Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Contents:

The following documents are made available to stakeholders:

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

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Consultation on the draft guidance document – deadline for comments 5pm on Thursday 25 July 2024.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:

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	• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology. • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UCB Pharma Ltd (Company)

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

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. The use of a blended standard of care 'basket' as comparator (Section 3.4 in the draft guidance)	The company strongly disagrees with the blended standard of care 'basket' as a comparator against zilucoplan, and believes the decision is inappropriate based on the evidence presented. UCB maintains that zilucoplan will displace intravenous immunoglobulin (IVIg) and plasma exchange (PLEX) in clinical practice in refractory patients who have failed standard of care alone and therefore IVIg and PLEX are the only relevant comparators to zilucoplan. This agrees with what is stated in the section of the ACD titled 'Why the committee made these recommendations' (paragraph 1, lines 5–8): 'Zilucoplan would be used as an add-on to standard treatment for people who test positive for anti-acetylcholine receptor antibodies and whose condition has not improved with standard of care alone'. The NICE manual (PMG36) states that pairwise comparisons are relevant and justified when the technology is expected to specifically displace individual comparators (1) The proposed positioning of zilucoplan is in line with a myasthenia gravis treatment algorithm being developed by the Association of British Neurologists myasthenia gravis specialist interest group and discussed in a recent NICE Heath Technology Assessment submission for newly licensed targeted therapies for myasthenia gravis. The algorithm places targeted treatments, including complement inhibitors such as zilucoplan, as a fourth line option, displacing chronic IVIg and PLEX. The rationale behind the EAG preference for a basket of care approach is that some centres do not have access to IVIg and/or PLEX. The company is unaware whether this preference was due to evidence generated by EAG discussions with clinicians or to other sources. It is the company's understanding that patients with refractory generalised myasthenia gravis needing IVIg and/or PLEX are referred to specialist neurology centres/hospitals where both treatments are available. However, the company acknowledges the view of the committee that some refractory patients who have received IVIg and/or PLEX may have periods in which they do not receive treatment for various clinical reasons. The company believes that this scenario would be better modelled in subsequent treatments for those patients who have lost response as it avoids the conclusion that cheaper and better versions of currently used interventions would not be recommended. The company has now modelled the use of subsequent treatments including a proportion of patients receiving standard of

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	care; this proportion of patients remains constant across time but would represent patients moving between IVIg/PLEX and standard of care. The company believes that this approach provides a more accurate estimate of the ICER than using a blended comparator. UCB understands the concern that all refractory patients could potentially be considered for zilucoplan should it be approved. However, as submitted by the clinical experts, zilucoplan is expected to be used following review by a multidisciplinary team at an MG specialists' centre and funding approval managed through Blueteq. Additionally, the EAG based the proportion of people receiving each comparator on the published efgartigimod Early Access to Medicines Scheme (EAMS) patient cohort (2, 3). While this evidence adds to UK published literature in MG, there are limitations pointed out in the study publication (4). The company disagrees with the composition and proportions of the basket assumptions based on the following points: • The full dataset was not reported • On page 9 of the draft guidance, reports that the EAG noted ‘‘refractory was defined in a slightly different way’ in the efgartigimod EAMS. The efgartigimod EAMS paper reports only 77% [n=37] of patients were refractory (2, 3). The population recruited in the efgartigimod EAMS is broader than the population presented in zilucoplan company submission. The entry criteria used in the efgartigimod EAMS is patients with acetylcholine receptor-antibody-positive generalised myasthenia gravis, including **but not limited** to patients with refractory generalised myasthenia gravis (2, 3). Therefore, as not all patients were refractory, the population in the efgartigimod EAMS does not match the population under consideration in this single technology appraisal for zilucoplan • In addition, the publicly available results do not specify the standard of care therapies in the refractory subgroup. In total, 4.2% (n=2) of patients were provided efgartigimod as a bridging treatment which is outside of the proposed positioning of zilucoplan. Three patients (6.3%) were reported as having no immunosuppressive/immunomodulatory treatment, but it is unknown if these patients were refractory patients or otherwise.

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	The company has based the above considerations on the available published data and is unaware of whether the EAG or the committee have had access to additional data concerning the efgartigimod EAMS population. As part of this response, the company has submitted an updated model, requested by the committee, that includes in the base case a standard of care basket as subsequent treatment for patients who discontinue due to lack of response to zilucoplan and its comparators (IVIg and PLEX) (see point 5).
2. Unmet need in refractory MG (Section 3.1 in the draft guidance)	There is an urgent unmet need for a new treatment for patients with refractory generalised myasthenia gravis who are not sufficiently responding to acetyl cholinesterase inhibitors, corticosteroids, or non-steroidal immunosuppressants. The only routinely available treatment options in England and Wales are regular IVIg and PLEX. As mentioned in the draft guidance, IVIg and PLEX both pose a significant treatment burden for the patient and are resource-intensive for the healthcare system. Patients on IVIg and/or PLEX typically attend hospital every 4 weeks. At the time of writing, no targeted treatment for generalised myasthenia gravis has received a positive recommendation from a NICE committee, which is in stark contrast to other disease areas, e.g. multiple sclerosis and lupus. As a result, access to innovative treatments for generalised myasthenia gravis is limited to clinical trials, compassionate use schemes, or individual funding requests. This contrasts with access to targeted treatments for generalised myasthenia gravis in France, Germany, Italy, Spain Austria, Belgium, the Netherlands, Greece and countries outside of Europe Further highlighting the need for a targeted treatment, [redacted] patient applications for zilucoplan have been approved, and 48 patients accessed efgartigimod for acetylcholine receptor antibody-positive generalised myasthenia gravis via the EAMS (4). Patients with generalised myasthenia gravis experience debilitating symptoms that severely impact all aspects of their lives (5). Living with refractory generalised myasthenia gravis has a substantial negative impact on education and work, with careers interrupted or ended prematurely. In addition, patients feel that living with generalised myasthenia gravis impacts their decision to have a family.

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	Concerns about the effects of uncontrolled generalised myasthenia gravis symptoms on daily living, and their ability to cope as a parent, can deter patients from planning a pregnancy (5). Contraindications to therapy during pregnancy and lactation mean women may face a difficult choice between starting a family and managing symptoms of generalised myasthenia gravis (5). Younger patients in particular may feel a sense of loss of life due to restrictions in activity and limitations in life choices (5). Patients with refractory generalised myasthenia gravis are sub-optimally managed with the treatments currently available on the NHS. The consequences of patients staying on standard of care despite being refractory to treatment include poor symptom control, increased risk of myasthenic crisis (6-10) and the debilitating side effects of corticosteroids (diabetes, osteoporosis, depression and infection, which can trigger a myasthenic exacerbation) (7, 11-14). Current treatments also have delayed onset of action (usually 6–18 months, but it can take up to 2 years to achieve maximal clinical benefit), contributing to poor disease control and leaving patients with a high symptom burden and at risk of exacerbation and crisis (6-8). Currently available treatments for patients with refractory generalised myasthenia gravis may require patients to travel long distances for treatment at specialist centres, and even stay in hospital for repeat treatment if they live too far away to travel for each session (15, 16), which is burdensome for patients and the NHS. Zilucoplan is a fast-acting, efficacious, targeted treatment for generalised myasthenia gravis that can be administered at home by the patient, which will not only reduce burden on patients, carers and the healthcare system, but also significantly improve quality of life for the currently under-served patients with refractory generalised myasthenia gravis. To further minimise the treatment burden on both patients and the NHS, UCB has commissioned a service to offer home delivery of zilucoplan. The use of zilucoplan in place of IVIg and PLEX would enable more IVIg (which is a finite supply) and PLEX to be made available to patients with other diseases who need it The NICE manual states that although decisions about the acceptability of the technology as an effective use of NHS resources will consider the degree of certainty around the value for money, the committee will be mindful that there are certain technologies or populations for which evidence generation is particularly difficult, because they are rare diseases

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	and/or the technology is innovative (1). UCB would also like to highlight that a priority of the Rare Disease Action Plan 2024 is to improve access to specialist care, treatments, and drugs (17). Zilucoplan presents an opportunity for patients living with a severe and debilitating disease such as refractory generalised myasthenia gravis to access an efficacious treatment that reduces the symptom burden, with no new significant capital investment or service development required and is a candidate for the interim innovative medicines fund.
3. How the company sought to address the uncertainties in the CS (Section 3.16 in the draft guidance)	The company would like to emphasise that given the paucity of data in refractory generalised myasthenia gravis; a substantial effort has been made to address the uncertainties in the company submission. In addition, the company has presented new evidence that will address some of the uncaptured health benefits of zilucoplan. The new evidence submission includes: • Updated cost-effectiveness model that seeks to address subsequent treatments and other uncaptured benefits of zilucoplan (please see Section 3 in the supporting document) • New indirect treatment comparison methodologies that show consistent outcomes, despite underlying heterogeneity in the studies, particularly those of IVIg (please see Section 2 in the supporting document) • New data on the steroid-sparing and minimum symptom expression achieved with zilucoplan, highlighting the value of zilucoplan (please see Sections 2.1 and 2.3 in the supporting document, respectively) UCB would also like to highlight that a priority of the Rare Disease Action Plan 2024 is to improve access to specialist care, treatments, and drugs (17).
4. Bivariate NMA (Section 3.8 in the draft guidance)	There is a lack of published studies on the use of IVIg and PLEX in myasthenia gravis, as IVIg and PLEX do not have marketing authorisation for use in generalised myasthenia gravis. IVIg and PLEX are therefore used off licence in England in Wales to treat generalised myasthenia gravis in the absence of approved targeted treatments.

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	The updated analysis (section 2 of supporting document) shows that: • Zilucoplan has a numerically better proportion of responders compared with IVIg, and has demonstrated a significantly increased change from baseline when compared with IVIg in the network meta-analysis (and in the matched-adjusted indirect comparison) Despite data limitations causing uncertainty with wide credible intervals, there is general concordance with point estimates across analyses (matched-adjusted indirect comparison, network meta-analysis, bivariate network meta-analysis and the naive treatment comparison). Please see section 2.3 in the supporting document.
5. Modelling subsequent treatments (Section 3.10 in the draft guidance)	Formally modelling treatment sequences would be challenging as the results would be too uncertain due to the lack of available data. There is uncertainty around the number lines of subsequent treatments needed, what treatments clinicians will consider after failure on IVIg/PLEX and whether lack of response to index will be a treatment effect modifier. However, UCB acknowledge that the validity of a model which did not allow for repeat attempts of treatment and switching of treatment may be challenged. Similarly, a model which kept patients on IVIg or PLEX persistently despite loss of response might also be challenged. Therefore, the company has submitted an adapted model where subsequent treatments are assumed to be in steady state but reflecting movement of patients between treatment with IVIg/PLEX and standard of care. UCB also acknowledge the statements (3.12) from patient and clinical experts that generalised myasthenia gravis requires lifelong management.
6. Substantial placebo response in RAISE (Sections 3.5 and 3.11 of the draft guidance)	A BL risk-adjusted network meta-analysis was conducted, which showed that the placebo response was not significantly different between the studies, and that the results for change from baseline in myasthenia gravis-activities of daily living score were similar to those from the conventional network meta-analysis (please see the supporting document for methods and full results).

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	One possibility for a higher placebo response in RAISE compared with efgartigimod is that, with daily self-administration, patients felt empowered by having a way to improve their health after a long period with uncontrolled symptoms. An analogue is a study in osteoarthritis that reported that the more frequently administered an intervention, the higher the placebo effect (18).
7. Referent response rate (Section 3.11 in the draft guidance)	The data applied in the model are limited by the small number of studies available. In the updated model, the referent response rate is calculated as the overall mean of log odds based on individual log odds for each study reporting MG-ADL response for placebo. In the previous version of the model, on which the draft guidance is based, the referent response rate was calculated as the average response rate for the placebo arms across studies identified in the network meta-analysis. Neither of these calculations offer a substantially different outcome, with the mean of log odds giving 31.5% response, vs a 32% simple average of included studies reporting MG-ADL response.
8. Include uncertainties from NMA in modelling (Section 3.8 in the draft guidance)	The bivariate network meta-analysis is associated with uncertainties due to the lack of clinical evidence, but UCB has incorporated the CODA from this analysis into the PSA in the CEM Further, scenarios have been used to explore uncertainty around the response rate and change from baseline, including: • Setting change from baseline data to –3 for all comparators for stable responder (instead of the network meta-analysis outcomes) • Extreme values for IVIg/PLEX responder rates, i.e. 70% primary response rate
9. Response assessment timepoint of 3 weeks	Thank you for your comments. UCB agrees with a response assessment timepoint of 3 weeks, as defined in the draft guidance document, and has made the required changes to the cost-effectiveness model.

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(Section 3.12 in the draft guidance)	
10. Administration costs of IVIg and PLEX applied every 4 weeks (Section 3.14 in the draft guidance)	Thank you for your comments. UCB agrees with the committee's assumptions and has made the required changes to the cost-effectiveness model.
11. PLEX administration costs (SA44A) (Section 3.14 in the draft guidance)	Thank you for your comments. UCB agrees with the committee's assumptions on PLEX administration costs and has made the required changes to the cost-effectiveness model.
12. Response rates from Barth et al (Section 3.11 in the draft guidance)	The response rates for IVIg and PLEX were not back calculated but taken directly from Barth et al (19) (page 4 of the article, third paragraph [see below]) and expressed as the proportion (%) of responders. Patients were classified as responders if they achieved a quantitative myasthenia gravis score improvement of 3.5 points as reported by Barth et al (19). The model presents both response rates and odds ratios. For the other treatments, the odds ratios from the network meta-analysis were transformed into response rates. Although the response rates from Barth et al were converted to odds ratios, the odds ratios were not used in the model; only the response rate was used to inform the transition probabilities. Please see section 2.1 in the supporting information.
13. Uncaptured benefits: corticosteroid sparing (Section 3.19 in the draft guidance) and minimum symptom expression	Patients face a severe treatment burden from currently available therapies and must balance the benefits of controlling symptoms with severe, debilitating treatment side effects. Corticosteroids are associated with severe side effects such as diabetes, osteoporosis, depression and infection, which can trigger a myasthenic exacerbation and affect QoL (7, 11-14, 20-22). Paradoxically, high dose corticosteroids are

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	associated with a temporary worsening of symptoms and an extended hospital stay (23, 24). Long-term corticosteroids use is also associated with a cost burden (25). A post-hoc analysis of data from RAISE-XT shows that patients receiving zilucoplan were able to reduce or discontinue corticosteroids (see supporting document). The model was updated to include costs and disutilities of corticosteroids and the corticosteroids-sparing effect of zilucoplan (please see Section 2.1 in the supporting document). In addition to the corticosteroid-sparing effect of zilucoplan, an analysis of MSE as a proportion of patients responding to zilucoplan in the RAISE-XT trial was conducted. Of patients in response at week [redacted] (defined as 3-point change from baseline in MG-ADL), [redacted] had MSE. Therefore, of patients responding to zilucoplan, [redacted] become free or virtually free of MG symptoms please see Section 2.3 in the supporting document).
14. Uncaptured benefits: convenience associated with at-home sc administration (Section 3.19 in the draft guidance)	There are benefits to both patients (improved quality of life) and the NHS (reduced healthcare resource utilisation) associated with at-home self-administration of zilucoplan, compared with highly burdensome in-hospital intravenous administration of treatments such as IVIg and PLEX. PLEX and IVIg are also associated with the risk of rare but life-threatening side effects (such as infection and hypotension with anaphylactic shock) (26, 27). It is evident from the literature that patients prefer to receive subcutaneous at-home administration to IVIg in hospital. A systematic literature review on patient preferences for subcutaneous injection versus intravenous administration of treatment for chronic immune system disorders reported that, of 18 studies comparing intravenous and subcutaneous immunoglobulin therapy, 16 concluded that patients prefer subcutaneous administration (28). Patients who preferred subcutaneous administration preferred treatment at home due to the convenience and comfort of home treatment and the ability to avoid hospital attendance. A study in patients with multiple sclerosis showed that 87.8% of patients preferred subcutaneous administration over intravenous, and 82.9% of patients specified “requires less time in the clinic” as the reason for the preference for subcutaneous administration (29).

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	There remains limited data relating to the difference in utility between intravenous and subcutaneous administration, but of the few studies found, the increment ranges from 0.03 to 0.12 (30-37).
15. Uncaptured benefits: adherence associated with at-home sc administration (Section 3.19 in the draft guidance)	Compliance to zilucoplan is high. In a post-hoc study on compliance in RAISE-XT, patients reported taking [redacted] of their medication, and [redacted] of them reported [redacted] compliance, over a median study medication duration of [redacted], suggesting that long-term compliance to zilucoplan administration is high (please see the supporting document for the abstract). Compliance by age, sex, duration of disease, and baseline myasthenia gravis-activities of daily living are similar to overall compliance.
16. Uncaptured benefits: carer cost and disutility (Section 3.19 in the draft guidance)	Myasthenia gravis is associated with a significant carer burden. Burden on family and friends of patients with generalised myasthenia gravis were highlighted by expert patients at the ACD meeting on 14 June 2024. Societal costs for patients (work time lost) and caregiver burden (time spent caring for a patient with generalised myasthenia gravis) by MG-ADL range have now been included as an option in the updated model and scenarios have been provided with these options included (please see the supporting document). The company recommends that expert patients and clinicians are invited to present at ACM2 so that detailed perspectives can be shared on the burden that both generalised myasthenia gravis and the currently available treatments have on patients, carers, and the NHS.

Insert extra rows as needed

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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 5pm on Thursday 25 July 2024. Please submit via NICE Docs.

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Overview of new evidence and modelling updates and results

1. Executive summary

In the draft guidance published by NICE for zilucoplan for treating antibody-positive generalised myasthenia gravis, the committee has requested the following:

- An indirect treatment comparison (ITC) that includes intravenous immunoglobulin (IVIg) and plasma exchange (PLEX), and accounts and adjusts for differential placebo response observed in the clinical trials
- Including subsequent IVIg and PLEX in the modelling and the effect on the -cost-effectiveness estimates
- Scenario analyses incorporating some of the uncaptured benefits of zilucoplan and testing the robustness of the model assumptions.

This document includes an overview of new evidence for zilucoplan (Section 2) referred to in the ACD response comments form. Section 3 presents updates made to the model following the draft guidance consultation. This document only presents the data that is not included in the supporting files being submitted (NMA, MAIC reports and global CEM technical report). No studies comparing PLEX with placebo were identified, so it was not possible to include PLEX as a treatment in the bivariate network meta-analysis.

The findings of the indirect treatment comparisons conducted (bivariate NMA, MAIC and NMA) demonstrate that zilucoplan is significantly better than standard of care (SoC) alone in patients with gMG, with similar results in refractory patients and despite a high placebo response on some endpoints. Zilucoplan is associated with a numerically larger proportion of treatment responders, and has demonstrated a significantly larger change from baseline, when compared with IVIg in the NMA and MAIC. Despite data limitations causing uncertainty in the results with wide credible intervals, there is general concordance with point estimates across the analyses (MAIC, NMA, NMA, naive comparison).

In addition, there are uncaptured benefits and non-health factors that could not be included in the modelling, for example patient and nurse time lost when in-hospital treatment is needed, and the benefits associated with the NSIST-sparing effect of zilucoplan

Section 3.3 provides the results of the cost-utility analysis utilising the base-case settings described in Section 3.2 as well as the results of scenario analyses. In the base-case, zilucoplan was [redacted] compared with both IVIg and PLEX. The results of the probabilistic sensitivity analysis and scenario analyses were consistent with the base-case. The deterministic sensitivity analysis identified that the assumptions on resource use associated with IVIg and PLEX in uncontrolled health state for subsequent treatments was consistently influential on ICERs for both comparisons.

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

2. New evidence

2.1. Corticosteroid and NSIST-sparing data

Among patients receiving zilucoplan in RAISE and RAISE-XT, [redacted] of those with a CS dose above the Cushing threshold (≥7.5 mg) at baseline reduced their CS dose at Week [redacted] ([redacted]), of which [redacted] discontinued their CS. Of patients with a CS dose above the Cushing threshold (≥7.5 mg) at DB baseline who reduced or discontinued their CS dose at Week [redacted] ([redacted]), CS dose decreased on average by [redacted] mg, while MG-ADL improved on average by [redacted] from baseline.

These data suggest that patients receiving zilucoplan may reduce or discontinue their use of CS, whilst maintaining disease control.

Long term data from RAISE-XT also suggest that zilucoplan offers the potential to reduce reliance on long term NSIST use.

Among zilucoplan 0.3mg/kg patients with NSIST dose ≥0 mg at DB baseline, [redacted] reduced their NSIST dose by Week [redacted], including [redacted] who discontinued ≥1 NSIST. Mean MG-ADL CFB was [redacted] among those who decreased dose for ≥1 NSIST [redacted] among those who discontinued ≥1 NSIST).

The model was updated to include costs (Table 1 and Table 2) and disutilities (Table 3) of corticosteroids and the corticosteroid-sparing effect of zilucoplan. Due to scarcity of data, NSIST-sparing effects are not included in the model, and the costs and benefits of this are assumed to be accounted for by the CS sparing.

There are no data available on the costs or utility values associated with CS use in gMG; therefore, proxy conditions had to be used to incorporate the CS cost and disutility in the model.

For cost data, a study was identified that reported the costs of different doses of CS in 715 patients with systemic lupus erythematosus in the UK, using Clinical Practice Research Datalink (CPRD) and hospital episode statistics (HES) (1).

Table 1. Annual treatment cost of corticosteroids by dose

Daily dose of CSs	Annual cost, £
No CSs	3,842
<5 mg	5,699
5–7.5 mg	7,884
7.5–15 mg	9,241
≥15 mg	13,929

Abbreviations: CS, corticosteroids.
Source: Cost-effective model and Stirnadel-Farrant et al, 2023 (1).

Whilst the reported costs are for lupus erythematosus, which has more diverse symptoms than gMG and therefore potentially higher costs, this should be accounted for by removing the cost of those patients taking no CS. There were no data reported in literature for the HCRU or costs of CS use related to dose for patients with gMG.

The mean (SD) dose in this study was 3.2 (6.0) mg/per day, which is much lower than the doses that are seen in the RAISE study and used in the treatment of refractory gMG. The

study notes as a limitation that disease activity is not controlled for, and it is likely that higher disease activity is associated with higher CS use, which is likely to be the same in gMG.

Patients in the uncontrolled health state are assumed to have the annual cost associated with a daily CS dose of >15 mg, minus the costs for no steroids. Patients in the stable response health state are assumed to have an average annual cost of a daily CS dose of <5 mg, 5–7.5 mg, and 7.5–15 mg, minus the costs for no steroids. For zilucoplan only, patients in the continued response health state are assumed to have no costs associated with CS use. For IVIg, the Bril 2023 (2) study provides evidence that IVIg is not more effective than placebo at steroid sparing in gMG, and PLEX is assumed the same as IVIg.

Table 2. Assumed costs per health state

	Zilucoplan	IVIg/PLEX
CS costs assigned to continuous response health state	£0	£4,670.50
CS costs assigned to stable response health state	£ 4670.50	£4,670.50
CS costs assigned to uncontrolled health state	£10,087	£10,087

Abbreviations: CS, corticosteroids.
Source: Cost-effective model.

Table 3. Utility decrements with CS use

Steroid use	Health state	Utility decrement
High dose (≥10 mg/day)	Uncontrolled	0.18
Low dose (<10 mg/day)	Stable response	0.07

Abbreviations: CS, corticosteroids.
Source: Cost-effective model.

Please refer to the supporting document (technical report for the cost-effective model [version 4]) for full methodology and results.

2.2. Minimum symptom expression

The proportion of patients with gMG who achieve complete stable remission is low with current treatments available in England and Wales (3).

Minimal symptom expression (MSE), defined as achieving an MG-ADL score of 0 or 1 and representative of patients who become free or virtually free of MG symptoms, has been used as an evaluation tool for MG treatment goals in recent years (3).

In an analysis of MSE as a proportion of patients responding to zilucoplan in the RAISE-XT trial, of responders in RAISE (defined as 3-point change from baseline [CFB] in MG-ADL at Week [redacted]), [redacted] had MSE (Table 4). Therefore, of patients responding to zilucoplan, [redacted] become free or virtually free of MG symptoms. Please see Section 3.1.5 for the model updates.

Table 4. MSE as a proportion of anytime responders to zilucoplan

Week	R	NR	n	%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MSE, minimum symptom expression; NR, non-responders; R, responders.

2.3. Bivariate NMA

A bivariate network meta-analysis was conducted, on recommendation from the committee to consider a multivariate analysis, to obtain estimates of relative differences in studies containing IVIg so that they could be included. No studies comparing PLEX with placebo were identified, so it was not possible to include PLEX as a treatment in the bivariate network meta-analysis. Challenges with the evidence base for IVIg precluded a full multivariate approach incorporating three outcomes, as very wide credible intervals and significantly non-concordant results were observed; these are included in the report for transparency. For IVIg, CFB data from Wolfe 2002 and NCT02473952 showed a greater CFB for placebo compared with IVIg, whilst Zinman 2007 found the opposite; the only responder data, from NCT02473952, showed limited benefit for IVIg compared with placebo.

2.3.1. Responder outcomes

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

A total of eleven studies were included in the responder network; five studies reported both MG-ADL and QMG responder data as measured by a ≥3-point improvement in score, four studies reported only QMG responder data at a threshold of ≥3 points of improvement, and two studies only reported MG-ADL responder data for ≥3-point improvement.

The results for MG-ADL responder suggest an odds ratio (95% CrI) for zilucoplan of [redacted] and [redacted] for IVIg. Despite the uncertainty, the results show that zilucoplan is significantly better than placebo, whilst IVIg is not. Using the referent 31.5% (calculated as per Section 3.1.6) this translates into a responder rate in the CEM of [redacted] for zilucoplan and [redacted] for IVIg. To mitigate the remaining uncertainty, UCB has produced scenarios with extreme values to demonstrate the impact on the ICER.

2.3.2. Change from baseline outcomes:

Data for change from baseline in MG-ADL and QMG scores were assessed separately as continuous outcomes. A total of 14 studies were included in the network; 12 reported change

from baseline in both MG-ADL and QMG scores and 2 studies only reported CFB QMG data.

The results for MG-ADL CFB (95% CrI) were [redacted] for zilucoplan and [redacted] for IVIg, suggesting that, whilst zilucoplan demonstrates a significant CFB vs placebo, IVIg has a non-significant worsening effect on MG-ADL.

These incongruent outcomes for IVIg (improved responder and worsened CFB) and the unavailability of quality data for IVIg and PLEX are the reason that UCB believes there is limited utility in further network meta-analyses.

Please refer to the supporting document (Multivariate Bayesian Network Meta_Short Report) for full methodology and results.

2.4. MAIC

Acknowledging the limitations of the NMA not including all IVIg studies due to a lack of link to the network, or the lack of reporting of relevant outcomes, UCB has further performed two matched adjusted indirect comparisons of zilucoplan versus IVIg studies that could not be included in any of the NMAs.

Barth et al, 2011 (4), report on a 4-point QMG response at Week 2 (69% on IVIg vs 65% on PLEX) and QMG CFB. Bril et al, 2023 (2), report the secondary endpoint of MG worsening by Week 39, defined as a QMG score ≥4 points from baseline; IVIg showed no significant difference vs placebo.

For both studies, unanchored MAIC was used to compare the outcomes. Bril 2023 (2) was used to compare the outcome at 39 weeks and therefore, only unanchored MAIC can be performed using RAISE-XT open-label data. In Barth 2011 (4) IVIg was compared with PLEX, and in the absence of a common comparator only an unanchored MAIC can be performed. UCB chose to compare with the IVIg arm as this performed marginally better in the study and results could be conservatively generalised to PLEX.

The results showed that zilucoplan had significantly lower odds of MG worsening at Week 39 compared with placebo, had numerically higher QMG response at Week 2, and a significantly deeper QMG CFB at week 2 compared with IVIg. These results are consistent across all scenarios tested but have the limitations associated with unanchored comparisons.

Please refer to the supporting technical document (ZLP vs IVIg_ Technical report) for full methodology and results.

2.5. Baseline risk-adjusted NMA

As proposed by the committee, to assess the probable impact of the difference in placebo response, a baseline risk-adjusted (BR) NMA was conducted as per the guidelines laid down by Dias et al (5). The primary outcome of interest was a 3-point MG-ADL response. The regression estimate of beta from the NMA indicated that the baseline risk (placebo response) is not statistically significant.

Please refer to the supporting document (Multivariate Bayesian Network Meta_Short Report) for methodology and results.

3. Modelling

3.1. Updates to the model

Please refer to the separate supporting document (technical report for the cost-effective model) for full description on model methodology, assumptions, inputs and functionality. Adaptations made for this submission are summarised below.

3.1.1. Response assessment timepoint

The response assessment timepoint used in the model for zilucoplan and all comparators is 3 weeks in line with committee's preferred assumption.

3.1.2. Dosing frequency of IVIg and PLEX

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

3.1.3. PLEX administration costs (SA44A)

The updated model uses £455 for PLEX-specific administration cost every cycle (2 weeks) which aligns with committee's assumption of £910 every 4 weeks (NHS reference cost SA44A – Single Plasma Exchange).

3.1.4. Change from baseline for the 'continued response' health state

Change from baseline to for the 'continued response' health state was updated to reflect minimum symptom expression and new minimum symptom expression data was used to inform the proportions in each health state.

3.1.5. Minimum symptom expression

The data in Section 2.2 have been 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 [redacted] in the continued response health state, which achieves a 0.5 score from the baseline MG-ADL score in the model of [redacted]

UCB sought expert clinical opinion (n=5 clinical experts) on the estimated proportion of patients receiving IVIg or PLEX that achieve MSE. The expert opinion informed the [redacted] rate that was used in the model base case. No patients on standard of care (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 [redacted].

3.1.6. Response rates

The updated referent response rate (31.5%) is on the overall mean of log odds based on individual log odds for each study reporting MG-ADL response for placebo (Table 5). The odds ratios for response of [redacted] for IVIg and [redacted] for zilucoplan are from the bivariate NMA (please see Section 2.5). The odds ratio of [redacted] for PLEX is informed by the 57% responder rate for PLEX from Barth et al (4).

Table 5. Response rates in studies reporting MG-ADL response for placebo

Study	Treatment	N	n	Response Rate	logit
REGAIN	Placebo	63	25	0.40	-0.42
Howard 2019	Placebo	12	4	0.33	-0.69
RAISE	Placebo	88	47	0.53	0.14
ADAPT	Placebo	64	23	0.36	-0.58
CHAMPION MG	Placebo	89	30	0.34	-0.68
MycarinG	Placebo	64	13	0.20	-1.37
Bril 2021	Placebo	22	3	0.14	-1.85

3.1.7. Subsequent treatments

Acknowledging the paucity of data from patients with refractory gMG, UCB believes that the EAMS cohort data for use as subsequent treatment requires further analysis to make it relevant to the population appropriate for zilucoplan treatment. Not all patients are considered refractory (n=37/48 are refractory), and three patients received no treatment (these patients would not be eligible for zilucoplan, as zilucoplan is licenced as an add-on therapy and not a monotherapy) and 10 patients are on corticosteroids only (these patients would likely be considered for an NSIST prior to initiation of zilucoplan). Removing these patients from the cohort results in a total of 35 patients. To match the number of refractory patients (n=37), UCB suggests including two of the CS-only patients. This leaves a remaining 73% (n=35/48) of patients using IVIg/PLEX in the refractory subgroup. In respect of this, UCB has now applied the ongoing costs of this refractory SoC basket to the uncontrolled health state, where patients move to after treatment discontinuation or lack/loss of response. UCB believes this is a conservative approach.

Table 6. Patients receiving subsequent treatments in the reweighted EAMS basket

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

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

As four weekly cycles of IVIg or PLEX would be received by a patient on chronic IVIg/PLEX, an annual resource use of 13 cycles would be applied in the model should 100% of patients receive either intervention. As 56.7% of patients receive IVIg (Table 6), 7.37 cycles of IVIg are applied in the uncontrolled health state. For PLEX, 2.46 cycles are applied to account for 18.9% of patients. The remaining 24.3% of patients receive only low-cost SoC ongoing in the model.

To account for the ongoing health effects, UCB has applied the stable response MG-ADL value (and thus associated utility score) to the period post-discontinuation.

3.1.8. Benefit of at-home subcutaneous administration

The “AdminTime” worksheet of the updated model reports the NHS staff and patient time for zilucoplan and comparators. The model assumes 52 minutes for a round trip to and from the hospital per infusion in addition to the time spent at the hospital. This calculation considers the distribution of the population between rural and urban areas, the percentage of people using cars in each area, and the travel times to the hospital for both public transport and car travel (6-8). The model only calculates the number of hours associated with administration during the time-on-treatment period. Compared with IVIg, zilucoplan saves [redacted] hours of NHS staff time and [redacted] hours of patient time; for the comparison with PLEX, [redacted] staff hours and [redacted] patient hours are saved.

0.05 per-administration utility of self-administration is assumed in the model based on the values suggested in available literature (9-13).

3.1.9. Duration of exacerbation and crisis

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

3.1.10. Caregiver disutility

The updated model incorporated the parameters for caregiver disutilities, considering the proportion of patients requiring caregiver support according the MD-AGL score ranges and utility decrements reported in previous submissions to NICE for relevant populations (14).

Table 7. Caregiver disutility assumptions

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

Source: National Institute for Health and Care Excellence, 2023 (14).

3.2. Base case inputs and settings

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

3.2.1. Decision problem definitions

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

Table 8. 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>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>UCB data on file, 2022 (15)</td></tr>
<tr><td>Males, %</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>UCB data on file, 2022 (15)</td></tr>
<tr><td>Average MG-ADL score at the start</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>UCB data on file, 2022 (15)</td></tr>
<tr><td>Average weight (kg)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>UCB data on file, 2022 (15)</td></tr>
<tr><td>Average BSA (m^2)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Mosteller, 1987 (16); UCB data on file, 2022 (15)</td></tr>
<tr><td>Baseline BMI (kg/m^2)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>UCB data on file, 2022 (15)</td></tr>
</table>
Abbreviations: BSA, body surface area; BMI, body mass index; MG-ADL; Myasthenia Gravis Activities of Daily Living.</td></tr>
<tr><td>Intervention</td><td>Zilucoplan</td></tr>
<tr><td>Comparators</td><td>• IVIg/SCIg
• PLEX</td></tr>
<tr><td>Analysis type</td><td>Cost-utility analysis</td></tr>
<tr><td>Perspective</td><td>NHS and Personal Social Services in England</td></tr>
<tr><td>Discount rate</td><td>3.5% for costs and QALYs</td></tr>
<tr><td>Model type</td><td>State-transition cohort (Markov model)</td></tr>
<tr><td>Health states</td><td>• Uncontrolled on high-dose steroids and ISTs
• Continued response
• Stable response
• Loss of response
• Acute exacerbation
• Myasthenic crisis
• Death</td></tr>
<tr><td>Cycle length</td><td>2 weeks</td></tr>
<tr><td>Time horizon</td><td>Lifetime ([redacted] 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: GBP, British pound sterling; gMG, generalized Myasthenia Gravis; IST, immunosuppressive therapies; IVIg, intravenous immunoglobulin; NHS, National Health Service; PLEX, plasma exchange; QALY, quality-adjusted life year; SCIg, subcutaneous immunoglobulin; WTP, willingness to pay.

3.2.2. Efficacy assumptions and inputs

Table 9. Primary response rate and response assessment timepoint

Treatment	Odds Ratios (SE)	Response rate used in the model	Response assessment timepoint used in the model (weeks)	Source
Referent response rate	1.00	31.50%	NA	Per Section 3.1.6
Zilucoplan	[redacted]	[redacted]	3.00	mvNMA
IVIg/SCIg	[redacted]	[redacted]	3.00	mvNMA
Refractory standard of care	[redacted]	[redacted]	3.00	mvNMA
PLEX	[redacted]	57.00%	3.00	Barth 2011 (4)

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

The maximum treatment duration (treatment-stopping rule) was 2 years (104 weeks) for 100% of patients for all treatments.

Table 10. Treatment-specific MG-ADL score CFB

Treatment	Continued Response	Loss of response	Stable response	Source
Zilucoplan	[redacted]	[redacted]	[redacted]	Section 3.1.5
IVIg/SCIg	[redacted]	3.00	3.00	Section 3.1.5
Refractory standard of care	[redacted]	3.00	3.00	Section 3.1.5
PLEX	[redacted]	3.00	3.00	Section 3.1.5

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

Time of last response assessment from trial was 3 weeks for zilucoplan and all comparators.

Table 11. Response distribution

	Continued response	Loss of response	Stable response	Source
Zilucoplan	[redacted]	[redacted]	[redacted]	Section 2
IVIg/SCIg	[redacted]	[redacted]	[redacted]	Section 2
Refractory standard of care	[redacted]	[redacted]	[redacted]	Section 2
Plasma exchange	[redacted]	[redacted]	[redacted]	Section 2

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

Long-term MG-ADL score assumes a period of 14 weeks was assumed before 0% of patients return to the new uncontrolled level.

Table 12. Clinical event rates

Health state	Event	Mean	Lower range	Upper range	Source
Annual event rate					
Uncontrolled	Exacerbation	0.651	0.59	0.72	Abuzinadah et al 2021 (17)
Response	Exacerbation	0.244	0.194	0.307	Abuzinadah et al 2021 (17)
Uncontrolled	Myasthenic crisis	0.062	0.06	0.07	Abuzinadah et al 2021 (17)
Response	Myasthenic crisis	0.023	0.011	0.048	Abuzinadah et al 2021 (17)
2-week event rate					
Exacerbation	Myasthenic crisis	0.184	0.166	0.202	Gajdos, 2005 (18)

Table 13. Mortality parameters

Health state/event	Mean	Lower range	Upper range	Source
Uncontrolled/response/exacerbation	1.00	0.90	1.10	
Myasthenic crisis	4.47%	4.02%	4.92%	Alshekhlee et al, 2009 (19)

3.2.3. Cost assumptions and inputs

The model assumptions were as follows:

- Vial sharing is excluded
- SOC costs are included in the targeted therapies
- 100% adherence is assumed

Table 14. Administration costs per treatment

	Mean	Lower	Upper	Source
Intravenous				
Initial (£)	195.74	£176.17	£215.32	
Subsequent (£)	184.23	£165.81	£202.65	
IG-specific (£)	504.67	454.200	555.133	
PLEX-specific (£)	455	409.500	500.500	Section 3.1.3
Subcutaneous				
Initial (£)	41.00	£36.90	£45.10	
Oral				
Initial (£)	0.00	£0.00	£0.00	

Abbreviations: IG, immunoglobulin; PLEX, plasma exchange.

Table 15. 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
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 16. Refractory standard of care basket costs

Medication	Bundle composition			Average treatment cost per model cycle (£)	Admin costs per model cycle (£)
	Mean	Lower	Upper		
Azathioprine	17.80%	16.02%	19.58%	5.88	0.00
Cyclophosphamide	0.00%	0.00%	0.00%	0.00	0.00
Cyclosporine	7.50%	6.75%	8.25%	95.59	0.00
IVIg	56.7%	51.0%	62.4%	2,322.00	757.00
Methotrexate	2.30%	2.07%	2.53%	2.20	0.00
Mycophenolate mofetil	19.00%	17.10%	20.90%	6.70	0.00
PLEX	18.9%	17.0%	20.8%	6,468.63	1,137.50
Corticosteroids	63.20%	56.88%	69.52%	2.42	0.00
Rituximab	0.00%	0.00%	0.00%	3,230.64	379.97
SCIg	0.00%	0.00%	0.00%	0.00	0.00
Tacrolimus	5.70%	5.13%	6.27%	202.31	0.00
Pyridostigmine	80.50%	72.45%	88.55%	6.36	0.00
Average cost per model cycle (£)				2,565.34	644.21
Average add-on cost per model cycle for ZLP/IVIg/PLEX (£)				26.19	0

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

Table 17. 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	7.37	11.70-14.30†	0.00	0	0.00	0
PLEX	12,937.25	2.46	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 (£)		94,417.54		9,111.33		4,440.83	
Total cost for IVIg and PLEX		94,417.54		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 18. 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.

3.2.4. 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 19. MG0010 outcomes

	Mean	Lower	Upper	Source
Baseline EQ-5D	[redacted]	[redacted]	[redacted]	UCB data on file (15, 20)
Baseline BMI (kg/m^2)	[redacted]	[redacted]	[redacted]	UCB data on file (15, 20)
Intercept	[redacted]	[redacted]	[redacted]	UCB data on file (20, 21)
Coefficient of baseline EQ-5D	[redacted]	[redacted]	[redacted]	UCB data on file (20, 21)
Coefficient of MG-ADL score	[redacted]	[redacted]	[redacted]	UCB data on file (20, 21)
Coefficient of BMI	[redacted]	[redacted]	[redacted]	UCB data on file (20, 21)

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

Table 20. 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 21. Clinical event disutility

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

Table 22. Annual disutility of steroid use

	Disutility	Duration (days)
Uncontrolled - High-dose (> 10mg/day)	0.18	365.25
Stable response - Low-dose (< 10mg/day)	0.07	365.25

Continued response - no steroid use	0.00	365.25

Table 23. Per-administration utility of self-administration

Utility	Duration (days)
0.05	1.00

3.3. Model results and scenario analyses

3.3.1. Base case results (discounted)

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

Table 25 presents the estimated total costs and QALYs for zilucoplan and comparators as well as the pairwise comparison in terms of incremental costs, QALYs, and ICER (£/QALYs) assuming the £30,000 WTP threshold. [redacted].

Table 24: Base case results (discounted)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.6468			
IVIg/SCIg	[redacted]	9.4413	[redacted]	0.2055	[redacted]
Plasma exchange	[redacted]	9.4713	[redacted]	0.2055	[redacted]

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

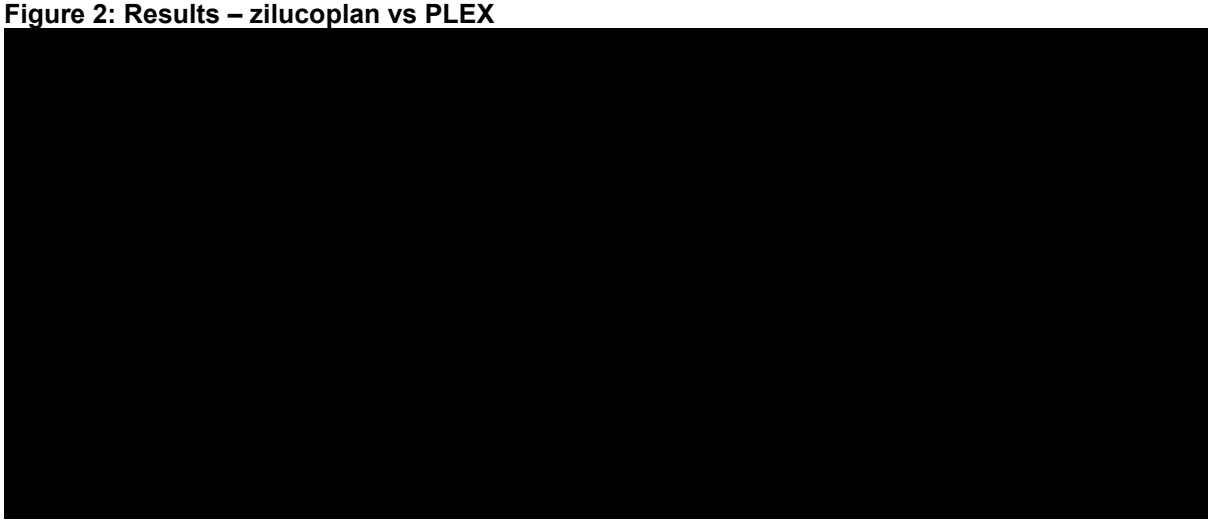
3.3.2. Deterministic sensitivity analysis results

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 a 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, accordingly.

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.

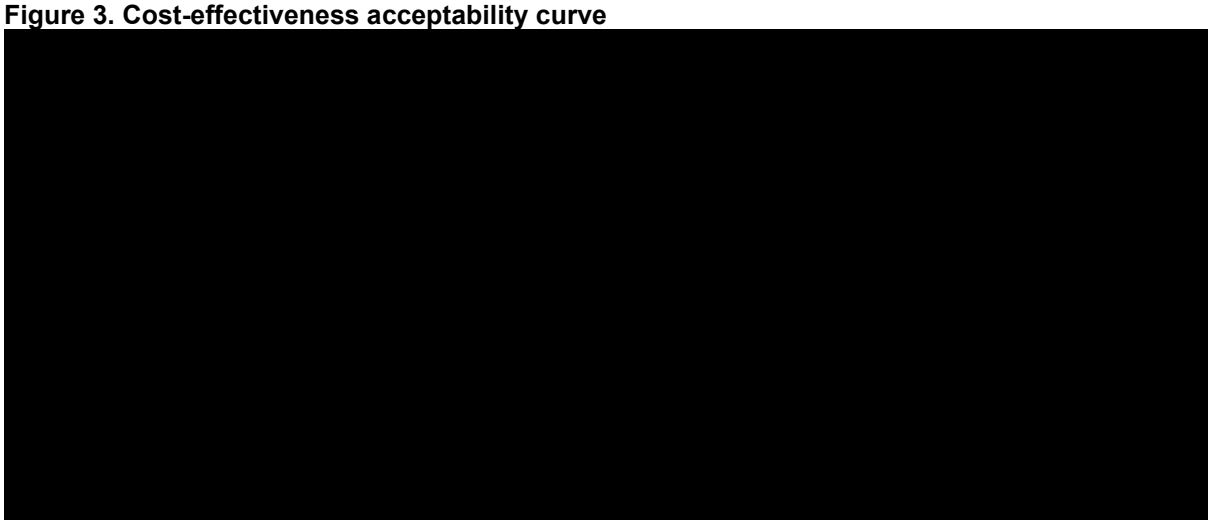
3.3.3. Probabilistic sensitivity analysis results

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. In the PSA all parameters varied 10% around the mean, except parameters informed by the CODA and mvNMA. Results are shown in Table 25 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 is reflective of the intervention arm relative to the comparator arm, and the level of uncertainty surrounding the point estimates. Across all comparisons, 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 25. Probabilistic sensitivity results (all parameters varied 10% around mean, except parameters informed by CODA and mvNMA)

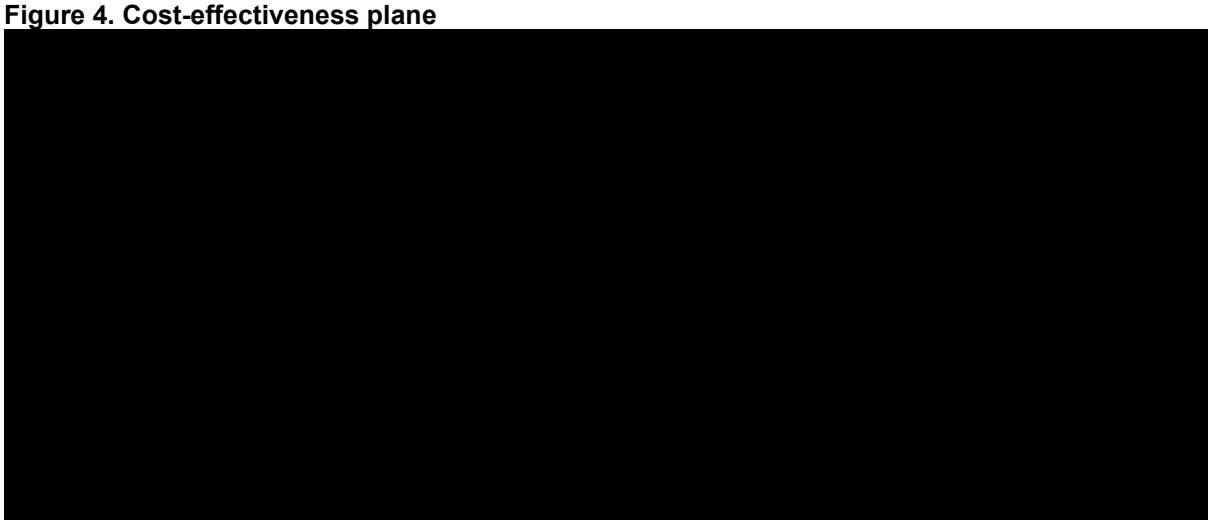
Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.6384			
IVIg/SCIg	[redacted]	9.4485	[redacted]	0.1899	[redacted]
Plasma exchange	[redacted]	9.4537	[redacted]	0.1848	[redacted]

Figure 3. Cost-effectiveness acceptability curve



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

Figure 4. Cost-effectiveness plane



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

3.3.4. Scenario analyses

3.3.4.1. 70% response rate for IVIg and PLEX for Zilucoplan based on mvNMA)

This scenario illustrates the summary of model results when a 70% primary response rate is assumed for IVIg and PLEX, which are consistent with base-case pairwise ICER results.

Table 26: Scenario analysis results - 70% response rate for IVIg and PLEX

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan		9.6468			
IVIg/SCIg		9.5135		0.1333	
Plasma exchange		9.5135		0.1333	

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

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

This scenario provides estimates when societal costs and utilities are integrated in the model as described in the Section 3.1.10 and the global CEM technical report (Section 2.4.5). The results of this scenario show higher total costs and lower total QALYs across all interventions compared with the base-case. Given that both the cost increase and QALY decrease (vs base case) is lower with zilucoplan than the comparators, the incremental savings and QALYs for zilucoplan vs the comparators are greater than in the base case.

Table 27: Scenario analysis results - Societal perspective

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	8.2371			
IVIg/SCIg	[redacted]	8.0022	[redacted]	0.2349	[redacted]
Plasma exchange	[redacted]	8.0520	[redacted]	0.1851	[redacted]

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

3.3.4.3. Absolute health state values using the definition of mild/moderate/severe

This scenario uses the absolute health state definitions and values to test the robustness of ITT regression for utility parameters chosen in the base case. The results show robustness of the chosen approach.

Table 28: Health state definitions and utility values

Health State	Definition	Utility value
Severe	Uncontrolled, patients with high disease activity	[redacted]
Moderate	Stable response, patients with some disease activity	[redacted]
Mild	Continued response, patients with limited disease activity	[redacted]
The steroid assumptions of severe = high dose, moderate = lower dose, and mild = no dose have face validity also.		

Table 29: Scenario analysis results - Absolute health state values using the definition of mild/moderate//severe stated in Table 26

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	6.9155			

IVIg/SCIg	[redacted]	6.6774	[redacted]	0.2381	[redacted]
Plasma exchange	[redacted]	6.7520	[redacted]	0.1635	[redacted]

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

3.3.4.4. Exclude disutility of corticosteroids

In this scenario, QALYs are higher across all comparators in comparison with the base case. However, the impact on total and incremental QALY results is minimal, owing to the per-cycle disutility of corticosteroids being low.

Table 30: Scenario analysis results – Steroid disutility removed

Technologies	**Total**		**Incremental**		**Pairwise ICER (£/QALY)**
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.8410			
IVIg/SCIg	[redacted]	9.6399	[redacted]	0.2011	[redacted]
Plasma exchange	[redacted]	9.6677	[redacted]	0.1733	[redacted]

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

3.3.4.5. Self-administration utility removed

Although the total QALYs for Zilucoplan decreased slightly in this scenario, the effect is minimal, owing to the per-cycle parameter being so low. The pairwise ICER in this scenario is consistent with base-case results.

Table 31: Scenario analysis results - Self-administration utility gain removed

Technologies	**Total**		**Incremental**		**Pairwise ICER (£/QALY)**
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.5703			
IVIg/SCIg	[redacted]	9.4413	[redacted]	0.1289	[redacted]
Plasma exchange	[redacted]	9.4713	[redacted]	0.0990	[redacted]

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

3.3.4.6. Steroid costs removed

The pairwise ICER in this scenario is consistent with base-case results.

Table *32*: Scenario analysis results - Steroid costs removed

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.6468			
IVIg/SCIg	[redacted]	9.4413	[redacted]	0.2055	[redacted]
Plasma exchange	[redacted]	9.4713	[redacted]	0.1755	[redacted]

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

3.3.4.7. If PLEX has a 10% lower acquisition cost and is 10% more effective (62.70% primary response rate)

This scenario investigates hypothetical new PLEX with slightly cheaper price and slightly improved effectiveness versus the blended standard of care.

Table 33: Scenario analysis results - PLEX has a 10% lower acquisition cost and is 10% more effective

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Plasma exchange	1,862,420.84	9.4892			
Blended standard of care 'basket'	1,879,923.77	9.3860	-17,502.93	0.1	Dominant

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

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	• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology. • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UCB Pharma Ltd (Company)

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

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. The use of a blended standard of care 'basket' as comparator (Section 3.4 in the draft guidance)	The company strongly disagrees with the blended standard of care 'basket' as a comparator against zilucoplan, and believes the decision is inappropriate based on the evidence presented. UCB maintains that zilucoplan will displace intravenous immunoglobulin (IVIg) and plasma exchange (PLEX) in clinical practice in refractory patients who have failed standard of care alone and therefore IVIg and PLEX are the only relevant comparators to zilucoplan. This is in agreement with what stated in the section of the ACD titled 'Why the committee made these recommendations' (paragraph 1, lines 5–8): 'Zilucoplan would be used as an add-on to standard treatment for people who test positive for anti-acetylcholine receptor antibodies and whose condition has not improved with standard of care alone'. The NICE manual (PMG36) states that pairwise comparisons are relevant and justified when the technology is expected to specifically displace individual comparators (1) The proposed positioning of zilucoplan is in line with a myasthenia gravis treatment algorithm being developed by the Association of British Neurologists myasthenia gravis specialist interest group and discussed in a recent NICE Heath Technology Assessment submission for newly licensed targeted therapies for myasthenia gravis. The algorithm places targeted treatments, including complement inhibitors such as zilucoplan, as a fourth line option, displacing chronic IVIg and PLEX. The rationale behind the EAG preference for a basket of care approach is that some centres do not have access to IVIg and/or PLEX. The company is unaware whether this preference was due to evidence generated by EAG discussions with clinicians or to other sources. It is the company's understanding that patients with refractory generalised myasthenia gravis needing IVIg and/or PLEX are referred to specialist neurology centres/hospitals where both treatments are available. To demonstrate that the standard of care 'basket' is not suitable as comparator, the company analysed the EAG's version of the model, including a scenario in which a new version of PLEX has a 10% lower acquisition cost and is 10% more effective than the version of PLEX currently available in the NHS (see supporting information document Section 3.3.4.7). This analysis results in incremental costs of £106,098 and incremental quality adjusted life years of 0.1 versus the

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	standard of care 'basket' as a comparator. The resulting incremental cost-effectiveness ratio is £1,028,234 per quality adjusted life year. This is far above (~34 times) the top end of the willingness-to-pay threshold accepted by NICE, and would result in this less costly, more effective version of PLEX to be refused reimbursement, which is clearly an incorrect outcome. The method of blended comparator is therefore not appropriate and would reach the illogical conclusion that a cheaper and more effective PLEX would not be recommended. However, the company acknowledges the view of the committee that some refractory patients who have received IVIg and/or PLEX may have periods in which they do not receive treatment for various clinical reasons. The company believes that this scenario would be better modelled in subsequent treatments for those patients who have lost response as it avoids the conclusion that cheaper and better versions of currently used interventions would not be recommended. The company has now modelled the use of subsequent treatments including a proportion of patients receiving standard of care; this proportion of patients remains constant across time but would in reality represent patients moving between IVIg/PLEX and standard of care. The company believes that this approach provides a more accurate estimate of the ICER than using a blended comparator. UCB understands the concern that all refractory patients could potentially be considered for zilucoplan should it be approved. However, as submitted by the clinical experts, zilucoplan is expected to be used following review by a multidisciplinary team at an MG specialists' centre and funding approval managed through Blueteq. Additionally, the EAG based the proportion of people receiving each comparator on the published efgartigimod Early Access to Medicines Scheme (EAMS) patient cohort (2, 3). While this evidence adds to UK published literature in MG, there are limitations pointed out in the study publication (4). The company disagrees with the composition and proportions of the basket assumptions based on the following points: • The full dataset was not reported • On page 9 of the draft guidance, reports that the EAG noted ''refractory was defined in a slightly different way' in the efgartigimod EAMS. The efgartigimod EAMS paper reports only 77% [n=37] of patients were refractory (2, 3).

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	The population recruited in the efgartigimod EAMS is broader than the population presented in zilucoplan company submission. The entry criteria used in the efgartigimod EAMS is patients with acetylcholine receptor-antibody-positive generalised myasthenia gravis, including **but not limited** to patients with refractory generalised myasthenia gravis (2, 3). Therefore, as not all patients were refractory, the population in the efgartigimod EAMS does not match the population under consideration in this single technology appraisal for zilucoplan • In addition, the publicly available results do not specify the standard of care therapies in the refractory subgroup. In total, 4.2% (n=2) of patients were provided efgartigimod as a bridging treatment which is outside of the proposed positioning of zilucoplan. Three patients (6.3%) were reported as having no immunosuppressive/immunomodulatory treatment, but it is unknown if these patients were refractory patients or otherwise. The company has based the above considerations on the available published data and is unaware of whether the EAG or the committee have had access to additional data concerning the efgartigimod EAMS population. As part of this response, the company has submitted an updated model, requested by the committee, that includes in the base case a standard of care basket as subsequent treatment for patients who discontinue due to lack of response to zilucoplan and its comparators (IVIg and PLEX) (see point 5).
2. Unmet need in refractory MG (Section 3.1 in the draft guidance)	There is an urgent unmet need for a new treatment for patients with refractory generalised myasthenia gravis who are not sufficiently responding to acetyl cholinesterase inhibitors, corticosteroids, or non-steroidal immunosuppressants. The only routinely available treatment options in England and Wales are regular IVIg and PLEX. As mentioned in the draft guidance, IVIg and PLEX both pose a significant treatment burden for the patient and are resource-intensive for the healthcare system. Patients on IVIg and/or PLEX typically attend hospital every 4 weeks. At the time of writing, no targeted treatment for generalised myasthenia gravis has received a positive recommendation from a NICE committee, which is in stark contrast to other disease areas, e.g. multiple sclerosis, and lupus. As a result, access to innovative treatments for generalised myasthenia gravis is limited to clinical trials, compassionate use schemes,

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	or individual funding requests. This contrasts with access to targeted treatments for generalised myasthenia gravis in France, Germany, Italy, Spain Austria, Belgium, the Netherlands, Greece, and countries outside of Europe Further highlighting the need for a targeted treatment, [redacted] patient applications for zilucoplan have been approved, and 48 patients accessed efgartigimod for acetylcholine receptor antibody-positive generalised myasthenia gravis via the EAMS (4). Patients with generalised myasthenia gravis experience debilitating symptoms that severely impact all aspects of their lives (5). Living with refractory generalised myasthenia gravis has a substantial negative impact on education and work, with careers interrupted or ended prematurely. In addition, patients feel that living with generalised myasthenia gravis impacts their decision to have a family. Concerns about the effects of uncontrolled generalised myasthenia gravis symptoms on daily living, and their ability to cope as a parent, can deter patients from planning a pregnancy (5). Contraindications to therapy during pregnancy and lactation mean women may face a difficult choice between starting a family and managing symptoms of generalised myasthenia gravis (5). Younger patients in particular may feel a sense of loss of life due to restrictions in activity and limitations in life choices (5). Patients with refractory generalised myasthenia gravis are sub-optimally managed with the treatments currently available on the NHS. The consequences of patients staying on standard of care despite being refractory to treatment include poor symptom control, increased risk of myasthenic crisis (6-10) and the debilitating side effects of corticosteroids (diabetes, osteoporosis, depression and infection, which can trigger a myasthenic exacerbation) (7, 11-14). Current treatments also have delayed onset of action (usually 6–18 months, but it can take up to 2 years to achieve maximal clinical benefit), contributing to poor disease control and leaving patients with a high symptom burden and at risk of exacerbation and crisis (6-8). Currently available treatments for patients with refractory generalised myasthenia gravis may require patients to travel long distances for treatment at specialist centres, and even stay in hospital for repeat treatment if they live too far away to travel for each session (15, 16), which is burdensome for patients and the NHS.

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	Zilucoplan is a fast-acting, efficacious, targeted treatment for generalised myasthenia gravis that can be administered at home by the patient, which will not only reduce burden on patients, carers, and the healthcare system, but also significantly improve quality of life for the currently under-served patients with refractory generalised myasthenia gravis. To further minimise the treatment burden on both patients and the NHS, UCB has commissioned a service to offer home delivery of zilucoplan. The use of zilucoplan in place of IVIg and PLEX would enable more IVIg (which is a finite supply) and PLEX to be made available to patients with other diseases who need it. The NICE manual states that although decisions about the acceptability of the technology as an effective use of NHS resources will consider the degree of certainty around the value for money, the committee will be mindful that there are certain technologies or populations for which evidence generation is particularly difficult, because they are rare diseases and/or the technology is innovative (1). UCB would also like to highlight that a priority of the Rare Disease Action Plan 2024 is to improve access to specialist care, treatments, and drugs (17). Zilucoplan presents an opportunity for patients living with a severe and debilitating disease such as refractory generalised myasthenia gravis to access an efficacious treatment that reduces the symptom burden, with no new significant capital investment or service development required and is a candidate for the interim innovative medicines fund.
3. How the company sought to address the uncertainties in the CS (Section 3.16 in the draft guidance)	The company would like to emphasise that given the paucity of data in refractory generalised myasthenia gravis; a substantial effort has been made to address the uncertainties in the company submission. In addition, the company has presented new evidence that will address some of the uncaptured health benefits of zilucoplan. The new evidence submission includes: • Updated cost-effectiveness model that seeks to address subsequent treatments and other uncaptured benefits of zilucoplan (please see Section 3 in the supporting document)

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	• New indirect treatment comparison methodologies that show consistent outcomes, despite underlying heterogeneity in the studies, particularly those of IVIg (please see Section 2 in the supporting document) • New data on the steroid-sparing and minimum symptom expression achieved with zilucoplan, highlighting the value of zilucoplan (please see Sections 2.1 and 2.3 in the supporting document, respectively) UCB would also like to highlight that a priority of the Rare Disease Action Plan 2024 is to improve access to specialist care, treatments, and drugs (17).
4. Bivariate NMA (Section 3.8 in the draft guidance)	There is a lack of published studies on the use of IVIg and PLEX in myasthenia gravis, as IVIg and PLEX do not have marketing authorisation for use in generalised myasthenia gravis. IVIg and PLEX are therefore used off licence in England in Wales to treat generalised myasthenia gravis in the absence of approved targeted treatments. The updated analysis (section 2 of supporting document) shows that: • Zilucoplan has a numerically better proportion of responders compared with IVIg, and has demonstrated a significantly increased change from baseline when compared with IVIg in the network meta-analysis (and in the matched-adjusted indirect comparison) Despite data limitations causing uncertainty with wide credible intervals, there is general concordance with point estimates across analyses (matched-adjusted indirect comparison, network meta-analysis, bivariate network meta-analysis and the naive treatment comparison). Please see section 2.3 in the supporting document.
5. Modelling subsequent treatments (Section 3.10 in the draft guidance)	Formally modelling treatment sequences would be challenging as the results would be too uncertain due to the lack of available data. There is uncertainty around the number lines of subsequent treatments needed, what treatments clinicians will consider after failure on IVIg/PLEX and whether lack of response to index will be a treatment effect modifier.

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	However, UCB acknowledge that the validity of a model which did not allow for repeat attempts of treatment and switching of treatment may be challenged. Similarly, a model which kept patients on IVIg or PLEX persistently despite loss of response might also be challenged. Therefore, the company has submitted an adapted model where subsequent treatments are assumed to be in steady state but reflecting movement of patients between treatment with IVIg/PLEX and standard of care. UCB also acknowledge the statements (3.12) from patient and clinical experts that generalised myasthenia gravis requires lifelong management.
6. Substantial placebo response in RAISE (Sections 3.5 and 3.11 of the draft guidance)	A BL risk-adjusted network meta-analysis was conducted, which showed that the placebo response was not significantly different between the studies, and that the results for change from baseline in myasthenia gravis-activities of daily living score were similar to those from the conventional network meta-analysis (please see the supporting document for methods and full results). One possibility for a higher placebo response in RAISE compared with efgartigimod is that, with daily self-administration, patients felt empowered by having a way to improve their health after a long period with uncontrolled symptoms. An analogue is a study in osteoarthritis that reported that the more frequently administered an intervention, the higher the placebo effect (18).
7. Referent response rate (Section 3.11 in the draft guidance)	The data applied in the model are limited by the small number of studies available. In the updated model, the referent response rate is calculated as the overall mean of log odds based on individual log odds for each study reporting MG-ADL response for placebo. In the previous version of the model, on which the draft guidance is based, the referent response rate was calculated as the average response rate for the placebo arms across studies identified in the network meta-analysis. Neither of these calculations offer a substantially different outcome, with the mean of log odds giving 31.5% response, vs a 32% simple average of included studies reporting MG-ADL response.
8. Include uncertainties from NMA in modelling	The bivariate network meta-analysis is associated with uncertainties due to the lack of clinical evidence, but UCB has incorporated the CODA from this analysis into the PSA in the CEM

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(Section 3.8 in the draft guidance)	Further, scenarios have been used to explore uncertainty around the response rate and change from baseline, including: • Setting change from baseline data to –3 for all comparators for stable responder (instead of the network meta-analysis outcomes) • Extreme values for IVIg/PLEX responder rates, i.e. 70% primary response rate
9. Response assessment timepoint of 3 weeks (Section 3.12 in the draft guidance)	Thank you for your comments. UCB agrees with a response assessment timepoint of 3 weeks, as defined in the draft guidance document, and has made the required changes to the cost-effectiveness model.
10. Administration costs of IVIg and PLEX applied every 4 weeks (Section 3.14 in the draft guidance)	Thank you for your comments. UCB agrees with the committee's assumptions and has made the required changes to the cost-effectiveness model.
11. PLEX administration costs (SA44A) (Section 3.14 in the draft guidance)	Thank you for your comments. UCB agrees with the committee's assumptions on PLEX administration costs and has made the required changes to the cost-effectiveness model.
12. Response rates from Barth et al (Section 3.11 in the draft guidance)	The response rates for IVIg and PLEX were not back calculated but taken directly from Barth et al (19) (page 4 of the article, third paragraph [see below]) and expressed as the proportion (%) of responders. Patients were classified as responders if they achieved a quantitative myasthenia gravis score improvement of 3.5 points as reported by Barth et al

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	(19). The model presents both response rates and odds ratios. For the other treatments, the odds ratios from the network meta-analysis were transformed into response rates. Although the response rates from Barth et al were converted to odds ratios, the odds ratios were not used in the model; only the response rate was used to inform the transition probabilities. Please see section 2.1 in the supporting information.
13. Uncaptured benefits: corticosteroid sparing (Section 3.19 in the draft guidance) and minimum symptom expression	Patients face a severe treatment burden from currently available therapies and must balance the benefits of controlling symptoms with severe, debilitating treatment side effects. Corticosteroids are associated with severe side effects such as diabetes, osteoporosis, depression and infection, which can trigger a myasthenic exacerbation and affect QoL (7, 11-14, 20-22). Paradoxically, high dose corticosteroids are associated with a temporary worsening of symptoms and an extended hospital stay (23, 24). Long-term corticosteroids use is also associated with a cost burden (25). A post-hoc analysis of data from RAISE-XT shows that patients receiving zilucoplan were able to reduce or discontinue corticosteroids (see supporting document). The model was updated to include costs and disutilities of corticosteroids and the corticosteroids-sparing effect of zilucoplan (please see Section 2.1 in the supporting document). In addition to the corticosteroid-sparing effect of zilucoplan, an analysis of MSE as a proportion of patients responding to zilucoplan in the RAISE-XT trial was conducted. Of patients in response at week [redacted] (defined as 3-point change from baseline in MG-ADL), [redacted] had MSE. Therefore, of patients responding to zilucoplan, [redacted] become free or virtually free of MG symptoms (please see Section 2.3 in the supporting document).
14. Uncaptured benefits: convenience associated with at-home sc	There are benefits to both patients (improved quality of life) and the NHS (reduced healthcare resource utilisation) associated with at-home self-administration of zilucoplan, compared with highly burdensome in-hospital intravenous administration of treatments such as IVIg and PLEX. PLEX and IVIg are also associated with the risk of rare but life-threatening side effects (such as infection and hypotension with anaphylactic shock) (26, 27).

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administration (Section 3.19 in the draft guidance)	It is evident from the literature that patients prefer to receive subcutaneous at-home administration to IVIg in hospital. A systematic literature review on patient preferences for subcutaneous injection versus intravenous administration of treatment for chronic immune system disorders reported that, of 18 studies comparing intravenous and subcutaneous immunoglobulin therapy, 16 concluded that patients prefer subcutaneous administration (28). Patients who preferred subcutaneous administration preferred treatment at home due to the convenience and comfort of home treatment and the ability to avoid hospital attendance. A study in patients with multiple sclerosis showed that 87.8% of patients preferred subcutaneous administration over intravenous, and 82.9% of patients specified “requires less time in the clinic” as the reason for the preference for subcutaneous administration (29). There remains limited data relating to the difference in utility between intravenous and subcutaneous administration, but of the few studies found, the increment ranges from 0.03 to 0.12 (30-37).
15. Uncaptured benefits: adherence associated with at-home sc administration (Section 3.19 in the draft guidance)	Compliance to zilucoplan is high. In a post-hoc study on compliance in RAISE-XT, patients reported taking [redacted] of their medication, and [redacted] of them reported [redacted] compliance, over a median study medication duration of [redacted], suggesting that long-term compliance to zilucoplan administration is high (please see the supporting document for the abstract). Compliance by age, sex, duration of disease, and baseline myasthenia gravis-activities of daily living are similar to overall compliance.
16. Uncaptured benefits: carer cost and disutility (Section 3.19 in the draft guidance)	Myasthenia gravis is associated with a significant carer burden. Burden on family and friends of patients with generalised myasthenia gravis were highlighted by expert patients at the ACD meeting on 14 June 2024. Societal costs for patients (work time lost) and caregiver burden (time spent caring for a patient with generalised myasthenia gravis) by MG-ADL range have now been included as an option in the updated model and scenarios have been provided with these options included (please see the supporting document).

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	The company recommends that expert patients and clinicians are invited to present at ACM2 so that detailed perspectives can be shared on the burden that both generalised myasthenia gravis and the currently available treatments have on patients, carers, and the NHS.

Insert extra rows as needed

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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 5pm on Thursday 25 July 2024. Please submit via NICE Docs.

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Overview of new evidence and modelling updates and results

1. Executive summary

In the draft guidance published by NICE for zilucoplan for treating antibody-positive generalised myasthenia gravis, the committee has requested the following:

- An indirect treatment comparison (ITC) that includes intravenous immunoglobulin (IVIg) and plasma exchange (PLEX), and accounts and adjusts for differential placebo response observed in the clinical trials
- Including subsequent IVIg and PLEX in the modelling and the effect on the -cost-effectiveness estimates
- Scenario analyses incorporating some of the uncaptured benefits of zilucoplan and testing the robustness of the model assumptions.

This document includes an overview of new evidence for zilucoplan (Section 2) referred to in the ACD response comments form. Section 3 presents updates made to the model following the draft guidance consultation. This document only presents the data that is not included in the supporting files being submitted (NMA, MAIC reports and global CEM technical report).

The findings of the indirect treatment comparisons conducted (bivariate NMA, MAIC and NMA) demonstrate that zilucoplan is significantly better than standard of care (SoC) alone in patients with gMG, with similar results in refractory patients and despite a high placebo response on some endpoints. Zilucoplan is associated with a numerically larger proportion of treatment responders, and has demonstrated a significantly larger change from baseline, when compared with IVIg in the NMA and MAIC. Despite data limitations causing uncertainty in the results with wide credible intervals, there is general concordance with point estimates across the analyses (MAIC, NMA, NMA, naive comparison).

In addition, there are uncaptured benefits and non-health factors that could not be included in the modelling, for example patient and nurse time lost when in-hospital treatment is needed, and the benefits associated with the NSIST-sparing effect of zilucoplan

Section 3.3 provides the results of the cost-utility analysis utilising the base-case settings described in Section 3.2 as well as the results of scenario analyses. In the base-case, zilucoplan was [redacted] compared with both IVIg and PLEX. The results of the probabilistic sensitivity analysis and scenario analyses were consistent with the base-case. The deterministic sensitivity analysis identified that the assumptions on resource use associated with IVIg and PLEX in uncontrolled health state for subsequent treatments was consistently influential on ICERs for both comparisons.

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

2. New evidence

2.1. Corticosteroid and NSIST-sparing data

Among patients receiving zilucoplan in RAISE and RAISE-XT, [redacted] of those with a CS dose above the Cushing threshold (≥7.5 mg) at baseline reduced their CS dose at Week [redacted] ([redacted]), of which [redacted] discontinued their CS. Of patients with a CS dose above the Cushing threshold (≥7.5 mg) at DB baseline who reduced or discontinued their CS dose at Week [redacted] ([redacted]), CS dose decreased on average by [redacted] mg, while MG-ADL improved on average by [redacted] from baseline.

These data suggest that patients receiving zilucoplan may reduce or discontinue their use of CS, whilst maintaining disease control.

Long term data from RAISE-XT also suggest that zilucoplan offers the potential to reduce reliance on long term NSIST use.

Among zilucoplan 0.3mg/kg patients with NSIST dose ≥0 mg at DB baseline, [redacted] reduced their NSIST dose by Week [redacted], including [redacted] who discontinued ≥1 NSIST. Mean MG-ADL CFB was [redacted] among those who decreased dose for ≥1 NSIST ([redacted] among those who discontinued ≥1 NSIST).

The model was updated to include costs (Table 1 and Table 2) and disutilities (Table 3) of corticosteroids and the corticosteroid-sparing effect of zilucoplan. Due to scarcity of data, NSIST-sparing effects are not included in the model, and the costs and benefits of this are assumed to be accounted for by the CS sparing.

There are no data available on the costs or utility values associated with CS use in gMG; therefore, proxy conditions had to be used to incorporate the CS cost and disutility in the model.

For cost data, a study was identified that reported the costs of different doses of CS in 715 patients with systemic lupus erythematosus in the UK, using Clinical Practice Research Datalink (CPRD) and hospital episode statistics (HES) (1).

Table 1. Annual treatment cost of corticosteroids by dose

Daily dose of CSs	Annual cost, £
No CSs	3,842
<5 mg	5,699
5–7.5 mg	7,884
7.5–15 mg	9,241
≥15 mg	13,929

Abbreviations: CS, corticosteroids.
Source: Cost-effective model and Stirnadel-Farrant et al, 2023 (1).

Whilst the reported costs are for lupus erythematosus, which has more diverse symptoms than gMG and therefore potentially higher costs, this should be accounted for by removing the cost of those patients taking no CS. There were no data reported in literature for the HCRU or costs of CS use related to dose for patients with gMG.

The mean (SD) dose in this study was 3.2 (6.0) mg/per day, which is much lower than the doses that are seen in the RAISE study and used in the treatment of refractory gMG. The

study notes as a limitation that disease activity is not controlled for, and it is likely that higher disease activity is associated with higher CS use, which is likely to be the same in gMG.

Patients in the uncontrolled health state are assumed to have the annual cost associated with a daily CS dose of >15 mg, minus the costs for no steroids. Patients in the stable response health state are assumed to have an average annual cost of a daily CS dose of <5 mg, 5–7.5 mg, and 7.5–15 mg, minus the costs for no steroids. For zilucoplan only, patients in the continued response health state are assumed to have no costs associated with CS use. For IVIg, the Bril 2023 (2) study provides evidence that IVIg is not more effective than placebo at steroid sparing in gMG, and PLEX is assumed the same as IVIg.

Table 2. Assumed costs per health state

	Zilucoplan	IVIg/PLEX
CS costs assigned to continuous response health state	£0	£4,670.50
CS costs assigned to stable response health state	£ 4670.50	£4,670.50
CS costs assigned to uncontrolled health state	£10,087	£10,087

Abbreviations: CS, corticosteroids.
Source: Cost-effective model.

Table 3. Utility decrements with CS use

Steroid use	Health state	Utility decrement
High dose (≥10 mg/day)	Uncontrolled	0.18
Low dose (<10 mg/day)	Stable response	0.07

Abbreviations: CS, corticosteroids.
Source: Cost-effective model.

Please refer to the supporting document (technical report for the cost-effective model [version 4]) for full methodology and results.

2.2. Minimum symptom expression

The proportion of patients with gMG who achieve complete stable remission is low with current treatments routinely available in England and Wales (3).

Minimal symptom expression (MSE), defined as achieving an MG-ADL score of 0 or 1 and representative of patients who become free or virtually free of MG symptoms, has been used as an evaluation tool for MG treatment goals in recent years (3).

In an analysis of MSE as a proportion of patients responding to zilucoplan in the RAISE-XT trial, of responders in RAISE (defined as 3-point change from baseline [CFB] in MG-ADL at Week [redacted]), [redacted] had MSE (Table 4). Therefore, of patients responding to zilucoplan, [redacted] become free or virtually free of MG symptoms. Please see Section 3.1.5 for the model updates.

Table 4. MSE as a proportion of anytime responders to zilucoplan

Week	R	NR	n	%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MSE, minimum symptom expression; NR, non-responders; R, responders.

2.3. Bivariate NMA

A bivariate network meta-analysis was conducted, on recommendation from the committee to consider a multivariate analysis, to obtain estimates of relative differences in studies containing IVIg so that they could be included. No studies comparing PLEX with placebo were identified, so it was not possible to include PLEX as a treatment in the bivariate network meta-analysis. Challenges with the evidence base for IVIg precluded a full multivariate approach incorporating three outcomes, as very wide credible intervals and significantly non-concordant results were observed; these are included in the report for transparency. For IVIg, CFB data from Wolfe 2002 and NCT02473952 showed a greater CFB for placebo compared with IVIg, whilst Zinman 2007 found the opposite; the only responder data, from NCT02473952, showed limited benefit for IVIg compared with placebo.

2.3.1. Responder outcomes

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

A total of eleven studies were included in the responder network; five studies reported both MG-ADL and QMG responder data as measured by a ≥3-point improvement in score, four studies reported only QMG responder data at a threshold of ≥3 points of improvement, and two studies only reported MG-ADL responder data for ≥3-point improvement.

The results for MG-ADL responder suggest an odds ratio (95% CrI) for zilucoplan of [redacted] and [redacted] for IVIg. Despite the uncertainty, the results show that zilucoplan is significantly better than placebo, whilst IVIg is not. Using the referent 31.5% (calculated as per Section 3.1.6) this translates into a responder rate in the CEM of [redacted] for zilucoplan and [redacted] for IVIg. To mitigate the remaining uncertainty, UCB has produced scenarios with extreme values to demonstrate the impact on the ICER.

2.3.2. Change from baseline outcomes:

Data for change from baseline in MG-ADL and QMG scores were assessed separately as continuous outcomes. A total of 14 studies were included in the network; 12 reported change from baseline in both MG-ADL and QMG scores and 2 studies only reported CFB QMG data.

The results for MG-ADL CFB (95% CrI) were [redacted] for zilucoplan and [redacted] for IVIg, suggesting that, whilst zilucoplan demonstrates a significant CFB vs placebo, IVIg has a non-significant worsening effect on MG-ADL.

These incongruent outcomes for IVIg (improved responder and worsened CFB) and the unavailability of quality data for IVIg and PLEX are the reason that UCB believes there is limited utility in further network meta-analyses.

Please refer to the supporting document (Multivariate Bayesian Network Meta_Short Report) for full methodology and results.

2.4. MAIC

Acknowledging the limitations of the NMA not including all IVIg studies due to a lack of link to the network, or the lack of reporting of relevant outcomes, UCB has further performed two matched adjusted indirect comparisons of zilucoplan versus IVIg studies that could not be included in any of the NMAs.

Barth et al, 2011 (4), report on a 4-point QMG response at Week 2 (69% on IVIg vs 65% on PLEX) and QMG CFB. Bril et al, 2023 (2), report the secondary endpoint of MG worsening by Week 39, defined as a QMG score ≥4 points from baseline; IVIg showed no significant difference vs placebo.

For both studies, unanchored MAIC was used to compare the outcomes. Bril 2023 (2) was used to compare the outcome at 39 weeks and therefore, only unanchored MAIC can be performed using RAISE-XT open-label data. In Barth 2011 (4) IVIg was compared with PLEX, and in the absence of a common comparator only an unanchored MAIC can be performed. UCB chose to compare with the IVIg arm as this performed marginally better in the study and results could be conservatively generalised to PLEX.

The results showed that zilucoplan had significantly lower odds of MG worsening at Week 39 compared with placebo, had numerically higher QMG response at Week 2, and a significantly deeper QMG CFB at week 2 compared with IVIg. These results are consistent across all scenarios tested but have the limitations associated with unanchored comparisons.

Please refer to the supporting technical document (ZLP vs IVIg_ Technical report) for full methodology and results.

2.5. Baseline risk-adjusted NMA

As proposed by the committee, to assess the probable impact of the difference in placebo response, a baseline risk-adjusted (BR) NMA was conducted as per the guidelines laid down by Dias et al (5). The primary outcome of interest was a 3-point MG-ADL response. The regression estimate of beta from the NMA indicated that the baseline risk (placebo response) is not statistically significant.

Please refer to the supporting document (Multivariate Bayesian Network Meta_Short Report) for methodology and results.

3. Modelling

3.1. Updates to the model

Please refer to the separate supporting document (technical report for the cost-effective model) for full description on model methodology, assumptions, inputs and functionality. Adaptations made for this submission are summarised below.

3.1.1. Response assessment timepoint

The response assessment timepoint used in the model for zilucoplan and all comparators is 3 weeks in line with committee's preferred assumption.

3.1.2. Dosing frequency of IVIg and PLEX

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

3.1.3. PLEX administration costs (SA44A)

The updated model uses £455 for PLEX-specific administration cost every cycle (2 weeks) which aligns with committee's assumption of £910 every 4 weeks (NHS reference cost SA44A – Single Plasma Exchange).

3.1.4. Change from baseline for the 'continued response' health state

Change from baseline to for the 'continued response' health state was updated to reflect minimum symptom expression and new minimum symptom expression data was used to inform the proportions in each health state.

3.1.5. Minimum symptom expression

The data in Section 2.2 have been 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 [redacted] in the continued response health state, which achieves a 0.5 score from the baseline MG-ADL score in the model of [redacted].

UCB sought expert clinical opinion (n=5 clinical experts) on the estimated proportion of patients receiving IVIg or PLEX that achieve MSE. The expert opinion informed the [redacted] rate that was used in the model base case. No patients on standard of care (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 [redacted].

3.1.6. Response rates

The updated referent response rate (31.5%) is on the overall mean of log odds based on individual log odds for each study reporting MG-ADL response for placebo (Table 5). The odds ratios for response of [redacted] for IVIg and [redacted] for zilucoplan are from the bivariate NMA (please see Section 2.5). The odds ratio of [redacted] for PLEX is informed by the 57% responder rate for PLEX from Barth et al (4).

Table 5. Response rates in studies reporting MG-ADL response for placebo

Study	Treatment	N	n	Response Rate	logit
REGAIN	Placebo	63	25	0.40	-0.42
Howard 2019	Placebo	12	4	0.33	-0.69
RAISE	Placebo	88	47	0.53	0.14
ADAPT	Placebo	64	23	0.36	-0.58
CHAMPION MG	Placebo	89	30	0.34	-0.68
MycarinG	Placebo	64	13	0.20	-1.37
Bril 2021	Placebo	22	3	0.14	-1.85

3.1.7. Subsequent treatments

Acknowledging the paucity of data from patients with refractory gMG, UCB believes that the EAMS cohort data for use as subsequent treatment requires further analysis to make it relevant to the population appropriate for zilucoplan treatment. Not all patients are considered refractory (n=37/48 are refractory), and three patients received no treatment (these patients would not be eligible for zilucoplan, as zilucoplan is licenced as an add-on therapy and not a monotherapy) and 10 patients are on corticosteroids only (these patients would likely be considered for an NSIST prior to initiation of zilucoplan). Removing these patients from the cohort results in a total of 35 patients. To match the number of refractory patients (n=37), UCB suggests including two of the CS-only patients. This leaves a remaining 73% (n=35/48) of patients using IVIg/PLEX in the refractory subgroup. In respect of this, UCB has now applied the ongoing costs of this refractory SoC basket to the uncontrolled health state, where patients move to after treatment discontinuation or lack/loss of response. UCB believes this is a conservative approach.

Table 6. Patients receiving subsequent treatments in the reweighted EAMS basket

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

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

As four weekly cycles of IVIg or PLEX would be received by a patient on chronic IVIg/PLEX, an annual resource use of 13 cycles would be applied in the model should 100% of patients receive either intervention. As 56.7% of patients receive IVIg (Table 6), 7.37 cycles of IVIg are applied in the uncontrolled health state. For PLEX, 2.46 cycles are applied to account for 18.9% of patients. The remaining 24.3% of patients receive only low-cost SoC ongoing in the model.

To account for the ongoing health effects, UCB has applied the stable response MG-ADL value (and thus associated utility score) to the period post-discontinuation.

3.1.8. Benefit of at-home subcutaneous administration

The “AdminTime” worksheet of the updated model reports the NHS staff and patient time for zilucoplan and comparators. The model assumes 52 minutes for a round trip to and from the hospital per infusion in addition to the time spent at the hospital. This calculation considers the distribution of the population between rural and urban areas, the percentage of people using cars in each area, and the travel times to the hospital for both public transport and car travel (6-8). The model only calculates the number of hours associated with administration during the time-on-treatment period. Compared with IVIg, zilucoplan saves [redacted] hours of NHS staff time and [redacted] hours of patient time; for the comparison with PLEX, [redacted] staff hours and [redacted] patient hours are saved.

0.05 per-administration utility of self-administration is assumed in the model based on the values suggested in available literature (9-13).

3.1.9. Duration of exacerbation and crisis

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

3.1.10. Caregiver disutility

The updated model incorporated the parameters for caregiver disutilities, considering the proportion of patients requiring caregiver support according the MD-AGL score ranges and utility decrements reported in previous submissions to NICE for relevant populations (14).

Table 7. Caregiver disutility assumptions

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

Source: National Institute for Health and Care Excellence, 2023 (14).

3.2. Base case inputs and settings

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

3.2.1. Decision problem definitions

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

Table 8. 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>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>UCB data on file, 2022 (15)</td></tr>
<tr><td>Males, %</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>UCB data on file, 2022 (15)</td></tr>
<tr><td>Average MG-ADL score at the start</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>UCB data on file, 2022 (15)</td></tr>
<tr><td>Average weight (kg)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>UCB data on file, 2022 (15)</td></tr>
<tr><td>Average BSA (m^2)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Mosteller, 1987 (16); UCB data on file, 2022 (15)</td></tr>
<tr><td>Baseline BMI (kg/m^2)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>UCB data on file, 2022 (15)</td></tr>
</table>
Abbreviations: BSA, body surface area; BMI, body mass index; MG-ADL; Myasthenia Gravis Activities of Daily Living.</td></tr>
<tr><td>Intervention</td><td>Zilucoplan</td></tr>
<tr><td>Comparators</td><td>• IVIg/SCIg
• PLEX</td></tr>
<tr><td>Analysis type</td><td>Cost-utility analysis</td></tr>
<tr><td>Perspective</td><td>NHS and Personal Social Services in England</td></tr>
<tr><td>Discount rate</td><td>3.5% for costs and QALYs</td></tr>
<tr><td>Model type</td><td>State-transition cohort (Markov model)</td></tr>
<tr><td>Health states</td><td>• Uncontrolled on high-dose steroids and ISTs
• Continued response
• Stable response
• Loss of response
• Acute exacerbation
• Myasthenic crisis
• Death</td></tr>
<tr><td>Cycle length</td><td>2 weeks</td></tr>
<tr><td>Time horizon</td><td>Lifetime ([redacted] 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: GBP, British pound sterling; gMG, generalized Myasthenia Gravis; IST, immunosuppressive therapies; IVIg, intravenous immunoglobulin; NHS, National Health Service; PLEX, plasma exchange; QALY, quality-adjusted life year; SCIg, subcutaneous immunoglobulin; WTP, willingness to pay.

3.2.2. Efficacy assumptions and inputs

Table 9. Primary response rate and response assessment timepoint

Treatment	Odds Ratios (SE)	Response rate used in the model	Response assessment timepoint used in the model (weeks)	Source
Referent response rate	1.00	31.50%	NA	Per Section 3.1.6
Zilucoplan	[redacted]	[redacted]	3.00	mvNMA
IVIg/SCIg	[redacted]	[redacted]	3.00	mvNMA
Refractory standard of care	[redacted]	[redacted]	3.00	mvNMA
PLEX	[redacted]	57.00%	3.00	Barth 2011 (4)

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

Table 10. Treatment-specific MG-ADL score CFB

Treatment	Continued Response	Loss of response	Stable response	Source
Zilucoplan	[redacted]	[redacted]	[redacted]	Section 3.1.5
IVIg/SCIg	[redacted]	3.00	3.00	Section 3.1.5
Refractory standard of care	[redacted]	3.00	3.00	Section 3.1.5
PLEX	[redacted]	3.00	3.00	Section 3.1.5

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

Time of last response assessment from trial was 3 weeks for zilucoplan and all comparators.

Table 11. Response distribution

	Continued response	Loss of response	Stable response	Source
Zilucoplan	[redacted]	[redacted]	[redacted]	Section 2
IVIg/SCIg	[redacted]	[redacted]	[redacted]	Section 2
Refractory standard of care	[redacted]	[redacted]	[redacted]	Section 2
Plasma exchange	[redacted]	[redacted]	[redacted]	Section 2

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

Long-term MG-ADL score assumes a period of 14 weeks before 0% of patients return to the new uncontrolled level.

Table 12. Clinical event rates

Health state	Event	Mean	Lower range	Upper range	Source
Annual event rate					
Uncontrolled	Exacerbation	0.651	0.59	0.72	Abuzinadah et al 2021 (17)
Response	Exacerbation	0.244	0.194	0.307	Abuzinadah et al 2021 (17)
Uncontrolled	Myasthenic crisis	0.062	0.06	0.07	Abuzinadah et al 2021 (17)
Response	Myasthenic crisis	0.023	0.011	0.048	Abuzinadah et al 2021 (17)
2-week event rate					
Exacerbation	Myasthenic crisis	0.184	0.166	0.202	Gajdos, 2005 (18)

Table 13. Mortality parameters

Health state/event	Mean	Lower range	Upper range	Source
Uncontrolled/response/exacerbation	1.00	0.90	1.10	
Myasthenic crisis	4.47%	4.02%	4.92%	Alshekhlee et al, 2009 (19)

3.2.3. Cost assumptions and inputs

The model assumptions were as follows:

- Vial sharing is excluded
- SOC costs are included in the targeted therapies
- 100% adherence is assumed

Table 14. Administration costs per treatment

	Mean	Lower	Upper	Source
Intravenous				
Initial (£)	195.74	£176.17	£215.32	
Subsequent (£)	184.23	£165.81	£202.65	
IG-specific (£)	504.67	454.200	555.133	
PLEX-specific (£)	455	409.500	500.500	Section 3.1.3
Subcutaneous				
Initial (£)	41.00	£36.90	£45.10	
Oral				
Initial (£)	0.00	£0.00	£0.00	

Abbreviations: IG, immunoglobulin; PLEX, plasma exchange.

Table 15. 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
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 16. Refractory standard of care basket costs

Medication	Bundle composition			Average treatment cost per model cycle (£)	Admin costs per model cycle (£)
	Mean	Lower	Upper		
Azathioprine	17.80%	16.02%	19.58%	5.88	0.00
Cyclophosphamide	0.00%	0.00%	0.00%	0.00	0.00
Cyclosporine	7.50%	6.75%	8.25%	95.59	0.00
IVIg	56.7%	51.0%	62.4%	2,322.00	757.00
Methotrexate	2.30%	2.07%	2.53%	2.20	0.00
Mycophenolate mofetil	19.00%	17.10%	20.90%	6.70	0.00
PLEX	18.9%	17.0%	20.8%	6,468.63	1,137.50
Corticosteroids	63.20%	56.88%	69.52%	2.42	0.00
Rituximab	0.00%	0.00%	0.00%	3,230.64	379.97
SCIg	0.00%	0.00%	0.00%	0.00	0.00
Tacrolimus	5.70%	5.13%	6.27%	202.31	0.00
Pyridostigmine	80.50%	72.45%	88.55%	6.36	0.00
Average cost per model cycle (£)				2,565.34	644.21
Average add-on cost per model cycle for ZLP/IVIg/PLEX (£)				26.19	0

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

Table 17. 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	7.37	11.70-14.30†	0.00	0	0.00	0
PLEX	12,937.25	2.46	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 (£)		94,417.54		9,111.33		4,440.83	
Total cost for IVIg and PLEX		94,417.54		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 18. 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		

	Unit cost (£)	Frequency of resource use per event					
		Exacerbation			Myasthenic crisis		
		ZLP/SoC	IVIg	PLEX	ZLP/SoC	IVIg	PLEX
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.

3.2.4. 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 19. MG0010 outcomes

	Mean	Lower	Upper	Source
Baseline EQ-5D	[redacted]	[redacted]	[redacted]	UCB data on file (15, 20)
Baseline BMI (kg/m^2)	[redacted]	[redacted]	[redacted]	UCB data on file (15, 20)
Intercept	[redacted]	[redacted]	[redacted]	UCB data on file (20, 21)
Coefficient of baseline EQ-5D	[redacted]	[redacted]	[redacted]	UCB data on file (20, 21)
Coefficient of MG-ADL score	[redacted]	[redacted]	[redacted]	UCB data on file (20, 21)
Coefficient of BMI	[redacted]	[redacted]	[redacted]	UCB data on file (20, 21)

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

Table 20. 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 21. Clinical event disutility

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

Table 22. Annual disutility of steroid use

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

Table 23. Per-administration utility of self-administration

Utility	Duration (days)
0.05	1.00

3.3. Model results and scenario analyses

3.3.1. Base case results (discounted)

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

Table 25 presents the estimated total costs and QALYs for zilucoplan and comparators as well as the pairwise comparison in terms of incremental costs, QALYs, and ICER (£/QALYs) assuming the £30,000 WTP threshold. [redacted]

Table 24: Base case results (discounted)

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.6468			
IVIg/SCIg	[redacted]	9.4413	[redacted]	0.2055	[redacted]
Plasma exchange	[redacted]	9.4713	[redacted]	0.1755	[redacted]

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

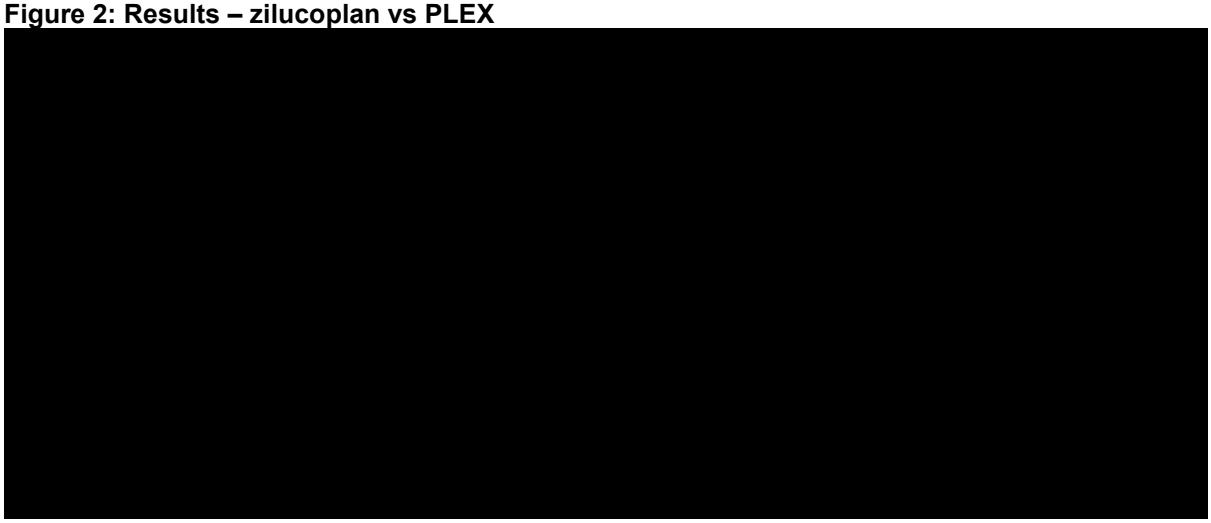
3.3.2. Deterministic sensitivity analysis results

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.

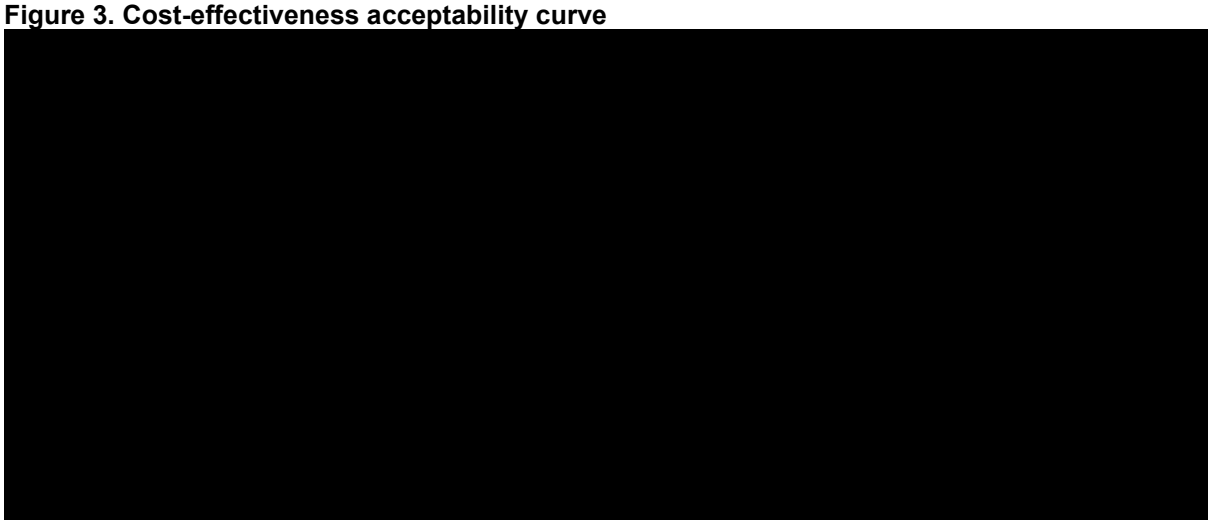
3.3.3. Probabilistic sensitivity analysis results

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. In the PSA all parameters varied 10% around the mean, except parameters informed by the CODA and mvNMA. Results are shown in Table 25 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 plasma exchange, 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 25. Probabilistic sensitivity results (all parameters varied 10% around mean, except parameters informed by CODA and mvNMA)

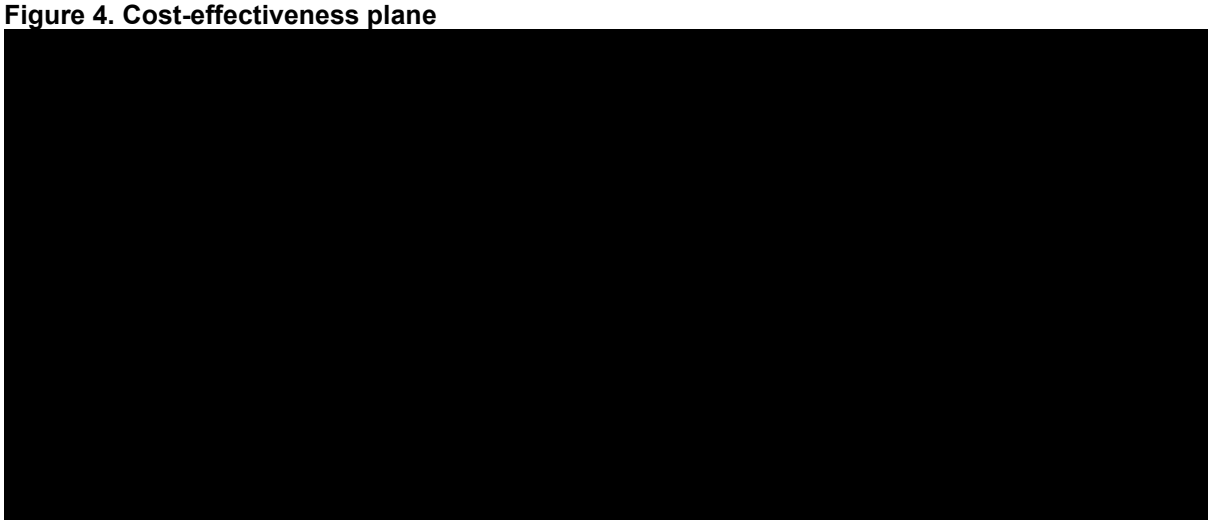
Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.6300			
IVIg/SCIg	[redacted]	9.4390	[redacted]	0.19	[redacted]
Plasma exchange	[redacted]	9.4451	[redacted]	0.18	[redacted]

Figure 3. Cost-effectiveness acceptability curve



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

Figure 4. Cost-effectiveness plane



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

3.3.4. Scenario analyses

3.3.4.1. 70% response rate for IVIg and PLEX ([redacted] for Zilucoplan from RAISE at 12 weeks)

This scenario illustrates the summary of model results when a 70% primary response rate is assumed for IVIg and PLEX, which are consistent with base-case pairwise ICER results.

Table 26: Scenario analysis results - 70% response rate for IVIg and PLEX

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.7196			
IVIg/SCIg	[redacted]	9.5135	[redacted]	0.2061	[redacted]
Plasma exchange	[redacted]	9.5135	[redacted]	0.2061	[redacted]

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

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

This scenario provides estimates of when societal costs and utilities are integrated in the model as described in Section 3.1.10 and the global CEM technical report (Section 2.4.5). The results of this scenario show higher total costs and lower total QALYs across all interventions compared with the base case. Given that both the cost increase and QALY decrease (vs base case) are lower with zilucoplan than the comparators, the incremental savings and QALY gain for zilucoplan vs the comparators are greater than in the base case.

Table 27: Scenario analysis results - Societal perspective

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	8.2371			
IVIg/SCIg	[redacted]	8.0022	[redacted]	0.2349	[redacted]
Plasma exchange	[redacted]	8.0520	[redacted]	0.1851	[redacted]

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

3.3.4.3. Absolute health state values using the definition of mild/moderate/severe

This scenario uses the absolute health state definitions and values to test the robustness of ITT regression for utility parameters chosen in the base case. The results show the robustness of the chosen approach.

Table 28: Health state definitions and utility values

Health State	Definition	Utility value
Severe	Uncontrolled, patients with high disease activity	[redacted]
Moderate	Stable response, patients with some disease activity	[redacted]
Mild	Continued response, patients with limited disease activity	[redacted]
The steroid assumptions of severe = high dose, moderate = lower dose, and mild = no dose.		

Table 29: Scenario analysis results - Absolute health state values using the definition of mild/moderate//severe stated in Table 26

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	6.9155			
IVIg/SCIg	[redacted]	6.6774	[redacted]	0.2381	[redacted]
Plasma exchange	[redacted]	6.7520	[redacted]	0.1635	[redacted]

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

3.3.4.4. Exclude disutility of corticosteroids

In this scenario, QALYs are higher across all comparators in comparison with the base case. However, the impact on total and incremental QALY results is minimal, owing to the per-cycle disutility of corticosteroids being low.

Table 30: Scenario analysis results – Steroid disutility removed

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.8410			
IVIg/SCIg	[redacted]	9.6399	[redacted]	0.2011	[redacted]
Plasma exchange	[redacted]	9.6677	[redacted]	0.1733	[redacted]

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

3.3.4.5. Self-administration utility removed

Although the total QALYs for Zilucoplan decreased slightly in this scenario, the effect is minimal, owing to the per-cycle parameter being so low. The pairwise ICER in this scenario is consistent with base-case results.

Table 31: Scenario analysis results - Self-administration utility gain removed

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.5703			
IVIg/SCIg	[redacted]	9.4413	[redacted]	0.1289	[redacted]
Plasma exchange	[redacted]	9.4713	[redacted]	0.0990	[redacted]

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

3.3.4.6. Steroid costs removed

The pairwise ICER in this scenario is consistent with base-case results.

Table *32*: Scenario analysis results - Steroid costs removed

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Zilucoplan	[redacted]	9.6468			
IVIg/SCIg	[redacted]	9.4413	[redacted]	0.2055	[redacted]
Plasma exchange	[redacted]	9.4713	[redacted]	0.1755	[redacted]

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

3.3.4.7. If PLEX has a 10% lower acquisition cost and is 10% more effective (62.70% primary response rate)

This scenario investigates a hypothetical version of PLEX with a 10% lower acquisition cost and 10% higher response rate (compared with standard PLEX) versus the blended standard of care. This illustrates the inappropriateness of the SoC 'basket' as a comparator, as it would result in this hypothetical, less costly, more effective version of PLEX to be refused reimbursement since the ICER is far above the willingness-to-pay threshold accepted by NICE, which is clearly a perverse outcome.

Table 33: Scenario analysis results - PLEX has a 10% lower acquisition cost and is 10% more effective

Technologies	Total		Incremental		Pairwise ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Blended standard of care 'basket'	1,920,515.88	9.3860			
Plasma exchange	2,026,613.88	9.4892	-106,098	0.1	£1,028,234.33

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

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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 5pm on Thursday 25 July 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):	Joint submission by myaware and Muscular Dystrophy UK (MDUK).

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Myaware has received funding from UCB totalling £334.78 to cover the cost of accommodation associated with attendance of the MG: Connects meeting in Manchester. Myaware has received funding from Merck totalling £19,641.93 to cover the cost of projects relating to awareness and literature library refresh. Muscular Dystrophy UK received £500 from UCB Pharma in March 2024 for corporate attendance of the UCL Neuromuscular Translational Research Conference. Not ongoing. Muscular Dystrophy UK received £8,750.00 (plus VAT) from comparator treatment company Pfizer Ltd in March 2024 for sponsorship of the UCL Neuromuscular Translational Research Conference. Muscular Dystrophy UK are due to receive from the comparator treatment company Argenx £2,610 (plus VAT) fee for support provided in May 2023 for the gathering of carer insight into the carer disutility caused by generalised myasthenia gravis. Not ongoing. Muscular Dystrophy UK received £2,750 (plus VAT) from the comparator treatment company Alexion in February 2024 for sponsorship of virtual patient information seminar series. Not ongoing. Muscular Dystrophy UK received £45,000 in November 2023 from comparator company Novartis as funding for the UK SMA Newborn Screening Alliance. MDUK is co-secretariat of the alliance with responsibility for processing and administering funding requests. Not ongoing. Muscular Dystrophy UK have received the following funding from comparator treatment company Roche as funding for the UK SMA Newborn Screening Alliance. MDUK is co-secretariat of the alliance with responsibility for processing and administering funding requests. • £25,000.00 in August 2023 from Roche as funding for the UK SMA Newborn Screening Alliance. MDUK is co-secretariat of the alliance with responsibility for processing and administering funding requests. A further £25,000 was received in March 2024. Not ongoing beyond that. • £900.00 fee for participation by Director of Care, Campaigns and Support in the Roche Neuromuscular Summit: Advocacy Panel on 5 September 2023. Not ongoing. Not ongoing. • £417.50 reimbursement for Conservative Party Conference Not-for-Profit ticket fee to participate in a Health and Care Forum fringe event on 2 October 2023. Not ongoing.

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Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

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	• £318.00 has been pledged in July 2024 as reimbursement for Labour 2024 Party Conference Not-for-Profit pass through Roche donation scheme. • £190.00 covering of accommodation costs associated with participation in Health and Care Forum fringe event at Conservative Party Conference on 2 October 2023. Not ongoing. • £2,750 (plus VAT) in October 2023 for sponsorship of virtual patient information seminar series. Not ongoing.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No such links exist between either patient organisation.
Name of commentator person completing form:	[redacted] ([redacted], myaware) [redacted] ([redacted], Muscular Dystrophy UK)

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that this recommendation may imply that IVIg/PLEX usage for refractory patients provides equal benefit to those who have received zilucoplan. We believe these two treatments provide different levels of benefit in terms of administration, response time, and sustainability.
2	We would urge the consideration of zilucoplan and its mode of administration, subcutaneous injection, and the benefit this provides over treatments such as IVIg/PLEX. Patients have been treated with zilucoplan at home, with some self-administering. This is a contrast to the lengthy and disruptive IVIg/PLEX treatments that may require hospital stays. At-home treatment also directly benefits families and carers and reduces the emotional, financial, and physical burden of myasthenia gravis.
3	Our concerns also extend to treatment response time and duration between IVIg/PLEX and zilucoplan. We surveyed MG patients who had experience of IVIg treatment as a maintenance therapy, rescue therapy, or both. Patients from the RAISE-XT trial compared IVIg to zilucoplan, stating '…(zilucoplan) gives me a very consistent and predictable MG that can be managed and allows me to have an active life in both work, sport and home life (compared to IVIg).' In comparison to plasma exchange, one patient who had received zilucoplan said 'Zilucoplan is like being straight after plasma exchange only the effects don't fade away like from plasma exchange'. Patients that we surveyed reported that zilucoplan treatment provided a symptomatic benefit within 48 hours of treatment, whereas others have stated on average it can take days to feel the effect of IVIg.
4	Finally, we are concerned that once again, the testimony of patients isn't having the impact it should have for what has been a lifechanging treatment for those who have trialled it. The committee has heard from patients who have had their life returned to them, who have suffered from myasthenia gravis for several years and felt like burdens to their own families. Treatment with

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	zilucoplan has benefited not only the patients but their support systems – parents, partners, children, and carers. There are more refractory patients in the UK that would benefit from zilucoplan and we can only hope that this option is opened to them on the NHS.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- 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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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	ABN Neuromuscular Advisory Group

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	All relevant evidence data available has been taken into account. The systematic review of the literature is complete. However, we do not feel that the particular data chosen for comparison with zilucoplan are appropriate: see below.

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2	The summaries of clinical effectiveness and interpretation of the phase 3 and OLE studies are sensible. However, we have a number of concerns regarding how this data has been compared to SOC in an NHS context: • we do not feel that Barth et al. 2011 is an appropriate comparator dataset: While the 70% response rate suggested for either IVIg or PLEX would be an accurate estimate of effectiveness of either treatment in isolation based how we use these treatments in the ABN MG treatment algorithm (Sussman et al. ,2015) it does not tell us about how we use IVIg and PLEX maintenance in the context of refractory MG. In this scenario, the scenario in which we are exploring the utility of zilucoplan, regular IVIg or PLEX are used alongside SOC (corticosteroids and steroid-sparing immunosuppression) in an attempt to provide additive effect in the 20-30% of MG patients in whom first and second-line treatments have been ineffective/ partially effective or are not tolerated. Therefore, by definition, representing a much lower response rate than the general MG population, i.e. less than 70%. • If we are trying to explore the role for additive use of zilucoplan compared to current SOC would it not be better to compare to evidence for rituximab in the refractory sub-set? The committee papers rightly acknowledge that the commissioning of rituximab for treatment of refractory AChR antibody positive MG has been less than satisfactory and the medical literature published since the 2018 commissioning policy for rituximab in generalised MG back this up (*Vesperinas-Castro, Cortes Vicente. Rituximab treatment in myasthenia gravis. Front Neurol. 2023;14: 1275533*). In AChR antibody positive MG response to rituximab in 50%. • We agree that the time to response in Rituximab is often slow and that there is an unmet clinical need for a rapidly acting, well tolerated, self-administered therapeutic such as zilucoplan. Therefore we would suggest that comparison with published data on the role of rituximab in the treatment of refractory MG is more suitable as a basis for exploring the comparative efficacy of zilucoplan than the Barth et al. 2011 paper. With potential for a greater demonstration of unmet clinical need. • The EAMS information on efgartigimod is highly relevant as this is representative of the subset of individuals in which zilucoplan is likely to be considered in the NHS. It would be interesting to know what proportion of that cohort was previous treated with rituximab and whether it was effective or not, considering cost and impact on patient of additive holding therapies while rituximab was tried and then further treatment deemed necessary. Although the 2015 ABN MG treatment guidelines do not include rituximab, this drug is used in a widespread manner for refractory cases in line with the 2018 NHSE commissioning policy. Therefore if we are trying to establish improved efficacy of a novel therapeutic: zilucoplan then comparison to the effectiveness/ tolerance and cost of rituximab should not be left out.

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

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	• Comparison to effectiveness of efgartigimod in the ADAPT study is not important because it is a completely different drug with a different mechanism of action. There is an unmet clinical need for novel therapeutics in gMG (as stated clearly in the committee papers) but, although these drugs may be placed at similar points in the MG treatment algorithm, nothing can be learned about their individual values from comparing one to the other based on the initial phase 3 trial data. • The point around self-delivery/ home delivery of zilucoplan as a reason for its superiority to current options is noted. However, if being compared to immunoglobulin – subcutaneous home-delivery options including pre-filled syringes are now available. And there is NHS availability of single point of access with plasma exchange centrifugal machines – albeit not geographically equitable throughout the UK.
3	We do not feel the model is a true demonstration of the potential cost effectiveness of zilucoplan beyond consideration of cost savings of IVIg/ PLEX requirements in the refractory MG group. Further points to be considered beyond the saving of IVIg/ PLEX spend include: • reduction in hospital visits/ working days gained from home administration • reduction in cost of rituximab/ time spent on supplementary treatments when rituximab is unsuccessful (50% of refractory ACHR ab positive MG) given current commissioning of rituximab for refractory MG by NHSE • reduction in symptom fluctuation given significant improvement in MG-ADL with QOL impact on patients/ improved independence
4	We have no clinical evidence that zilucoplan is superior to IVIG or PLEX as there have been no head to head comparison. However, as stated above, the response rates referenced for IVIg or PLEX in gMG do not refer to the refractory population or the mode of IVIg/ PLEX utilisation (regular maintenance infusions/ exchanges in addition to SOC) in this cohort. The response rates refer to how we use IVIg or PLEX in MG crisis situations or to induce remission while maintenance treatment is introduced. A relatively poor response rate of just 50% is seen in AChR antibody positive patients to rituximab which is currently commissioned for refractory MG by NHSE – this would be a more appropriate comparator to the suggested role of zilucoplan in refractory cases. We have concerns about how the guidance document refers to the response rate in the placebo group in the trial. We would like to highlight that (i) this is not a true placebo group as the trial drug has been added to SOC and there is considerable benefit already well established from SOC (ii) although there were some refractory patients within the trial, the trial was not designed to test the drug in a refractory cohort and so some response to SOC alongside placebo is to be expected. We agree with the clinical experts and would like to emphasise the importance of the added improvement/ response seen in the treatment group, as this represents the impact of zilucoplan over and above SOC.

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5	The response rate with Zilucoplan is longer than the response rate on the plasma exchange data in MG patients. There is evidence that patients on PLEX has shorter response time versus IVIG and were off ventilator faster. In clinical practice we know PLEX has a dramatic effect on MG patients within days of starting treatment with a more rapid response rate versus IVIG and Zilucoplan (Ipe TS, Davis AR, Raval JS. Therapeutic Plasma Exchange in Myasthenia Gravis: A Systematic Literature Review and Meta-Analysis of Comparative Evidence. Front Neurol. 2021 Aug 31;12:662856.)
6	We would like to highlight the fact that early onset MG is more common in females and therefore disproportionately effects women of childbearing and working age. The potential impact of refractory disease and inability to access effective novel therapeutics is likely to have a greater burden on females than males.

Insert extra rows as needed

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Zilucoplan for treating antibody-positive generalised myasthenia gravis

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

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

The evaluation committee is interested in receiving comments on the following:

- ☐ Has all of the relevant evidence been taken into account?
- ☐ Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- ☐ Are the recommendations sound and a suitable basis for guidance to the NHS?
- ☐ Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: July 2024

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

After consultation:

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

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

The key dates for this evaluation are:

- ☒ Closing date for comments: 25 July 2024
- ☒ Second evaluation committee meeting: to be confirmed
- ☒ Details of the evaluation committee are given in section 4

Issue date: July 2024

1 Recommendations

1.1 Zilucoplan is not recommended, within its marketing authorisation, as an add-on to standard treatment for generalised myasthenia gravis in adults who test positive for anti-acetylcholine receptor antibodies.

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

Why the committee made these recommendations

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

Clinical trial evidence suggests that zilucoplan plus standard treatment improves symptoms and people's ability to carry out their normal activities compared with standard treatment alone. But zilucoplan has not been compared with intravenous immunoglobulin and plasma exchange, so it is unclear how well it works compared with these treatments.

As well as the uncertainties in the clinical evidence, there are uncertainties in the economic model and the cost-effectiveness estimates for zilucoplan. The most likely estimates are substantially above what NICE considers an acceptable use of NHS resources. So, zilucoplan is not recommended.

what are the uncertainties?

1. Clinical trial designs in MG excludes concurrent use of PLEX or IVIG with the IMP. therefore a diret head to head comparison doesnt exist.
2. Could the company provide an ICT of Zilucoplan with PLEX/IVIG bearing the caveat of differences in study population characteristics
3. IVIG/PLEX are used as rescue therapy and NHSE commissioning guidance discourages use of IVIG as maintenance therapy

therefore NICE request to compare Zilucoplan with IVIG/PLEX is concerning (unless NICE suggests a preferred ICT method/ indicates the rationale

2 Information about zilucoplan

Marketing authorisation indication

2.1 Zilucoplan (Zilbrysq, UCB Pharma) is indicated 'as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of zilucoplan is £3,653.97 for 7 pre-filled syringes of 16.6 mg solution for injection, £5,041.78 for 7 pre-filled syringes of 23.0 mg solution for injection, and £7,114.70 for 7 pre-filled syringes of 32.4 mg solution for injection (all excluding VAT, BNF online, accessed June 2024).

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

3 Committee discussion

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

The condition

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

This needs to be changed to "In those who only have an ocular onset 80% can generalise over 1-2 years.

substantial physical, emotional and financial impacts on the person with gMG, as well as their family. They noted that the typical symptoms of fatigue, and problems with breathing, speaking, seeing, and concentrating, substantially impact daily activities and ability to work. The symptoms of gMG mean that many people regularly need a high level of care. All current treatments for gMG aim to suppress the condition to reduce symptoms and there is no cure. The patient experts noted that treatments for gMG are associated with side effects, and it is particularly difficult to manage the side effects of multiple treatments simultaneously. Many people with gMG take corticosteroids, but it can be difficult to optimise the lowest effective dose (to minimise side effects) without increasing the risk of exacerbations (an acute worsening of symptoms) or myasthenic crisis. People with gMG and their carers spend their lives fearing a myasthenic crisis, a life-threatening complication of gMG in which the muscles that are needed for breathing are affected and hospitalisation is required. The patient experts explained that there are limited options available for people whose condition does not improve with standard treatment (refractory gMG). Typically, people with refractory gMG will have intravenous immunoglobulin (IVIg) or plasma exchange (PLEX), or try a different type of immunosuppressant. IVIg and PLEX both require regular hospital visits or stays. These can be difficult to fit around work and family commitments, and place substantial burden on carers. The patient experts highlighted the unmet need for treatments for refractory gMG. The committee concluded that gMG is a debilitating condition with a high treatment burden.

This section undermines the impact of steroid on MG patients.

Approx 75% of patients in both arms of several MG clinical trials have indicatetd that gMG patients with an MGADL ≥6 are on corticosteroids. When gMG patients are started on steroids they tend to stay on high doses of steroids for a long time causing significant side effects. Rapid withdrawal can result in crisis or exaxerbation.

It is not only the crisis patients live in anxiety, MG causes signifiant impact by creating both unpredictability of MG status causing uncertainty to their lives, from going to a restaurant, answering the phone to maintaining employment.

gMG patients lack not only treatment for refrctory MG but also
- there are no fast acting safe drugs to help bridge periods of brittle MG, post crisis

Clinical management

Treatment options

3.2 gMG is a long-term condition and most people need lifelong treatment. The clinical experts explained that people would usually have treatments outlined in the Association of British Neurologists (ABN) guidelines. But, at the time of this evaluation, the ABN guidelines are being updated. The

ABN (2015) guidelines recommend that people are first offered pyridostigmine at the lowest effective dose and that surgery to remove the thymus gland (thymectomy) can be considered for people under 45 years. The clinical experts noted that, after publication of the ABN guidelines, thymectomy is now offered to people under 65 years. If symptoms continue, people are offered prednisolone. The clinical experts explained that corticosteroids like prednisolone are associated with notable side effects and that they aim to use minimal effective doses to reduce these. The ABN guidelines recommend non-steroidal immunosuppressants such as azathioprine if remission is not achieved on corticosteroids alone. If there is insufficient response to immunosuppressants or people experience notable side effects on increasing corticosteroid doses, expert advice should be sought on the use of IVIg or PLEX. The NHS England commissioning criteria policy for the use of therapeutic immunoglobulin recommends IVIg should be used:

Though experts try to use minimal effective dose of steroids, this is often too high andtoo long resulting in significant life changing side effects

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

This clause is discouraging to use IVIG for a proportion of patients and causes significant inconvenience to patient

Rescue treatments for a myasthenic exacerbation or crisis include IVIg or PLEX. The clinical experts explained that zilucoplan would be used as an alternative to long-term maintenance IVIg or PLEX, but would not replace rescue use. They highlighted that IVIg and PLEX are time-consuming and resource-intensive treatments, and that access to PLEX is highly variable across the NHS.

Effect of Rituximab takes 6-12 months but IVIG beneefit is observeed in 1-2 weeks

NHS England also considers rituximab, an anti-B-cell monoclonal antibody treatment, to be equally effective to IVIg. It has stated that rituximab should be considered for refractory gMG. But clinical advice received by the company and EAG suggested that the evidence for rituximab in refractory gMG is limited, and it takes a long time to start

working. The clinical experts advised that rituximab is being used earlier in the treatment pathway and is less widely used for refractory gMG. The committee concluded that an effective, fast-acting, and easy-to-administer treatment option would be welcomed by people with gMG and healthcare professionals.

This is incorrect. Rituximab as per NHSE guidance is used when a patient is deemed refractory.

however the RINOMAX study supports the use of Rituximab earlier in the disease course.

such a treatment for maintenance use doesnt exist for UK MG patients. Which is sad and disappointing compared to European and

Target population

3.3 Zilucoplan has a marketing authorisation as an add-on to standard treatment for AChR antibody-positive gMG. In its submission, the company positioned zilucoplan for a narrower population, people with refractory AChR antibody-positive gMG, based on the following criteria:

- the condition 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 condition is uncontrolled, defined by a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 6 or more or a Quantitative Myasthenia Gravis (QMG) score of 12 or more, and:
  - an additional therapy such as IVIg or PLEX is being considered, or
  - people are having long-term treatment with IVIg or PLEX, or
  - efgartigimod would be an alternative option (subject to NICE approval).

The clinical experts considered that these criteria broadly describe the population that zilucoplan would be used for in the NHS. The committee noted that in the RAISE clinical trial (see section 3.5), refractory criteria also included that people had to be on 1 year or more of standard treatment. The clinical experts did not consider it appropriate to set a time limit when defining refractory gMG, because sometimes it is straightforward to identify who has refractory gMG and they would not wait 1 year before trying other treatments. The committee agreed with the clinical experts that the

Unsure if this is correct. RAISE did not define a refractory criteria, in retrospect if the company had reviewed the data with a new lens Im not clear

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

Comparators

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

- ☐ Standard care without zilucoplan (including corticosteroids and immunosuppressants, with or without IVIg or PLEX)
- ☐ efgartigimod (subject to NICE evaluation)
- ☐ ravulizumab (subject to NICE evaluation, now terminated).

will need to include Steroids and NSITs, however steroids will be reduced if we can

Zilucoplan is proposed as an add on treatment to SOC, therefore SOC should be part of the comparator

The company proposed the following comparators: efgartigimod, IVIg and PLEX, excluding corticosteroids and non-steroidal immunosuppressants. At the time of the first committee meeting (13 June 2024), the NICE evaluation of efgartigimod for treating gMG was ongoing and so efgartigimod was not considered as established NHS practice. The committee noted that zilucoplan, IVIg and PLEX are intended to be used as an add-on treatment to corticosteroids and immunosuppressants. So, corticosteroids and immunosuppressants should be included in both arms of the model. The clinical experts commented on the substantial variation in access to IVIg and PLEX across the NHS. Some centres may exclusively use IVIg, some may use a mix of IVIg and PLEX, and some may have access to neither. So, there would be some people who instead try another type of immunosuppressant instead of IVIg or PLEX. To reflect this, the EAG preferred to use a 'basket' of standard care as the comparator. In this, some people have IVIg (plus corticosteroids and immunosuppressants), some have PLEX (plus corticosteroids and immunosuppressants), and some would have corticosteroids and immunosuppressants only.

I agree with NICE

I agree with this

The EAG assumed that data on the proportion of people having each treatment from the efgartigimod Early Access to Medicines Scheme

(EAMS) would be relevant for this evaluation. The EAG noted that, although 'refractory' was defined in a slightly different way, people in the efgartigimod EAMS were comparable to the population who would have zilucoplan in the NHS. The EAMS cohort included 48 people with refractory gMG in the NHS. At the time of starting efgartigimod:

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

I agree with NICE/ERG Reliable IVIG and PLEX use info from UK refractory gMG cases dont exist.

These are generous estimates and I am not sure EAMS data represents UK refractory population given the nature of the sampling and selection bias.

The committee concluded that a 'basket' of standard care is consistent with the NICE scope, is more reflective of NHS practice and is the relevant comparator. The committee agreed with the EAG that corticosteroids and immunosuppressants should be included in both arms. The committee also agreed that the efgartigimod EAMS population was sufficiently similar to the zilucoplan target population, and that the proportions of people having each treatment could be taken from the EAMS population.

Clinical effectiveness

RAISE

3.5 RAISE was a phase 3, randomised, multicentre, double-blind, placebo-controlled trial. It recruited adults with gMG with positive serology for anti-AChR antibodies, with an MG-ADL score of 6 or more and a QMG score of 12 or more. Of the 239 people screened, 174 were randomised to zilucoplan (n=86) or placebo (n=88). People in both arms also continued to have standard treatment with existing corticosteroids and immunosuppressants. The primary outcome was reduction in MG-ADL score at 12 weeks (a higher MG-ADL score shows more severe symptoms). From baseline to week 12, people who had zilucoplan had a

statistically significantly greater reduction in MG-ADL score compared with people who had placebo (4.39 versus 2.30, least squares mean difference of -2.09 [standard error: 0.58; 95% confidence interval: -3.24, -0.95; p<0.001]). RAISE also reported the number of people who had an MG-ADL response, defined as a 3-point or more improvement in MG-ADL score, as a secondary outcome. At week 12, statistically significantly more people who had zilucoplan had an MG-ADL response than people who had placebo (73.1% versus 46.1% [odds ratio: 3.18; 95% confidence interval: 1.66, 6.10; p<0.001]). The EAG noted that a high proportion of people who had placebo showed an MG-ADL response. The patient and clinical experts explained that people with refractory gMG can feel hopeless because there are no further treatment options. They thought it was plausible that the high level of expectation that a new treatment will work could translate to a perceived improvement in symptoms. The committee noted that gMG can relapse and remit over time. It questioned whether people might enter the trial when their gMG is particularly bad, and the improvement seen after starting treatment is partly a regression to the mean effect. The clinical experts thought this was possible, but highlighted the difference in response observed between the treatment groups as evidence of the benefits of zilucoplan.

The whole idea of a RCT is to account for a possible placebo effect especially daily injections could reinforce

RAISE also included a pre-planned subgroup of people with refractory gMG. Refractory gMG was defined similarly to the definition of the target population in the company's submission (see section 3.3), with the additional criterion that people had at least 1 year of standard treatment. A total of 88 people (51%) in RAISE had gMG that met the refractory definition. The outcomes of people in the refractory subgroup are considered confidential by the company and so cannot be reported here.

The committee concluded that zilucoplan as an add-on to standard treatment is more effective at improving MG-ADL score than standard treatment alone. The committee noted the substantial response in the

placebo group and emphasised the need for this to be accounted for in any indirect treatment comparisons.

RAISE-XT

3.6 RAISE-XT is an ongoing open-label extension trial. People could enter RAISE-XT after completing 12 weeks of RAISE, or after completing a zilucoplan phase 2 trial. A total of 200 people entered RAISE-XT. People who had placebo in RAISE could switch to zilucoplan. At the RAISE-XT data cut (May 2023), people who had zilucoplan had a reduced MG-ADL score compared with baseline, and this reduction was maintained through extension week 84 (96 total weeks of treatment). The exact results are considered confidential by the company and so cannot be reported here. The committee concluded that RAISE-XT provided evidence that the effectiveness of zilucoplan was sustained for up to 2 years.

Generalisability

3.7 In its submission, the company positioned zilucoplan for people with refractory gMG. The EAG noted that people with refractory gMG were only a subgroup of the RAISE trial population. It was concerned that the outcomes observed in the whole RAISE trial population would not generalise to the refractory population that would have zilucoplan in the NHS. It also noted that of the studies included in the network meta-analysis (NMA; see section 3.8), only RAISE had a pre-defined refractory subgroup, and therefore the assumption of generalisability may not hold for any indirect comparisons. But clinical advice to the EAG explained that the baseline characteristics of the whole RAISE trial population approximated the refractory population in the NHS who would be considered for IVIg or PLEX. The clinical experts at the committee meeting also considered that refractory gMG may be expected to respond as well as non-refractory gMG in trials of new treatments. This is because treatments like zilucoplan have a novel mechanism of action, which people with refractory gMG will not have previously tried, and to which their gMG may respond. The committee concluded that the outcomes of

The evidence from the refractory cohort is available to NICE i understand. Refractory group also showe benefit compared to placeboo+SOC

Refractory MG patients could be considered the sub group with highest unmet need.

In my opinion and as PI of the RAISE study, I did not expect a dramatic responseto Zilucoplan as the patients I recruited were all refractory and considered to have lasting damage. But allof them improved. Therefore I believe whilst non refractory patient may theoretically could respond better (likely to have less end organ damage than a protracted refractory patient), practically I have observed that refractory cases also

I agree with NICE

the whole trial populations in RAISE and RAISE-XT could be generalised to the refractory gMG population in the NHS.

Indirect treatment comparisons

3.8 The company did NMAs to estimate the comparative effectiveness of zilucoplan with the comparators. NMAs were done for several outcomes, but the only outcome used in the economic model was MG-ADL response. The MG-ADL response NMA compared zilucoplan and efgartigimod, connected through the common placebo comparator. IVIg or PLEX studies were not included in this NMA because none included the MG-ADL response outcome. The results of the NMAs are considered confidential by the company and so cannot be reported here.

The EAG had several concerns with the NMAs. It noted differences in baseline characteristics and placebo response rates between RAISE and the efgartigimod trial. The NMAs did not account or adjust for these differences. Also, the EAG was concerned that the uncertainty in the NMAs was not carried through into the modelling because the response rate estimates were included as point estimates, without credible intervals. The EAG previously asked the company to try different methods, such as a matching-adjusted indirect comparison, but the company declined to do so. The company explained that it had assessed the feasibility of doing an adjusted NMA but concluded that it was not possible because of the small number of studies identified. It also explained that a matching-adjusted indirect comparison would be limited by heterogeneity in reporting across trials and by small sample sizes after population matching.

IVIG and PLEX are not SOC and they are used as rescue therapy. Due to shortages, requirement of infusion centre space, regular visits to the hospitals, reaction to IVIG, serious lack of accessibility to PLEX on chronic use, make these therapies not directly comparable.

The committee noted that there were several IVIg and PLEX studies that were excluded from the NMA because they did not report the MG-ADL response outcome. The committee would have preferred the company to try using different methods to obtain estimates of relative differences in those studies so that IVIg and PLEX could be included. One method that the committee thought could be useful was multivariate NMA in which the

RAISE and ADAPT trials have different trialdesigns and treatment modalities, treatmentdosing, cyclical approach in one and continuous daily treatment in another, whilst primary outcome was read at cycle one of ADAPTand at 12 weeks in RAISE. Therefore attempting to compare the two is riddled with complexities, casting doubt to any outcome

relationship between outcomes can be used to impute relative effect estimates for missing outcomes. A second method suggested by the committee would be to do an NMA of standardised mean differences for MG-ADL and other outcomes, from which odds ratios could then be approximated. The committee concluded that there were multiple issues with the NMA that meant that the comparative effectiveness of zilucoplan was highly uncertain. So, the committee asked the company to provide additional analyses to improve the indirect comparisons and provide scenarios using all relevant evidence.

Economic model

Company's modelling approach

3.9 The company used a cohort state transition model to estimate the cost effectiveness of zilucoplan against the comparators. The model included 7 health states. People start in the 'uncontrolled' health state and transition to the 'response' health state if they meet the treatment response criteria (decrease of 3 or more in MG-ADL score) at the response assessment timepoint. Responders are further divided into 3 subhealth states: 'stable response' (MG-ADL score remains stable after time of response assessment), 'loss of response', and 'continued response' (MG-ADL score continues to improve after time of response assessment). The exact proportion who transition into each is considered confidential by the company and so cannot be reported here. Within each health state (except death), people in the model can transition to the 'exacerbation', 'myasthenic crisis', or 'death' states. The model has a cycle length of 2 weeks and a time horizon of 52.5 years. The committee concluded that the model could be appropriate for decision making if it accounted for subsequent treatment use (see section 3.10).

RAISE has set a higher standard upon defining response by setting an MG ADL improvement by ≥3 points

Subsequent treatments

3.10 Over time, people in the model return to the 'uncontrolled' health state, and only have corticosteroids and immunosuppressants. The model does

Patients wit MG can move health status too exacerbation or crisis at any time (less likely if well controlled, unless well controlled situation leads to down titration of steroids or NSISTs, additionally even if the gMG patients stop zilucoplan as added therapy to SOC and if they dont respond as expected to Zilucoplan, then SOC will continue with clinicians exploring other options such as another DMT, IVIG, PLEX or even a new clinical trial

not account for any future use of IVIg or PLEX for people who stop either zilucoplan or the comparators. The committee recalled statements from the patient and clinical experts that gMG requires lifelong management. So, the committee thought it was implausible that someone with refractory gMG would stop zilucoplan and never have another treatment other than corticosteroids and immunosuppressants. The clinical experts noted that they would consider IVIg or PLEX for people who stop zilucoplan. They explained that if a person's refractory gMG did not previously respond to a particular treatment, they would not use it again. So, there may be differences in the choice and proportion of subsequent treatments in the zilucoplan and comparator arms. The committee concluded that it would like to see the company account for subsequent treatments in the model.

I agree with NICE

Treatment response rates

3.11 The company used the NMA results to estimate the MG-ADL response rates for zilucoplan and efgartigimod. The company converted the odds ratios of zilucoplan compared with placebo, and efgartigimod compared with placebo, into relative risks. Then, the relative risks were applied to the referent response rate. The referent response rate was calculated as the average response rate across studies identified in the NMA. The company considers the response rates for zilucoplan and efgartigimod, and the referent response rate, to be confidential and so they cannot be reported here. IVIg or PLEX response rates in the company model were based on data from Barth et al. (2011), a Canadian randomised controlled trial of 84 people with gMG who had either IVIg or PLEX. The company back-calculated the odds ratios for IVIg and PLEX from Barth et al., before using the same methodology to convert to relative risks and response rates, as with zilucoplan and efgartigimod. The calculated response rates were 51% (IVIg) and 57% (PLEX). The EAG noted several limitations with using data from Barth et al., including that:

- The population was not explicitly defined as refractory

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

Because of these uncertainties, the EAG chose to use the unadjusted response rates from the zilucoplan and efgartigimod trial arms of 73.1% and 73%, respectively. For IVIg and PLEX, the EAG received clinical advice that the expected response is much higher than estimated using Barth et al., with approximately 70% of people with gMG in clinical practice having a response. So, the EAG preferred to use the 70% MG-ADL response for both IVIg and PLEX. The clinical experts noted that they expect about two-thirds of people with gMG who have IVIg or PLEX would have an MG-ADL response, and so considered 70% plausible. The committee concluded that there was uncertainty in the estimates of the comparative effectiveness of zilucoplan. It noted that the company's approach used results from the uncertain NMA, and estimated IVIg and PLEX response from a study with several limitations. The committee also noted that the EAG's approach did not adjust for the placebo response observed in both RAISE and the efgartigimod trial. It noted that it would prefer response rates to be based on clinical data rather than expert opinion. The committee concluded that it had not been presented with accurate estimates of treatment response for any of the treatments. It asked the company to provide more analyses to clarify this.

Response assessment timepoint

3.12 The company selected the response assessment timepoint from the zilucoplan and the efgartigimod trials (12 weeks and 10 weeks, respectively), and used an assumption for IVIg and PLEX (6 weeks). The EAG noted that it had received clinical advice that treatment effects are seen much earlier, after 1 to 2 weeks, and response is often assessed 3 to 4 weeks after starting IVIg or PLEX. It also noted that later response

assessment may mean someone's gMG responds and then that response is lost. The EAG chose to use a response assessment timepoint of 3 weeks for all treatments in the model. The clinical experts at the committee meeting agreed that they would typically assess a person who had IVIg or PLEX after 2 to 4 weeks. The committee concluded that a response assessment timepoint of 3 weeks reflected NHS practice.

This is correct approximation:

for IVIG - 2 weeks after treatment and PLEX 3-4 weeks after starting the treatment

Utility values

3.13 Health-related quality of life data was captured in RAISE through the EQ-5D-5L. EQ-5D-5L scores were mapped to the EQ-5D-3L in line with the NICE reference case. Utility values based on EQ-5D scores from RAISE were used in a regression model and fitted for all people in the trial. Changes in utility depended on the person's baseline EQ-5D score, MG-ADL score, and body mass index. The model applied disutilities for exacerbations and myasthenic crises, sourced from the REGAIN trial for eculizumab. The model did not apply disutilities for adverse events, because the company noted that there were no serious adverse events with an incidence of 5% or more in RAISE. The model also did not apply disutilities for caregiver burden. The EAG noted that the company's approach for modelling utilities was appropriate. The committee thought that there were several uncaptured benefits associated with zilucoplan and asked the company to provide scenarios that consider these (see section 3.19).

Pre filled syringe
Not requiring to attend hospital several days a month
Not disrupting education/ employment
Non cyclical- therefore minimises the significant fluctuations

Costs

Resource use

3.14 The company's model applied treatment costs for IVIg every 3 weeks and for PLEX every 4 weeks. The EAG received clinical advice that, in the NHS, IVIg and PLEX are typically given every 4 to 8 weeks, with the interval between treatments sometimes extended to 12 weeks or, rarely, 16 weeks. The clinical experts noted that treatment intervals of 8 weeks or longer are not common and that 4 weeks is typical. The company also

Administration of IVIG I assume is less resource intense cmpared to PLEX Additionally there is a challenge in sourcing human Albumin for PLEX as of 30th of July 2024 Albumin is essential for PLEX

assumed that the PLEX administration cost was equal to the administration cost of subcutaneous immunoglobulin. The EAG disagreed, preferring to use the NHS reference cost SA44A – Single Plasma Exchange (£910). The committee concluded that IVIg and PLEX costs should be applied every 4 weeks and that the NHS reference cost for PLEX should be used.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.15 Because of confidential commercial arrangements for zilucoplan and some of the comparators, the exact cost-effectiveness results are confidential and cannot be reported here. Although some of the company's base-case incremental cost-effectiveness ratios (ICERs) were within the range NICE normally considers to be a cost-effective use of NHS resources, they did not include the committee's preferred assumptions. The EAG's base-case ICER was substantially above this range.

As a clinician awaiting novel therapies to a disease that has significant unmet therapeutic needs, it is disheartening to note that Zilucoplan is required to be compared to another treatment such as Efgartigimod, IVIG or PLEX. In the absence of head to head studies, statistical modeling used will no doubt create uncertainty when comparing apples with oranges. I appreciate NICE request to the sponsor to select a conservative model, however the drugs administered differently, mode of action is different, and in the case of IVIG/PLEX outcomes used were different. The current report has some guidance to the sponsor to follow from NICE guidance hopefully that would be acceptable to the sponsor.

Acceptable ICER

3.16 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically that:

- the model does not account for subsequent treatments (see section 3.10)
- the comparative effectiveness of zilucoplan is highly uncertain, and that uncertainty is not reflected in the model (see section 3.8 and section 3.11)

- ☐ There are uncaptured benefits of zilucoplan that the committee would like the company to try to account for (see section 3.13 and section 3.19).

The committee was unwilling to state an acceptable ICER threshold until these uncertainties are addressed.

The committee's preferred assumptions

3.17 The committee's preferred assumptions included:

- ☐ The comparators should be modelled as a 'basket' of standard care, with some people having IVIg, some having PLEX, and some having neither. All people should have corticosteroids and immunosuppressants. Efgartigimod should not be included as a comparator (see section 3.4).

Majority of the refractory patients yes should be ideally on SOC including steroids+NSIT

Text

- ☐ The results of the whole trial populations of RAISE and RAISE-XT can be generalised to the NHS population (see sections 3.5 to 3.7).
- ☐ Neither the company's nor the EAG's methods of estimating MG-ADL response were satisfactory. The committee would prefer an indirect comparison that incorporates data from all available studies, includes IVIg and PLEX, and adjusts for the placebo response. Also, any uncertainty from indirect comparisons should be incorporated in the model (see section 3.8 and section 3.11).

why is the response to treatment analysed at 3 weeks but costs are applied at 4 weekly.

Zilucoplan patients continued to improve until 12 weeks and some afterwards.

- ☐ The response assessment timepoint should be 3 weeks for all treatments (see section 3.12).
- ☐ There are uncaptured benefits of zilucoplan that may affect the utility of people who have it. The committee would prefer the company to present scenario analyses incorporating some of these uncaptured benefits in the modelling (see section 3.13 and section 3.19).
- ☐ Costs of IVIg and PLEX should be applied every 4 weeks, and the NHS reference cost should be used for PLEX administration (see section 3.14).

Other factors

Equality

Equality is a major issue when it comes to UL patients accessing novel therapies compared to the rest of the world and Europe. Our MG patients in the UK are disadvantaged compared to other developed economies.

3.18 The committee considered that gMG may have a different burden on women than men. gMG is more prevalent in women, women are typically younger at disease onset, and women typically have higher mortality. Furthermore, pregnancy may contraindicate some types of treatment. Sex is a protected characteristic under the Equality Act 2010. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed this was not a potential equality issue.

Uncaptured benefits

3.19 The committee considered if zilucoplan was innovative. The patient experts clearly noted that treatment with IVIg or PLEX was time-consuming, requiring regular hospital stays. They thought that zilucoplan, as a subcutaneous treatment that can be taken at home, would be much more convenient and could improve adherence. The clinical experts noted how resource intensive IVIg and PLEX are to administer. They also explained that people who have zilucoplan may be able to reduce their corticosteroid dose. This could lead to fewer corticosteroid-related adverse effects. Both patient and clinical experts considered zilucoplan to have advantages for patients, carers, and healthcare professionals. But the committee noted that similar QALYs were generated by each treatment in the model. The committee therefore concluded that there were benefits of zilucoplan that were uncaptured in the modelling. The committee asked the company to present scenario analyses that account for some of these benefits.

Additional analyses

3.20 The committee would like the company to provide the following analyses:

- ☒ an improved indirect treatment comparison that:
  - ☐ uses data from more of the identified studies

- ☐ includes IVIg and PLEX
- ☐ considers outcomes other than MG-ADL response rate to produce estimates of relative effectiveness
- ☐ accounts and adjusts for the differential placebo response observed in the trials
- ☐ respects randomisation.

☐ ☒ including subsequent IVIg and PLEX in the modelling and the effect on the cost-effectiveness estimates

☐ ☒ scenario analyses incorporating some of the uncaptured benefits of zilucoplan.

Conclusion

Recommendation

3.21 The committee considered that the cost-effectiveness estimates presented by the company and EAG were highly uncertain, and that given the uncertainty, it would like to see additional analyses. But the committee considered that, given its preferred assumptions, and based on the analysis it had seen, the cost-effectiveness estimates were highly likely to be above the range that NICE considers a cost-effective use of NHS resources. The committee concluded that zilucoplan could not be recommended for treating refractory gMG in adults.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

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

Issue date: July 2024

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

Chair

Dr Charles Crawley

Chair, technology appraisal committee B

NICE project team

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

Tom Palmer

Technical lead

Eleanor Donegan and Yelan Guo

Technical advisers

Jeremy Powell

Project manager

ISBN: [to be added at publication]

Issue date: July 2024

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 5pm on Thursday 25 July 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):	UCB

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Oct/2022 to 2024, I have served on advisory and educational boards and acted as a speaker at UCB organised and sponsored educational events. These advisory boards have been focussed on the management and treatment of myasthenia gravis and UCB treatments under development for the treatment of myasthenia gravis (zilucoplan and rozanolixizumab). The contracted parties for the above were UCB and Oxford University. Oct/2022 to 2023, I have served on advisory board and acted as speaker at an argenx organised and sponsored educational event. Those activities have focussed on the management of myasthenia gravis, in general, and on medical treatments, including that developed for generalised myasthenia gravis by argenx (efgartigimod) . The contracted parties for the above were argenx and Oxford University Oct/2022 to 2024, I have served on advisory boards I am a member of the steering committee for a clinical trial developed by Horizon for generalised myasthenia gravis (MINT) and acted as chairman in two educational sessions presented in international meetings, organised and sponsored by Horizon. The contracted parties for the above were Horizon and Oxford University
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No; I have no disclosures of any type or at any time in relation to funding from the tobacco industry.
Name of commentator person completing form:	Maria Isabel Leite (Dr & Associate Professor, Consultant Neurologist)

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 feel that all of the evidence available has been taken into account if we consider the available studies, publications and the modelling proposed sufficient. There is however great amount of unpublished valuable information that can still be captured if we make an effort to gather such data to show the potential and real “uncaptured” benefits of the zilucoplan. This can be provided by

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	experts with large cohorts of patients, including those with large experience on the management of patients with refractory disease and on the effects of zilucoplan in such patients, by providing real patient scenarios. Two UK centres contributed with 10% of the patients globally randomized to the Raise / Raise XT clinical trials.
2	If that data is captured and analysed (e.g. real number of patients on IVIG or PLEX, number of courses, complications, days in the hospital and other direct and indirect costs per patient / year) the committee will be able to estimate more accurately costs and benefits of zilucoplan vs standard treatment. It is important that, as noted in the committee report another proportion of patients with refractory disease have no access to either PLEX or IVIG and are unable to work, attend education / school, have a family and so on, and are often admitted to the hospital with MG exacerbations, have significant complications of very high dose steroids and of more prolonged hospital admissions than those who receive IVIG or are treated with PLEX. I am concerned that if the model includes the use and costs of IVIG / PLEX and not the significant costs of not reaching such treatments, we will be missing real data that needs to be taken into account.
3	Scenarios of the above based on patients randomised in the raise/raise XT in UK: (1) onset disease early teens; for 8 years: severe/refractory disease, on a sequence of standard immunosuppression and continuous steroids + very frequent PLEX for half of the disease course (multiple complications of such therapies, some life threatening and others will remain for life; house bound; no school; dependent of family); (2) onset 25; again severe disease, multiple therapies and complications; managed to live on regular IVIG for 20 years; (3) onset 18 years; on steroids and azathioprine all adult life with very modest effect (for 35 years); no access to PLEX or IVIG; no other immunosuppression offered; unable to work; no children; 20 years after disease and treatment onset, skin complications of azathioprine were already irreversible and severe, including skin cancers in multiple areas of the body (areas exposed) requiring surgeries and radiotherapy. These problems required many admissions. MG caused some crises and prolonged admissions, some with some serious complications, including pulmonary embolism. All patients had been initially treated as per usual guidelines, including thymectomy. These are just illustrative cases similar to a proportion of the refractory gMG patients we see in our practice and need to manage. How could we estimate the direct and indirect costs of each of these patients? I fear that, some of such patients will die earlier than their peers from school; they do already look much older than them. Have diabetes, osteoporosis and are overweight and suffer of sleep apnoea and depression; their vascular risk factors are high. I would be very keen and happy to participate in gathering relevant information on such cases and provide it to include in a health economical model to allow incorporation of uncaptured benefits of zilucoplan in such cases (similar to those who we hope will benefit from the zilucoplan). Going back to those 3 examples, all received zilucoplan and 2 are in remission (absolutely normal life, of steroids or immunosuppression and back to the activities they missed for many years; one (with skin cancer, who did not have access to different immunosuppression, or IVIG or PLEX) improved but is still symptomatic; missed opportunities and has irreversible damage of neuromuscular junction and many other organs affected by poorly optimised management.
4	To your point on whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, my answer is yes, but there is evidence missing; this is the problem. The examples above, multiplied by *n* nationally, are difficult to capture and analyse as a whole in a way that could translate easily in valuable evidence. I think, however, that it is still possible to collect such data from two distinct centres with large and diverse cohorts of patients.
5	The provisional recommendations seem to me a suitable basis for guidance to the NHS. I appreciated the request for scenario analyses incorporating some of the uncaptured benefits of zilucoplan. There are plenty of them (direct and indirect), but one may need to make an effort to gather that evidence.

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

	I liked the adjustments for the assessment of the benefit of the zilucoplan to match IVIG and PLEX (around 3 weeks); it is appropriate and will benefit all (patients and NHS). I felt that the concern or uncertainties of the Committee around the placebo effect could be eased. In my experience, any new treatment, including immunosuppression, in patients very symptomatic, leads to some apparent improvement which may not be constant or significant when compared to those who respond really well. I am aware that in the clinical trial, the patients, assessors and treating physician were able to "guess" early on what they were injecting (zilucoplan or placebo). I am confident that outside of the trial, there will be clear distinction between responders and non-responders. Furthermore, those who do not respond well will not tolerate daily subcutaneous injection without clear benefit. I do not expect problems in this aspect of the treatment in future.
6	Regarding equal access to the treatment, I think that unfortunately it will be difficult to avoid inequalities regarding the potential access to the new therapies in general, including zilucoplan. This is because we see already great differences in access to specialised centres and certain treatments considered standard. We see that on a daily bases: (1) managers refuse referrals from "out of the area" without the doctor who the patient has been referred to being aware of that letter from another consultant asking to review the patient and / or advice; (2) many general neurologists without expertise on MG prefer not to refer patients to specialised centres as they feel confident it is easy to manage MG; they only refer the patient when there are significant problems or when the patients insist to be referred; opportunities, even if it is simply to change doses or from one drug to another within standard regimes; (3) this is also seen in relation to thymectomy where there are patients operated by surgeons who do thymectomies weekly and others by surgeons who do a couple of year; (4) there is also a great difference based on the patients' difficulties caused by low education and socio-economic status and location (one of all together); such patients will require more than a referral to a myasthenia centre. They need to get there, pay transport, and so on. So, we need to work to improve the current system as much as possible. We neurologists in specialised centres will have the knowledge and ability to assess the patients and consider any particular treatment thought to be beneficial (standard or new). We need to improve the current practice to benefit every patient and, especially, to ensure that certain specific patient groups will have the same access to the relevant treatments as any other patients.
	I do not see any particular adverse impact on people with a particular disability or disabilities, unless for example blind and requiring someone to drive/bring them to the hospital / clinic. Having access to appropriate (new) treatments will probably only have positive impact on disease and life. The question is more whether they gain access to the treatments knowing that only specialised centres will be able to prescribe following rigorous clinical assessment and MDT discussions & recommendations. Another example could be blind people having difficulty self-injecting and needing a carer available and reliable.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.

Please return to: **NICE DOCS**

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 5pm on Thursday 25 July 2024. Please submit via NICE Docs.

- 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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Single Technology Appraisal

Zilucoplan for treating antibody-positive generalised myasthenia gravis [ID4008]

Comments on the draft guidance received through the NICE website

Name	[redacted]
ID	1
Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: I do not feel that the research for Zilucoplan versus IvIg have been properly addressed. We need to be able to compare the efficacy of Zilucoplan against Immunoglubulins/plasma exchange.

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

Answer: I do not believe so. You must look at long term benefits both at the burden on patients as well as the financial burden of the NHS of current treatments. If this can be shown as an available alternative to IVIG/plasma exchange it can impact greatly on both. As someone who currently has prophylactic Plasma and subcutaneous IG the impact can be great. My QoL can be greatly affected.

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

Answer: Without the inclusion of IvIg and plasma exchange I do not think there is enough data to say they are sound.

Question: 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?

Answer: The burden on those with a disability as unpredictable as MG getting to a hospital to have either or both Plasma and IViG at times can be impossible. At times needing hospitalisation can cause both homelife to suffer as well as the economic burden placed on those that are employed. For instance mothers, or single parent families, especially if there is no one to help. If Zilucoplan is a subcut treatment then the administering of it at

home will impact greatly on those with extreme disability or those who are relied on to provide financially or as a parent.

Name	[redacted]
ID	2
Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: Not in my opinion. Myasthenia Gravis is a rare disease and getting suitable treatment is both difficult and time consuming. Medical opinions vary greatly across the country and finding a suitably qualified professional is very difficult primarily because of its rareity. Access to Ivig or plex therapy is patchy to say the least and fraught with widely differing opinions and unnecessarily complex and beaurocratic. It is no surprise therefore that zilucoplan has not been compared to either Plex or IVIG.
It can take years to get a) a diagnoses and b) appropriate treatment - if ever!
Indeed access to other non standard therapies like rituximab is unnecessarily complex and time consuming leading to patients not having appropriate therapy for years!

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

Answer: There are no real summary of cost effectiveness included in the summary. Whilst it does state that it is clinically effective no comparison is made between IVIG and PLEX or indeed between other high cost treatments like monoclonal antibody treatments. To rule it solely by comparison to these two points is unreasonable and will lead to further delays in treatment for a very small cohort of patients! With an incidence of around 15 per 100,000 the vast majority of patients are successfully treated with Acetylcholine esterase inhibitors an steroid, the numbers who would need to access this treatment are very small probably less than 0.1 per 100,000

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

Answer: No for the reasons given above. If there is evidence of efficacy then getting the comparison between 2nd and 3rd line and novel therapies need to considered as does the affect of poor and patchy treatment of Myasthenia generally.

Question: 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?

Answer: No

Name	[redacted]
ID	3
Organisation	N/A
Conflict	No
Comments on the DG:	

Comment on section 1, Recommendations

Not all drugs suit every patient. Zilucoplan, along with efgartigimod, offers potential treatment for those for whom rituximab is ineffective or intolerable. Drugs such as these help conserve limited IVIg supplies for patients for whom it is an essential treatment, such as primary immunodeficiencies.

Name	[redacted]
ID	4
Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: Yes - all relevant data has been taken into account. There are limitations to the data reviewed by the committee, however. Specifically, NICE has reviewed evidence from the EAMS scheme for efgartigimod in defining a treatment refractory population of myasthenia. Despite the consensus of myasthenia specialists to only offer treatment to patients with refractory MG (failed two or more non steroid immunosuppressive treatments), the patient cohort in the EAMS scheme includes patients who do not meet this criteria. Therefore, the target population for zilucoplan identified by the drug company (patients on maintenance treatment with IVIg and PLEX) is NOT the same as patients reported on the EAMS scheme.

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

Answer: Recruitment to randomised controlled clinical trials in rare diseases such as myasthenia is difficult. For an adequately powered RCT, trials have to recruit patients with active disease to demonstrate if a treatment is clinically effective and not restrict recruitment to the small proportion of patients with refractory disease. As such, it would NOT be possible to recruit to a clinical trial to compare effectiveness of interventions like plasma exchange (PLEX) and IVIg to the new targeted treatments such as

zilucoplan. There are therefore no RCTs comparing PLEX or IVIg to the new targeted treatments.

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

Answer: There are very few proven effective treatments for myasthenia. There is one RCT supporting use of azathioprine and negative RCTs for mycophenolate. These non steroid immunosuppressive treatments for myasthenia take over 12 months for clinical effect with no options available to treat patients with explosive onset disease, typically admitted to hospital for prolonged inpatient stays and receiving very expensive treatments (typically ICU with plasma exchange or IVIg). Also, the only available RCT for Rituximab did not provide evidence of benefit in myasthenia. Although targeted treatments have not been explicitly studied in this patient population, for reasons given in a previous answer, it is reasonable to extrapolate data from the available RCTs to suggest that zilucoplan, and other targeted treatments, are likely to be effective and offer early benefit in this treatment refractory group of patients.

Question: 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?

Answer: No.

Name	[redacted]
ID	5
Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: No, in my experience there are refractory MG patients are less responsive to IVIg and PLEX therefore, having an alternative for this patient group to improve quality of life should be considered.

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

Answer: no because it does not account for the amounts of IVIg required in patients with gMg to keep them functioning at a suboptimal level.

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

Answer: No, I think further consideration is necessary on the effects of Mg on patients daily functioning and how severe symptoms can get become, especially in refractory patients who do not respond well to the standard treatments or IVIg/Plex. Having other options available is needed

Question: 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?

Answer: no

Name	[redacted]
ID	6
Organisation	N/A
Conflict	No
Comments on the DG:	

Comment on section 1, Recommendations

Having read the recommendations and the committee discussions it seems the present decision is solely based upon a economic model which is uncertain, the actual cost of Zilucoplan is not clearly defined as it states that "The company has a commercial arrangement, which would have applied if zilucoplan had been recommended." Unless this is defined then the economic model cannot be valid.

I have refractory gMG and so am desperate for an effective modern treatment to become available, the impact upon one's life is difficult to put into words, but stopping life about covers it. Imagine going through life struggling with speech for instance, try walking a mile in my shoes (if I could actually walk a mile).

The treatments we have available to us at present are very limited in their effectiveness and come with horrendous side effects (especially steroids), a therapy which may eliminate the need for these is long overdue.

I wonder if the committee whilst looking at the cost of treating a gMG patient also consider the additional costs involved, for instance exacerbations requiring hospital admission (four in my case), all the other medications required (pyridostigmine, prednisolone, omeprazole, alendronic acid to name but a few), I realise the cost of therapeutic IvIg is considered but that's not the only cost, also what are the costs of hospitalisation for IvIg or PLEX?

Perhaps also to be considered is the economic impact of the inability to work and live a productive life, I didn't want to quit work but had no choice, perhaps Zilucoplan could enable sufferers to return to useful lives.

In conclusion we gMG suffers just want to be free of the symptoms of this cursed disease and it is in the hands of NICE to do this, other modern therapies for gMG have been rejected perhaps authorising one which, it would appear, is very effective would, in the long run, be beneficial.

Name	[redacted]
ID	7
Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: It seems that little account has been taken of the severity of the impact of side effects of, for example anticholinesterases, on a patients quality of life. This can be as simple as not having the courage to leave home, even for exercise.
The current reliance on Pyrodostigamine as the main (only) first stage treatment engenders further lose of confidence. What is a patient to do if this treatment causes distress. Unfortunately most GPs have little knowledge of myasthenia and accessing specialised neurologists can be a lengthy process.
Knowledge that there is a readily available backup or treatment would be extremely useful

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

Answer: No comment

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

Answer: No, for the reasons given above

Question: 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?

Answer: Yes everyone wants to lead a useful and productive life. The lack of a benign alternative or supplement to anticholinesterases would benefit all the groups listed

Name	[redacted]
ID	8

Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: Yes.

Comment on section 1, Recommendations

As someone who has lived with Myasthenia Gravis for 24 years (I'm 37 years old), I have experienced the challenges of managing this condition firsthand. The condition has been quite active throughout the years, I have never been in remission, and have tried numerous treatments, with only IVIG proving successful. Since the pandemic, I have faced particularly tough moments, culminating in a long-term crisis where I became dependent again. Therefore, I am deeply concerned by NICE's initial decision not to approve Zilucoplan for MG patients as another treatment alternative.
When I was first diagnosed, there were very few treatments and medications available for MG. Today, we are fortunate to have more treatment options, offering patients the chance to find something that truly works and helps manage this chronic condition.
At the end of last year, I experienced a respiratory arrest and survived by a miracle. I was intubated for a week and hospitalized for two months. Recently, I began treatment with Zilucoplan after an unsuccessful trial with Efgartigimod last year. Already, I have seen significant improvements in my strength and energy. I have been able to do things and activities that I haven't done in ages. Besides, this treatment doesn’t require me to go to the hospital to be able to have it (in 24 years I’ve never been more than 4 weeks without going to the hospital), I administrate it myself from the comfort of my home or wherever I am. Zilucoplan is definitely working for me, giving me hope, freedom, and the path to the independence needed to return to work and resume my life as it was before the pandemic.

We are all different, and not every treatment works for everyone. Thus, excluding a treatment option when we still don't have many available, and that is responsive to every patient, should not be an option. MG is a complex condition that is difficult to manage when not under control. Many treatments and medications take a long time to show effectiveness, if they show any at all, and the side effects can be severe. Zilucoplan acts quickly, allowing both patients and consultants to know soon if it is effective. Its prompt action can significantly improve the quality of life for patients (the trials say so), providing a much-needed alternative for those who have not found success with other treatments.
I strongly urge NICE to reconsider its decision and approve Zilucoplan, giving MG patients the opportunity to benefit from this promising treatment.

Name	[redacted]

ID	9
Organisation	Myaware and Moorfields Eye Hospital, [redacted]
Conflict	No
Comments on the DG:	

Comment on section 1.2 (Recommendations), text "Zilucoplan would be used as an add-on to standard treatment for people who test positive for anti-acetylcholine receptor antibodies and whose condition has not improved with standard treatment alone."

I fit into this category as standard treatment alone is not improving my condition, Myasthenia Gravis, MG. I would welcome a prescription from my General Practitioner,GP for Zilucoplan with guidance from Moorfields Eye Hospital, Dr and consultant [redacted] for the correct dosage post ratification and clearance by National Institute for Clinical Excellence, NICE.

Comment on section 1.2 (Recommendations), text "Clinical trial evidence suggests that zilucoplan plus standard treatment improves symptoms and people's ability to carry out their normal activities compared with standard treatment alone. But zilucoplan has not been compared with intravenous immunoglobulin and plasma exchange, so it is unclear how well it works compared with these treatments."

Perhaps further clinical trials are required to carry out those comparisons? Furthermore I highly recommend working with Myaware the charity organisation behind Myasthenia Gravis, MG as they also carry out research and have a laboratory with research assistance with fully qualified and working neurophysicians.

Comment on section 1.2 (Recommendations), text "As well as the uncertainties in the clinical evidence, there are uncertainties in the economic model and the cost-effectiveness estimates for zilucoplan. The most likely estimates are substantially above what NICE considers an acceptable use of NHS resources. So, zilucoplan is not recommended."

With this I highly recommend contacting or if already established work with [redacted] at Moorfields Eye Hospital, London as she has a research group, of which I am a member, researching the causes of Myasthenia Gravis, MG. This should also provide evidence of how an economic model can be created that is cost-effective and an acceptable use of NHS resources.

Name	[redacted]
ID	10
Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: The relevant trials have been taken into account but given the nature of MG (a rare disease with frequent fluctuations), placebo controlled trials are difficult in this condition and this must be recognised. It's often unethical to include patients who are acutely deteriorating or dependant on regular IVIG or PLEX in trials - hence the comparison of Zilucoplan to these treatments will be difficult.

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

Answer: To a point...however, I do not think factors such as the side effects of steroids have been emphasised enough. This is a huge cost issue (requiring different medications to counteract side effects, bone scans, additional clinic appointments such as bone clinic reviews etc) and is a major quality of life issue for patients with MG.
Steroids are known to be associated with weight gain - has the major public health issue of obesity been considered when considering the potential impact of steroid reduction from targeted therapy?

MG is a major cause of unplanned hospital admissions, day care attendances etc and i think these factors should be continued. Has the impact of MG on ability to work been considered?

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

Answer: I think the decision not to recommend Zilucoplan puts the NHS and the country in a backward position compared to our European peers. The landscape for MG has changed - for a small select proportion of patients with refractory MG there is now the option for targeted therapy that is more efficacious and faster acting. Depriving these patients of an efficacious treatment option puts them at a substantial disadvantage to our neighbouring countries.
The MG specialists are very clear that these drugs will be used judiciously. We are drawing up very specific guidelines to this effect.
It is our opinion that these drugs should only be used after an MDT discussion with multiple MG specialists. There is already a flourishing and active MG MDT network and this can be expanded formalised and audited.

Patients with refractory MG will use healthcare resources in different ways including unplanned admissions, prolonged hospital stays, treatment related complications as well as the inability to work that many suffer from.

Provision of a proven effective safe self administered treatment in a small select group of patients would seem sensible and indeed ethical.

Question: 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?

Answer: The geography of the NHS in England means that there is massive variation in the equity of access to IVIG and PLEX - a self administered drug would help reduce the variations in access to care.

Comment on section 1, Recommendations

It would be very difficult to have a clinical trial comparing IVIG to Zilucoplan - given that IVIg is generally used for acute severe deteriorations - it would be difficult to do this trial from an ethical point of view. It is difficult / impossible / borderline unethical to recruit acutely deteriorating MG patients into trials.
Non trial evidence from severe patients who were previously on IVIg who then received Zilucoplan exists - I had one such patient - after years of severe symptoms requiring IVIg and steroids, she was able to stop both treatments once she received Ziluocplan suggesting that in her case at least Zilucoplan was more effective than IVIg. Clinician colleagues have shared similar stories with me.

Comment on section 3.1 (Committee discussion, The condition), text "ids"
The side effects of long term steroids should not be minimised. This is a major course of morbidity for patients with MG

Comment on section 3.2 (Committee discussion, Treatment options), text "NHS England also considers rituximab, an anti-B-cell monoclonal antibody treatment, to be equally effective to IVI"

There is no evidence comparing Rituximab to IVIg in refractory MG. I do not think that it makes sense to regard them as equivalent. It is certainly contrary to may clinical experience.

Rituximab is indeed often ineffective in longstanding refractory AchR positive MG and the BEAT MG Phase 2 trial of Rituximab in Mg was negative.

Comment on section 3.3 (Committee discussion, Target population), text "The clinical experts considered that these criteria broadly describe the population that zilucoplan would be used for in the NHS."

THere have been weekly meetings for MG experts regarding rewriting the guidelines for MG. The experts are very clear that if approved, the newer targeted therapies would only be used in very specific subgroups of patients. We have also suggested the setting up of a national MDT / multiple regional MDTs in which cases could be discussed to ensure appropriate use of targeted therapies.

Comment on section 3.4 (Committee discussion, Comparators)

There is a big issue with equity of access to IVIg and PLEX across the NHS. PLEX services are few and far between and not every Trust has equal access to IVIg. An alternative (assuming it had been approved by a committee of MG experts) would help improve equity of access to treatments for refractory patients

Comment on section 3.8 (Committee discussion, Indirect treatment comparisons)

I understand the reasons for the committee suggesting these comparisons but I think it is really difficult to compare different trials that used different outcome measures even with the adjustments that are suggested.

Comment on section 3.10 (Committee discussion, Subsequent treatments)

For most targeted treatments especially those that work quickly like complement inhibitors it would be reasonable to try treatment holidays on a yearly basis - MG can rarely go into remission and treatments should not be continued if not needed. This may mean that a % of patients who start Zilucoplan may be able to stop it if their condition stabilises.

Comment on section 3.11 (Committee discussion, Treatment response rates)

The placebo response rate is not unique to targeted therapies in MG. It is a disease that does fluctuate so a placebo response is not unexpected.
I also would like to point out that real world evidence will look beyond the ADL - the MG ADL score does not capture all the factors of MG (eg distal weakness, head drop etc are not counted) Moreover there are other factors that indicate treatment response eg a drop in steroid dose, ability to stop regular IVIG and PLEX and unplanned admission rates that should be considered.

Comment on section 3.14 (Committee discussion, Resource use)

Do the PLEX costs quoted reflect all factors involved - including need for specialised machines, vascular access, blood products, admission to hospital when needed etc?

Furthermore there are risks of both IVIg and PLEX including clotting/bleeding/ ischaemic events etc. Have the potential impact of these events been considered?

Name	[redacted]
ID	11
Organisation	N/A

Conflict	No

Comments on the DG:

Question: Has all of the relevant evidence been taken into account?

Answer: Yes

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

Answer: No

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

Answer: No

Question: 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?

Answer: I dint feel the needs of the Mysthenia community have been taken into account.

It shouldn't be about cost, it should be about quality of life.

An injection a day is far less invasive than iVig. You have to go ibto hospital for iVig. An injection could be administered at home. Surely that is more cost effective.

Comment on section 1, Recommendations

I am 48 years old and was diagnosed with AchR positive Myasthenia Gravis in Jan 2020.

I take immunosuppresents every day and had a thymectomy in 2020 to remove a malignant thymoma.

I was put on a course of steroids after going into crisis in Sept 2020. I gained 3 stone in weight in 6 months and it took till June 2023 to reduce off these steroids completely.

I was also treated with Ivig whilst going into crisis, in hospital. Crisis is extremely scary and can lead to being put on a ventilator because your diaphram doesn't work.

After all this treatment I still live with symptoms of MG every day. It has changed my whole world, and my families. I have had to completely change

the way I live. I can't do physical activity because the weakness will return. I've had to give up work completely recently because I'm an administrator and the muscles in my eyes can't take the constant movement and it now causing fatigue, brain fog, and cognitive problems.

If this treatment was approved and I could lead a normal, or close to normal life again it would be life changing for me.

I'm 48 now but how much worse will it get as I get older?

I would be happy to administer an injection or have someone do it at home if would mean I could have a better quality of life.

For us Myasthenics, Ivig is a last chance saloon. Its what your given when your already going into crisis. This new medication would prevent us from even going into crisis.

There is not 1 drug out that has specifically been made for people with Myasthenia. We have to take medication that is used to treat other illnesses. I take Mycophenolate, this is used to treat people who have had organ replacement.

I would welcome any new treatment if it meant a better quality of life.

With many thanks
[redacted]

Name	[redacted]
ID	12
Organisation	N/A
Conflict	No
Comments on the DG:	

Comment on section 3.1 (Committee discussion, The condition)

Myasthenia Gravis has a significant impact on family life. Before diagnosis I was an avid fell walker and scuba diver and worked full time as did my wife. Now because of my condition I am in a wheelchair with multiple co morbidities all caused by Myasthenia or the treatments. I am totally reliant on my wife for everything. I can no longer work and my wife has had to give up work to become my full time carer. We have had alterations made to the house including converting the bathroom to a wet room, having a ramp installed so we can get the wheelchair out. The car has been changed to accommodate the wheelchair and a boot hoist has been fitted so the wheelchair can be easily lifted in and out. I also need a hospital bed so I can sleep upright which enables me to breathe and an air mattress to help with bed sores. Although we have had some help with this we have had to use our savings to pay for a lot of it. This condition causes numerous problems

for lots of people who are affected by it and any new potential treatments are to be welcomed. Many treatments currently available are not suitable for patients. I have tried every drug available to me since diagnosis and nothing has worked so far. I now see a psychologist as I have PTSD as a result of my lengthy stay in ICU when I had a crisis. I live in hope that one day something will work for me

Comment on section 3.2 (Committee discussion, Treatment options)

I have tried all the usual treatments that are available to me so far to no effect. I have had Pyridostigmine, corticosteroids, Mycophenolate, Methotrexate and Rituximab infusions all to no avail. The other immunosuppressant drugs are not suitable for me due to other conditions I have. These drugs, in particular the steroids, have caused numerous other problems as follows:
Steroid induced myopathy - I have very limited use of my legs
Severe breathing difficulties
Type 2 diabetes controlled by insulin
Sleep aponea - I use a CPAP machine
Neuropathy in my feet and toes which is painful all the time
Pancreatitis and gallbladder issues caused by the steroids. My gallbladder needs to be removed but I am deemed to ill for this to be done. I have pancreatic necrosis and have a fistula going from the wall of the pancreas to my bowel which they cannot do anything about as I am too ill.
I went into septic shock as a result of a kidney infection I got which has resulted in me having CKD stage 3b. I still suffer from numerous infections each year some of which require a hospital stay
I had a myasthenic crisis which meant a stay in ICU for almost two weeks where I received IVIg. Whether this helped or not we don't know as at the same time I had sepsis. This resulted in a hospital stay of over 6 months
I have had cataracts removed from both eyes which appeared more or less overnight due to the steroids
I attend a hospice as an outpatient to help me to cope with the impact this has had on my life
All this has happened because of the condition and because there are no treatments available to me at present that will help my condition. The next stage, if my neurologist can gain approval is for me to try IVIg as a maintenance treatment. I think all treatments should be available on the NHS regardless of cost. If the treatment works for just a few people then this will help to give them their life back and will probably result in fewer costly hospital admissions. Until you live with this condition you have no idea of the impact it has on your life

Name	[redacted]
ID	13
Organisation	N/A
Conflict	No
Comments on the DG:	
Question: Has all of the relevant evidence been taken into account?	

Answer: I do not believe so as there is no evidence based on the efficacy of Zilucoplan versus IVIG or Plasma Exchange which would be the target for being able to reduce or replace the need for.

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

Answer: I do not think so as I do not feel you are looking at the long term benefits of the drug. Plasma exchange and IVIG are both still expensive and also require clinical space and staff to administer them whereas Zilucoplan does not. Also the benefit to the patient and their family/carer(s) far outweighs any financial burdens of Plasma exchange or IVIG which can be a lot for the hospital and also for the patient. I can speak of this first hand as I used to regularly have plasma exchange and depending on how far away you live (1.5 hours) for me those fuel and parking costs add up. I have since been having Efgartigimod which until recently was working for me and saved all that hassle but due to a venous issue I now find myself in need of a drug like Zilucoplan once more and I know it works because I speak to a lot of people in the USA who think it is wonderful!

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

Answer: I do not feel that there is enough data to say there is a sound and suitable guidance to the NHS because IVIG and Plasma Exchange has not been included.

Question: 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?

Answer: If you think about a group of patients as a whole you need to remember that although most will likely need treatment not all will be at the same severity and some will be parents, single parents or working, or even working single parents who just cannot make it into hospital for other treatments that could help them. Zilucoplan could therefore be the one drug that helps them due to being able to self administer it from home and it could really make a huge difference to their quality of life and that of their family too. Some children end up being carers for their parents which is so unfortunate but this drug could change their lives and that of their children's too and not just in terms of care but financially for some because they do not need to make their way to the hospital constantly.

Name	[redacted]
ID	14
Organisation	N/A

Conflict	No
Comments on the DG:	

Comment on section 3.2 (Committee discussion, Treatment options), text "The clinical experts explained that corticosteroids like prednisolone are associated with notable side effects and that they aim to use minimal effective doses to reduce these."

As noted steroids are associated with significant side effects which patients find difficult to tolerate. there is also a cost to the health service with increased incidence of diabetes, fractures, cataracts etc which need to be factored into the cost equation.

Comment on section 3.2 (Committee discussion, Treatment options), text "The ABN guidelines recommend non-steroidal immunosuppressants such as azathioprine if remission is not achieved on corticosteroids alone."

The evidence for use of other immunosuppressants in MG is poor. If they work they take months - years before benefits can be noticed, they come with significant side effects including increased risk of skin cancers and require regular blood tests. Furthermore most are contraindicated in pregnancy which makes managing women of childbearing potential a challenge.

Comment on section 3.2 (Committee discussion, Treatment options), text "NHS England also considers rituximab, an anti-B-cell monoclonal antibody treatment, to be equally effective to IVIg."

I question where this data comes from. As far as I am aware there are no trials comparing these treatment modalities. In clinical practice IVIG provides most patients with short term benefit (4-12 week) while rituximab takes longer to work but if beneficial, provides longer benefit.

Comment on section 3.5 (Committee discussion, RAISE), text "From baseline to week 12, people who had zilucoplan had a statistically significantly greater reduction in MG-ADL score compared with people who had placebo"

In my clinical experience it can take longer for the benefits of zilucoplan to be realised. Therefore it should not be stopped too soon.

Comment on section 3.5 (Committee discussion, RAISE), text "It questioned whether people might enter the trial when their gMG is particularly bad, and the improvement seen after starting treatment is partly a regression to the mean effect."

I'm not sure how likely this is. Refractory patients do fluctuate but around a pretty low baseline. I think it is unlikely that natural fluctuations explain the changes in the ADL score

Comment on section 3.10 (Committee discussion, Subsequent treatments), text "The clinical experts noted that they would consider IVIg or PLEX for people who stop zilucoplan."
I have a patient on this treatment which has effectively kept the patient out of hospital (they were admitted to hospital several times during the previous 6 months with at least one period of time on ITU). The patient has not required PLEX or IVIG and has been able to reduce their steroid dose substantially. Although not symptom free their MG ADL has reduced significantly and they are pleased with the response. If they stopped it they would have to go back onto PLEX or IVIG.

Comment on section 3.12 (Committee discussion, Response assessment timepoint), text "The EAG chose to use a response assessment timepoint of 3 weeks for all treatments in the model"

In my limited clinical experience of zilucoplan it can take a lot longer for benefits to be realised. Patients continue to improve for several months.

Comment on section 3.14 (Committee discussion, Resource use), text "4 weeks is typical"

I think this is quite a short time interval and think that 6-8 weekly is more typical.

Comment on section 3.19 (Committee discussion, Uncaptured benefits), text "zilucoplan, as a subcutaneous treatment that can be taken at home"

There is a huge benefit to patients being able to self administer at home. They can still work, care for children, study etc. This is difficult to capture but very important to patients.

Name	[redacted]
ID	15
Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: No I do not think it has, as a patient I have been poorly with three crisis's in the last year.
I was given IVIG and had terrible side effects along with Atopic meningitis.
I was given Efgartigimod but unfortunately this did not suit me and I ended up in a crisis.
I have not been suitable for any other treatments due to my complicated health problems.

Zilucoplan has given me a new lease of life, saved it if I am honest, and I have reduced the steroids because I have negative side effects, along with immunosuppressant medications of which I hope to reduce too.

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

Answer: If it helps to give a reasonable life back then cost should not have to come into it.
Zilucoplan, which is a revolutionary and unique medicine should be highly recommended.
Not only does it give near normality back to a patient along with a good quality of life, It also has ease of use and patients can travel, vacation etc with the simple daily injection that is well tolerated.
Plasma exchange is costly and time consuming by putting unnecessary stress on patients, not every patient has good veins, therefore can be risky.
IVIG is also time consuming, it does not always work and too many side effects, considering I am not allowed the flu vaccination, or the Covid 19, IVIG is not screened from these.
Both the above treatments put a heavy burden on the NHS, staff, equipment, transport, risk of infections along with immunosuppressive patients being at risk mixing with others.

Name	[redacted]
ID	16
Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?

Answer: Misses out patients not responding to standard care.

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

Answer: I think a smaller population of patients need to be taken into account eg this drug would be outside of standard care if that is defined as try 2 NSIMs, then rituximab and then zilucoplan.

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

Answer: I think there are issues that remain unresolved. At the moment there is an unmet need for additional medications to be available to patients who have tried standard of care and failed standard of care. I don't think the consultation takes outside of standard of care into account. Most patients are controlled on standard medical care but a proportion are not. By standard of are I mean trying 2 non-steroidal immunosuppressive agents

and then rituximab. After rituximab there is no data for other drugs that could potentially work apart from zilucoplan and other targeted therapies eg efgartigimod. If we don't have access to these drugs we know that patients who live with an unacceptable burden of disease as that is the reason to consider other drugs and cycle through other drugs. We need essentially drugs that have been shown to be effective rather than relying on drugs with no clinical RCT data. We currently have no guidance on what to use after rituximab and these drugs would fill a void for what we use after rituximab if this drug fails and the patient still remains with an unacceptable disease burdon.

Question: 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?

Answer: No

Name	[redacted]
ID	17
Organisation	N/A
Conflict	No
Comments on the DG:	

Comment on section 1, Recommendations

I have Myasthenia Gravis. It has significantly changed my life!! As it progresses, I am likely to have to cut my dose of Prednisolone. Drugs, such as Zilucoplan, which can potentially be used as an alternative to intravenous treatments and plasma exchange, are literally vital. I appreciate that cost is always a limiting factor, but if effective, costs such as ongoing care, further medical intervention, etc must surely be weighed against the initial cost of the drug to the NHS. Thank you for this opportunity to comment as one who has to live with MG in perpetuity.
Regards,

[redacted]

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

Zilucoplan for treating generalised myasthenia gravis (ID 4008)

Appendix: EAG critique of the company's updated economic analyses following the first Appraisal Committee Meeting

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Date completed	26th September 2024

[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)
CEM	Cost-effectiveness model
CFB	Change from baseline
CS	Corticosteroid
DGD	Draft Guidance Document
EAG	External Assessment Group
EAMS	Early Access to Medicine Scheme
gMG	Generalised myasthenia gravis
HCRU	Healthcare resource use
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
IVIg	Intravenous immunoglobulin
SCIg	Subcutaneous immunoglobulin
MAIC	Matching-adjusted indirect comparison
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living scale
MSE	Minimum symptom expression
NMA	Network meta-analysis
NSIST	Non-steroidal immunosuppressant
PLEX	Plasma exchange
QALYs	Quality adjusted life years
QMG	Quantitative Myasthenia Gravis scale
RCT	Randomised controlled trial
SoC	Standard of care
SLR	Systematic literature review

1 INTRODUCTION

This document is the External Assessment Group's (EAG's) critique of the response by the company, UCB, to the NICE Draft Guidance Document (DGD) (issue date 27th June 2024) for the technology appraisal on zilucoplan for treating generalised myasthenia gravis (ID4008). The EAG received the company's response documents and the revised economic model on 28th August 2024. The EAG noted some errors in the model and we were unable to verify which changes to the model had been made since the first Appraisal Committee Meeting (ACM1).

We requested clarification from the company via NICE on 11th September 2024 and received a revised version of the company response and economic model on 15th September 2024. The EAG was subsequently informed that the company had identified errors in their analysis and we were provided with an updated company response and economic model on 23rd September 2024.

The present EAG critique is based on the company's response received on 15th September 2024, because we were given insufficient time to critique the version received on 23rd September. The EAG cannot verify the changes that the company have made to their model since ACM1 in any of the three versions of the model received.

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

Table 1 Documents provided by the company

Company document name	Document name used in this report
gMG global CEM – Technical report v4	Model Technical Manual
ID4008 Zilucoplan_ACD response_ supporting information	Company Response Document
Network Meta Analyses for NICE_Short Report	Company NMA Report
ZLP vs IVIg_MAIC Technical report v3	Company MAIC Report

The DGD provides a series of NICE preferences and recommendations which can be divided into five issues relating to the clinical effectiveness evidence and seven issues relating to the economic analysis, as follows:

Clinical effectiveness:

- Indirect treatment comparison (ITC) should use data from all relevant studies
- ITC should include both IVIg and PLEX
- ITC should consider all relevant outcomes
- ITC should account for placebo response heterogeneity
- ITC should respect treatment randomisation

Economic analysis:

- Uncertainty in clinical effectiveness should be incorporated in the economic analysis
- The comparators should be modelled as a 'basket' of standard care
- Uncaptured benefits of zilucoplan to patients should be considered
- Subsequent treatments should be accounted for in the economic analysis
- Costs of IVIg and PLEX should be applied every 4 weeks
- The response assessment timepoint should be 3 weeks for all treatments
- Results of the whole-trial populations of the RAISE and RAISE-XT trials can be generalised to the NHS

The company's responses to these issues are summarised in Table 2 below and are critiqued in further detail in the subsequent sections of this report.

In addition to the issues noted in the DGD, the company provided additional evidence for:

- Corticosteroid sparing and NSIST sparing (Company Response Document section 2.1).
- Minimum symptom expression (MSE) (Company Response Document sections 2.2 and 3.1.5).
- Treatment stopping rule (Model Technical Manual section 2.4.3).

This additional evidence is summarised in Table 3 below and critiqued further in the subsequent sections of this report.

The company present the results of their revised base case analysis and sensitivity analyses in section 3 of the Company Response Document.

In this report we present the following:

- Our critique of the company's response and new evidence (section 2)

- A validation of the results of the company's updated cost-effectiveness analysis based on the company's revised model received on 15th September 2024 (section 3).
- The EAG's preferred assumptions (section 4)

As noted above, we were unable to revert the company's revised base case results to the version that was considered at the first Appraisal Committee Meeting. The company have not provided a table documenting the changes made to the model and we are uncertain whether any further changes have been made to the model, beyond those stated in the company's response documents. We are therefore uncertain whether results of our base case analysis (Table 16 below) and scenario analyses on our base case (Table 17 below) are reliable.

Table 2 Summary of the NICE Committee's preferred assumptions and recommendations in the Draft Guidance Document (DGD) and the company's responses

NICE Committee's preferred assumptions and recommendations in the DGD		Company's approach	EAG comments
Clinical effectiveness: Studies included	An improved indirect treatment comparison that uses data from all available studies (DGD sections 3.17 and 3.20)	As outlined in the Company Response Document, the company conducted new NMA analyses (conventional NMA, bivariate NMA, baseline-risk-adjusted NMA). An additional study of IVIg versus placebo (NCT02473952) was included NMAs and an additional study of IVIg versus placebo (Bril et al. 2023 [1]) was included in a MAIC analysis.	The company have included some new evidence but have not provided an update to their systematic search or feasibility assessment for studies to confirm whether any further studies, particularly of PLEX (e.g. real-world evidence cohorts), could be relevant. The EAG could not verify that NMA and MAIC analyses were conducted appropriately, because statistical code was not provided. For further discussion see section 2.1 below.
Clinical effectiveness: Treatments included	An improved indirect treatment comparison that includes IVIg and PLEX (DGD sections 3.17 and 3.20)	As noted above, the company's updated NMAs and MAIC analysis included two additional studies on IVIg.	One of the additional IVIg studies is included in an NMA that informs the economic analysis (bivariate NMA), but the NMA is subject to the limitations noted above. No new evidence for PLEX has been provided. For further discussion see section 2.2 below.

NICE Committee's preferred assumptions and recommendations in the DGD		Company's approach	EAG comments
Clinical effectiveness: Outcomes included	An improved indirect treatment comparison that considers outcomes other than MG-ADL response rate to produce estimates of relative effectiveness (DGD section 3.20)	The company conducted a bivariate NMA that included both MG-ADL and QMG outcomes to enable estimation of MG-ADL where this outcome was missing (Company Response Document section 2.3 and Company NMA Report)	Company NMA Report Table 2 shows that the bivariate NMA, which informs the economic analysis, allowed one additional study of IVIg to be included (NCT02473952). However, the bivariate NMA does not resolve the lack of MG-ADL response outcomes for PLEX, which is a key source of uncertainty among the comparators. For further discussion see section 2.3 below.
Clinical effectiveness: Placebo response heterogeneity	An improved indirect treatment comparison that accounts and adjusts for the differential placebo response observed in the trials (DGD sections 3.17 and 3.20)	The company conducted a baseline risk adjusted NMA to account for placebo response heterogeneity between trials (Company Response Document section 2.5 and Company NMA Report).	The baseline-risk-adjusted NMA to adjust for placebo response heterogeneity does not inform the economic analysis. The company do not discuss how results of this NMA should be interpreted in relation to the way that placebo heterogeneity is handled in the economic analysis. For further discussion see section 2.4 below.
Clinical effectiveness: Randomisation	An improved indirect treatment comparison that respects randomisation (DGD section 3.20)	No change to the modelling approach has been made. For zilucoplan and IVIg the economic model utilises odds ratios for each treatment versus placebo which are adjusted using a referent placebo response rate.	The NMA that informs the economic model respects randomisation (provides an odds ratio). However, the original company economic analysis converted the odds ratio to a response rate point estimate via a referent placebo rate calculation and this remains unchanged in the company's updated analysis. For further discussion see section 2.5 below.

NICE Committee's preferred assumptions and recommendations in the DGD		Company's approach	EAG comments
Economic analysis: Uncertainty in clinical effectiveness inputs	Any uncertainty from indirect treatment comparisons should be incorporated in the model (DGD section 3.17)	No change to the modelling approach has been made. The credible intervals of NMAs or confidence intervals of primary studies are not used in the company's model.	This recommendation in the DGD has not been addressed by the company. For further discussion see section 2.6 below.

NICE Committee's preferred assumptions and recommendations in the DGD		Company's approach	EAG comments
Economic analysis: Comparators	The comparators should be modelled as a 'basket' of standard care, with some people having IVIg, some having PLEX, and some having neither. All people should have corticosteroids and immunosuppressants. Efgartigimod should not be included as a comparator (DGD section 3.17)	The company compared zilucoplan directly with IVIg or PLEX. They did not model the comparator as a 'basket' of standard of care treatments.	Within the revised company model, the functionality to use a 'basket' of standard of care (called the 'refractory standard basket') as a comparator was hidden in the model, which the EAG reactivated. We have used the refractory standard basket as the comparator in our base case as well as the scenario analyses. For further discussion see section 2.7 below.
Economic analysis: Uncaptured benefits	There are uncaptured benefits of zilucoplan that may affect the utility of people who have it. The committee would prefer the company to present scenario analyses incorporating some of the uncaptured benefits in the modelling (DGD section 3.17)	The company provide data from RAISE and RAISE-XT showing that some patients may reduce or discontinue their use of corticosteroids and, in some cases NSISTs. This information is used for adjusting treatment costs (Company Response Document section 2.1). They include annual utility decrements associated with corticosteroid use in their base case (Company Response Document section 3.2.4). Furthermore, they apply a 0.005 per-administration utility to account for the health-related benefit of self-administered zilucoplan in their revised base case (Company Response Document section 3.1.8). Finally, they also incorporate carer disutilities as part of their scenario analyses (Company Response Document section 3.1.10).	We disagree with the company's approach for including extra costs from corticosteroid use. We also disagree with the company regarding including the utility increment associated with self-administration of zilucoplan at home and the utility decrement associated with corticosteroid use. We consider that these have already been captured in patients' global EQ-5D scores. Lastly, we agree with the company regarding excluding carer disutilities from their base case. For further discussion, see section 2.8 below.

NICE Committee's preferred assumptions and recommendations in the DGD		Company's approach	EAG comments
Economic analysis: Subsequent treatments	The committee would like to see the company account for subsequent treatments in the model (DGD section 3.10).	The company applied subsequent treatment costs for patients who do not respond, or lose response, to first-line treatment. (Company Response Document section 3.17)	While the company incorporated subsequent treatment in their revised model, the EAG have concerns with their approach, because the costs for IVIg and PLEX are applied in the subsequent treatment of patients who received IVIg or PLEX. The EAG do not consider this to be appropriate, because if patients did not respond the first time, they would not be offered this treatment again. We acknowledge that patients receiving IVIg may switch to PLEX and vice versa, but there is no information available to inform the proportions of patients doing this in refractory standard of care. Clinical advice about the proportions of patients who switch from IVIg to PLEX, and vice versa, if the index treatment is unsuccessful would be helpful. The EAG's preferred assumptions for modelling subsequent treatments are discussed in detail in section 2.9 below.
Economic analysis: Treatment costs	Costs of IVIg and PLEX should be applied every 4 weeks, and the NHS reference cost should be used for PLEX administration (DGD section 3.17)	The company use a dosing frequency of 4 weeks for both IVIg and PLEX, as preferred by the committee. Furthermore, they use £455 for PLEX administration cost for every cycle (2 weeks), which aligns with the committee's preference of £910 every 4 weeks (based on NHS reference cost SA44A).	No further comment (for related discussion see section 2.10 below)

NICE Committee's preferred assumptions and recommendations in the DGD		Company's approach	EAG comments
Economic analysis: Response assessment timepoint	The response assessment timepoint should be 3 weeks for all treatments (DGD section 3.17)	Within the company's revised model, the response assessment timepoint is 3 weeks for all treatments.	No further comment (for related discussion see section 2.11 below)
Economic analysis: Population	The results of the whole trial populations of RAISE and RAISE-XT can be generalised to the NHS population (DGD section 3.17)	The company presented their results for the refractory gMG patient population based on the population of RAISE.	The EAG agrees with the generalisability of the target population in the company's revised model to the NHS population. For further discussion see section 2.12 below.

Table 3 New evidence provided by the company in addition to the NICE Committee's preferences and recommendations

Company's additional evidence	EAG comments
Corticosteroid and NSIST-sparing data (Company Response Document section 2.1)	The company provide data from RAISE and RAISE-XT showing that some patients may reduce or discontinue their use of corticosteroids and, in some cases NSISTs. The model was updated to include increased HCRU costs associated with corticosteroid use. Due to lack of data, NSIST-sparing effects are not included in the model; the company assumes the costs and benefits of this are accounted for by sparing the use of corticosteroids. We disagree with the company's approach and remove these costs in our base case. For further discussion see section 2.8.1 below.
Minimum symptom expression (MSE) data (Company Response Document section 2.2)	The company have adjusted MG-ADL response rates to reflect MSE. However, the economic model does not include a MSE health state, and the company do not explain why the MSE adjustment of MG-ADL is now considered relevant, given that this adjustment was not applied in their original economic analysis. We have conducted a scenario analysis to show how the MSE adjustment affects ICER results, although this is subject to the limitation that we could not validate the economic model. For further discussion see section 2.13.2 below.
Treatment stopping rule (Company Response Document section 3.2.2)	The company's revised base case assumes a maximum treatment duration (treatment-stopping rule) of two years (104 weeks) for all patients on all treatments. The EAG notes that this stopping rule was not included in the company's ACM1 model. We remove the stopping rule in our base case because generalised MG is a chronic disease requiring lifelong treatment, and none of the therapies under consideration are curative. Further clinical advice regarding the appropriateness of using a two-year treatment stopping rule would be beneficial. For further discussion see section 2.13.3 below.

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

2.1 Clinical effectiveness: Studies included in indirect treatment comparisons

The DGD recommends an improved indirect treatment comparison that uses data from all available studies (DGD sections 3.17 and 3.20).

In their response to the DGD the company provided three sets of NMAs in the Company NMA Report: (i) a 'conventional' NMA, (ii) a bivariate NMA that enables both MG-ADL and QMG outcomes to be included, and (iii) a baseline risk-adjusted NMA that adjusts for heterogeneity between the studies in the placebo response (results from these NMAs are summarised in Table 4 below). The company also provided a multivariate NMA with three variables (referred to as "MVNMA-3" in Company NMA Report Figures 4-7) but without explaining what the three variables are; this tri-variate NMA does not inform the economic analysis and we do not discuss it in this report. The company further provided a MAIC analysis (Company MAIC Report) to compare zilucoplan against IVIG, although this does not inform the economic analysis.

In general, the statistical approaches for conducting the NMAs and MAIC analyses appear to be broadly appropriate. However, as noted in section 2.3 below some key information is missing and the company did not provide any statistical code for the NMA or MAIC analyses and so we are unable to verify whether these analyses have been implemented correctly.

The EAG understands that the main uncertainty relating to the clinical effectiveness studies is the lack of studies on PLEX and (to a lesser extent) IVIg. In view of the need to identify all available real-world evidence for IVIg and PLEX the search terms for observational studies in the company's original systematic literature review could have been extended to be more comprehensive of terms relevant to real-world evidence. However, the company have not extended their original search nor updated their screening eligibility criteria or ITC feasibility assessment in a methodical or transparent way and so uncertainty remains whether further relevant evidence, particularly for PLEX, could be available.

2.1.1 NMAs

Of the NMAs conducted by the company, only the bivariate NMA informs the economic analysis (Table 4). As noted below (section 2.3) the company's bivariate NMA enabled an additional RCT comparing IVIg against placebo (NCT02473952) to be included.

2.1.2 MAICs

The company conducted two matching-adjusted indirect comparisons (Company MAIC Report section 4.2.1):

(1) An unanchored MAIC comparing the zilucoplan arm of RAISE-XT against the IVIg arm of a placebo-controlled RCT reported by Bril et al. 2023.[1] It was not feasible to include the Bril et al. study in an anchored MAIC, or in NMAs, because the relevant outcome reported by Bril et al. (proportion with worsening of QMG score ≥4 points from baseline) was assessed at 39 weeks and therefore the relevant comparison was against the zilucoplan arm of the RAISE-XT study rather than utilising the RAISE RCT (we assume the company used the zilucoplan → zilucoplan arm of RAISE-XT although this is not stated). Results of this MAIC statistically favoured zilucoplan (Company MAIC Report Table 11).

(2) An unanchored MAIC comparing the zilucoplan arm of the RAISE study against the IVIg arm of the Barth et al. 2011 study[2] for the outcomes of QMG response at 2 weeks and change from baseline in QMG score at 2 weeks and at 4 weeks (Company MAIC Report section 4.2.3.2). The results for the change in QMG score [redacted] zilucoplan over IVIg at 2 weeks and 4 weeks. However, the QMG response rates were [redacted] between zilucoplan and IVIg, either when compared at 2 weeks, or in a further analysis when the zilucoplan 12 week assessment was compared against the IVIg 2 week assessment (Company MAIC Report Table 15).

Neither MAIC informs the economic model, and therefore the MAICs do not reduce any uncertainty in the economic analysis. The MAICs are unsuitable for informing the economic model for two reasons. First, the economic analysis requires odds ratios for the response outcomes for each treatment versus placebo, not the odds ratio of zilucoplan versus IVIg provided by the MAICs. Second, the economic model uses MG-ADL outcomes, not QMG outcomes. Furthermore, the assessment timepoint of 39 weeks in the first MAIC is markedly longer than the other response assessment timepoints so would not be consistent with the other response outcomes used in the economic model.

EAG conclusion: The company have included one additional study of IVIg versus placebo in the NMA which informs the economic analysis. The company also conducted MAIC analyses which included a further additional study comparing zilucoplan against IVIg but the MAIC does not inform the economic analysis. The company have not extended their search, nor updated their screening eligibility criteria or feasibility assessment in a methodical or transparent way, so uncertainty remains whether there could be further relevant evidence.

The EAG was not able to verify whether the reported NMA and MAIC statistical approaches were implemented correctly.

2.2 Clinical effectiveness: Treatments included in indirect treatment comparisons

The DGD recommends an improved indirect treatment comparison that includes IVIg and PLEX (DGD sections 3.17 and 3.20).

As noted in section 2.1 above the company included additional studies of IVIg in their NMA and MAIC analyses. However, as shown in Table 4 below, no additional studies of PLEX were included. The EAG appreciate that data on PLEX are limited, but the company have not provided an update of their search or a feasibility assessment to confirm whether other studies on PLEX (e.g. real-world evidence cohorts) could be available.

In their MAIC using the Barth et al. 2011 study[2] noted in section 2.1 above the company used only the IVIg arm, to compare zilucoplan against IVIg. The company argue that the MAIC IVIg results could be conservatively generalised to PLEX (Company Response Document section 2.4). The EAG disagree with this approach since it fails to acquire a point estimate or credible interval for the PLEX comparison to help characterise the uncertainty. Although we believe the company should have included the PLEX arm from Barth et al., this would be inconsequential because, as explained in section 2.1.2 above, the MAIC analysis does not inform the economic model. If, hypothetically, a new PLEX cohort was identified (e.g. real-world evidence), including this in a MAIC would not be directly applicable to the economic analysis unless the MAIC is modified to compare PLEX against placebo.

EAG conclusion: The company have not included PLEX in any of their updated indirect treatment comparisons and have not fully explored whether further relevant PLEX studies (e.g. real-world evidence cohorts) could be available.

2.3 Clinical effectiveness: Outcomes included in indirect treatment comparisons

The DGD recommends an improved indirect treatment comparison that considers outcomes other than MG-ADL response rate to produce estimates of relative effectiveness (DGD section 3.20).

The company's bivariate NMA enabled imputation of missing MG-ADL response outcomes for studies that reported only QMG response. This has resulted in one additional study comparing IVIg against placebo being included in the NMA (NCT02473952) (Company NMA Report Table 2). The bivariate NMA provides an odds ratio used to calculate the IVIg response rate for the economic analysis that replaces IVIg response data calculated from

the Barth et al. 2011 study (section 2.14.2 below). However, as no studies of PLEX are included in the bivariate NMA the PLEX response rate used for the economic analysis is still calculated from the Barth et al. study (see section 2.14.2).

The EAG have been unable to verify that the data from NCT02473952 reported by the company in NMA Report Tables 1 and 2 are accurate and the company have not reported the analysis timepoint used in this RCT nor the analysis timepoint for the NMA results. Moreover, no heterogeneity or feasibility assessment has been reported to confirm that including NCT02473952 in the bivariate NMA is appropriate.

Company NMA Report section 3.3 implies that the company's focus of interest for the bivariate NMA was to improve the evidence for IVIg and does not discuss whether uncertainty in the response outcome for PLEX could be reduced. The Barth et al. 2011 study[2] (which reports only QMG response) could in theory have been connected to the network via IVIg as the common comparator, to give a PLEX study in the bivariate NMA for which MG-ADL could be imputed. The Barth et al. study had several limitations (summarised in EAG Report section 4.2.6.1), including that the response outcome was only reported at 2 weeks, which is inconsistent with the assessment timepoints reported in the other studies. However, as the company's current source of PLEX response data for the economic analysis is from Barth et al. 2011 (see section 2.14.2) this suffers from the same limitations.

EAG conclusion: The company's bivariate NMA enabled the inclusion of an additional study of IVIg to inform the economic analysis, but the EAG are unable to verify whether this is appropriate due to lack of information provided by the company, and the assessment timepoint used for the analysis is unclear. The bivariate NMA does not resolve the lack of MG-ADL outcomes for comparisons involving PLEX.

2.4 Clinical effectiveness: Placebo response heterogeneity

The DGD recommends an improved indirect treatment comparison that accounts and adjusts for the differential placebo response observed in the trials (DGD sections 3.17 and 3.20). The company's baseline-risk adjusted NMAs adjust for the heterogeneity of placebo responses between studies. However, these NMAs do not inform the economic analysis. Conversely, the NMA which does inform the economic analysis (bivariate NMA) (see Table 4 below) does not account for the heterogeneity in placebo response rates. Therefore, the odds ratios that are used in the economic analysis are not adjusted for placebo response heterogeneity and instead the company have retained their original placebo referent response rate adjustment (see section 2.14.2 below). We also note that the baseline-risk-

adjusted NMAs indicate that both the placebo response heterogeneity and the odds ratios for the results are [redacted], but the company do not discuss the interpretation and implications of this.

EAG conclusion: Placebo response heterogeneity has not been adjusted for in the odds ratios that inform the economic analysis; instead, the company's original approach of using a referent placebo response rate adjustment has been retained.

2.5 Clinical effectiveness: Randomisation

The DGD recommends an improved indirect treatment comparison that respects randomisation (DGD section 3.20). The existing NMAs which inform the economic analysis do respect randomisation, as they provide odds ratios for the relative treatment comparisons. However, the model is not designed to utilise odds ratios for the logical comparisons in the NMAs (i.e. zilucoplan versus each comparator) but is instead informed by odds ratios for zilucoplan and each active comparator versus placebo and derives response rates for each therapy via the referent placebo response rate calculation.

We note that the company's MAIC analyses are unanchored comparisons and so do not consider randomisation, but as explained in section 2.2 above the MAICs do not inform the economic analysis.

EAG conclusion: The format of the input parameters for response outcomes used in the economic model remains unchanged from the approach employed in the model in the original CS, as discussed at ACM1.

2.6 Economic analysis: Uncertainty in clinical effectiveness inputs

The DGD recommends that any uncertainty from indirect treatment comparisons should be incorporated in the model (DGD section 3.17). The company have not made any changes to their modelling approach that would directly capture uncertainty from the indirect comparisons. The credible intervals of NMAs or confidence intervals of primary studies are not used in the company's model.

EAG conclusion: The company have not changed their modelling approach to directly capture uncertainty from the indirect comparisons. In our EAG Report we ran scenario analyses to illustrate the uncertainty indicated by the NMA credible intervals. Given the limitations of the company's clinical effectiveness inputs to the current economic model

noted in sections 2.1 to 2.5 above, and the fact that the EAG cannot verify that the NMAs were conducted correctly nor validate the economic model (section 3), we have not updated the EAG scenario analyses.

Table 4 Odds ratios for MG-ADL response (≥3-point improvement) from the company's updated NMAs

Analysis [a]	Treatment	OR vs placebo (95% CrI)	Source
Conventional NMA (random effects), non-informative prior	Zilucoplan	[redacted]	NMA Report Figures 4, 6
	IVIg	Stated "NA" (no IVIg study included in the network)	
	PLEX	No studies in the network	
Bivariate NMA (random effects) - These results inform the economic model	Zilucoplan	[redacted]	NMA Report Figure 4
	IVIg	[redacted]	
	PLEX	No studies in the network (odds ratio from Barth et al. 2011[2] used instead for the economic model)	
Baseline risk-adjusted NMA (random effects), 0,1 uniform prior for SD	Zilucoplan	[redacted]	NMA Report Figure 8
	IVIg	Stated in NMA Report section 3.4 that the data for IVIg was not available, without explanation (an IVIg versus placebo study had been included in the conventional NMA)	
	PLEX	No studies in the network	
Baseline risk-adjusted NMA (random effects), 0,2 uniform prior for SD	Zilucoplan	[redacted]	NMA Report Figure 8
	IVIg	No studies in the network	
	PLEX	No studies in the network	
Baseline risk-adjusted NMA (random effects), half-normal prior distribution for SD with median 0.3	Zilucoplan	[redacted]	NMA Report Figure 9
	IVIg	No studies in the network	
	PLEX	No studies in the network	

[a] The results presented here have limitations as discussed in sections 2.1 to 2.5 above. The company did not provide the statistical code so the EAG were unable to verify that the reported statistical analyses had been implemented correctly.
NS, not statistically significant.

2.7 Economic analysis: Comparators

The company present results for zilucoplan compared directly with IVIg or PLEX. The comparator is not modelled as a 'basket' of standard of care treatments as per the committee's preferred assumptions from ACM1.

The functionality to use a 'basket' of standard of care (called the 'refractory standard basket') as a comparator was hidden in the model, which the EAG reactivated. We prefer to use the refractory standard basket as the comparator in our base case.

EAG conclusion: The company have not included the refractory standard basket (that included IVIg, PLEX and SoC) in their analyses as preferred by the committee. We included this in the EAG analyses.

2.8 Economic analysis: Uncaptured benefits

2.8.1 Corticosteroid and NSIST-sparing data

The company suggest that patients receiving zilucoplan may reduce or discontinue their use of corticosteroids, while maintaining disease control. Consequently, the company have updated the healthcare resource use (HCRU) costs for corticosteroid use in their revised model (Table 2).

In addition, patients receiving IVIg or PLEX and exhibiting a continued response also accrue annual healthcare resource use (HCRU) costs of £4,671 for corticosteroid use. The EAG considers this to be inappropriate because MG-ADL scores continue to fall over time in patients experiencing a continued response and it is expected patients would not therefore need to use corticosteroids continually.

Table 5 Annual corticosteroid healthcare resource use, company original and revised model

Health state	ACM1 model	Revised model
Uncontrolled	£7,743	£10,087
Stable response	£2,950	£4,671

The corticosteroid costs are taken from Stirnadel-Farrant (2023).[3] The company's response states that these costs are for the proxy condition lupus erythematosus, because no data are available for costs associated with corticosteroid use in generalised MG.

The EAG notes that treatment costs for corticosteroids are already costed in the model (£2.42 per model cycle, annual cost of £62.92), so we assume the HCRU corticosteroid costs are for managing the complications arising from corticosteroid use.

The HCRU costs included in the company's original model seen at ACM1 (hereafter 'ACM1 model') also included costs for corticosteroid use, also taken from Stirnadel-Farrant (2023).[3] The EAG considers that these ACM1 model costs already included managing the adverse clinical outcomes from corticosteroid use. We disagree with the costs for corticosteroid use that the company have applied and prefer to use the HCRU corticosteroid costs from the ACM1 model in our base case. Further clinical advice regarding the annual costs of managing complications associated with corticosteroid use in generalised MG would be helpful.

We note that the NICE committee assessing the efgartigimod appraisal accepted the weighted average of NHS reference costs for the intolerable adverse events reported in Lee et al. (2018)[4] for estimating corticosteroid complication costs associated with generalised MG treatment (ID4003 Efgartigimod draft guidance 2-pdf section 3.17 p.23).[5]

The company response explains that, due to lack of data, NSIST-sparing effects are not included in the model.

2.8.2 Benefit of at-home subcutaneous administration

Using their economic model, the company have calculated the advantages of at-home administration of zilucoplan in terms of time saved for patients and NHS staff, which are:

- [redacted] hours of NHS staff time and [redacted] hours of patient time for zilucoplan compared with IVIg
- [redacted] staff hours and [redacted] patient hours are saved for zilucoplan compared with PLEX

The company apply a 0.05 per-administration utility to account for the health-related benefit of self-administering zilucoplan and explore removing this utility in a scenario analysis (Company Response Document section 3.3.4.5). The total QALYs for zilucoplan are reduced from 9.65 to 9.57 when removing the self-administration QALY gain.

The EAG notes that none of the company's references regarding the utility gain relate to generalised MG, and instead are for: Gaucher disease (a rare, genetic lysosomal storage disorder), bone metastases, pulmonary arterial hypertension, transfusion-dependent β-thalassemia and haemophilia A. We note that:

- Hadi et al. (2018)[6] (Gaucher disease) - list health state utility valuations for intravenous and oral treatment, not subcutaneous injections
- Matza et al. (2013)[7] (Bone metastases; patients not receiving chemotherapy) - disutility of subcutaneous injection = -0.004; disutility of 30min intravenous infusion -0.02, disutility of a 2 hour infusion = -0.04
- Davies et al. (2018)[8] (Pulmonary arterial hypertension) - present information for a continuous subcutaneous infusion, not a subcutaneous injection
- Matza et al. (2020)[9] (β-thalassemia) - present information for oral chelation compared with subcutaneous chelation
- Johnston et al. (2021)[10] (Haemophilia A) – present data for weekly and monthly subcutaneous injections, but not daily.

The EAG prefers to remove this utility benefit; we consider that it is already captured in a patient's global EQ-5D score.

2.8.3 Annual disutility of steroid use

Company response 2.1, Table 3 presents the utility decrements associated with corticosteroid use, which the company include in their base case. The EAG do not consider it appropriate to include this decrement, because this disutility has already been captured in patients' global EQ-5D scores. The company remove this utility decrement in their scenario analysis described in Company response section 3.3.4.4. The EAG have removed the utility decrement from our base case.

2.8.4 Caregiver disutility

The company explore the impact of generalised MG on a patient's carer's health-related quality of life in a scenario analysis. The source of the caregiver disutilities used is given in Company Response Document section 3.1.10. The EAG note that the company are using caregiver utility decrements from a study in multiple sclerosis by Acaster et al. (2013)[11] as a proxy. These data were also presented at the first committee meeting for efgartigimod for treating generalised myasthenia gravis [ID4003].[5]

The EAG agree with the company and do not consider that caregiver disutilities should be included in the model, because there is no evidence that multiple sclerosis is a suitable proxy for generalised MG. We note that the committee assessing efgartigimod preferred to exclude caregiver disutilities (Efgartigimod DGD section 3.12 bullet 4, discussed fully in section 3.10)[5] and to consider the effect of generalised MG on caregivers qualitatively.

EAG conclusion

We disagree with the company's approach to including costs accrued from corticosteroid use, as these costs are already included in the HCRU costs for corticosteroid use. We also disagree with the company regarding including a utility increment associated with at-home subcutaneous administration of zilucoplan and a utility decrement associated with corticosteroid use, because these have already been captured in patients' global EQ-5D scores. We agree with the company concerning excluding carer disutilities from the model.

2.9 Economic analysis: Subsequent treatments

The company apply subsequent treatment costs for patients who do not respond, or lose response, to first-line treatment. We observe that the costs associated with the subsequent treatment have a significant impact on the costs for patients in the uncontrolled condition. We explain the mechanism below and present a critique of the company's approach.

The company have refined the description of the EAMS population used in the refractory standard of care arm, and when applying the ongoing costs of this refractory standard of care basket to the uncontrolled health state. The refined EAMS population includes: 56.7% of patients receiving IVIg, 18.9% receiving PLEX, the remaining 24.4% receiving only corticosteroids, NSISTs or a combination of both. The company's full rationale for this refinement is given in their response document, section 3.1.7. The EAG considers this refinement to be reasonable.

The EAG notes a substantial increase in total costs for all treatments in the company's revised model (Table 4). Table 5 shows the breakdown of zilucoplan total costs as an example. The EAG notes the difference in total costs is predominantly due to the increase in costs for patients in the uncontrolled condition. In the company's ACM1 model, the annual uncontrolled health state resource use was £14,896; it is £94,417 in the revised model.

Table 6 Treatment total costs

Treatment	ACM1 model (£)	Revised model (£)
Zilucoplan	[redacted]	[redacted]
IVIg/SCIg	535,341	1,968,712
(Refractory) standard of care	614,382	1,943,092
Plasma exchange	696,316	1,928,092

Table 7 Breakdown of total costs for zilucoplan

Cost	ACM1 model (£)	Revised model (£)
Treatment cost	[redacted]	[redacted]
Admin costs	-	[redacted]
Admins	-	[redacted]
Uncontrolled	[redacted]	[redacted]
Continued response	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]
Stable response	[redacted]	[redacted]
Exacerbation	[redacted]	[redacted]
Crisis	[redacted]	[redacted]
Terminal costs	[redacted]	[redacted]
Total costs	[redacted]	[redacted]

The EAG considers the difference in total costs for the uncontrolled condition is due to how the company are applying subsequent treatment costs for patients who do not respond, or lose response, to first-line treatment. However, costs for IVIg and PLEX are applied in the subsequent treatment of patients who received IVIg or PLEX first-line. The EAG do not consider this to be appropriate, because if patients did not respond the first time, they would not be offered this treatment again.

Figure 1 and Figure 2 show the subsequent treatment flowcharts for the company's base case and the EAG's preferred approach for zilucoplan and the comparator arm. **Please note: the flowchart is specific to subsequent treatment and does not include our other preferred assumptions.**

We acknowledge that patients receiving IVIg may switch to PLEX and vice versa, but there is no information available to inform the proportions of patients doing this in refractory standard of care. Clinical advice about the proportions of patients who switch from IVIg to PLEX, and vice versa, if the index treatment is unsuccessful would be helpful.

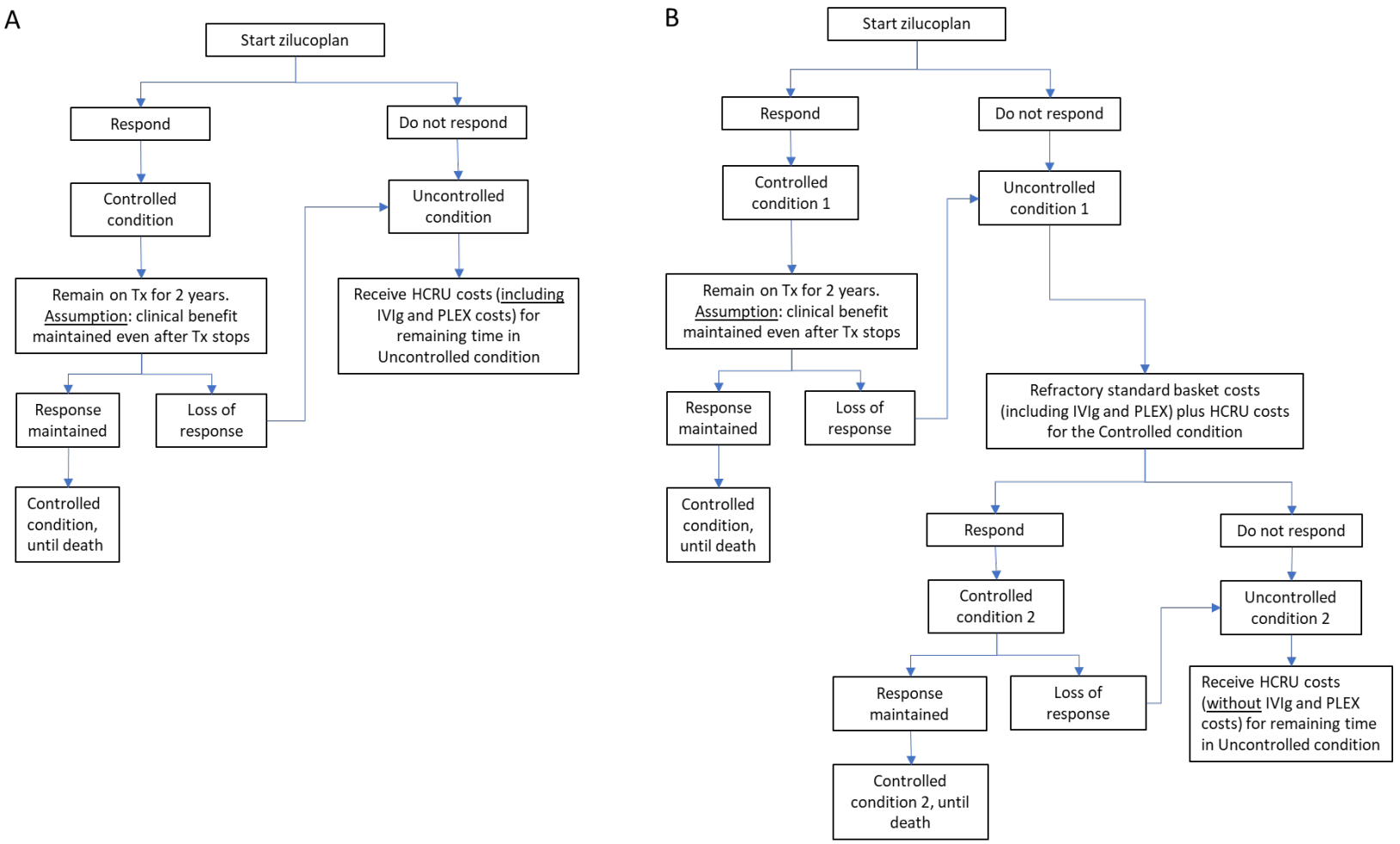

Figure 1 Flow chart of subsequent treatment for zilucoplan. A) Company model; B) EAG preferred approach

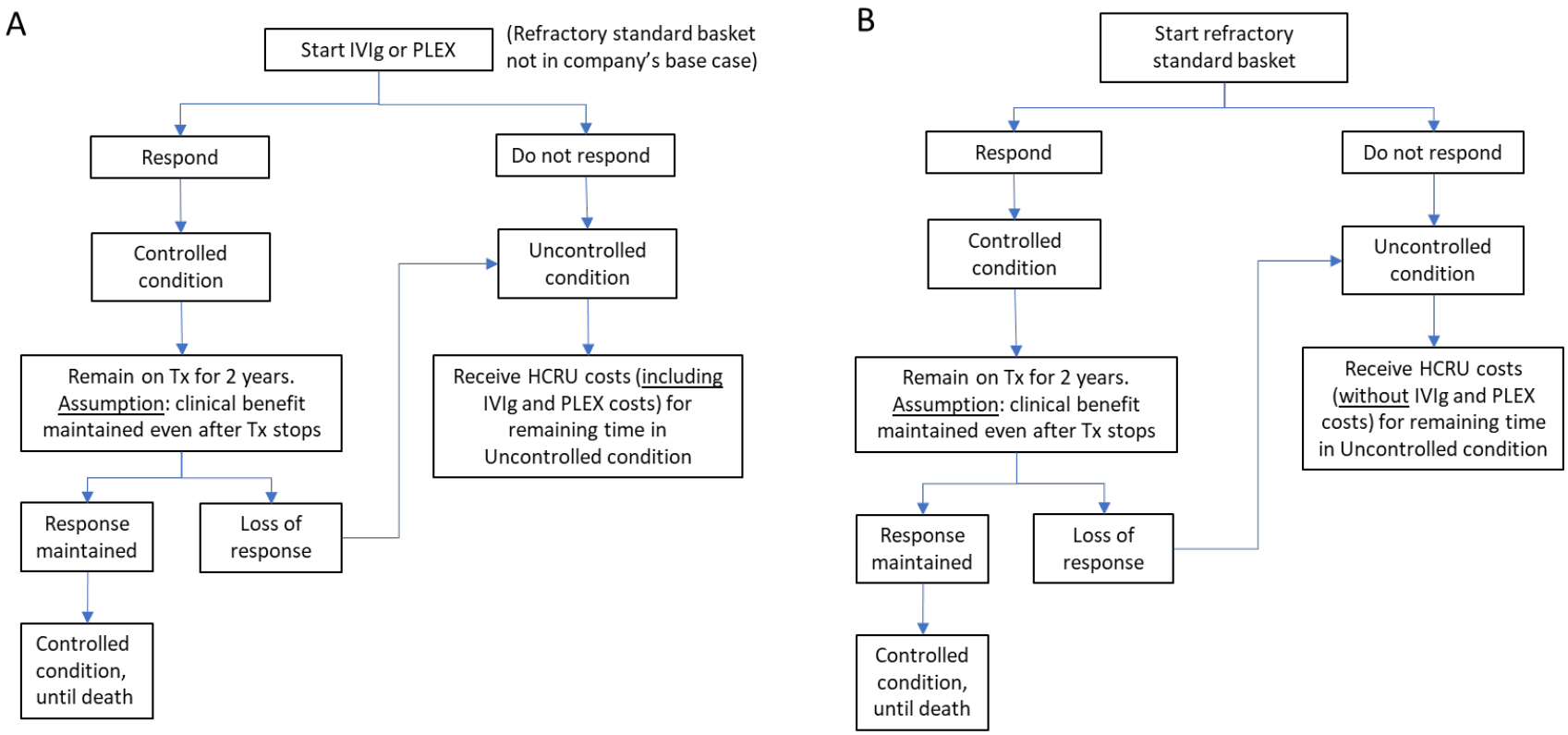

Figure 2 Flow chart of subsequent treatment for the comparator arm. A) Company model; B) EAG preferred approach

We prefer that for the uncontrolled condition:

- Of patients receiving zilucoplan first-line:
  - [redacted]% (the EAG's estimate of the proportion of patients receiving refractory standard of care (section 2.14.2)) accrue costs for the refractory standard basket (including IVIg and PLEX) plus HCRU costs for the controlled condition
  - The remainder, [redacted]%, accrue HCRU costs (without IVIg and PLEX costs) for the uncontrolled condition, plus costs for the refractory standard basket without IVIg or PLEX costs
  - Cost per model cycle is estimated as: ([redacted]% x (£[redacted] + £[redacted])) + ([redacted]% x £[redacted] + £[redacted]) = £[redacted]
- Of patients receiving IVIg first-line:
  - 10.77% (i.e. the 18.9% in EAMS who receive PLEX in the refractory standard basket, multiplied by the 57% who respond) accrue costs for the refractory standard basket (excluding IVIg costs) plus HCRU costs for the controlled condition
  - The remainder, 89.23%, accrue HCRU costs (without IVIg and PLEX costs) for the uncontrolled condition, plus costs for the refractory standard basket without IVIg or PLEX costs.
  - Cost per model cycle is estimated as: (10.77% x (£[redacted] + £[redacted])) + (89.23% x £[redacted] + £[redacted]) = £[redacted] per model cycle
- Of patients receiving PLEX first line:
  - [redacted]% (i.e. the 57.6% in EAMS who receive IVIg in the refractory standard basket, multiplied by the [redacted]% who respond) accrue costs for the refractory standard basket (excluding PLEX costs) plus HCRU costs for the controlled condition
  - The remainder, [redacted]%, accrue HCRU costs (without IVIg and PLEX costs) for the uncontrolled condition, plus costs for the refractory standard basket without IVIg or PLEX costs.
  - Cost per model cycle is estimated as: ([redacted]% x (£[redacted] + £[redacted])) + ([redacted]% x £[redacted] + £[redacted]) = £[redacted] per model cycle
- Patients receiving refractory standard of care first-line receive HCRU costs without either IVIg or PLEX costs plus costs for the refractory standard basket without IVIg or PLEX costs.
  - Costs per model cycle is estimated as: (£[redacted] / [redacted]) + £[redacted] = £[redacted]

Table 8 illustrates the effect of these subsequent treatment cost changes. We note that the total QALYs do not change between the two scenarios, indicating that the health benefits

associated with receiving IVIg or PLEX as part of subsequent treatment have not been included in the model.

Table 8 EAG preferred subsequent treatment costs, company revised base case

Scenario		Treatment	Total costs (£)	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
1	Revised company base case	Zilucoplan	[redacted]	9.65	-	-	-
		IVIg/SCIg	1,968,712	9.44	[redacted]	0.205	[redacted]
		Refractory std care	1,943,093	9.39	[redacted]	0.261	[redacted]
		PLEX	1,928,093	9.47	[redacted]	0.176	[redacted]
2	EAG preferred approach to subsequent treatment	Zilucoplan	[redacted]	9.65	-	-	-
		IVIg/SCIg	717,707	9.44	[redacted]	0.205	[redacted]
		Refractory std care	632,155	9.39	[redacted]	0.261	[redacted]
		PLEX	771,388	9.47	[redacted]	0.176	[redacted]

EAG conclusion

While the company incorporates subsequent treatment in their revised model, the EAG have concerns with their approach, because the costs for IVIg and PLEX are applied in the subsequent treatment of patients who received IVIg, PLEX or refractory standard of care first-line. The EAG do not consider this to be appropriate, because if patients did not respond the first time, they would not be offered this treatment again. We acknowledge that patients receiving IVIg may switch to PLEX and vice versa, but there is no information available to inform the proportions of patients doing this in refractory standard of care. Clinical advice about the proportions of patients who switch from IVIg to PLEX, and vice versa, if the index treatment is unsuccessful would be helpful.

2.10 Economic analysis: Treatment costs

Table 11 presents the treatment costs for zilucoplan, IVIg and PLEX used in the company's revised model, received on 15th September. The company later confirmed their revised PAS for zilucoplan on 20th September as [redacted].

We note a cost issue in the model – the company are assuming 100% of patients are treated with IVIg (DrugCostsDetailPopup!J10), we consider this should be 50% receiving IVIg and 50% receiving SCIg, in line with the company's ACM1 model.

Table 9 Treatment acquisition costs, company model

Treatment	Per cycle drug cost		Annual drug cost	
	ACM1 model	Revised model	ACM1 model	Revised model
Zilucoplan (15 Sep 2024)	[redacted]	[redacted]	[redacted]	[redacted]
IVIg/SCIg	£3,898	£2,322	£101,348	£60,372
Refractory standard of care	N/A	£2,567	N/A	£66,742
PLEX[a]	£6,469	£6,469	£168,184	£168,184
[a] Costs are for the first cycle of treatment				

2.10.1 Dosing Frequency of IVIg and PLEX

The company use a dosing frequency of 4 weeks for both IVIg and PLEX, as preferred by the committee. The EAG have no further comments on this issue.

2.10.2 PLEX administration costs (SA44A)

The company use £455 for PLEX administration cost for every cycle (2 weeks), which aligns with the committee's preference of £910 every 4 weeks (based on NHS reference cost SA44A). The EAG have no further comments on this issue.

EAG conclusion

The company have adhered to the committee's preferred assumptions and recommendations in the DGD for dosing frequency of IVIg and PLEX and PLEX administration costs. However, they assume 100% of patients being treated with IVIg; we view this should be 50% receive IVIg and 50% receive SCIg, in line with the company's ACM1 model.

2.11 Economic analysis: Response assessment timepoint

The company use a response assessment timepoint of 3 weeks for all treatments, as preferred by the committee. The EAG have no further comments on this issue.

2.12 Economic analysis: Population

The company's analyses use the refractory gMG patient population from RAISE. The EAG agrees with the generalisability of the target population in the company's revised model to the NHS population.

2.13 New evidence provided by the company

2.13.1 Corticosteroid and NSIST-sparing data

See section 2.8.1 above.

2.13.2 Minimum symptom expression

In their revised model, the company assume that patients in the continued response health state have reached MSE. MSE is defined as achieving an MG-ADL score of 0 or 1; the company use the average and apply a mean MG-ADL score of 0.5 for patients in the continued response health state. This is expressed in the model as a change from baseline MG-ADL score of 10.2 (the average MG-ADL score at the start is 10.7).

In their base case, the company assumes [redacted]% of patients receiving zilucoplan achieve MSE, 10% of patients receiving IVIg or PLEX achieved MSE and no patients receiving refractory standard of care achieve MSE.

The EAG notes that the Model Technical Manual (section 2.1.1, p.11) states that the MSE health state was not included in the final model structure; instead, the model uses a 'continued response' health state to capture the potential improvement in a patient's symptoms over time. In addition, MSE was not used in the company's original submission and the Company Response Document does not explain why it is being used now.

We are uncertain if the use of MSE in this model structure is appropriate and consequently prefer to revert to using the patient distribution of [redacted] with loss of response, [redacted] with continued response, and [redacted] with stable response in our base case, using the treatment-specific change from baseline MG-ADL scores reported in the technical report Table 8.

2.13.3 Treatment stopping rule

The company's revised base case assumes a maximum treatment duration (treatment-stopping rule) of two years (104 weeks) for all patients on all treatments (Company Response Document section 3.2.2). The Model Technical Manual (section 2.4.3 p.34) states that "A treatment stopping rule was also included to simulate patient intolerance to treatment or a physician choice to limit long-term use of some treatments, assuming that improvements in symptoms mean patients may be able to taper their treatment." The Model Technical Manual further states that the company's revised base case assumes that "patients who have received two years of treatment will maintain the health improvements for the rest of their lifetime, with no ongoing treatment costs." The EAG notes that this stopping rule was not included in the company's ACM1 model.

The EAG prefers to remove the stopping rule in our base case, because generalised MG is a chronic disease requiring lifelong treatment, and none of the therapies under consideration are curative. Further clinical advice regarding the appropriateness of using a two-year treatment stopping rule would be helpful.

2.14 Other updates to the company's revised model (not covered in the above sections)

2.14.1 Change from baseline for the 'continued response' health state

The company updated the change from baseline for the 'continued response' health state to reflect minimum symptom expression, which was used to inform the proportions of patients in each health state. The EAG have concerns with the use of minimum symptom expression, which we discuss in detail in Section 2.13.2 of this report.

2.14.2 Response rates

The company's updated response rates used in the revised model are shown in Table 10. These are from the odds ratios from the bivariate NMA for zilucoplan vs placebo and IVIg vs placebo shown in Table 4 above (discussed in section 2.3 above). However, the PLEX odds ratio is still back calculated from Barth et al. (2011).[2]

The EAG notes that the response rate for refractory standard of care is the same as the referent rate (i.e. the average placebo response). Patients receiving refractory standard of care include people receiving IVIg and PLEX, consequently we consider the response rate for refractory standard of care to be [redacted]%, based on the following calculation:

- 56.7% of patients receive IVIg, 18.9% receive PLEX, the remaining 24.4% receive corticosteroids and/or NSISTs (please see section 2.9 regarding the refined EAMS cohort data)
- (56.7% x [redacted]%) + (18.9% x 57.00%) + (24.4% x 31.50%) = [redacted]%

Table 10 Treatment response rates used in the model

Treatment	Response rate used in the revised model	Response rate used in the ACM1 model
Referent	31.50%	[redacted]
Zilucoplan	[redacted]	[redacted]
IVIg/SCIg	[redacted]	[redacted]
Refractory standard of care	[redacted]	[redacted]
Plasma exchange	57.00%	57.00%

2.14.3 Duration of exacerbation and crisis

The duration of myasthenic crisis and exacerbations are 28 days each in the company's revised model, following expert clinical opinion and discussions at the committee meeting. The EAG have no further comments on this issue.

2.14.4 Healthcare resource use costs

Company Response Document Table 17 presents the HCRU costs per health state used in the revised company model. As discussed above in section 2.9, IVIg and PLEX are given as subsequent treatments (proportions derived using the EAMS cohort data), even if a patient received IVIg or PLEX first-line. We do not consider this is appropriate, because if a patient did not respond initially, we do not expect they would be offered the same treatment again second-line.

In addition, patients receiving IVIg or PLEX and experiencing a continued response (i.e. their MG-ADL scores continue to fall over time) accrue costs for complications from corticosteroid use of £4,670 per year, the same as for patients achieving a stable response on these treatments. The EAG do not agree with this assumption, and we have removed this cost for patients experiencing a continued response in our base case.

2.14.5 Time horizon

The time horizon of the company's ACM1 model was 52.5 years but is 48.2 years in the revised model; the company are now using data for the refractory population. The average age at model entry in the revised model is 51.8 years, so the model runs until patients are 100 years old. The EAG have no concerns regarding the revised time horizon.

2.14.6 MG-ADL change from baseline and response distribution

The response distribution for the comparators used in the company's revised model is reproduced below in Table 11. The EAG notes these values are different to the distributions used in the ACM1 model of [redacted] for continued response, [redacted] for loss of response and [redacted] for stable response, because the company are using the minimum symptom expression in their revised model (discussed above in section 2.13.2).

The EAG does not consider using the MSE data to be appropriate and we prefer to revert to the response distributions used in the ACM1 model, using the treatment-specific change from baseline MG-ADL scores for the refractory population provided in Table 8 of the Model Technical Manual and reproduced in Table 12.

Table 11 Response distribution, company's revised model

Treatment	Continued response	Loss of response	Stable response
Zilucoplan	[redacted]	[redacted]	[redacted]
IVIg/SCIg	10.0%	[redacted]	[redacted]
Refractory standard of care	[redacted]	[redacted]	[redacted]
Plasma exchange	10.0%	[redacted]	[redacted]

Table 12 Treatment-specific change from baseline MG-ADL scores, refractory population

Treatment	Continued response	Loss of response	Stable response
Zilucoplan	[redacted]	[redacted]	[redacted]
IVIg/SCIg	[redacted]	[redacted]	[redacted]
Refractory standard of care	[redacted]	[redacted]	[redacted]
Plasma exchange	[redacted]	[redacted]	[redacted]
Adapted from: Model Technical Manual section 2.2.3.4, Table 8			

2.14.7 Utilities: baseline EQ-5D

The company's revised model uses a baseline utility of [redacted], which was [redacted] in the company's ACM1 model. The revised utility score is derived from data for refractory population, which the EAG considers to be appropriate.

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 CMU costs for all treatments are presented in a separate confidential addendum.

The company reports their revised base case ICER result in Company Response Document Table 24. Zilucoplan [redacted]. A comparison with refractory standard of care was not presented in the company's base case. The EAG activated this analysis and present results in Table 13. Results suggest zilucoplan [redacted].

Table 13 Base case results, company revised model

Treatment	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Zilucoplan	[redacted]	9.65	-	-	
Refractory standard of care	1,943,093	9.39	[redacted]	0.261	[redacted]

We attempted to replicate the changes made between the company's ACM1 model (seen at Committee Meeting 1) and their revised base case. Due to the complex coding changes added to the new version of the model (e.g. the treatment stopping rule), we had to start with the company's revised base case and work back to their previous version (rather than vice versa).

Table 14 shows the changes to the company's base case (that we are aware of) between the ACM1 model seen at Committee Meeting 1 and the revised version of the company's model received on 15th September 2024. We were unable to reproduce the results of the previous version of the model using the revised model.

The EAG contacted NICE on 11th September 2024 requesting a model change log from the company outlining the change in results from incorporating the committee's preferred assumptions as stated in the DGD. The company have not provided this information.

Table 14 Cumulative results for the changes between the company's revised and previous base case

Assumption	Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company revised base case	Zilucoplan	[redacted]	9.65			
	IVIg/SCIg	1,968,712	9.44	[redacted]	0.205	[redacted]
	Ref std care	1,943,093	9.39	[redacted]	0.261	[redacted]
	PLEX	1,928,093	9.47	[redacted]	0.176	[redacted]
Use previous response assessment timepoints	Zilucoplan	[redacted]	9.87			
	IVIg/SCIg	1,945,041	9.49	[redacted]	0.379	[redacted]
	Ref std care	1,933,929	9.43	[redacted]	0.437	[redacted]
	PLEX	1,928,174	9.52	[redacted]	0.345	[redacted]
Use response rates from the ACM1 model including the referent response rate for standard care	Zilucoplan	[redacted]	9.91			
	IVIg/SCIg	1,936,737	9.50	[redacted]	0.405	[redacted]
	Ref std care	1,926,465	9.44	[redacted]	0.465	[redacted]
	PLEX	1,928,174	9.52	[redacted]	0.385	[redacted]
Use previous response distributions and MG-ADL change-from-baseline data	Zilucoplan	[redacted]	9.81			
	IVIg/SCIg	1,936,737	9.41	[redacted]	0.395	[redacted]
	Ref std care	1,926,465	9.40	[redacted]	0.411	[redacted]
	PLEX	1,928,174	9.42	[redacted]	0.384	[redacted]
Use previous durations for exacerbations and crises	Zilucoplan	[redacted]	9.81			
	IVIg/SCIg	1,871,288	9.41	[redacted]	0.395	[redacted]
	Ref std care	1,860,063	9.40	[redacted]	0.411	[redacted]
	PLEX	1,863,148	9.42	[redacted]	0.384	[redacted]
Use previous time horizon	Zilucoplan	[redacted]	9.80			
	IVIg/SCIg	1,872,364	9.41	[redacted]	0.395	[redacted]
	Ref std care	1,861,107	9.39	[redacted]	0.411	[redacted]
	PLEX	1,864,171	9.42	[redacted]	0.384	[redacted]
Use unrefined EAMS cohort data (43.8% IVIg, 14.8% PLEX in standard basket)	Zilucoplan	[redacted]	9.80			
	IVIg/SCIg	1,872,364	9.41	[redacted]	0.395	[redacted]
	Ref std care	1,846,685	9.39	[redacted]	0.411	[redacted]
	PLEX	1,864,171	9.42	[redacted]	0.384	[redacted]
Use previous administration costs for PLEX	Zilucoplan	[redacted]	9.80			
	IVIg/SCIg	1,872,364	9.41	[redacted]	0.395	[redacted]
	Ref std care	1,841,706	9.39	[redacted]	0.411	[redacted]
	PLEX	1,842,336	9.42	[redacted]	0.384	[redacted]
	Zilucoplan	[redacted]	9.80			

Assumption	Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Use previous treatment cost for zilucoplan	IVIg/SCIg	1,872,364	9.41	[redacted]	0.395	[redacted]
	Ref std care	1,841,706	9.39	[redacted]	0.411	[redacted]
	PLEX	1,842,336	9.42	[redacted]	0.384	[redacted]
Use previous HRCU costs, including corticosteroid costs	Zilucoplan	[redacted]	9.80			
	IVIg/SCIg	489,794	9.41	[redacted]	0.395	[redacted]
	Ref std care	511,186	9.39	[redacted]	0.411	[redacted]
	PLEX	637,505	9.42	[redacted]	0.384	[redacted]
Use previous baseline utility	Zilucoplan	[redacted]	9.74			
	IVIg/SCIg	489,794	9.35	[redacted]	0.395	[redacted]
	Ref std care	511,186	9.33	[redacted]	0.411	[redacted]
	PLEX	637,505	9.36	[redacted]	0.384	[redacted]
Remove disutility associated with corticosteroid use	Zilucoplan	[redacted]	9.93			
	IVIg/SCIg	489,794	9.54	[redacted]	0.390	[redacted]
	Ref std care	511,186	9.53	[redacted]	0.403	[redacted]
	PLEX	637,505	9.55	[redacted]	0.381	[redacted]
Remove utility for at home subcutaneous administration of zilucoplan	Zilucoplan	[redacted]	9.75			
	IVIg/SCIg	489,794	9.54	[redacted]	0.202	[redacted]
	Ref std care	511,186	9.53	[redacted]	0.215	[redacted]
	PLEX	637,505	9.55	[redacted]	0.193	[redacted]
50% patients treated with IVIg	Zilucoplan	[redacted]	9.75			
	IVIg/SCIg	494,700	9.54	[redacted]	0.202	[redacted]
	Ref std care	503,938	9.53	[redacted]	0.215	[redacted]
	PLEX	637,505	9.55	[redacted]	0.193	[redacted]
No IVIg or PLEX in standard of care	Zilucoplan	[redacted]	9.75			
	IVIg/SCIg	494,700	9.54	[redacted]	0.202	[redacted]
	Ref std care	465,893	9.53	[redacted]	0.215	[redacted]
	PLEX	637,505	9.55	[redacted]	0.193	[redacted]
Remove treatment stopping rule	Zilucoplan	[redacted]	9.75			
	IVIg/SCIg	580,281	9.54	[redacted]	0.202	[redacted]
	Ref std care	466,430	9.53	[redacted]	0.215	[redacted]
	PLEX	824,294	9.55	[redacted]	0.193	[redacted]
EAG's approximation of ACM1 company model	Zilucoplan	[redacted]	9.75			
	IVIg/SCIg	580,281	9.54	[redacted]	0.202	[redacted]
	Ref std care	466,430	9.53	[redacted]	0.215	[redacted]
	PLEX	824,294	9.55	[redacted]	0.193	[redacted]
	Zilucoplan	[redacted]	9.81			

Assumption	Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Actual company model results from ACM1 model	IVIg/SCIg	628,862	9.65	[redacted]	0.165	[redacted]
	Ref std care	469,374	9.64	[redacted]	0.180	[redacted]
	PLEX	783,124	9.66	[redacted]	0.158	[redacted]

The company presents the results of their deterministic sensitivity analysis (DSA) as tornado diagrams in company response section 3.3.2, and results of their probabilistic sensitivity analysis (PSA) in company response section 3.3.3; zilucoplan [redacted]

3.2 Company scenario analyses

The company presents the results of their scenario analyses in Company Response Document section 3.3.4. Zilucoplan [redacted]. The EAG reproduced the company's scenarios using refractory standard of care as the comparator. Zilucoplan [redacted].

We present the results of the company's scenario analyses in a separate confidential addendum, applying the appropriate CMU costs for all treatments.

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:

1. Use a 'basket' of standard of care treatments, as per the committee's preferred assumptions, for the comparator (section 2.7)
2. Remove the extra HCRU costs for managing the complications associated with corticosteroid use; use HCRU corticosteroid costs from the ACM1 model (section 2.8.1)
3. Not use the minimum symptom expression data and revert to using the patient distributions used in the ACM1 model ([redacted] for continued response, [redacted] for loss of response and [redacted] for stable response) along with treatment-specific change from baseline MG-ADL scores for the refractory population (Table 10) (section 2.13.2 and section 2.14.1)
4. Use a refractory standard of care response rate of [redacted]% (section 2.14.2)
5. Use the EAG's preferred assumptions for subsequent treatment (section 2.9)
6. Remove the utility benefit associated with the subcutaneous injection of zilucoplan (section 2.8.2)
7. Remove the additional disutility associated with corticosteroid use (section 2.8.3)
8. 50% of patients receive IVIg; 50% receive SCIg, rather than 100% receive IVIg (section 2.10)
9. Remove the treatment stopping rule (section 2.13.3)

The cumulative effect of these changes results in an ICER of [redacted] per QALY for zilucoplan compared with refractory standard of care (Table 13). The EAG base case produces an ICER of [redacted] for zilucoplan compared with IVIg, and [redacted] per QALY for zilucoplan compared with PLEX.

Please note: Because we were unable to validate the company's revised model, we are unsure if the results of our base case (Table 16) and scenarios on our base case (Table 17) are reliable.

Table 15 Cumulative effect of the EAG's preferred assumptions, zilucoplan compared with refractory standard of care

Assumption	Incr. costs (£)	Incr. QALYs	Cumulative ICER (£/QALY)
Use refractory standard of care as the comparator, **company revised base case**	[redacted]	0.261	[redacted]
+ Remove the added HCRU costs for managing the complications associated with CS use	[redacted]	0.261	[redacted]
+ Use the previous patient distribution (5%/5%/90%) and MG-ADL CFB data for the refractory population from the NMA (Tech report Table 8)	[redacted]	0.157	[redacted]
+ Use refractory standard of care response rate of [redacted]%	[redacted]	0.117	[redacted]
+ Use the EAG's approximation of subsequent treatment	[redacted]	0.117	[redacted]
+ Remove the utility benefit of s.c. admin of zilucoplan	[redacted]	0.041	[redacted]
+ Remove the disutility associated with CS use	[redacted]	0.038	[redacted]
+ 50% of patients receive IVIg; 50% receive SCIg	[redacted]	0.038	[redacted]
+ Remove the treatment stopping rule	[redacted]	0.038	[redacted]
EAG base case	[redacted]	0.038	[redacted]

4.2 Scenario analyses on the EAG's preferred assumptions

The EAG ran scenario analyses on our base case assumptions (Table 17). Using the company's approach to modelling subsequent treatment had the most significant effect on the ICER for zilucoplan compared with refractory standard of care (scenario 4), reducing it to [redacted] per QALY because incremental costs are reduced by [redacted].

Table 16 Scenario results for zilucoplan versus refractory standard of care, EAG base case

No.	Scenario description	Incr. Costs	Incr. QALYs	ICER (£/QALY)
EAG base case		[redacted]	0.038	[redacted]
1	Include the added HCRU costs for managing the complications associated with CS use and the disutilities associated with CS use	[redacted]	0.041	[redacted]
2	Include the utility benefit of s.c. admin of zilucoplan	[redacted]	0.115	[redacted]
3	Use the minimum symptom expression data	[redacted]	0.148	[redacted]
4	Use the company's approximation of subsequent treatment	[redacted]	0.038	[redacted]
5	Include the treatment stopping rule	[redacted]	0.038	[redacted]
6	Use response rates for the refractory gMG population from the bivariate NMA ('ZLP refractory data in NMA')	[redacted]	0.109	[redacted]

5 EAG CONCLUSION

5.1 Clinical effectiveness

The company provided three sets of NMAs (conventional, bivariate and baseline-risk-adjusted) and two MAIC analyses. Of these, only the bivariate NMA informs the economic analysis, providing updated MG-ADL response rates for zilucoplan and IVIg. No new evidence has been provided for PLEX. Whilst the EAG appreciate that PLEX data are limited, the company have not systematically and convincingly demonstrated that there are no further potentially relevant PLEX studies that could be considered.

Results of the baseline-risk-adjusted NMA account for heterogeneity in placebo responses but are not used in the economic model. The company do not explain how they intend this NMA to be interpreted. The EAG assume that the results cannot be used to inform the current model because the model already utilises the referent placebo response rate adjustment. Results from the baseline-risk-adjusted NMA are not statistically significant, with wide credible intervals which, if included in the economic modelling, would show high uncertainty around the response rates.

The company's MAIC analyses provide odds ratios (zilucoplan versus active comparators) that are incompatible with the odds ratios needed to inform response rates in the economic model (zilucoplan or active comparators versus placebo). The company have not considered modifying the MAIC analyses to provide odds ratios that can inform the economic analysis.

In summary, whilst the company has conducted new analyses, these largely do not inform the economic analysis and therefore do not substantively address the uncertainties in the cost-effectiveness results. Specifically, the following aspects of uncertainty have not been reduced:

- No new evidence has been found for PLEX. The response rate for PLEX remains sourced from the Barth et al. 2011 study which has substantial limitations, including a 2-week assessment timepoint and response rate based on QMG not MG-ADL.

- The company have included an additional placebo-controlled study of IVIg, in the bivariate NMA that informs the economic analysis. However, insufficient details of the analysis are reported for the EAG to be confident that it has been appropriately included, and the assessment timepoint for the NMA results is unclear.

- As noted above, the company's investigation of placebo response heterogeneity does not inform the economic analysis.

- Statistical estimates of uncertainty in the NMAs are not utilised in the economic analysis. The company instead make heterogeneity assumptions in their sensitivity analyses, as in their original submission.

- The DGD raises a question about how randomisation is preserved from the clinical effectiveness analyses. The company's economic analysis does not address this.

- The company did not provide any statistical code or confirm the data that were input to statistical analyses so the EAG is unable to verify that the NMAs and MAICs have been implemented correctly.

5.2 Economic analysis

The EAG received three versions of the company's revised economic model on: 28th August, 15th September and 23rd September 2024. We cannot verify the changes the company have made to their model since ACM1 in any of the versions of the model we received. Consequently, we are unsure if the company's, and our, base case and scenario results are reliable.

Zilucoplan [redacted] in the company's base case and in all of their scenarios. In contrast, the EAG's base case produced an ICER of [redacted] per QALY, and is sensitive to any changes. Our base case is most sensitive to the way that subsequent treatment is modelled.

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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 [ID4008]

Addendum to the EAG critique of the company's response to the first appraisal consultation document (ACD1): Results with the Patient Access Scheme price for zilucoplan and British National Formulary (BNF) and electronic Market Information Tool (eMIT) prices for comparators and subsequent treatments

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Commercial in confidence (CIC) information in blue

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1 INTRODUCTION

A confidential discount for the price for zilucoplan has been agreed under a Patient Access Scheme (PAS). Table 1 shows the PAS discount for zilucopan, and the British National Formulary (BNF) and eMIT costs (date of price check 16-Sep-2024) for subsequent treatments included in the company's economic evaluation of zilucoplan for generalised myasthenia gravis (MG).

The company's response to the NICE Draft Guidance Document (DGD) (issue date 27th June 2024) for the technology appraisal on zilucoplan for treating generalised MG (ID4008) and the External Assessment Group's (EAG's) critique of the company's response present cost-effectiveness results based on the PAS price for zilucoplan and the list prices for the comparators and subsequent treatments. In this addendum, we reproduce tables of the company's and the EAG's cost effectiveness results with all available discounts applied. This document should be read in conjunction with the EAG's critique of the Company Response Document.

We note the following:

- The PAS price for zilucoplan was confirmed by the company on 20-Sep-2024
- The company provided a new version of their model on 23-Sep-2024; this did not allow sufficient time for us to update our analyses so **this addendum presents results using the 15-Sep-2024 version of the model**
- The Commercial Medicines Unit (CMU) prices are no longer active for IVIg, SCIg, and ciclosporin; BNF prices have been used instead

Table 1 Costs for drugs with PAS discounts and eMIT prices

Treatment	Formulation (mg)	List price per pack	PAS discount	PAS, BNF or eMIT price per pack
Zilucoplan	Subcutaneous formulation for injection; 7 pre-filled syringes; 32.4mg/0.810ml	£7114.70	[redacted]	[redacted]
Intravenous immunoglobulin	Solution for infusion; 1000mg		N/A	£69.00
Intravenous immunoglobulin	Solution for infusion; 2000mg		N/A	£138.00
Subcutaneous immunoglobulin	Solution for infusion; 1000mg		N/A	£73.50
Subcutaneous immunoglobulin	Solution for infusion; 2000mg		N/A	£147.00

Treatment	Formulation (mg)	List price per pack	PAS discount	PAS, BNF or eMIT price per pack
Corticosteroids (prednisolone)	10mg tablet, pack of 28		N/A	£9.70
Azathioprine	25mg tablets, pack of 28	£2.04	N/A	£0.81
Mycophenolate	500mg tablets, pack of 50	£8.21	N/A	£6.55
Cyclosporine	100mg tablets, pack of 30		N/A	£41.59
Tacrolimus	1mg capsule, pack of 50		N/A	£55.69
Methotrexate	10mg tablets, pack of 100		N/A	£55.07
Pyridostigmine	60mg tablets, pack of 200		N/A	£22.27

2 COMPANY ANALYSES

2.1 Company base case

This addendum presents results using the company's revised base case (15-Sep-2024). The company's deterministic cost-effectiveness results (zilucoplan compared with comparators) using the BNF and eMIT costs are shown in Table 2. Zilucoplan [redacted].

Table 2 Company base case results, pairwise results, with PAS and eMIT prices

Technologies	Total		Incremental vs. zilucoplan		ICER (£/QALY) zilucoplan vs comparator
	Costs	QALYs	Costs	QALYs	
Zilucoplan	[redacted]	9.65	-	-	-
IVIg/SCIg	2,136,314	9.44	[redacted]	0.205	[redacted]
Ref std care	2,119,983	9.39	[redacted]	0.261	[redacted]
PLEX	2,102,609	9.47	[redacted]	0.176	[redacted]

QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; PLEX: plasma exchange; Ref std care, refractory standard of care; SCIg: subcutaneous immunoglobulin

2.2 Company scenarios

The company conducted six scenarios and we were able to reproduce them (Table 3).

Table 3 Company scenario analyses results, pairwise comparison with PAS and eMIT prices

Scenario		Treatment	ICER(£/QALY)
1	70% response rate for IVIg and PLEX ([redacted]% for Zilucoplan based on mvNMA)	Zilucoplan	-
		Ref std care	[redacted]
		IVIg/SCIg	[redacted]
		PLEX	[redacted]
2	Societal perspective (both societal costs and carer disutilities)	Zilucoplan	-
		Ref std care	[redacted]
		IVIg/SCIg	[redacted]
		PLEX	[redacted]
3	Exclude disutility of corticosteroids	Zilucoplan	-
		Ref std care	[redacted]
		IVIg/SCIg	[redacted]
		PLEX	[redacted]
4	Self-administration utility removed	Zilucoplan	-
		Ref std care	[redacted]
		IVIg/SCIg	[redacted]
		PLEX	[redacted]
5	Steroid costs removed[a]	Zilucoplan	-
		Ref std care	[redacted]

		IVIg/SCIg	[redacted]
		PLEX	[redacted]
6	If PLEX has a 10% lower acquisition cost and is 10% more effective (62.70% primary response rate)	Zilucoplan	-
		Ref std care	[redacted]
		IVIg/SCIg	[redacted]
		PLEX	[redacted]

[a] In this scenario the EAG reverted the HCRU 'cost of managing steroid use' costs for all treatments to those used in the previous version of the model

QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; PLEX: plasma exchange; Ref std care, refractory standard of care; SCIg: subcutaneous immunoglobulin

3 EAG ANALYSES

3.1 EAG preferred assumptions

The EAG's preferred model assumptions are listed in section 4 of the EAG critique document. Table 4 shows the cumulative effect of each of our assumptions on the ICER for zilucoplan versus refractory standard of care, using the zilucoplan PAS discount and eMIT prices. The EAG base case ICER for zilucoplan versus refractory standard of care is [redacted] per QALY.

Please note: Because we were unable to validate the company's revised model, we are unsure if the results of our base case (Table 4) and scenarios on our base case (Table 5) are reliable.

Table 4 Cumulative effect of the EAG's preferred assumptions, zilucoplan versus refractory standard of care (with PAS and eMIT prices)

Assumption	Incr. costs (£)	Incr. QALYs	Cumulative ICER (£/QALY)
Use refractory standard of care as the comparator, **company revised base case**	[redacted]	0.261	[redacted]
+ Remove the added HCRU costs for managing the complications associated with CS use	[redacted]	0.261	[redacted]
+ Use the previous patient distribution (5%/5%/90%) and MG-ADL CFB data for the refractory population from the NMA (Tech report Table 8)	[redacted]	0.157	[redacted]
+ Use refractory standard of care response rate of [redacted]%	[redacted]	0.117	[redacted]
+ Use the EAG's approximation of subsequent treatment	[redacted]	0.117	[redacted]
+ Remove the utility benefit of s.c. admin of zilucoplan	[redacted]	0.041	[redacted]
+ Remove the disutility associated with CS use	[redacted]	0.038	[redacted]
+ 50% of patients receive IVIg; 50% receive SCIg	[redacted]	0.038	[redacted]
+ Remove the treatment stopping rule	[redacted]	0.038	[redacted]
EAG base case	[redacted]	**0.038**	[redacted]

3.2 Scenario analyses on the EAG's preferred assumptions

The EAG ran scenario analyses on our base case assumptions (Table 5). Using the company's approach to modelling subsequent treatment had the most significant effect on the ICER for zilucoplan compared with refractory standard of care (scenario 4), reducing it to [redacted] per QALY.

Table 5 Scenario results for zilucoplan versus refractory standard of care, EAG base case

No.	Scenario description	Incr. Costs	Incr. QALYs	ICER (£/QALY)
EAG base case		[redacted]	0.038	[redacted]
1	Include the added HCRU costs for managing the complications associated with CS use and the disutilities associated with CS use	[redacted]	0.041	[redacted]
2	Include the utility benefit of s.c. admin of zilucoplan	[redacted]	0.115	[redacted]
3	Use the Minimum Symptom Expression data	[redacted]	0.148	[redacted]
4	Use the company's approximation of subsequent treatment	[redacted]	0.038	[redacted]
5	Include the treatment stopping rule	[redacted]	0.038	[redacted]
6	Use response rates for the refractory gMG population from the bivariate NMA ('ZLP refractory data in NMA')	[redacted]	0.083	[redacted]