EAMS cohort (43.8% receive IVIg, 14.6% receive PLEX, 41.6% receive standard care)
4. Including the disutility of corticosteroids
5. Response rates from the two-stage NMA (including RCTs + non-RCTs): Zilucoplan ([redacted]); IVIg ([redacted]), PLEX ([redacted]), SoC ([redacted]).
6. Subsequent treatment removed
7. Same subsequent treatment proportions for comparators as zilucoplan: IVIg ([redacted]), PLEX ([redacted]), SoC ([redacted]).
8. Reduced response rate for subsequent treatments (shown in Table 20)
9. Lee et.al.[2] as the source for costs for corticosteroid management

Table 20 Assumed reduction in response rate for subsequent treatments versus first-line treatments, stratified by first-line treatment, based on expert clinical opinion

Response rate	Zilucoplan	IVIg/SCIg	Plasma exchange	Standard of care blended comparator
IVIg	[redacted]	[redacted]	[redacted]	[redacted]
PLEX	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company Results Document 1.2.4.8, Table 29
IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SCIg, subcutaneous immunoglobulin.

We have reproduced scenarios 1-9 for zilucoplan compared with the comparator basket, using the company's revised model 06-Jan-2025 (Table 21). In response to Clarification Question B3, the company conducted scenario analyses exploring a range of time on treatment assumptions (as requested by the committee in the second Draft Guidance Document). These scenarios do not directly model zilucoplan time-on-treatment but use transitions to the 'loss of response' health state as a proxy. We have reproduced these analyses for zilucoplan compared with the comparator basket in scenarios 10-12, Table 21. Note: Zilucoplan 'loss of response' is [redacted] in the company's revised base case.

Using the original EAMS cohort to inform the proportion of patients on treatment in the comparator basket (scenario 3) has the most influence on the ICER, increasing it to [redacted] per QALY.

Table 21 Company scenario analyses for zilucoplan compared with the comparator basket, company revised base case 06-Jan-2025

No.	Scenario description	Incr. Costs	Incr. QALYs	ICER (£/QALY)
Company revised base case		[redacted]	0.146	[redacted]
1	Use the overall gMG population	[redacted]	-0.007	[redacted]
2	Use the societal perspective (both societal costs and carer disutilities)	[redacted]	0.167	[redacted]
3	Use proportions from the EAMS study (43.8% receive IVIg, 14.6% receive PLEX, 41.6% receive standard care) for the comparator basket	[redacted]	0.152	[redacted]
4	Include the disutility of corticosteroids	[redacted]	0.205	[redacted]
5	Use the two-stage NMA (RCTs + non-RCTs) response rate	[redacted]	0.170	[redacted]
6	Remove subsequent treatment	[redacted]	0.136	[redacted]
7	Use the same subsequent treatment proportions for comparators as zilucoplan	[redacted]	0.130	[redacted]
8	Reduced response rate for subsequent treatments	[redacted]	0.153	[redacted]
9	Use Lee et.al.[2] as the source for costs for corticosteroid management	[redacted]	0.146	[redacted]
10	Zilucoplan loss of response = [redacted]	[redacted]	0.148	[redacted]
11	Zilucoplan loss of response = [redacted]	[redacted]	0.147	[redacted]
12	Zilucoplan loss of response = [redacted]	[redacted]	0.142	[redacted]

Source: EAG created table
EAMS, Early access to medicines scheme; gMG, generalised myasthenia gravis; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; NMA, network meta-analysis; PLEX, plasma exchange; QALY, quality-adjusted life-year; RCT, randomised controlled trial

As part of their response to Clarification Question B1, the company provided more commentary and scenario analyses, which were unrelated to our clarification question and that we did not request. Owing to time constraints, and that these analyses were unsolicited, we have not assessed this information fully. However, we note that:

- Scenario 1 (company Response Form Table 5) includes inappropriate comparators (direct comparisons of zilucoplan to IVIg, to PLEX and to blended treatment (75% of patients receive IVIg and 25% receive PLEX).
- Scenario 2 (company Response Form Table 6) involves changing the intervention arm such that a not all patients receive zilucoplan, and a proportion receive standard care (i.e. NSISTs and corticosteroids) only instead.

- Scenario 3 (company Response Form Table 7) explores the company's estimate of cheaper and more effective IVIg treatment; we present results using current MPSC costs for IVIg in our confidential addendum.

4 EAG ANALYSES

4.1 EAG preferred assumptions

Based on the EAG's critique of the company's model (discussed in section 2), we have identified several aspects of the company's revised base case with which we disagree. Our preferred model assumptions are to:

- Use the original EAMS cohort to inform the proportions of patients on each treatment in the comparator basket (43.8% receive IVIg, 14.6% receive PLEX, 41.6% receive standard care; discussed in section 2.1)
- Response rate – use response rates derived from the two-stage NMA (discussed in section 2.2 and section 2.7)
- Incorporate the proportions of patients receiving IVIg and PLEX into the minimum symptom expression proportions in the comparator basket (discussed in section 2.5.2). Note: This proportion depends on the make-up of the comparator basket and is [redacted] in the EAG base case, because we use data from the original EAMS cohort
- Use the lowest expert estimate of the proportions of patients switching treatments in the comparator arm ([redacted] from IVIg to PLEX, and [redacted] from PLEX to IVIg) (discussed in section 2.6.1)
- Use our calculation for the proportions of patients on IVIg and PLEX subsequent treatment in comparator arm (discussed in section 2.6.1, Table 13)
- Subsequent treatment in the zilucoplan arm to match the initial comparator basket in the comparator arm (discussed in section 2.6.2)
- Remove the disutilities for IVIg and PLEX treatment use (discussed in section 2.8)
- Use costs for corticosteroid management from Lee et al. (2018) (discussed in section 2.9)
- Add costs for corticosteroid management to the zilucoplan arm for patients achieving minimum symptom expression (discussed in section 2.9)

The cumulative effect of these changes results in an ICER of [redacted] per QALY for zilucoplan compared with the comparator basket (Table 22).

Please note: Because we were unable to validate the company's revised model, and because of uncertainty in the bivariate and two-stage NMA results (section 2.2.4) we are unsure if the results of our base case (Table 22) and scenarios on our base case (Table 23) are reliable.

Table 22 Cumulative effect of the EAG's preferred assumptions, zilucoplan compared with the comparator basket

Assumption	Incr. costs (£)	Incr. QALYs	Cumulative ICER (£/QALY)
Company revised base case	[redacted]	0.146	[redacted]
Use the original EAMS cohort for the comparator basket (43.8% IVIg, 14.6% PLEX, 41.6% SoC)	[redacted]	0.152	[redacted]
Use response rates derived from the two-stage NMA (RCTs + non-RCTs)	[redacted]	0.178	[redacted]
Proportion of patients achieving MSE in comparator basket includes patients receiving IVIg and PLEX ([redacted]	[redacted]	0.150	[redacted]
Use the lowest expert estimate of the proportions of patients switching treatments in the comparator arm ([redacted] from IVIg to PLEX, and [redacted] from PLEX to IVIg)[a]	[redacted]	0.150	[redacted]
Use EAG calculated proportions of patients on IVIg ([redacted]) and PLEX ([redacted]) subsequent treatment in the comparator arm	[redacted]	0.258	[redacted]
Subsequent treatment in the zilucoplan arm matches the initial comparator basket in the comparator arm i.e. the original EAMS cohort	[redacted]	0.208	[redacted]
Remove the disutilities for IVIg and PLEX treatment use	[redacted]	0.247	[redacted]
Use costs for corticosteroid management from Lee et al.	[redacted]	0.247	[redacted]
Add costs for corticosteroid management to the zilucoplan arm for patients achieving MSE	[redacted]	0.247	[redacted]
EAG base case	[redacted]	**0.247**	[redacted]

Source: EAG created table
[a] This change has no effect until the EAG calculation of IVIg and PLEX subsequent treatment in the comparator arm is applied
EAMS, Early access to medicines scheme; gMG, generalised myasthenia gravis; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MSE, minimum symptom expression; NMA, network meta-analysis; PLEX, plasma exchange; QALY, quality-adjusted life-year; RCT, randomised controlled trial

4.2 Scenario analyses on the EAG's preferred assumptions

The EAG ran scenario analyses on our base case assumptions (Table 23). The model is sensitive to how subsequent treatment is applied, both in the zilucoplan arm (scenario 5) and especially in the comparator arm (scenarios 2, 3 and 4).

Table 23 Scenario analyses for zilucoplan compared with the comparator basket, EAG base case

No.	Scenario description	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
EAG base case		[redacted]	**0.247**	[redacted]
1	Use the company's modified EAMS cohort	[redacted]	0.27	[redacted]
2	Use the company's estimate of the proportions of patients switching treatments in the comparator arm: [redacted] from IVIg to PLEX, and [redacted]% from PLEX to IVIg	[redacted]	0.15	[redacted]
3	Use alternative proportions of patients switching treatments in the comparator arm: [redacted] from IVIg to PLEX, and [redacted]% from PLEX to IVIg	[redacted]	0.163	[redacted]
4	Use the company's proportions receiving IVIg and PLEX in subsequent treatment in the comparator basket: [redacted] on IVIg, [redacted] on PLEX, [redacted] on SoC	[redacted]	0.06	[redacted]
5	Use the company's estimate of subsequent treatment in the zilucoplan arm: [redacted] on IVIg, [redacted] on PLEX, [redacted] on SoC	[redacted]	0.34	[redacted]
6	Use response rates from the bivariate NMA (RCTs + non-RCTs): zilucoplan [redacted]; IVIg [redacted]; SoC [redacted]; PLEX [redacted]	[redacted]	0.21	[redacted]

Source: EAG created table
EAMS, Early access to medicines scheme; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; NMA, network meta-analysis; PLEX, plasma exchange; QALY, quality-adjusted life-year; RCT, randomised controlled trial; SoC (standard of care excluding IVIg and PLEX)

4.3 Economic analysis summary

The company presented the results of their revised base case (Table 19). We have reviewed the company's revised model and section 4.1 summarises our preferred assumptions. Applying the EAG's preferred assumptions increases the ICER for zilucoplan compared with the comparator basket from [redacted] to [redacted] per QALY.

We conducted scenarios on our revised base case to explore the remaining uncertainty when comparing the cost-effectiveness of zilucoplan with the comparator basket. The model is most sensitive to how IVIg and PLEX subsequent treatment is applied in the comparator arm (Table 23).

5 REFERENCES

1. Stirnadel-Farrant HA, Golam SM, Naisbett-Groet B, et al. Adverse Outcomes, Healthcare Resource Utilization, and Costs Associated with Systemic Corticosteroid use Among Adults with Systemic Lupus Erythematosus in the UK. *Rheumatol Ther* 2023;10(5):1167-82.
2. Lee I, Kaminski HJ, McPherson T, et al. Gender differences in prednisone adverse effects: Survey result from the MG registry. *Neurology: Neuroimmunology and NeuroInflammation* 2018;5(6):e507.
3. Moniz Dionisio J, Ambrose P, Burke G, et al. *Efgartigimod efficacy and safety in refractory Myasthenia Gravis - UK's first real-world experience*. https://www.medrxiv.org/content/10.1101/2024.01.31.24302082v1.
4. Barth D, Nabavi Nouri M, Ng E, et al. Comparison of IVIg and PLEX in patients with myasthenia gravis. *Neurology* 2011;76(23):2017-23.
5. Barnett C, Bril V, Kapral M, et al. Myasthenia Gravis Impairment Index. *Neurology* 2017;89(23):2357-64.
6. Duan W, Jiang F, Cai H, et al. Lymphoplasmapheresis versus plasma exchange in severe myasthenia gravis: a retrospective cohort study. *Frontiers in Neurology* 2023;14.
7. Leng B, Chen X-j, Wang C, et al. A short-term functional recovery comparison of therapeutic plasma exchange and immunoadsorption in severe acute neuroimmune diseases. *International Immunopharmacology* 2024;140:112796.
8. Zinman LNEBV. IV immunoglobulin in patients with myasthenia gravis: A randomized controlled trial. *Neurology* 2007;68(11):837-41.
9. Bril V, Berkowicz T, Szczudlik A, et al. Efficacy and safety of maintenance intravenous immunoglobulin in generalized myasthenia gravis patients with acetylcholine receptor antibodies: A multicenter, double-blind, placebo-controlled trial. *Muscle & Nerve* 2025;71(1):43-54.
10. Johnston K, Stoffman JM, Mickle AT, et al. Preferences and Health-Related Quality-of-Life Related to Disease and Treatment Features for Patients with Hemophilia A in a Canadian General Population Sample. *Patient Prefer Adherence* 2021;15:1407-17.
11. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual, 2023.