Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Contents:

The following documents are made available to stakeholders:

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

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

2. **Clarification questions and company responses**

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

4. **Expert personal perspectives** from:
   a. Abby Mabil – patient expert, nominated by Myaware & Muscular Dystrophy UK
   b. Gary Mahon – patient expert, nominated by Muscular Dystrophy UK

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

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

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

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Single technology appraisal (STA)

Zilucoplan for antibody positive generalised myasthenia gravis [ID 4008]

Document B

Company evidence submission

12th December 2023

File name	Version	Contains confidential information	Date
Document B	2.0	Yes	12th December 2023

Contents

List of Tables

Abbreviations

ABN	Association of British Neurologists
ACh	Acetylcholine
AChEI	Acetylcholinesterase inhibitor
AChR	Acetylcholine receptor
AChR-Ab+	AChR-antibody positive
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AHS	Accordant Health Services
ANCOVA	Analysis of covariance
BDI	Beck Depression Inventory
BIM	Budget impact model
BMI	Body mass index
C5	Complement component 5
CADTH	Canadian Agency for Drugs and Technologies in Health
CCDS	Company Core Data Sheet
CEM	Cost-effectiveness model
CFB	Change from baseline
CI	Confidence interval
CIE	Centre for International Economics
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CS	Corticosteroid
CSR	Complete Stable Remission
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Disease Area Review
DIC	Deviance information criterion
ECG	Electrocardiogram
EMA	European Medicines Agency
EMEA	Europe, the Middle East and Africa
EPAR	European Public Assessment Report

EQ-5D-5L	EuropeanQoL-5 dimensions
ER	Emergency room
EU	European Union
EU5	France, Germany, Italy, Spain and the United Kingdom
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FSS	Fatigue Severity Scale
GCP	Good clinical practice
GI	Gastrointestinal
gMG	Generalised myasthenia gravis
GVD	Global Value Dossier
HAS	Haute Autorité De Santé
HCP	Healthcare provider
HCRU	Healthcare resource use
HLT	High-level term
HRQoL	Health-related quality of life
HTA	Health technology assessment
HTN	Hypertension
IA	Immunoadsorption
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICF	Informed consent form
ICU	Intensive care unit
IgG	Immunoglobulin G
IMNM	Immune-mediated necrotising myopathy
IMP	Investigational medicinal product
IQR	Interquartile range
IST	Immunosuppressive therapy
ITT	Intent-to-treat
IV	Intravenous
IVIg	Intravenous immunoglobulin
LRP4	Low-density lipoprotein receptor-related protein 4
LS	Least squares
LSM	Least squares mean

MAC	Membrane attack complex
MCMC	Markov Chain Monte Carlo
MD	Mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living score
MGC	Myasthenia Gravis Composite score
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post-Interventional Status
MGII	Myasthenia Gravis Impairment Index
MGQoL15r	Myasthenia Gravis Quality of Life 15-Item scale
mITT	Modified intent-to-treat
MMF	Mycophenolate mofetil
MMRM	Mixed model with repeated measures
MMS	Minimal Manifestation Status
MoA	Mechanism of action
MSE	Minimal Symptom Expression
MTX	Methotrexate sodium
MuSK	Muscle-specific kinase
NA	Not applicable
NAbs	Neutralising antibodies
NEC	Not elsewhere classified
NIS	Nationwide Inpatient Survey
NMA	Network meta-analysis
NMD	Neuromuscular disease
NMJ	Neuromuscular junction
NR	Not reported
NSIST	Non-steroidal immunosuppressive therapies
ODD	Orphan Drug Designation
OHE	Office of Health Economics
OLE	Open-label extension
OR	Odds ratio
PD	Pharmacodynamics
PEG	Polyethylene glycol
PK	Pharmacokinetics

PLEX	Plasma exchange
PMDA	Pharmaceuticals and Medical Devices Agency
PML	Progressive multifocal leukoencephalopathy
PNDS	Protocole National de Diagnostic et de Soins
PNH	Paroxysmal nocturnal haemoglobinuria
PPS	Per Protocol Set
PT	Preferred Term
QMG	Quantitative Myasthenia Gravis
QoL	Quality of life
QTc	Corrected QT interval
RCT	Randomised controlled trial
RWE	Real world evidence
SAD	Single ascending dose
SAE	Serious adverse event
SC	Subcutaneous
SCIg	Subcutaneous immunoglobulin
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF-36	36 Item Short Form Survey
SIAQ	Self-Injection Assessment Questionnaire
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMQ	Standard MedDRA Query
SOC	System organ class
SoC	Standard of care
sRBC	Sheep erythrocyte
SS	Safety Set
T2DM	Type 2 diabetes mellitus
TBC	To be confirmed
TEAE	Treatment-emergent adverse events
TLS	Tumour lysis syndrome
TMPT	Thiopurine methyltransferase
UK	United Kingdom
US	United States

USD	United States dollar
VAS	Visual Analogue Scale
VM	Value Message
Wk	Week
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

Executive summary

Burden of generalised myasthenia gravis

Generalised myasthenia gravis (gMG) is a chronic autoimmune disease that causes severe weakness and fatigue in muscles responsible for breathing, swallowing and mobility (1, 2). The characteristic fluctuating muscle weakness is caused by inappropriate activation of the complement system which disrupts normal signalling between nerve fibres and muscles.

The severe and debilitating symptoms of gMG impose a substantial clinical, humanistic and financial burden on patients and their caregivers (3-18), and a considerable economic burden on the healthcare system (19-27). In addition to lifelong symptoms that impair day-to-day living (4), patients with gMG face the risk of myasthenic crisis (9-12), a life-threatening deterioration of muscle weakness and respiratory failure requiring intensive care with mechanical ventilation (9, 21, 28, 29).

While treatment options are available, around 15% patients with gMG are refractory to standard therapy and continue to experience poor symptom control, a severe disease burden, and poor quality of life (QoL) (30-33). These patients are at an increased risk of myasthenic exacerbation and crisis and are more likely to use healthcare resources, leading to a high economic burden (19-24, 34-36).

Unmet need

Patients with refractory gMG have an urgent unmet need for more effective and less burdensome treatments. Currently, the only treatments for these patients are chronic intravenous immunoglobulin (IVIg) or plasma exchange (PLEX), which have limitations related to availability and treatment burden and are costly to the healthcare system. In addition, IVIg and PLEX are not licensed for the chronic treatment of gMG (19, 20, 37-41).

Patients face a severe treatment burden from standard immunosuppressant therapies (ISTs) and must balance the benefits of controlling symptoms with severe, debilitating side effects. Long-term use of standard treatments is associated with side effects, for example skin cancer with azathioprine (42). Corticosteroids (CSs) in particular are associated with severe side effects such as diabetes, osteoporosis, depression and infection, which can trigger a myasthenic exacerbation (11, 34, 43-45).

There is an unmet need for a licensed targeted treatment with a fast onset of action that minimises the symptom burden, as well as the burden of therapy, reduces the risk of myasthenic exacerbations and crises, and improves QoL for patients who are refractory to available treatments.

Clinical effectiveness

Zilucoplan will be the first and only once-daily C5 complement inhibitor that can be self-administered at home by subcutaneous (SC) injection for patients with AChRAb-+ gMG who are refractory to standard treatments. The availability of zilucoplan is expected to reduce the devastating impact of uncontrolled disease, as well as the treatment burden

associated with non-specific treatments such as CSs and other ISTs, to patients, carers, and the healthcare system, improving QoL for patients with high unmet needs.

The clinical outcomes reported in Section B.2 demonstrate that zilucoplan provides statistically significant and clinically meaningful improvements in the signs and symptoms of disease activity, and QoL, with a fast onset of action (treatment effect of zilucoplan vs placebo was observed as early as Week 1) and durability of response [redacted] of the extension study [RAISE-XT]). A treatment that is fast-acting will reduce the disease burden for refractory patients, who may cycle through different ISTs without achieving symptom control and are at risk of myasthenic exacerbation and crisis whilst they wait for treatment effect (34, 46). Zilucoplan may also reduce the need for CSs and the associated side effects (47), as well as the need for rescue therapy (with IVIg or PLEX) (47, 48). Reducing the need for rescue therapy is expected to reduced medical resources and costs associated with managing exacerbations.

Zilucoplan as an add-on to standard of care (SoC) was associated with a favourable safety profile and was generally well tolerated by patients with gMG in the Phase III trial, RAISE. The safety profile of zilucoplan in RAISE-XT was consistent with findings in RAISE, with no new safety signals observed, demonstrating long-term safety and tolerability up to 96 weeks with zilucoplan 0.3 mg/kg.

Economic value

A state transition Markov model was developed to evaluate the cost effectiveness of zilucoplan as a treatment for adult patients with gMG from the perspective of the UK NHS/PSS. This structure captures the chronic nature of gMG and the variability in symptom severity experienced by gMG patients. The base case compared zilucoplan with efgartigimod, Ig/SCIg, and plasma exchange in adult patients utilising the RAISE trial as the source of clinical characteristics.

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

The model predicts discounted QALY gains of 0.0294 in comparison with efgartigimod, 0.0986 in comparison with IVIg/SCIg and 0.1077 in comparison with plasma exchange.

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

B.1.1 *Decision problem*

The full anticipated marketing authorisation for zilucoplan is as [redacted] in line with the scope issued by the National Institute for Health and Care Excellence (NICE) (Table 1).

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

- the disease has not responded to other systemic treatments, including pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate and ciclosporin, or these options are contraindicated or not tolerated, and
- the disease is uncontrolled, as defined by a MG-ADL score of ≥6 or a QMG score of ≥12, and
- an alternative option to efgartigimod (subject to NICE approval), and/or
- an additional therapy such as immunoglobulin (Ig) or PLEX is being considered, or patients are being treated chronically with Ig/PLEX

Patients with refractory gMG have an urgent unmet need for more effective and less burdensome treatments than what is currently available. There are currently no treatments for these patients other than chronic intravenous immunoglobulin (IVIg) or plasma exchange (PLEX), which have limitations related to availability and treatment burden, and are costly to the healthcare system. In addition, IVIg and PLEX are used off label as they are unlicensed for the chronic treatment of gMG. (see Sections B.1.3.3 and B.1.3.1.5) (19, 20, 37-41).The population of adult patients with AChR antibody-positive gMG who are refractory to treatment is in line with those who clinicians are expected to prioritise for targeted treatment. A pre-specified sub-group analysis was conducted on the cohort specified in this submission, with similar outcomes to the broad population.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with AChR antibody-positive generalised myasthenia gravis.	Adults with refractory† AChR antibody-positive generalised myasthenia gravis, if: • the disease has not responded to other systemic treatments, including pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate and ciclosporin, or these options are contraindicated or not tolerated, and • the disease is uncontrolled, as defined by a MG-ADL of 6 or more or a QMG of 12 or more, and • an alternative option to efgartigimod (subject to NICE approval), and/or • an additional therapy such as immunoglobulin (Ig) or PLEX is being considered, or patients are being treated chronically with Ig/PLEX	There is a high unmet need for a novel effective treatment with an acceptable safety profile in this patient population as there are currently no treatments other than chronic IVIg/PLEX, which are a burden to the patient and costly to the healthcare system. There is limited evidence available on the effectiveness of IVIg in MG, and issues with supply and access. In addition, IVIg and PLEX are used off label as they are unlicensed for the treatment of gMG. In addition, adult patients with AchR antibody-positive refractory gMG is in line with patients who clinicians are expected to prioritise. The evidence base for zilucoplan is based on a proportion of patients [redacted] who had refractory gMG at baseline in the pivotal phase III trial (RAISE) and as such provides sufficient subgroup data to perform meaningful indirect comparisons or allow cost cost-effectiveness analyses in refractory MG.
Intervention	Zilucoplan	Zilucoplan	-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Comparator(s)	• Efgartigimod (subject to NICE evaluation) • SoC without zilucoplan (including CSs and ISTs‡, with or without IVIg or PLEX)	• Efgartigimod (subject to NICE evaluation) • IVIg and PLEX	1. Is anticipated that efgartigimod will be approved for use in refractory gMG patients (subject to NICE evaluation) 2. IVIg/PLEX (added to CSs and ISTs‡) is the current SoC in patients who are refractory to treatment
Outcomes	• Improvement in MG • Time to clinically meaningful improvement • Mortality • Number of hospitalisations • Adverse effects of treatment • Health-related quality of life	• Improvement in MG (MG-ADL responder) • Time to clinically meaningful improvement • Mortality • Number of hospitalisations • Adverse effects of treatment • Health-related quality of life (in patients and carers)	Many patients with gMG require a caregiver for daily activities, which leads to reduced employment (productivity loss) and reduced QoL in those caring for gMG patients (14, 17, 18). Therefore, carer disutility was addressed in the submission

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	There is **geographic variability** in treatment availability and access to specialist centres, which introduces inequality among patients with MG in terms of access to care. The introduction of zilucoplan will improve equity of access to treatment, as access will not be restricted based on geography, and patients will be able to receive zilucoplan as a self-administered SC injection in their own homes. Treatment at home will reduce HCRU and help alleviate capacity challenges in hospitals and long waiting times in the NHS, compared with the comparators, which require in-hospital administration. In addition, the rapid onset of action of zilucoplan provides benefit to patients versus currently available treatment. There is **health inequality between males and females** in terms of the burden of MG. Like other autoimmune conditions, MG is more prevalent in female patients than male, with female patients making up 60% of the MG population (49, 50). As females are younger than males at disease onset (mean age of disease onset is 35±18 vs 45±18 years, respectively [p<0.001]) (51), they are exposed to a greater total burden throughout their lives than men, and through more of their working life.	-

†Refractory as defined in the RAISE clinical study: patients on treatment for ≥1 year with ≥2 of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, other ISTs, or history of treatment with ≥1 of these therapies for ≥1 year, and required chronic PLEX, IVIg, or SCIg at least every 3 months for the 12 months prior to enrolment.
‡ ISTs (including mycophenolate) are not currently licenced for MG in the UK (25, 26, 52-55).
Abbreviations: AChR, acetylcholine receptor; gMG, generalised myasthenia gravis, IST, immunosuppressant therapy, IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, MG Composite; MGQoL15r, MG Quality of Life 15-Item Scale; MSE, minimal symptom expression; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous; SCIg, subcutaneous immunoglobulin.

B.1.2 *Description of the technology being evaluated*

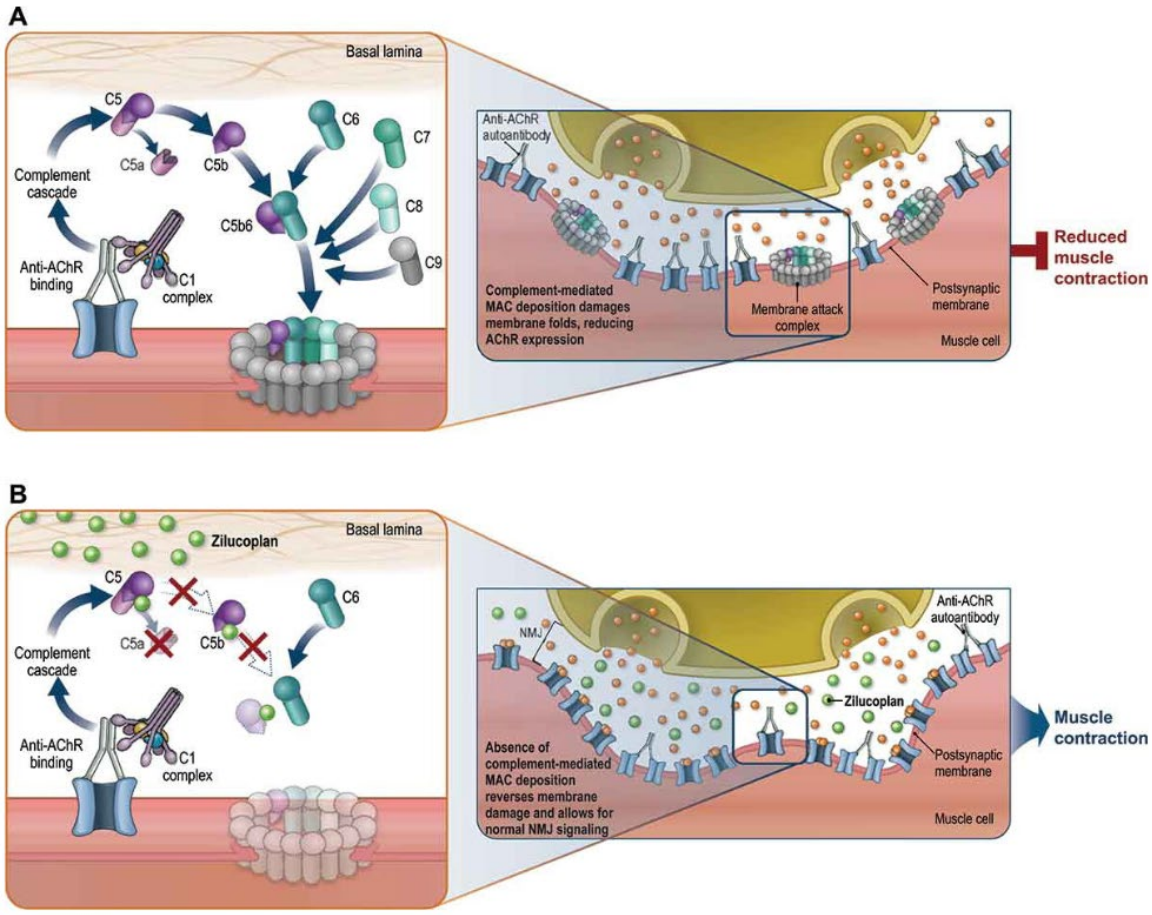
Zilucoplan is the first and only once-daily subcutaneous, targeted peptide inhibitor of component 5 (C5 complement inhibitor Figure 1), which can be self-administered at home by adult patients with refractory AChR antibody positive gMG – and is the newest addition to UCB's family of approved medicines (Table 2).

Table 2: Technology being evaluated

UK approved name and brand name	The generic name of the drug is zilucoplan. The brand name is ZILBRYSQ®.
Marketing authorisation/CE mark status	Positive CHMP opinion was issued on 15 September 2023. UK regulatory approval is expected in [redacted] via the European Commission Decision Reliance Procedure route.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	It is expected that zilucoplan will be indicated [redacted]
Mechanism of action	Zilucoplan is a peptide that inhibits the effects of the complement protein C5 through a dual mechanism of action. It specifically binds to C5, thereby inhibiting its cleavage by the C5 convertase to C5a and C5b, which results in a downregulation of the assembly and cytolytic activity of the membrane attack complex (MAC). Additionally, by binding to the C5b moiety of C5, zilucoplan sterically hinders binding of C5b to C6, which prevents the subsequent assembly and activity of the MAC, should any C5b be formed. Zilucoplan's rapid and sustained inhibition of C5 and the downstream complement cascade prevents functional impairment of the NMJ in patients with AChR antibody positive (AChR-Ab+) gMG (56-59).
Method of administration and dosage	• Zilucoplan is self-administered as a subcutaneous injection once daily from a prefilled syringe • Dosage of zilucoplan is based on patient weight at approximately 0.3 mg/kg/day: The total daily dose by body weight range (kg) is listed below: o <56 kg: 16.6 mg dose o ≥56 to <77 kg: 23 mg dose o ≥77 kg: 32.4 mg dose
Additional tests or investigations	None
List price and average cost of a course of treatment	List price: [redacted] Average cost of a course of treatment at list price: (cost of maintenance treatment for 1 year): [redacted]
Patient access scheme (if applicable)	This submission includes the confidential simple patient access scheme (PAS) for zilucoplan, implemented as [redacted]

Abbreviations: AChR-Ab, acetylcholine receptor antibody; C, complement; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; FDA, Food and Drug Administration; gMG, generalised myasthenia gravis; MAC, membrane attack complex; NHS, National Health Service; NMJ, neuromuscular junction; ODD, Orphan Drug Designation; PAS, SmPC, Summary of Product Characteristics; UK, United Kingdom.

Figure 1. Mechanism of action of zilucoplan



Source: Howard et al, 2021 (60).
(A) Activation of the terminal complement cascade in gMG and (B) inhibition by zilucoplan. Graphics are schematic representations and are not true to scale. In panel A, cross-linking of AChRs by anti-AChR antibodies initiates the classical complement cascade, leading to cleavage of C5 and assembly of the MAC. In panel B, zilucoplan binds C5 at the location corresponding to C5b, thereby inhibiting both the cleavage of C5 and the binding of C6 to pre-formed C5b, thus preventing assembly of the MAC.
Abbreviations: ACh, acetylcholine; AChR, acetylcholine receptor; C[x], complement component [x]; gMG, generalized myasthenia gravis; MAC, membrane attack complex; NMJ, neuromuscular junction.

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

Disease overview

- Generalised myasthenia gravis (gMG) is a chronic autoimmune disease that causes severe weakness and fatigue in muscles responsible for breathing, swallowing and mobility (1, 2)
- The severe and debilitating symptoms of gMG impose a substantial clinical and humanistic burden on patients and their caregivers (3-18), and a considerable financial burden on patients and the healthcare systems (19-27)
    - In addition to lifelong symptoms that impair day-to-day living (4), patients with gMG face the risk of myasthenic crisis (9-12), a life-threatening deterioration of muscle weakness and respiratory failure requiring intensive care with mechanical ventilation (9, 21, 28, 29)
- It is estimated that there are 19,053 people living with MG in England (61)

Current treatment pathway and position of technology

- There is a need for licensed targeted therapy for patients with refractory gMG (15% of the patient population (32, 33)). Established clinical management includes non-targeted treatments that have been repurposed for use in MG. Despite available treatment options, some patients with gMG are refractory to standard therapy and continue to experience poor symptom control, a severe disease burden and poor QoL (30, 31)
    - Currently available treatments are associated with limitations such as burdensome side effects, limited availability and delayed treatment effect of up to 18 months (11, 34, 37, 38, 42-46, 62)
    - Patients who are refractory to treatment are at an increased risk of myasthenic exacerbation and crisis and are more likely to use increased healthcare resources, leading to a high economic burden (19-24, 34-36)
    - Expert opinion suggests that a patient presenting in myasthenic crisis (explosive onset) can easily accumulate >£100,000 per patient in costs by remaining in intensive care for a month or more
- There is an unmet need for a licensed targeted treatment with a fast onset of action that minimises the symptom burden, as well as the burden of therapy, reduces the risk of myasthenic exacerbations and crises, and improves QoL for patients who are refractory to available treatments
- Zilucoplan will be the first and only once-daily C5 complement inhibitor that can be self-administered at home by subcutaneous (SC) injection for patients with AChR-Ab+ gMG who are refractory to standard treatments. The availability of zilucoplan is expected to reduce the devastating impact of uncontrolled disease, as well as the treatment burden associated with non-specific treatments such as CSs,

on patients and the healthcare system, improving QoL for patients with high unmet needs

- Clinical outcomes reported in Section B.2 demonstrate that zilucoplan provides statistically significant and clinically meaningful improvements in the signs and symptoms of disease activity, and QoL, as measured by MG-ADL, QMG, MGC, and MG-QoL15r, with a fast onset of action (treatment effect of zilucoplan vs placebo was observed as early as Week 1) and durability of response (up to week 96 of the extension study)
- A post-hoc analysis of patients receiving zilucoplan in the extension study, RAISE-XT, demonstrates that zilucoplan has a steroid-sparing effect, potentially reducing the need for patients to take concomitant CSs which have debilitating side effects (see Section B.2.7) (47)

B.1.3.1 *Disease overview*

Myasthenia gravis (MG) is a chronic autoimmune disease caused by antibody-mediated destruction of the neuromuscular junction (NMJ) (see Section B.1.3.1.2 for pathophysiology) (1, 2). Patients experience debilitating weakness and fatigue in muscles responsible for vital functions including breathing, swallowing and mobility. Symptoms of MG can significantly impact day-to-day living to such an extent that employment and working hours are impacted and caregiver support is needed (63). In addition, patients with MG experience poor mental health (64-68). Symptoms are relapsing and remitting in nature, and, during severe exacerbations, may lead to respiratory failure and the requirement for mechanical ventilation (myasthenia crisis is described in Section B.1.3.1.2) (69).

Some patients are refractory to treatment and experience high disease activity despite maximal immunosuppression. Clinical classification of MG with a description of symptoms is presented in Table 3.

Table 3. Clinical classification of MG (MGFA)

Class	Description
I	Any ocular muscle weakness.
II	**Mild** weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
IIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
III	**Moderate** weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
IIIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
IV	**Severe** weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

Class	Description
IVa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Abbreviations: MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America.
Source: The Myasthenia Gravis Foundation of America (70).

B.1.3.1.1 Epidemiology

Myasthenia gravis is a rare disease with low rates of incidence and prevalence globally (71, 72). In the UK, the annual incidence of MG is estimated at 25 cases per million people (2015–2019) (61), with an annual incidence rate of 17.6 per million people in England in 2021 as a replacement .The Clinical Practice Research Datalink (CPRD) collected epidemiology data for a range of neuromuscular diseases across the UK from 2000–2019 and reported a lifetime prevalence estimate for MG of 33.7 (95% CI; 32,7, 34.7) per 100,000 people in 2019 (61, 73). Overall, it is estimated that there are 19,053 people living with MG in England (61). Around 15% patients with gMG are refractory to standard therapy (32, 33).

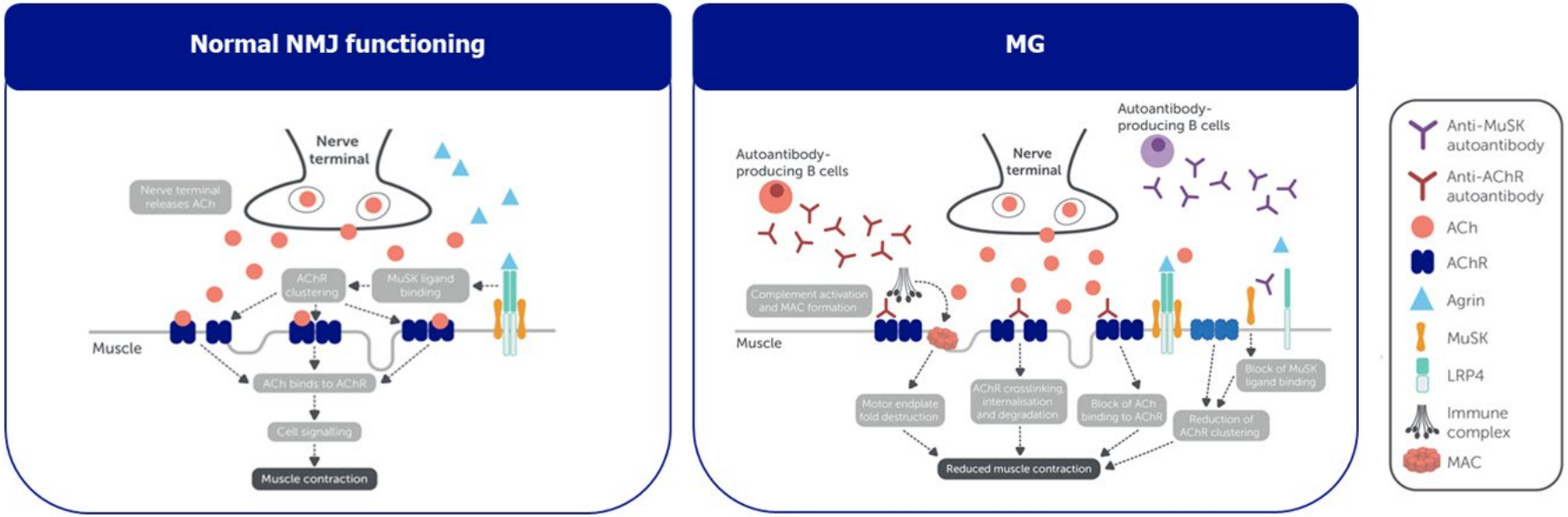
The number of people diagnosed with gMG is predicted to increase by an absolute annual growth rate of around 1% across the EU5, including England (74, 75).

Like other autoimmune conditions, MG is more prevalent in female than male patients, with female patients accounting for approximately 60% of the MG population (49, 50) (see Section B.1.4 for equality considerations related to women).

B.1.3.1.2 Pathophysiology

Muscle weakness is caused by defective synaptic transmission at the NMJ (Figure 2) (1, 2). At the healthy NMJ, acetylcholine (ACh) binds to acetylcholine receptors (AChRs) in the post-synaptic muscle-cell membrane, activating the muscle fibre and resulting in muscle contraction (76, 77). In MG, autoantibodies bind to components of the NMJ such as AChRs and/or muscle specific tyrosine kinase (MuSK), initiating the classical complement cascade. Activation of the complement system leads to cleavage of C5 and assembly of the membrane attack complex (MAC), disrupting normal signalling between nerve fibres and muscles and leading to the unpredictable, fluctuating muscle weakness and fatigue characteristic of gMG (clinical symptoms are described in more detail in Section B.1.3.1.2) (2, 76, 78-82). The majority of patients with MG (80–90%) have autoantibodies against AChRs (69, 83-85). A treatment directly targeting the complement system may minimise the loss of AChRs at the NMJ and the impact on muscle function (see Section B.1.2 for zilucoplan mechanism of action).

Figure 2. Pathogenesis of MG



Abbreviations: ACh: acetylcholine; AChR: acetylcholine receptor; LRP4: low-density lipoprotein receptor-related protein 4; MAC: membrane attack complex; MG: myasthenia gravis; MuSK: muscle specific tyrosine kinase; NMJ: neuromuscular junction.
Source: Adapted from Howard et al, 2018 (76), Gilhus et al, 2019 (63), Lindstrom et al, 2000 (77) and Kaminski et al, 1997 (80).

B.1.3.1.3 Clinical burden

Myasthenia gravis can be a severe and debilitating disease, characterised by muscle weakness with acute and chronic fatigue (3).

Approximately two-thirds of patients experience weakness confined to extraocular muscles at presentation, known as ocular MG (oMG) (86-88), which manifests as drooping of the upper eyelid (ptosis) and double vision (diplopia) and can cause difficulty with reading and driving (10, 83, 89, 90). Most (80–90%) patients with oMG will develop generalised MG (gMG[a]) within two years (10, 79, 86), which is associated with weakness in the muscles of the head, neck, arms, hands, chest, legs and torso (69). Of 1,518 patients with MG, 75% reported muscle weakness after physical strain, 71% had weakness of upper limbs and 70% had difficulty walking (91). Persistent fatigue is one of the most common symptoms of gMG, occurring in 44–70% of patients and interfering with daily activities such as walking, self-care and going to work (3, 79, 90-95). The debilitating symptoms of MG reduce patient QoL (see Section B.1.3.1.4).

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

In addition to the burdensome symptoms associated with gMG, the majority of patients (~75–90%) also experience comorbidities such as joint problems, cardiac and thyroid disease, dyslipidaemia, diabetes and other autoimmune conditions (35, 78, 82, 91, 97, 98).

Studies from Denmark, Norway, Sweden, France and Germany report excess mortality among patients with MG compared with the general non-MG population (99-101). The standardised mortality ratio (SMR) was higher for patients with MG in Denmark (1.42), Finland (1.30) and Sweden (1.21) compared with the respective general population (99). The mortality rate was 5.7% among German patients with MG (n=1,247) in 2019, compared with 1.1% for the general population in Germany (102). In France, MG was associated with an increased mortality in comparison with an age and gender matched control population, with a hazard ratio of 1.82 (95% CI; 1.74, 1.90]) (101).

Mortality is higher among younger female patients compared with the general population. In a Nordic study of patients from Denmark (n=2,248), Finland (n=2,306) and Sweden (n=4,500), SMR was numerically higher in women aged <65 years compared with the general population (99) (also see Section B.1.4, Equality considerations).

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

B.1.3.1.4 Impact on quality of life

Patients with gMG experience debilitating symptoms that severely impact all aspects of their lives (4).

Several studies have demonstrated that QoL is reduced in MG compared with the general population (5-8). In a multicentre study of health-related quality of life (HRQoL), 86.5% of patients with MG (n=37) reported moderate or severe problems in ≥1 dimension (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) of the European Quality of Life-5 Dimensions-3 Level Version (EQ-5D-3L) scale, and the percentage of patients with moderate or severe problems was substantially higher in patients with MG compared with the general population (6). Patients with MG also had a substantial reduction in QoL as measured by the SF-36 survey compared with the general population (6).

In an analysis of the MyRealWorld-MG observational study (1,859 participants with moderate to severe MG), QoL in those with MG was lower than in the general population (8). The mean MG-Activities of Daily Living (MG-ADL) score was higher in the MG group vs the general population (5.8 vs 1.2, respectively, $p<0.0001$), indicating a higher symptom burden and lower functional status among patients with MG. In addition, the MG group had significantly lower EQ-5D-5L utility values compared with the general population ($p<0.0001$), and those with severe disease had worse scores than those with mild symptoms (0.361 vs 0.872, respectively, $p<0.001$). As well as negatively impacting patient QoL, severe disease is also associated with caregiver burden ($p\leq0.0001$ vs mild gMG) (103). T

Patients with MG have lower QoL compared with other chronic diseases (8, 104, 105). The utility value for patients with MG (0.688, as measured by the EQ-5D-5L (106)) is lower than with type 2 diabetes in the UK (0.785; standard error [SE]: 0.007) and severe chronic obstructive pulmonary disease (0.743; 95% CI; 0.730, 0.756) (105, 107), and similar to that for patients with chronic heart failure (0.696; standard deviation [SD]: 0.302) (108), highlighting the severity of the disease burden and impact on QoL for patients with MG (8, 104, 105).

Patients with active disease despite maximal immunosuppression, or with severe disease, experience poor QoL (95, 109-113). In addition to the symptom burden, QoL is impacted by the effects of long-term corticosteroid (CS) use, which is associated with, comorbidities such as osteoporosis, diabetes and high rates of depression (see Section B.1.3.3) (67, 114, 115).

The negative impact of muscle weakness on QoL is compounded by the chronic fatigue experienced by many patients with MG (95). Between 44% and 70% of the MG population experience fatigue (defined either by Fatigue Severity Scale [FSS] scores ≥4 or a Fatigue Questionnaire score ≥4), and these patients have significantly poorer MG-QoL ($p<0.001$) and functional disability scores ($p<0.001$) than those without fatigue (93-95). Persistent fatigue may prevent patients with MG from performing daily tasks (3) and impact speech (due to tongue weakness), the ability to eat and nutritional status (10).

In a MG patient registry study (n=372), 50% of patients felt their disease impacted their ability to lead a full life (116). Of those with a MG-ADL score ≥6 (n=190) (representing

moderate to severe disease), 48% felt their ability to perform daily routines was considerably impaired by their disease (116).

The fluctuating, chronic symptoms of gMG negatively impact patients' mental health and are associated with depression, fear and anxiety (4, 64-66). Indeed, prevalence of depression is higher in patients with gMG compared with the general population (65, 114). In a European cross-sectional study (n=55), 64% of patients with MG had depression (assessed using the Beck Depression Inventory [BDI] Scale) and 46% of patients had moderate and severe anxiety (assessed using the State-Trait Anxiety Inventory) (68). High disease severity is associated with increased rates of depression (67, 114, 115). Using the Myasthenia Gravis Impairment Index [MGII] score, depression was associated with higher disease severity ($p<0.0001$) and generalised disease ($p=0.02$) (67). Fatigue is also associated with increased depressive symptoms (67). Due to the fluctuating nature of the symptoms, anxiety may be worsened by the fear of exacerbation and myasthenic crises, which cannot be predicted (68, 69). In a patient survey, symptoms of depression worsened HRQoL for patients with gMG and were associated with caregiver burden (103). Highlighting the severity of disease burden and the profound impact of MG on patients' lives, the risk of suicide is higher among patients with MG vs the general population (odds ratio [OR] 4.3 [95% CI; 2.0, 9.4], $p=0.0003$) (117).

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

B.1.3.1.5 Economic burden

Direct costs

Generalised myasthenia gravis is associated with a substantial economic burden related to treatment costs, high HCRU and lost productivity for patients and carers (see below for indirect costs) (19-24). Refractory patients with high disease activity incur high healthcare costs due to the need for hospitalisation, reliance on high cost rescue therapies and intensive care for symptom exacerbation and myasthenic crises.

The annual cost of treating patients with gMG in the UK was estimated to be £182.7 million, based on a cost analysis using data from the CPRD in the UK and the Hospital Episode Statistics (HES) database in England (Table 4) (19, 39). Treatment costs make up a significant proportion of expenditure in MG, with the annual cost of IVIg and PLEX in the UK for patients with gMG estimated at £159 million. The cost of consultant, nurse, and admin support time is £122.18 (£145.15 with overhead costs) per

PLEX session and £182.94 (£217.33 with overhead costs) per IVIg infusion. The treatment cost of IVIg per infusion is £1,312.00 (£1,558.66 with overhead costs) (20).

Patients with refractory disease account for 18.2% (£34 million) of the total cost, despite only making up 5.7% of the patient population (19), largely due to the use of IVIg and PLEX (£26,243,504) (Table 4). Hospitalisation (including for receiving intubation/ventilation and having surgery) of refractory patients is associated with a cost of £1,763,308.

Table 4. Annual treatment costs for treating MG in the UK

Category	Refractory patients (£)	Non-refractory patients (£)
Drug acquisition	4,426,898	22,154,812
IVIg and PLEX	26,243,504	132,829,917
Hospitalisation	1,253,210	7,317,020
Intubation	112,666	833,352
Ventilation	195,780	800,018
Outpatient visits	1,282,873	11,353,179
Surgery	201,652	1,160,382
ER visits	37,849	313,086
GP visits	319,518	2,308,100
Other healthcare professionals	379,693	2,323,324
Other resources	353,065	2,941,848
Total costs	**34,498,261**	**182,701,670**

Abbreviations: BNF, British National Formulary; CPRD, Clinical Practice Research Datalink; ER, emergency room; GP, general practice; HES, hospital episode statistics; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; UK, United Kingdom.
Source: Based on linked data from the CPRD in the UK and the HES database in England, reported in Harris et al, 2019 (19), the BNF and the NHS England integrated impact assessment report for unit costs for IVIg and PLEX (39).

Patients with refractory MG spend longer in hospital than non-refractory patients (19). In a retrospective cohort study of linked primary (CPRD) and secondary (HES) care medical records of 1,149 patients with MG (from 1997–2016), the total time in hospital was longer in the refractory MG cohort (median [IQR] = 33 [16–74] days) than in the non-refractory cohort (16 [6–45] days [p <0.0001 vs refractory MG]) (19).

Myasthenic crisis is associated with a substantial cost burden related to admission to ICU and intubation for assisted mechanical ventilation (in 66–90% of cases), provision of a feeding tube, and IVIg or PLEX treatment (21-24). Some patients experiencing myasthenic crisis or exacerbation of symptoms end up in hospital with uncontrolled symptoms for prolonged periods, incurring substantial costs to the healthcare system (25-27, 52). The high cost and HCRU burden of managing patients with gMG adds to the growing challenge of limited NHS resources against a backdrop of increased demand for treatment, staff shortages and long wait times (121).

Productivity loss

As patients with MG tend to be working age at diagnosis (mean age at disease onset is 45±18 years for men and 35±18 years for women [p<0.001]) (51)), much of their working lives will be impacted by having MG. Patients with MG and their caregivers face an economic burden related to unemployment and reduced working hours (13-18). Unemployment rates are higher for patients with MG than the general population or matched control groups, and higher compared with other chronic conditions (13-16). Patients with MG, especially those with uncontrolled symptoms, face unemployment (23–59%), long-term sickness absence (19–47%), and the resulting reduced income (36–53%) (13-16).

Caregiver disutility

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

Hours of work and caregiver time lost, categorised by MG-ADL score, are presented in Table 5 (122).

Table 5: Caregiver burden

MG-ADL score range	Days of work lost per month†	Average number of hours of work lost	Hours of caregiver time per week for those who require a caregiver	Proportion of patients requiring a caregiver (%)
0–1	12.3	4.31	25.16	6.0
2–3	11.5	6.71	50.00	10.4
4–5	13.6	12.38	27.55	28.6
6–7	15.3	16.79	25.78	40.0
8–9	9.4	14.48	18.60	50.0
10–11	14.0	19.28	19.19	57.1
12–13	24.0	34.17	27.23	74.2
14–24	26.7	34.28	35.00	84.6

Source: Jacob et al, 2022 (122).
Abbreviations: MG-ADL, myasthenia gravis activities of daily living.
†Some patients have more than one carer, which is why days of work per month are >20 in some cases.

B.1.3.2 *Clinical pathway of care*

There are currently no specific National Institute for Health and Care Excellence (NICE) or National Health Service (NHS) England guidelines for the full clinical pathway of care in MG, and there is limited published information on the care pathway for patients with MG. Recommendations from the Association of British Neurologists (ABN) management guidelines (25) are included in Sections B.1.3.2.1, B.1.3.2.2 and B.1.3.2.4. Following a diagnosis of MG (Section B.1.3.2.1), a number of treatments are available, depending on disease severity and symptom control (Section B.1.3.2.2).

B.1.3.2.1 Diagnosis

There is no formal diagnostic pathway recommended by NICE, and the diagnosis of MG may be challenging due to fluctuating symptoms (69). In addition, MG is a rare disease and therefore unfamiliar to many HCPs, and an overlap in symptoms with other neurological diseases can result in an MG diagnosis being missed or delayed (86, 123). UK guidelines advise physicians to seek the advice of a specialist neurologist with an interest in MG if the evidence base for diagnosis is too limited, where there is a range of treatment options, or when the disease is difficult to manage (124).

The focus of the diagnostic process is to look for the signs and symptoms, neurological findings and laboratory results that are characteristic of MG, while excluding other diagnoses (29, 125, 126). The ABN management guidelines and others recommend that MG is diagnosed through a combination of patient medical history, physical and neurological exams, autoantibody serum testing, and electrophysiological tests (25, 123-125, 127).

B.1.3.2.2 Management of generalised myasthenia gravis

Mild gMG is initially treated with cholinesterase inhibitors such as pyridostigmine (25, 26) (Figure 3). If treatment with cholinesterase inhibitors is not effective or only provides short-term relief, CSs such as prednisolone are used (25, 26).

Non-steroidal immunosuppressive therapies (NSIST) are offered in addition to steroids as current SoC, with the aim of reducing the CS dose over time (25, 26). Azathioprine, although an available option, generally would not be given as a first immunosuppressant therapy (IST), because of skin toxicity and slower mechanism of action than mycophenolate (≥12 months vs 6–12 months, respectively). In addition, an enzyme level check is required before initiating azathioprine; as if the patient lacks thiopurine methyltransferase (TPMT), then azathioprine is contraindicated and could cause liver failure (124).

If the disease does not respond to the first immunosuppressive treatment, alternative immunosuppressants may be offered (ISTs include mycophenolate, azathioprine, methotrexate, ciclosporin and rituximab, although these are not currently licensed for gMG in the UK) (25, 26, 53-55). Expert clinical opinion sought by the All Wales Therapeutic and Toxicology Centre (AWTTC) has suggested rituximab could be used as a first-line treatment for newly diagnosed antibody positive MG with steroids, as opposed to for refractory patients, based on emerging clinical evidence (128). In addition, there is limited evidence of its effectiveness, as well as safety concerns, in clinical trials and the real world for patients with refractory gMG (25, 129-131). Expert clinical opinion stated that rituximab has not fulfilled hopes for its use in refractory patients (129).

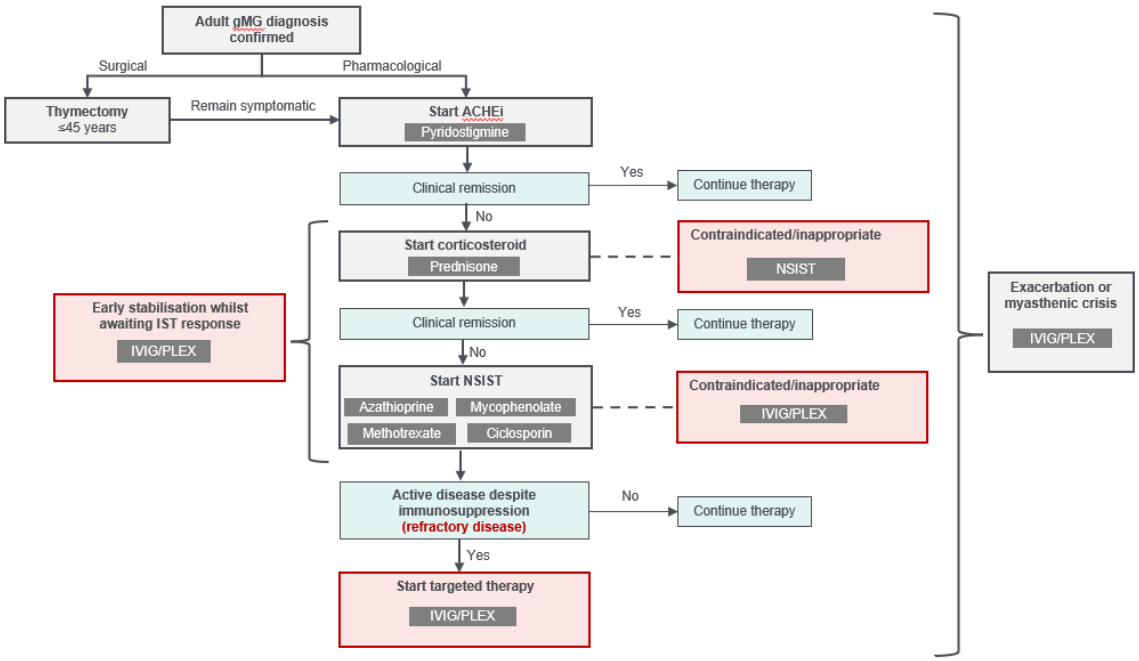
Surgery to remove the thymus (thymectomy) is an option for people age <50 years with mild disease and antibodies against AChR, and people with moderate disease (25, 26). Patients are treated before thymectomy to stabilise them as far as possible before the operation, as to under-treat them may result in ICU admission with respiratory crisis after the procedure . Pre-thymectomy treatments include pyridostigmine, corticosteroids, NSISTs, PLEX, and IVIg, with a preference for treatments with a fast onset of action. Thymectomy is an elective and not an emergency procedure, and it can take at least 12 months for to achieve maximum clinical benefit .

Chronic IVIg or PLEX can be used as a maintenance treatment for refractory patients under limited circumstances (25, 26, 38, 52, 132, 133). The IVIg commissioning policy on the use of maintenance IVIg and PLEX in MG states that in rare circumstances where a patient has failed all standard treatments (including steroids and immunosuppression), and where authorised by a specialist in MG from a centre with a specialist neuromuscular service, maintenance therapy may be considered (133). Chronic PLEX can be used as a maintenance treatment for refractory patients following failure on all standard therapies, for stabilisation whilst awaiting immunosuppressive therapy (IST) response or when CSs and ISTs are contraindicated or inappropriate (25, 26, 38, 132). Efgartigimod is available for patients with refractory gMG who have failed, not tolerated or are ineligible for current treatments, but only thorough the Early Access to Medicines Scheme.

In the event of a myasthenic crisis (see Section B.1.3.1.2), patients are treated in hospital with mechanical ventilation, IVIg from healthy donor blood, PLEX and supportive care (25, 26). For impending crisis (where treatment is needed to avert myasthenic crisis), bulbar or respiratory compromise is managed using IVIg and PLEX.

The current treatment pathway for gMG is presented in Figure 3. Available treatments for patients with gMG are listed in Table 6.

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



Source: Adapted from the ABN management guidelines and validated by UK clinical expert opinion (124).
Abbreviations: ABN, Association of British Neurology Guidelines; gMG, generalised myasthenia gravis; IST, immunosuppressant therapy; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant therapy; PLEX; plasma exchange; UK, United Kingdom.

Table 6. Currently available treatments for MG in the UK

Treatment	Method of administration	Indication	Time to onset of effect	Time to maximal effect	Efficacy	Safety	Other limitations
AChEIs (25, 26, 53-55);	Oral or IV	All patients with MG	15–30 minutes	2 hours	Limited RCT evidence	Nausea, diarrhoea abdominal cramping, increased salivation	Most gMG patients cannot be adequately managed with acetylcholinesterase inhibitors alone due to dose-limiting toxicities
Low-dose and high-dose CS	Oral or IV	Off-label	2–4 weeks	5–6 months	Limited RCT evidence	Skin atrophy, glaucoma, mood disorders, risk of infection, weight gain, osteoporosis, diabetes, hypertension	Significant side effects with chronic treatment
Non-CS ISTs	Oral or IV	Off-label	6–12 months	1–2 years	Limited RCT evidence	Bone marrow suppression, leukopenia, hypertension, GI intolerance, infection, hepatoxicity, nephrotoxicity, teratogenicity	Delayed onset of effect
PLEX	IV	Off-label	1–7 days	1–3 weeks	Limited RCT evidence	Allergic reactions, risk of infection, hypotension, nephrotoxicity, thrombosis	• Need for specialised equipment that may not be readily available • Burdensome intervention • Repeated interventions may be necessary due to rapidly declining effect
IVIg	IV	Off-label	1–2 weeks	1–3 weeks	Limited RCT evidence	Allergic reactions, nausea, hypotension, anaphylactic reactions, nephrotoxicity, thromboembolism	• Burdensome administration (long infusion time) • Specialised setting required for infusions

Treatment	Method of administration	Indication	Time to onset of effect	Time to maximal effect	Efficacy	Safety	Other limitations
							• Repeated interventions may be necessary due to rapidly declining effect
Rituximab	IV	Off-label	12 months	12 months	Phase III: significant difference in primary endpoint versus placebo in patients with early onset gMG	Risk of fatal infusion reactions, tumour lysis syndrome, severe mucocutaneous reactions and progressive multifocal leukoencephalopathy	• **Not licensed** • **Limited supportive clinical data** • Burdensome infusions • Delayed onset of effect

Abbreviations: AChEI, acetylcholinesterase inhibitor; AChR+, acetylcholine receptor-positive; CS, corticosteroids; GI, gastrointestinal; gMG, generalised myasthenia gravis; IST, immunosuppressive therapy; IVIG, intravenous immunoglobulin; PLEX: plasma exchange; RCT, randomised controlled trial.
References: Narayanaswami et al, 2020 (134); Piehl et al, 2022; (131) Sanders et al, 2016 (21); Farmakidis et al, 2018 (34); Howard et al, 2017 (135); Howard et al, 2019 (136); Nowak et al, 2018 (137); Sussman et al, 2015 (124).

B.1.3.2.3 Relevant NICE guidance, pathways or commissioning guides

There are currently no NICE technology appraisals or guidelines for gMG. A NICE technology appraisal for efgartigimod (ID4003) for gMG is currently in development. The appraisals for eculizumab (TA636) and ravulizumab (ID4019) have been terminated.

B.1.3.2.4 Clinical guidelines

The 2015 Association of British Neurologist (ABN) management guidelines were devised to guide physicians and general neurologists in the management of MG (124). They attempt to steer a path between evidence-based practice where available and established best practice where evidence is unavailable (25, 124). The ABN guideline was published in 2015, and therefore does not include all the treatments that are commissioned in MG. European guidelines (Euro Myasthenia) are aimed at European clinicians with limited experience in MG (GPs and neurologists) (138).

B.1.3.3 *Issues relating to current clinical practice*

B.1.3.3.1 Treatment burden

Patients face a severe treatment burden from standard therapies and must balance the benefits of controlling symptoms with severe, debilitating side effects. Current treatment options for MG are based on non-specific immunosuppression for symptom control (used off-label (25, 26, 53-55)), as there are no available therapies that specifically target the underlying pathophysiology in MG (25, 139). Long-term use of standard treatments is associated with side effects, for example skin cancer with azathioprine (42). Corticosteroids in particular are associated with severe side effects such as diabetes, osteoporosis, depression and infection, which can trigger a myasthenic exacerbation (11, 34, 43-45). Paradoxically, high dose CSs are associated with a temporary worsening of symptoms and an extended hospital stay (27, 140). Patients who are contraindicated to CSs have a high unmet need for another treatment option (25, 26). Interviews with MG experts in the UK also highlighted a group of patients that is not technically contraindicated to CS, but in whom CSs should be avoided if possible, for example, those with diabetes or osteoporosis and high BMI.

Despite available treatment options, many patients with gMG are refractory to standard therapy and continue to experience poor symptom control (30, 31). The only currently available treatments for patients who are refractory to standard therapies are IVIg and PLEX, both of which are used off-label as they are unlicensed for the chronic treatment of gMG in the UK (40, 41). In addition, IVIg and PLEX are associated with limitations related to availability, accessibility, high cost, and treatment burden. IVIg is in short supply in the UK because plasma is internationally imported owing to theoretical risks of variant Creutzfeldt-Jakob disease (37, 38). A global shortage coinciding with increased indications for IVIg has resulted in strict national clinical guidelines for the use of IVIg (37, 38, 62). Administration of PLEX requires treatment at specialist centres, which may involve patients having to travel long distances for treatment, and even staying in hospital for repeat treatment if they live too far away to travel for each session (25, 26). The IVIg infusion duration of 4–6 hours over 2–5 days is also burdensome for patients. PLEX and IVIg are associated with economic impacts for both patients and the NHS, related to high HCRU (from treatment and labour costs associated with treatment, see

Section B.1.3.1.5), opportunity cost, productivity loss and cost of travel for patients (19, 20, 39).

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

Despite available treatment options, many patients with gMG continue to experience a severe disease burden and poor symptom control (30, 31).

Delayed onset of treatment effect with NSISTs (usually 6–18 months, but it can take up to 2 years to achieve maximal clinical benefit) contributes to poor disease control, leaving patients with a high symptom burden and at risk of symptom exacerbation and crisis (34, 46, 141).

Patients may cycle through different ISTs until their symptoms are under control. Some patients remain refractory to available treatments and continue to experience active disease despite maximal immunosuppression. Patients who are refractory to currently available treatments are at an increased risk of myasthenic exacerbation and crisis, a life-threatening complication of gMG, and are more likely to use healthcare resources, leading to a high economic burden (19-24, 34-36) (see Sections B.1.3.1.2 and B.1.3.1.5). Of 1,149 patients with MG aged ≥18 years and receiving standard of care in the UK (median follow-up 47.2 months), 283 had ≥1 exacerbation (142). The only available options for patients with refractory disease are IVIg and PLEX, but both are associated with limitations related to treatment burden, tolerability and accessibility (see Section B.1.3.3.1).

B.1.3.3.3 Unmet need

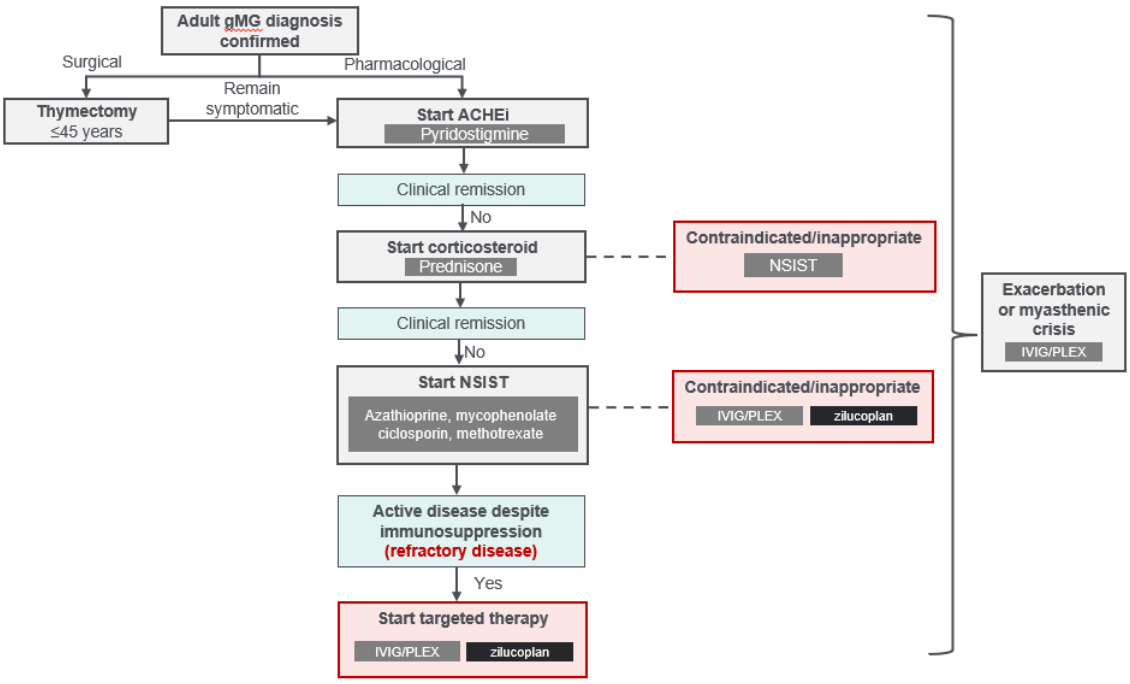
Given the limitations of current treatment options for patients with refractory gMG, there is an urgent unmet need for a new treatment option to control debilitating symptoms. A licensed, targeted treatment which controls symptoms may reduce the effects of burdensome symptoms on patients' lives, the need for CSs and the risk of myasthenic exacerbation (see section B.1.3.1.2) (143), as well as the impact on QoL, mental health and high HCRU associated with poor disease control. Patients will also benefit from a home-based treatment, which will also reduce NHS resource use.

A consensus report by the Health Innovation Network (HIN), developed by clinicians and patients, highlighted requirements to elevate standards of care for people with MG in the UK, which included faster diagnosis, increased awareness of rare diseases among healthcare professionals, better co-ordination of care and improved access to specialist care, treatments and drugs (144).

B.1.3.4 *Zilucoplan place in therapy*

Zilucoplan is positioned as an add-on therapy to SoC for patients with AChR-Ab+ gMG who are refractory[b] to current treatments and experience active disease despite receiving maximum immunosuppression, the disease is uncontrolled, as defined by a MG-ADL of 6 or more or a QMG of 12 or more, and an additional therapy such as IVIg or PLEX is being considered or patients are being treated chronically with IVIg/PLEX (Figure 4).

Figure 4. Proposed positioning of zilucoplan for gMG in the UK



Source: Adapted from the ABN management guidelines and validated by UK clinical expert opinion (124).
Abbreviations: ABN, Association of British Neurology Guidelines; gMG, generalised myasthenia gravis; IST, immunosuppressant therapy; IVIg, intravenous immunoglobulin; NSIST, non-steroidal immunosuppressant therapy; PLEX; plasma exchange; UK, United Kingdom.

The ongoing zilucoplan clinical trials have demonstrated sustained efficacy of zilucoplan up to 12 weeks (with open-label extension data up to [redacted] [RAISE-XT]) with a favourable safety profile in patients with gMG receiving concomitant SOC, as well as a fast onset of action (treatment effect of zilucoplan vs placebo was observed as early as Week 1). A treatment that is fast acting will reduce the disease burden for refractory patients, who may cycle through different ISTs without achieving symptom control. Similar results were seen in the refractory sub-group. Zilucoplan also has the potential to reduce the need for CSs and the associated side effects, as well as the need for rescue

[b] Refractory as defined in the RAISE clinical study: patients on treatment for ≥1 year with ≥2 of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, other ISTs, or history of treatment with ≥1 of these therapies for ≥1 year, and required chronic PLEX, IVIg, or SCIg at least every 3 months for the 12 months prior to enrolment.

therapy (with IVIg or PLEX) (47). This was highlighted in the favourable CS sparing effect seen at week extension (E) 48 in 40% (n=24/60) of patients who received zilucoplan in RAISE and the RAISE-XT. Reducing the need for rescue therapy may lead to reduced medical resource utilisation costs associated with managing exacerbations.

As a once-daily subcutaneous injection that can be self-administered at home, zilucoplan is anticipated to avoid the need for frequent IV administration, minimising the treatment burden to patients and providing cost savings. No new infrastructure or capital investment would be required for its introduction to the NHS.

B.1.4 *Equality considerations*

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

There is health inequality between males and females in terms of the burden of MG. As females are younger than males at disease onset (mean age of disease onset is 35±18 vs 45±18 years, respectively [p<0.001]) (51), women with MG are exposed to a greater total burden throughout their lives than men, and through more of their working life.

MG is more prevalent in female than male patients, with female patients accounting for approximately 60% of the MG population (49, 50). Studies of patients from Denmark, Finland and Sweden show increased mortality amongst younger (30–49 and 50–64 age groups) women compared with men with MG and the general population (99). In addition to a higher prevalence and mortality rates in females, females are younger than males at disease onset (51) and onset of MG at age <50 years is three times more common in women than in men (145-147). Women are therefore exposed to the negative impacts (economic, social, on quality of life [QoL]) earlier in life and for longer than men, amounting to a greater total burden. Women face a significant economic and social disadvantage if MG diagnosis occurs at a time in their lives when they may be building their careers and starting a family. Woman of childbearing age face contraindications to therapy during pregnancy and lactation and may face a difficult choice between starting a family and managing symptoms of MG (4).

B.2. Clinical effectiveness

Zilucoplan as an add-on treatment to SOC for patients with refractory gMG is associated with significant improvements in the signs and symptoms of disease activity and QoL, as measured by MG-ADL, QMG, MGC, and MG-QoL15r, with a fast onset of action (treatment effect of zilucoplan vs placebo was observed as early as Week 1), and sustained long-term efficacy. Zilucoplan may also reduce the need for CSs and the associated side effects, as well as the need for rescue therapy (with IVIg or PLEX) (47) (48)

- **RAISE**, a Phase III, randomised, placebo-controlled trial, provides pivotal clinical evidence for zilucoplan as an add-on treatment to SOC for patients with gMG.
- The ongoing open-label extension (OLE) phase of RAISE, **RAISE-XT** (interim results; cut-off date May 2023), demonstrate the long-term efficacy, durability and safety of zilucoplan in this patient population (ITT)
- In the RAISE study, the primary efficacy endpoint (CFB to Week 12 in MG-ADL score) was met
    - Treatment with zilucoplan 0.3 mg/kg resulted in significantly higher CFB to Week 12 MG-ADL scores compared with placebo (−4.39 vs −2.30, respectively). This significant difference vs placebo (LS mean difference −2.09, $p<0.001$) was also considered clinically meaningful
    - Zilucoplan demonstrated a rapid onset of action. Treatment effect with zilucoplan 0.3 mg/kg was observed from Week 1 and increased through Week 4 with stabilisation thereafter to Week 12
    - Zilucoplan was associated with consistently greater improvements from baseline to Week 12 in QMG and MGC scores (secondary endpoints) compared with placebo, with a fast onset of action
- All patients who received zilucoplan 0.3 mg/kg in RAISE-XT experienced improvements in the signs and symptoms of disease activity and QoL, as measured by MG-ADL, QMG, MGC, and MG-QoL15r. Patients continued to improve further through Week E12, which was maintained through Week E84 (May 2023 data cut), demonstrating long-term benefits of zilucoplan as an add-on to standard therapies for gMG. Zilucoplan may also reduce the need for rescue therapy (48)
    - At Week extension (E)12 (24 weeks total treatment), patients who received zilucoplan in both the parent study and in RAISE-XT experienced a mean reduction (SD) in MG-ADL score from parent study baseline [redacted] which was sustained up to Week E84 (96 weeks total)
    - A post-hoc analysis of patients receiving zilucoplan in RAISE-XT demonstrates that zilucoplan has a steroid-sparing effect, potentially reducing the need for patients to take concomitant CSs which have debilitating side effects (see Section B.2.7) (47)
    - Incidence of rescue therapy was [redacted] per 100 patients-years with zilucoplan compared with placebo, respectively, and [redacted] per 100 patients-years for patients who zilucoplan in the extension trial (see Section B.2.6.2.2) (48)

- Zilucoplan displayed a favourable tolerability profile in the RAISE study, which was maintained over time during RAISE-XT
    - The most common treatment-related TEAE in RAISE was injection-site bruising, occurring in 12 (6%) patients
    - No new safety concerns were identified in RAISE-XT

B.2.1 *Identification and selection of relevant studies*

B.2.1.1 *Search strategy*

A systematic literature review (SLR) was conducted to identify all available clinical evidence in patients with MG (report finalised on 25 September 2023).

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

B.2.1.1.1 Study selection

The methodology used for the SLR including the search strategy, databases searched, and selection criteria is presented in Appendix D. A summary of the inclusion and exclusion criteria is shown in Table 7.

Table 7. Eligibility criteria used in the search strategy

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

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

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

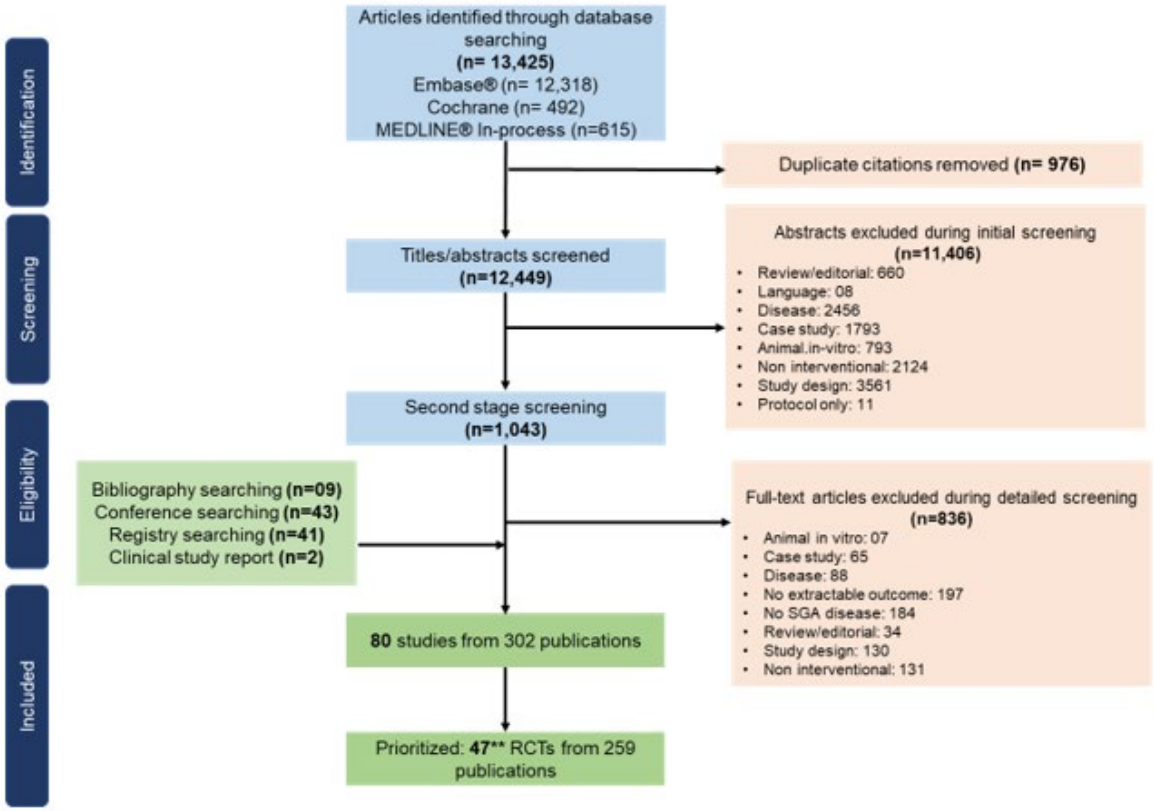
The PRISMA flow diagram of the numbers of records included and excluded at each stage of the selection process is shown in Figure 5.

Searches of electronic databases yielded 13,425 references, of which 976 were identified as duplicates and were excluded. The remaining 12,449 references were initially screened based on title and abstract, and 11,406 references were excluded, leaving 1,043 references to be screened on the basis of the full publications. Full-text screening led to the exclusion of 836 references, resulting in 207 publications to be included in the SLR. In addition, 41 references were identified from registry searching, 43 from conference searching, nine from bibliography searching and two from clinical study report searching. Following linking of multiple publications of any single study, a total of 80 randomised controlled trials (RCTs) from 302 publications were included in the clinical review. Of the identified RCTs (n=80), only those where the definition of gMG aligned with that used in RAISE were considered for further data extractions and reporting (n=47).

Based on these criteria, a total of 47 studies from 259 publications were included as relevant. These 47 studies represented the gMG population, of whom 13 were included patients with mild to moderate, nine with mild to severe, 11 with moderate to severe, seven with severe, three with refractory, and four with exacerbating MG.

Details of the study selection process and a complete list of included studies, along with the full list of excluded studies with the rationale for exclusion, are provided in Appendix D.

Figure 5. PRISMA flow diagram showing the study identification process



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

B.2.2 *List of relevant clinical effectiveness evidence*

The systematic review of clinical evidence identified a single Phase III RCT of zilucoplan in the population of interest to this submission – RAISE (Table 8). The ongoing OLE phase of the RAISE study (RAISE-XT) is also included in this submission. Interim results from this study (data from latest available cut-off point: May 2023) are of relevance to this submission, as they provide evidence of the long-term efficacy and safety of zilucoplan in the patient population of interest and informed the economic model for zilucoplan. The study is anticipated to be completed by the end of June 2026.

A Phase IIa trial (Study MG0009) evaluating zilucoplan as a treatment of gMG was also identified in the SLR. In MG0009, zilucoplan showed clinically meaningful, significant and sustained improvements over 12 weeks (and 24 weeks in the extension phase) in patients with gMG that warranted further investigation in a Phase III trial. MG0009 did not inform the economic model for zilucoplan; therefore, evidence from this trial is considered supportive for this submission and is not included in any further detail.

Table 8: Clinical effectiveness evidence

Trial no. (acronym) and primary study reference(s)	Study design	Population	Intervention	Comparator	Supports application for marketing authorisation	Used in the economic model	Is study excluded from further discussion? If yes state rationale	Reported outcomes specified in the decision problem
RAISE (NCT04115293/ MG0010) Phase III RCT (57, 148, 149)† CSR	Randomised, double-blind, placebo -controlled study	Patients with mild-to-severe AChR-Ab+ gMG	Zilucoplan 0.3 mg/kg/day, SC injection + SOC	SOC‡	Yes	Yes	No (pivotal Phase III trial)	See Table 1
RAISE-XT (NCT04225871/ MG0011) Phase III OLE CSR	OLE study	Patients who completed the RAISE Phase III study and Phase II study MG0009	Zilucoplan 0.3 mg/kg/day, SC injection + SOC	SOC‡	Yes	Yes	No (pivotal Phase III trial)	See Table 1
MG0009 NCT03315130 Phase II (150, 151) † CSR	Randomised, double-blind, placebo-controlled study	Patients with mild-to-severe AChR-Ab+ gMG	• Zilucoplan 0.1 mg/kg/day, SC injection + SOC • Zilucoplan 0.3 mg/kg/day, SC injection + SOC	SOC‡	No	No	Yes (only pivotal Phase III trials will be described in further detail)	See Table 1

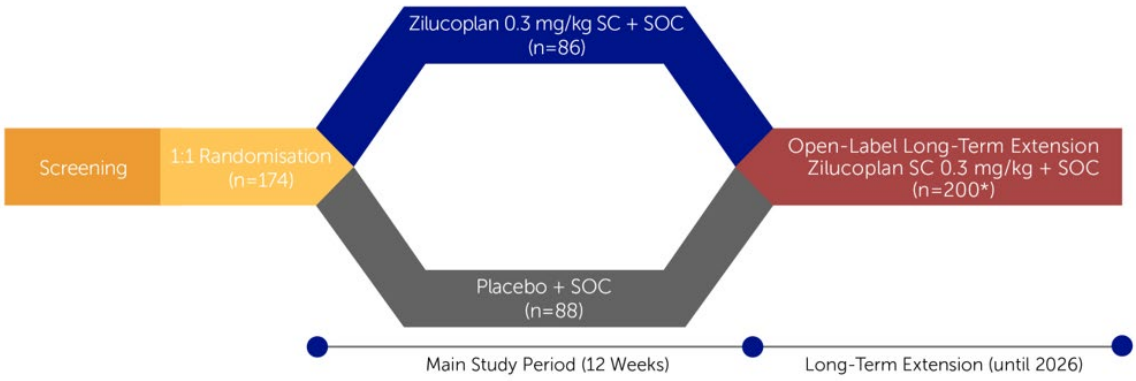
Abbreviations: AChR-Ab+, acetylcholine receptor antibody positive; CSs, corticosteroids; CSR, clinical study report; gMG, generalised myasthenia gravis; NCT, National Clinical Trials, NSISTs, non-steroidal immunosuppressive therapies; OLE, open-label extension; sc, subcutaneous; SOC, standard of care
† Sponsored by the parent company, Ra Pharmaceuticals, Inc.
‡Such as cholinesterase inhibitors, CSs and NSISTs.

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

B.2.3.1 *Comparative summary of RCT methodology*

The RAISE study was a Phase III, double-blind, randomised, placebo-controlled trial conducted to evaluate the efficacy and safety of zilucoplan in a broad population of patients with AChR-Ab$^+$ gMG. This trial consisted of a 12-week treatment phase, followed by an ongoing open-label phase, RAISE-XT, to evaluate long-term safety, tolerability, and efficacy of zilucoplan. RAISE-XT is estimated to continue until June 2026. The design and methodology of RAISE and RAISE-XT are summarised in Figure 6 and Table 9.

Figure 6. RAISE and RAISE-XT study design overview



Abbreviations: SC: subcutaneous; SOC; standard of care.
*MG0011 included patients from both MG0009 (Phase II) and MG0010.

Table 9: Comparative summary of trial methodology

Trial number (acronym)	**NCT04115293 RAISE Phase III**	**NCT04225871 RAISE-XT**
Location	Multiple sites across North America, Europe (including UK) and East Asia	
Trial design	Randomised, double-blind, placebo-controlled study	OLE study. Patients entered RAISE-XT following 12 weeks of treatment in RAISE
Eligibility criteria for participants	• gMG (MGFA Class II–IV) diagnosis at screening • Positive serology for anti-AChR autoantibodies • MG-ADL score ≥6 at screening and at baseline • QMG score ≥12 at screening and at baseline • No change in non-CS ISTs for ≥30 days prior to treatment or anticipated to occur during the study • No requirement to have failed multiple prior therapies	Completion of the RAISE Phase III or Phase II study

Settings and locations where the data were collected	Patients were recruited from North America, Europe (including the UK), and Japan	Patients were recruited from North America, Europe (including the UK), and Japan
Trial drugs	• Zilucoplan 0.3 mg/kg/day, SC injection + SOC (n=86) • Placebo + SOC (n=88)	Zilucoplan 0.3 mg/kg/day, SC injection + SOC (n=200)
Permitted concomitant medication	**Permitted** **AChEis, CSs, NSISTs**	**Permitted** **AChEis, CSs, NSISTs** • Pyridostigmine (n=171 [85.5%]) • Prednisone (n=109 [54.5%]) • MMF (n=54 [27.5%]) • Azathioprine (n=46 [23.0%]) (152)
Primary outcomes (including scoring methods and timings of assessments)	CFB up to Week 12 in MG-ADL score for patients with gMG receiving either zilucoplan + standard therapy or placebo + standard therapy	Long-term safety and tolerability of zilucoplan in patients with gMG who participated in a parent zilucoplan trial (either Phase III RAISE or Phase II MG0009)
Other outcomes used in the economic model/specified in the scope	**Secondary and exploratory endpoints** • QMG score • MGC score • Time to receipt of rescue therapy • Proportion of patients achieving MSE • Proportion of patients achieving a ≥3 point reduction in MG-ADL score without rescue therapy • Proportion of patients achieving a ≥5 point reduction in QMG score without rescue therapy o Mortality o Number of hospitalisations o Adverse effects of treatment o Time to clinically meaningful improvement o MGQoL15r score	The same efficacy, exploratory, quality of life, and safety endpoints for the RAISE study phase will also be used for RAISE-XT
Pre-planned subgroups	Patients who are treatment refractory, as per the definition used in the RAISE randomised controlled trial†	Patients who are treatment refractory, as per the definition used in the RAISE randomised controlled trial‡

Abbreviations: AChR, acetylcholine receptor; AChR-Ab+, acetylcholine receptor antibody positive; CFB, change from baseline; CSs, corticosteroids; (g)MG, (generalised) myasthenia gravis; IST, immunosuppressive therapy; MG-ADL, MG-Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MGQoL15r, MG Quality of Life 15-Item Scale; MMF, mycophenolate mofetil; MMS, minimal symptom expression; QMG, quantitative MG; NSISTs, non-steroidal immunosuppressive therapies; OLE, open-label extension; SC, subcutaneous; SOC, standard of care.
† Refractory as defined in the RAISE clinical study: patients on treatment for ≥1 year with ≥2 of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, other ISTs, or history of treatment with ≥1 of these therapies for ≥1 year, and required chronic PLEX, IVIg, or SCIg at least every 3 months for the 12 months prior to enrolment.

B.2.3.1.1 Patient disposition

RAISE (Phase III)

In total, 239 patients were screened across 75 sites (including North America, n=37; Europe, n=27 [19 from the UK]; and East Asia, n=11). Of the 239 patients who were screened, 63 patients (26.4%) failed screening and two patients (0.8%) withdrew prior to randomisation. The remaining 174 patients were randomised and exposed to treatment; 86 patients received zilucoplan and 88 patients received placebo (Table 10).
Of the 174 patients who entered the trial, 166 (95.4%) completed the study; 82/86 (95.3%) in the zilucoplan 0.3 mg/kg group and 84/88 (95.5%) in the placebo group (Table 10). Overall, [redacted] had refractory gMG. Of patients from the UK trial sites [redacted] were refractory and [redacted] were non refractory.

Table 10: Patient disposition–RAISE mITT population

Category, n (%)	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)	All study participants (n=174)
Started study	88 (100)	86 (100)	174 (100)
Completed study	84 (95.5)	82 (95.3)	166 (95.4)
Discontinued study	4 (4.5)	4 (4.7)	8 (4.6)
Primary reason for discontinuation			
AE	0	2 (2.3)	2 (1.1)
Lost to follow up	0	0	0
Withdrawal by study participant	2 (2.3)	1 (1.2)	3 (1.7)
Physician decision	1 (1.1)	0	1 (0.6)
Protocol violation	0	0	0
Death	1 (1.1)	1 (1.2)	2 (1.1)
Safety reason as determined by the Investigator or Sponsor	0	0	0
Intolerability of IMP	0	0	0
Other	0	0	0

Abbreviations: AE, adverse event; IMP, investigational medicinal product; mITT, modified intent to treat.
Source: RAISE CSR, 2022 (153).

RAISE-XT (open-label extension)

At the May 2023 data cut-off, [redacted] patients were enrolled and exposed to treatment in RAISE-XT. Patients transitioned to the extension study from either RAISE or the Phase II study MG0009 (Table 11) (see Section B.2.4.1 for definition of treatment groups and populations analysed).
Of the [redacted] patients who enrolled, [redacted] completed the trial period up to Week 12, including [redacted] patients from the placebo/zilucoplan 0.1/0.3 mg/kg, placebo/zilucoplan 0.3 mg/kg, zilucoplan 0.1/0.1/0.3 mg/kg, and zilucoplan 0.3/zilucoplan 0.3 mg/kg group,

respectively. Full patient disposition (September 2022 data cut [interim CSR]) is presented in Table 11.

Table 11: Patient disposition–RAISE-XT mITT population

Category, n (%)	Placebo/ zilucoplan 0.1/0.3 mg/kg (n=5)	Placebo/ zilucoplan 0.3 mg/kg (n=90)	Zilucoplan 0.1/0.1/0.3 mg/kg (n=12)	Zilucoplan 0.3/0.3 mg/kg (n=93)	All study participants (n=200)
Entered study	[redacted]	[redacted]	[redacted]	[redacted]	200 (100)
Completed Week E12	[redacted]	[redacted]	[redacted]	[redacted]	193 (96.5)
Ongoing	[redacted]	[redacted]	[redacted]	[redacted]	166 (83.0)
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]	34 (17.0)
Primary reason for discontinuation					
AE	[redacted]	[redacted]	[redacted]	[redacted]	6 (3.0)
Lost to follow up	[redacted]	[redacted]	[redacted]	[redacted]	2 (1.0)
Withdrawal from study participant	[redacted]	[redacted]	[redacted]	[redacted]	12 (6.0)
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]	6 (3.0)
Death	[redacted]	[redacted]	[redacted]	[redacted]	5 (2.5)
Safety reason as determined by the Investigator or Sponsor	[redacted]	[redacted]	[redacted]	[redacted]	1 (0.5)
Other	[redacted]	[redacted]	[redacted]	[redacted]	2 (1.0)

Abbreviations: AE, adverse event; mITT, modified intent to treat.
See Section B.2.4.1 for treatment groups and definitions.
Source: RAISE-XT interim CSR, September 2022 data cut (152).

B.2.3.1.2 Patient demographics and baseline characteristics

RAISE (Phase III)

Overall, the mean (SD) age was 53.0 (15.1) years (range: 19–75 years). More than half of patients were female (56.9% [99/174]), consistent with the real-world MG population (49, 50). Patients enrolled at European sites comprised 38.5% of study participants (67/174). The mean (SD) weight and BMI were 89.1 (24.77) kg and 31.0 (7.63) kg/m^2, respectively (Table 12).

Baseline demographics were generally well-balanced between the treatment groups except for sex, where there was a slightly higher proportion of females in the zilucoplan 0.3 mg/kg treatment group (60.5% [52/86]) compared with the placebo treatment group (53.4% [47/88]) (Table 12). Disease-specific baseline characteristics are presented in Table 13.

Table 12: Baseline demographics of patients enrolled in the RAISE study across treatment groups (ITT population)

MG0010 RAISE	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)	All study participants (n=174)
Age (years)†			
Mean (SD)	53.3 (15.7)	52.6 (14.6)	53.0 (15.1)
Median	55.5	54.5	55.0
Min, max	19, 75	21, 75	19, 75
Age group, n (%)‡			
≤18 years	0	0	0
19–64 years	62 (70.5)	64 (74.4)	126 (72.4)
≥65 years	26 (29.5)	22 (25.6)	48 (27.6)
Sex n (%)			
Female	47 (53.4)	52 (60.5)	99 (56.9)
Race, n (%)			
American Indian or Alaska Native	1 (1.1)	0	1 (0.6)
Asian	14 (15.9)	7 (8.1)	21 (12.1)
Black	7 (8.0)	6 (7.0)	13 (7.5)
White	62 (70.5)	66 (76.7)	128 (73.6)
Other/Mixed	0	0	0
Missing	4 (4.5)	7 (8.1)	11 (6.3)
Ethnicity, n (%)			
Hispanic or Latino	5 (5.7)	7 (8.1)	12 (6.9)
Not Hispanic or Latino	79 (89.8)	72 (83.7)	151 (86.8)
Missing	4 (4.5)	7 (8.1)	11 (6.3)
Region, n (%)			
East Asia	9 (10.2)	7 (8.1)	16 (9.2)
Europe	33 (37.5)	34 (39.5)	67 (38.5)
North America	46 (52.3)	45 (52.3)	91 (52.3)
BMI (kg/m^2)			
Mean (SD)	30.5 (8.02)	31.4 (7.22)	31.0 (7.63)
Median	29.0	30.5	30.0
Min, max	16, 54	19, 50	16, 54

Abbreviations: BMI, body mass index; gMG, generalised myasthenia gravis; MG, myasthenia gravis; SD, standard deviation.
†Age was calculated as: year informed consent signed – year of birth; ‡Clinicaltrials.gov age categories.
Source: RAISE CSR (153).

Table 13. Baseline disease characteristics of patients enrolled in the RAISE study across treatment groups (ITT population)

MG0010 RAISE	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)	All study participants (n=174)
MGFA class at screening, n (%)			
Class II	27 (30.7)	22 (25.6)	49 (28.2)
Class III	57 (64.8)	60 (69.8)	117 (67.2)
Class IV	4 (4.5)	4 (4.7)	8 (4.6)
Age at disease onset, years			
Mean (SD)	44.0 (18.7)	43.5 (17.4)	43.8 (18.0)
Median	44.5	43.0	44.0
Min, max	9.0, 73.0	13.0, 73.0	9.0, 73.0
Duration of disease, years			
Mean (SD)	9.0 (10.4)	9.3 (9.5)	9.2 (9.9)
Median	4.75	5.55	5.00
Min, max	0.2, 51.9	0.1, 42.3	0.1, 51.9
Symptoms at onset, n (%)			
Ocular	34 (38.6)	28 (32.6)	62 (35.6)
Generalised	54 (61.4)	58 (67.4)	112 (64.4)
Prior thymectomy, n (%)	37 (42.0)	45 (52.3)	82 (47.1)
Prior MG crisis	29 (33.0)	28 (32.6)	57 (32.8)
Time since most recent crisis (months)†			
Mean (SD)	72.3 (109.8)	75.6 (91.8)	73.9 (100.5)
Median	22.0	39.0	26.9
Min, max	1.4, 469.8	1.4, 277.6	1.4, 469.8
gMG refractory, n (%)‡			
	[redacted]	[redacted]	[redacted]
Baseline MG-ADL score			
Mean (SD)	10.9 (3.4)	10.3 (2.5)	10.6 (3.0)
Median	10.5	10.0	10.0
Min, max	6, 19	6, 16	6, 19
Baseline MG-ADL score, n (%)			
≤9	33 (37.5)	33 (38.4)	66 (37.9)
≥10	55 (62.5)	53 (61.6)	108 (62.1)

MG0010 RAISE	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)	All study participants (n=174)
Baseline QMG score			
Mean (SD)	19.4 (4.5)	18.7 (3.6)	19.1 (4.1)
Median	18.5	18.0	18.0
Min, max	13, 36	12, 31	12, 36
Baseline QMG score, n (%)			
≤17	38 (43.2)	38 (44.2)	76 (43.7)
≥18	50 (56.8)	48 (55.8)	98 (56.3)

Abbreviations: BMI, body mass index; gMG, generalised myasthenia gravis; IVIG, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; QMG, quantitative myasthenia gravis; SCIG, subcutaneous immunoglobulin; SD, standard deviation.
†Time since most recent crisis (months) was calculated as: (Date of Study Day 1–Date of crisis)/(365.25/12).
‡A study participant was considered "gMG Refractory" if they met the following criteria: (1) Treatment for at least 1 year with 2 or more of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, or other corticosteroids, or (2) History of treatment with at least 1 of the therapies listed in (1) for 1 year or more and required chronic plasma exchange or IVIG or SCIG at least every 3 months for the 12 months prior to enrolment.
Source: RAISE CSR (153).

RAISE-XT (open-label extension)

At the May 2023 data cut-off, [redacted] entered RAISE-XT[redacted] The other [redacted] patients enrolled in RAISE-XT had previously completed the Phase II study, MG0009. (Table 14).

Overall, baseline demographics and disease characteristics were balanced between treatment groups and are presented in Table 14 and Table 15, respectively. Prior MG crisis was consistent between treatment groups ([redacted] study participants [redacted] except for the placebo/zilucoplan 0.1/ 0.3 mg/kg group, which had no study participants with prior MG crisis. However, this was the treatment group with the smallest number of study participants [redacted] There was a similar distribution of gMG disease severity between all treatment groups, as measured by MGFA classification, with the majority of study participants in MGFA Class II (mild disease severity) or MGFA Class III (moderate disease severity).

Table 14: Baseline demographic characteristics of patients enrolled in the RAISE-XT study across treatment groups

MG0011 RAISE-XT	Placebo/ zilucoplan 0.1/0.3 mg/kg [redacted]	Placebo/ zilucoplan 0.3 mg/kg (n=90)	Zilucoplan 0.1/0.1/0.3 mg/kg [redacted]	Zilucoplan 0.3/0.3 mg/kg [redacted]	All study participants (n=200)
Age (years)†					
Mean (SD)	[redacted]	53.7 (15.5)	[redacted]	52.9 (14.5)	53.3 (15.0)
Median	[redacted]	[redacted]	[redacted]	[redacted]	56.0
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	19, 76
Sex n (%)					
Female	[redacted]	[redacted]	[redacted]	[redacted]	110 (55.0)
Race, n (%)					
Asian	[redacted]	[redacted]	[redacted]	[redacted]	23 (11.5)
Black	[redacted]	[redacted]	[redacted]	[redacted]	17 (8.5)
White	[redacted]	[redacted]	[redacted]	[redacted]	152 (76.0)
Missing	[redacted]	[redacted]	[redacted]	[redacted]	8 (4.0)
Ethnicity, n (%)					
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	14 (7.0)
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	179 (89.5)
Missing	[redacted]	[redacted]	[redacted]	[redacted]	7 (3.5)
Region, n (%)					
East Asia	[redacted]	[redacted]	[redacted]	[redacted]	16 (8.0)
Europe	[redacted]	[redacted]	[redacted]	[redacted]	65 (32.5)
North America	[redacted]	[redacted]	[redacted]	[redacted]	119 (59.5)
Source study protocol, n (%)					
MG0009	[redacted]	[redacted]	[redacted]	[redacted]	34 (17.0)
MG0010	[redacted]	[redacted]	[redacted]	[redacted]	166 (83.0)

Abbreviations: BMI, body mass index; gMG, generalised myasthenia gravis; IVIG, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; NA, not applicable; QMG, quantitative myasthenia gravis; SCIG, subcutaneous immunoglobulin; SD, standard deviation.
†Age was calculated as: year informed consent signed – year of birth. ‡Clinicaltrials.gov age categories.
Source: RAISE-XT CSR, May 2023 data cut (48).

Table 15. Baseline disease characteristics of patients enrolled in the RAISE-XT study across treatment groups

MG0011 RAISE-XT	Placebo/ zilucoplan 0.1/0.3 mg/kg [redacted]	Placebo/ zilucoplan 0.3 mg/kg [redacted]	Zilucoplan 0.1/0.1/0.3 mg/kg [redacted]	Zilucoplan 0.3/0.3 mg/kg [redacted]	All study participants (n=200)
MGFA class at screening, n (%)					
Class II	[redacted]	[redacted]	[redacted]	[redacted]	59 (29.5)
Class III	[redacted]	[redacted]	[redacted]	[redacted]	129 (64.5)
Class IV	[redacted]	[redacted]	[redacted]	[redacted]	12 (6.0)
Age at disease onset, years					
n	[redacted]	[redacted]	[redacted]	[redacted]	199
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	43.64 (17.94)
Median	[redacted]	[redacted]	[redacted]	[redacted]	44.0
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	9.0, 73.0
Missing	[redacted]	[redacted]	[redacted]	[redacted]	1
Duration of disease, years					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	9.38 (9.73)
Median	[redacted]	[redacted]	[redacted]	[redacted]	5.70
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	0.2, 51.9
Symptoms at onset, n (%)					
Ocular	[redacted]	[redacted]	[redacted]	[redacted]	79 (39.5)
Generalised	[redacted]	[redacted]	[redacted]	[redacted]	121 (60.5)
Prior thymectomy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	96 (48.0)
Prior MG crisis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	62 (31.0)
Time since most recent crisis (months)†					
n	[redacted]	[redacted]	[redacted]	[redacted]	62
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	72.27 (97.42)
Median	[redacted]	[redacted]	[redacted]	[redacted]	29.09
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	4.1, 472.6
gMG refractory, n (%)‡§					
	[redacted]	[redacted]	[redacted]	[redacted]	85 (51.2)
Baseline MG-ADL score					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	6.3 (4.3)
Median	[redacted]	[redacted]	[redacted]	[redacted]	6.0
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	0, 20

MG0011 RAISE-XT	Placebo/ zilucoplan 0.1/0.3 mg/kg [redacted]	Placebo/ zilucoplan 0.3 mg/kg [redacted]	Zilucoplan 0.1/0.1/0.3 mg/kg [redacted]	Zilucoplan 0.3/0.3 mg/kg [redacted]	All study participants (n=200)
Baseline MG-ADL score, n (%)					
≤9	[redacted]	[redacted]	[redacted]	[redacted]	151 (75.5)
≥10	[redacted]	[redacted]	[redacted]	[redacted]	49 (24.5)
Baseline QMG score					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	14.0 (5.9)
Median	[redacted]	[redacted]	[redacted]	[redacted]	14.0
Min, max	[redacted]	[redacted]	[redacted]	[redacted]	0, 38
Baseline QMG score, n (%)					
≤17	[redacted]	[redacted]	[redacted]	[redacted]	150 (75.0)
≥18	[redacted]	[redacted]	[redacted]	[redacted]	50 (25.0)

Abbreviations: gMG, generalised myasthenia gravis; IVIG, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; NA, not applicable; QMG, quantitative myasthenia gravis; SCIG, subcutaneous immunoglobulin; SD, standard deviation.
†Time since most recent crisis (months) was calculated as: (Date of Study Day 1–Date of crisis)/(365.25/12);
‡A study participant was considered "gMG Refractory" if they met the following criteria: (1) Treatment for at ≥1 year with two or more of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, or other corticosteroids, or (2) History of treatment with at least 1 of the therapies listed in (1) for 1 year or more and required chronic plasma exchange or IVIG or SCIG at least every 3 months for the 12 months prior to enrolment. § Refractory status was not recorded for MG0009.
Source: RAISE-XT CSR, May 2023 data cut (48).

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

B.2.4.1 *Populations analysed*

B.2.4.1.1 RAISE

All 174 randomised study participants were included in the modified ITT (mITT) population, i.e., 86 patients in the zilucoplan 0.3 mg/kg treatment group and 88 patients in the placebo treatment group (Table 16).

Table 16. Analysis sets

Category, n (%)	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)	All study participants (n=174)
RS	88 (100)	86 (100)	174 (100)
mITT population†	88 (100)	86 (100)	174 (100)
[redacted]‡	[redacted]	[redacted]	[redacted]
PPS§	77 (87.5)	70 (81.4)	147 (84.5)
SS¶	88 (100)	86 (100)	174 (100)
[redacted]††	[redacted]	[redacted]	[redacted]
[redacted]‡‡	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CFS, COVID-19 free set; COVID-19, coronavirus disease 2019; IMP, investigational medicinal product; ITT, intent-to-treat; mITT, modified intent-to-treat; PD-PPS, pharmacodynamic per-protocol set; PK-PPS, pharmacokinetic -per protocol set; PPS, per-protocol set; RS, randomised set; SS, safety set.
† All randomised study participants who received at least one dose of zilucoplan and had at least 1 post-dosing MG-ADL score. ‡ Participants in the mITT population who did not have a COVID-19-related important protocol deviation, visit reported as impacted by COVID-19, or a reported COVID-19 AE. § All study participants in the mITT population who completed the 12-week treatment period and had no important protocol deviations affecting the primary efficacy endpoint. ¶ All study participants who received at least 1 dose of zilucoplan. ††All study participants in the SS who received at least 1 dose of IMP and had at least 1 quantifiable PK measurement post-dose of zilucoplan without important protocol deviations that would have affected the PK. ‡‡ All study participants in the SS who received at least one dose of IMP and had at least 1 quantifiable PD measurement post-dose of zilucoplan without important protocol deviations that would have affected the PD.

B.2.4.1.2 RAISE-XT

The intention to treat (ITT), mITT and CFS analyses were based on the randomised treatment in the parent study (i.e., MG0009 or RAISE) and the planned treatment in RAISE-XT (zilucoplan 0.3 mg/kg), and were grouped as follows:

- Placebo/zilucoplan 0.1 mg/kg/0.3 mg/kg: MG0009 study participants who received placebo in the treatment period and then zilucoplan 0.1 mg/kg in the extension period, before entering MG0011 and receiving zilucoplan 0.3 mg/kg
- Placebo/zilucoplan 0.3 mg/kg: MG0010 study participants who received placebo in the treatment period then zilucoplan 0.3 mg/kg in MG0011. The group also included MG0009 study participants who were randomised to placebo in the treatment period and then zilucoplan 0.3 mg/kg in the extension period of MG0009 and in MG0011

- Zilucoplan 0.1 mg/kg/0.1 mg/kg/0.3 mg/kg: MG0009 study participants who were randomised to zilucoplan 0.1 mg/kg in both the treatment period and extension period of MG0009, before entering MG0011 and receiving zilucoplan 0.3 mg/kg
- Zilucoplan 0.3 mg/kg/0.3 mg/kg: MG0010 study participants who were randomised to zilucoplan 0.3 mg/kg in the treatment period of MG0010 and zilucoplan 0.3 mg/kg in MG0011. The group also included MG0009 study participants who were randomised to zilucoplan 0.3 mg/kg in both the treatment period and the extension portion of MG0009 and then in MG0011
- All zilucoplan doses: all study participants in MG0011, regardless of dose in the parent study

Analysis sets are presented in Table 17.

Table 17. Analysis sets

Category, n (%)	Placebo/ zilucoplan 0.1/0.3 mg/kg (n=5)	Placebo/ zilucoplan 0.3 mg/kg (n=90)	Zilucoplan 0.1/0.1/0.3 mg/kg (n=12)	Zilucoplan 0.3/0.3 mg/kg (n=93)	All study participants (n=200)
ITT population†	[redacted]	[redacted]	[redacted]	[redacted]	200 (100)
mITT population‡	[redacted]	[redacted]	[redacted]	[redacted]	200 (100)
CFS§	[redacted]	[redacted]	[redacted]	[redacted]	111 (55.5)
SS¶	[redacted]	[redacted]	[redacted]	[redacted]	(100)

Abbreviations: AE, adverse event; CFS, COVID-19 Free Set; COVID-19, coronavirus disease 2019; ITT, Intent-to-Treat; mITT, modified Intent-to-Treat; SS, Safety Set.
†All enrolled study participants. ‡ All randomised study participants who received at least one dose of zilucoplan and had at least one postdosing MG-ADL score. §Participants in the mITT population who did not have a COVID-19-related important protocol deviation, visit reported as impacted by COVID-19, or a reported COVID-19 AE ¶All study participants who received at least one dose of zilucoplan.
RAISE-XT interim CSR, [redacted] (152).

B.2.4.2 *Statistical information*

Table 18. Summary of statistical analyses in RCTs

Trial name	RAISE	RAISE-XT
Hypothesis/ objective	To measure CFB up to Week 12 in MG-ADL score for patients with gMG receiving either zilucoplan + standard therapy or placebo + standard therapy.	Long-term safety and tolerability of zilucoplan in patients with gMG who participated in a parent zilucoplan trial (either Phase III RAISE or Phase II MG0009).
Statistical analysis	The null statistical hypothesis for the primary endpoint was that the treatment difference between zilucoplan and placebo in CFB up to Week 12 in MG-ADL score was zero. The primary efficacy endpoint was Tested at the 2-sided 0.05 significance level. The primary endpoint and ranked secondary endpoints were evaluated using a fixed-sequential testing procedure to account for multiplicity. According to this procedure, the statistical testing	AEs were recorded from the time of informed consent until study completion. In addition, AEs were classified for severity according to the CTCAE Version 5.0.

Trial name	RAISE	RAISE-XT
	of an endpoint was investigated only if the null hypothesis for the previous endpoint had been rejected (i.e. if p≤0.05).	
Sample size, power calculation	For the primary efficacy endpoint, assuming a difference in treatment group LS means of 2.3, a SD of 3.7, and 78 study participants per treatment group (156 study participants in total), the study had approximately 94% power to detect a difference between an active and placebo treatment group based on a 2-sided alpha of 0.05. This assumed rates of rescue and dropout of up to 10% and 5%, respectively.	It was anticipated that approximately 200 study participants will be enrolled in this study from the parent studies (i.e., MG0009 or MG0010). Assuming study participants remain in this study for an average of 2 years, this study would provide approximately 400 participant-years of exposure for the zilucoplan safety database.
Data management, patient withdrawals	Quality assurance and quality control systems were implemented and maintained with written SOPs to ensure that the study was conducted, data were generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Quality control was applied to each stage of data handling to ensure that all data were reliable and had been processed correctly. Study participants with missing data at the timepoint of interest were treated as non-responders. Missing data for safety, PK, and PD endpoints were not imputed; observed cases were used. If a study participant received rescue therapy, efficacy endpoints that occurred after rescue therapy were censored. When a study participant withdrew consent from the study (or study procedure), the reason(s) for withdrawal was recorded by the Investigator.	

Abbreviations: AE, adverse event; CFB, change from baseline; CTCAE, Common Terminology Criteria for Adverse Events; GCP, good clinical practice; LS, least squares; MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation; SOP, standard operating procedure.

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

Quality assessment results for the RAISE and RAISE-XT studies are described in Table 19.

Table 19. Quality assessment results for parallel group RCTs

	RAISE	RAISE-XT
Was randomisation carried out appropriately?	Yes. Study participants who met inclusion criteria were randomized in a 1:1 ratio to receive daily zilucoplan 0.3mg/kg/day or placebo. Randomisation was stratified based on the Baseline MG-ADL score (≤9 versus ≥10), QMG score (≤17 versus ≥18), and geographical region (North America, Europe, and East Asia)	N/A. As RAISE-XT was an open-label extension study, all study participants received zilucoplan 0.3mg/kg and therefore no randomisation was required. Study participants retained their unique study participant number from their parent study
Was the concealment of treatment allocation adequate?	Yes. RAISE was a double-blind, placebo-controlled study. Study participants and staff remained blinded to treatment assignments until after the data had been cleaned, locked, and unblinded	N/A. Investigators and study participants were kept blinded to their original treatment in the parent studies (MG0009/RAISE) at the time of the clinical cut-off date. However, RAISE-XT is an open-label study and all study participants received zilucoplan 0.3mg/kg
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographics were balanced across treatment arms, apart from sex, where there was a slightly higher proportion of females in the zilucoplan 0.3mg/kg treatment group (60.5%) compared with the placebo treatment group (53.4%)	Yes. The demographics of the study population was generally well-balanced between groups with respect to the key demographic variables
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. Study participants and study staff remained blinded to treatment assignments until after the data had been cleaned, locked, and unblinded	N/A. As RAISE-XT is an open-label study and all study participants received zilucoplan 0.3mg/kg
Were there any unexpected imbalances in drop-outs between groups?	No. In total, four study participants discontinued RAISE in both the zilucoplan (4.7%) and placebo (4.5%) groups	No. Discontinuation from the study was defined as discontinuing at any point during MG0011, not limited to the first 12 weeks. In total, [redacted] discontinued the study, [redacted] in the placebo/ zilucoplan 0.3mg/kg treatment group

	RAISE	RAISE-XT
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All outcomes were related to the clinical goals of gMG therapy, and safety	No. All outcomes were related to the clinical goals of gMG therapy, and safety
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. The mITT population included all randomised study participants who received at least one dose of zilucoplan and had at least 1one post-dosing MG-ADL score Study participants with missing data at the timepoint of interest were treated as non-responders. If a study participant received rescue therapy, efficacy endpoints that occurred after rescue therapy were censored	Yes. The ITT population included all enrolled study participants in MG0011. The mITT population included all enrolled study participants in MG0011 who received at least one dose of zilucoplan and had at least one post-dosing MG-ADL score. Missing data for safety, PK, and PD endpoints were not imputed; observed cases were used. This included observations occurring after a study participant received rescue therapy. Missing total scores of QMG, MG-ADL, MGC, and MG-QoL15r were not imputed. In addition, data after rescue medication were not imputed

Abbreviations: gMG, generalised myasthenia gravis; ITT, intention to treat; mITT, modified intention to treat; MG-ADL, myasthenia gravis activities of daily living; MGC, myasthenia gravis composite; MG-QoL15r, Myasthenia Gravis-Quality of Life 15r; N/A, not applicable; PD, pharmacodynamics; PK, pharmacokinetics; QMG, quantitative myasthenia gravis; RCT, randomised controlled trial.

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

B.2.6.1 *Study RAISE*

Zilucoplan as an add-on treatment to SOC for patients with gMG is associated with significant improvements in the signs and symptoms of disease activity and QoL, as measured by MG-ADL, QMG, MGC, and MG-QoL15r, with a fast onset of action. Zilucoplan may also reduce the need for CSs and the associated side effects (47), as well as the need for rescue therapy (with IVIg or PLEX).

- **RAISE**, a Phase III, randomised, placebo-controlled trial, provides pivotal clinical evidence for zilucoplan as an add-on treatment to SOC for patients with gMG.
- In the RAISE study, the primary efficacy endpoint (CFB to Week 12 in MG-ADL score) was met
    - Treatment with zilucoplan 0.3 mg/kg resulted in significantly higher CFB to Week 12 MG-ADL scores compared with placebo (−4.39 vs −2.30, respectively). This significant difference vs placebo (LS mean difference −2.09, p<0.001) was also considered clinically meaningful
    - Zilucoplan demonstrated a rapid onset of action. Treatment effect with zilucoplan 0.3 mg/kg was observed from Week 1 and increased through Week 4 with stabilisation thereafter to Week 12
    - Zilucoplan was associated with consistently greater improvements from baseline to Week 12 in QMG and MGC scores (secondary endpoints) compared with placebo, with a fast onset of action
    - A numerically lower proportion of patients receiving zilucoplan treatment (5% [n=4/86]) required rescue therapy compared with placebo (12% [n=10/88]) over the course of the RAISE study, suggesting that zilucoplan reduces the risk of exacerbation of symptoms or myasthenic crisis
- Zilucoplan displayed a favourable tolerability profile in the RAISE study, with no new or additional safety signals

Zilucoplan is the only once-daily patient administered subcutaneous injection that can be self-administered at home (releasing capacity to the NHS by avoiding visits to specialist treatment centres) and requires no new infrastructure or capital investment for its incorporation in the NHS. In addition to the clinical benefits demonstrated in RAISE, it is estimated that the availability of zilucoplan for patients with gMG is associated with both humanistic benefits for patients (related to symptom reduction and being able to receive care at home) and reduced burden to the NHS (see Section B.3 for the cost effectiveness of zilucoplan for patients with gMG).

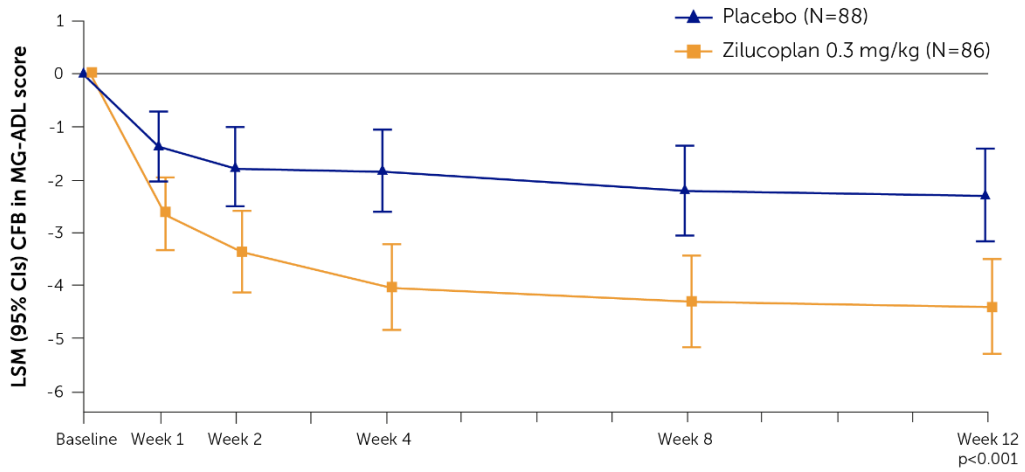
B.2.6.1.1 Primary efficacy outcome

The primary endpoint of CFB to Week 12 in MG-ADL score (higher scores indicate more severe symptoms) was met, with patients on receiving zilucoplan achieving a clinically meaningful and statistically significant reduction in MG-ADL scores vs placebo. From baseline to Week 12, patients receiving zilucoplan had a 4.39-point reduction in MG-ADL

score vs a 2.30-point reduction in the placebo group, with a least squares (LS) mean difference of −2.09 (SE: 0.58; p<0.001; 95% CI: −3.24, −0.95; mixed model repeated measure [MMRM] analysis of covariance [ANCOVA]). This 2.09 reduction is above what is commonly accepted as the clinically meaningful change threshold (2 points), indicating that zilucoplan meaningfully decreases symptom expression compared with current SoC alone and improves patients' abilities to perform daily activities.

The LS mean change from baseline through Week 12 in MG-ADL score using MMRM ANCOVA is presented in Figure 7 for the mITT population. There was a rapid onset of action in the zilucoplan 0.3 mg/kg treatment group, based on separation from placebo, in the change from Baseline in MG-ADL score using MMRM ANCOVA. This separation started at Week 1, increased through Week 4 with stabilisation thereafter, and was maintained through Week 12. At each visit after baseline, the 95% CI for the LS mean difference in MG-ADL score between the zilucoplan 0.3 mg/kg and the placebo treatment groups did not include 0. Additionally, no fluctuation of the placebo effect was observed for the change from baseline in MG-ADL score using MMRM ANCOVA.

Figure 7. LS mean change from Baseline to Week 12 in MG-ADL score (mITT population [MMRM ANCOVA])



The MG-ADL total score ranged from 0 to 24; higher score indicated more severe disability. A decrease from Baseline indicated improvement. Week 12 p-value was derived by a MMRM ANCOVA model (based on imputed data following to treatment failure) using an unstructured correlation matrix with treatment, Baseline MG-ADL score, Baseline QMG score, region (North America, Europe, and East Asia) and interactions terms treatment-by-visit and Baseline MG-ADL score-by-visit as fixed effects; study participants were added as random effects in the model.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from Baseline; CI, confidence interval; LSM, least squares mean; MG-ADL, Myasthenia Gravis Activities of Daily Living; mITT, modified intent-to-treat; MMRM, mixed model repeated measure.
Source: RAISE CSR (153).

A sensitivity analysis was performed (MMRM ANCOVA using a jump to reference [J2R] approach for the mITT Population) on the primary efficacy endpoint which supported the primary analysis, with no change to the results or conclusions from the main statistical analysis (Table 20).

The tipping point estimates using MMRM ANCOVA for change from Baseline to Week 12 in MG-ADL were shifts of 25.95 points for the zilucoplan 0.3 mg/kg treatment group and −17.26 points for the placebo treatment group.

When the primary efficacy endpoint was analysed using MMRM ANCOVA for the COVID-19 Free Set (CFS), the results supported the primary analysis. The LS mean change from Baseline to Week 12 in MG-ADL score using MMRM ANCOVA for the CFS was −4.42 in the zilucoplan 0.3 mg/kg treatment group and −2.18 in the placebo treatment group. A clinically meaningful improvement from Baseline to Week 12 in MG-ADL score using MMRM ANCOVA for the CFS was observed in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group, with an LS mean difference of −2.24 (nominal p <0.001).

Table 20. Change from Baseline to Week 12 in MG-ADL score (mITT Population [MMRM using J2R approach])

Visit and statistic	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)
Week 12		
LS mean (SE)	−2.44 (0.44)	−4.47 (0.45)
95% CI	−3.31, −1.58	−5.35, -3.59
LS mean difference (SE)†	-	−2.03 (0.58)
95% CI	-	3.16, −0.89
p-value‡	-	<0.001

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; J2R, jump to reference; LS, least squares; MG-ADL; Myasthenia Gravis Activities of Daily Living; mITT, modified Intent-to-Treat; MMRM, mixed model repeated measure; SE, standard error.
†The LS mean difference presented was zilucoplan 0.3 mg/kg minus placebo. ‡ p-value corresponded to the sensitivity analysis of the primary endpoint of change from Baseline to Week 12 in MG-ADL score.

B.2.6.1.2 Secondary efficacy outcome

Key secondary endpoints

CFB to Week 12 in the QMG score

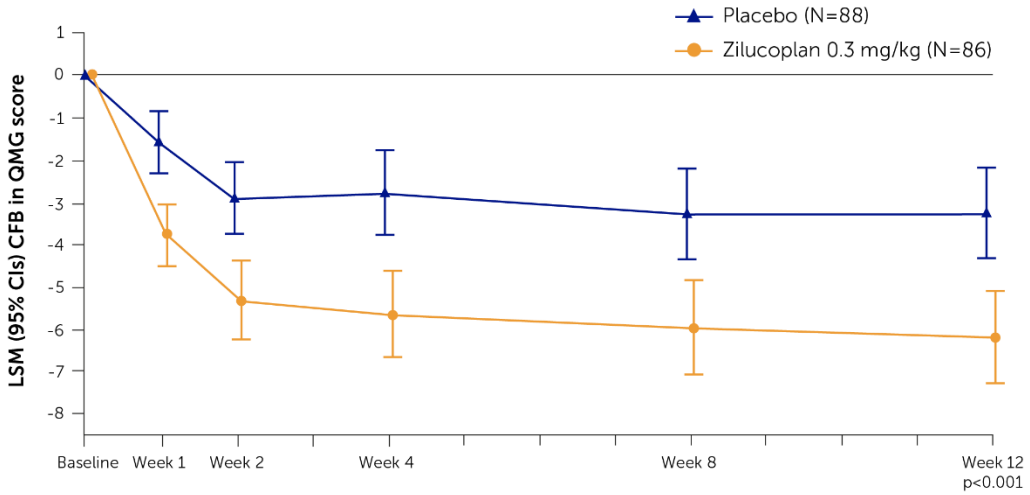
The Quantitative Myasthenia Gravis (QMG) system is a standardised and validated quantitative strength scoring system that was developed specifically for MG. Higher scores are representative of more severe impairment. A 3-point change in QMG score is considered clinically meaningful.

The secondary endpoint for the CFB in the QMG score was met in RAISE, with an improvement from Baseline to Week 12 in QMG score observed in patients treated with zilucoplan (−6.19) compared with those in the placebo treatment group (−3.25). There was a significant LS mean difference of −2.94 (SE: 0.73) compared with placebo (MMRM ANCOVA; p<0.001; 95% CI: −4.39, −1.49), which is comparable with the threshold for a clinically meaningful difference of −3.00 (Figure 8).

There was a rapid onset of action in the zilucoplan 0.3 mg/kg treatment group, based on separation from placebo, in the change from Baseline in QMG score using MMRM ANCOVA. This separation started at Week 1, increased through Week 4 with stabilisation thereafter, and was maintained through Week 12. At each visit after Baseline, the 95% CI for the LS mean difference in QMG score between the zilucoplan

0.3 mg/kg and the placebo treatment groups did not include 0. Additionally, no fluctuation of the placebo effect was observed for the change from Baseline in QMG score using MMRM ANCOVA.

Figure 8. LS mean change from Baseline to Week 12 in QMG score (mITT population [MMRM ANCOVA])



The QMG scores range from 0–39; higher scores indicate more severe disability. A decrease from Baseline indicated improvement. The Week 12 p-value was derived by a MMRM ANCOVA model (based on imputed data following to treatment failure) using an unstructured correlation matrix with treatment, Baseline MG-ADL score, Baseline QMG score, region (North America, Europe, and East Asia) and interactions terms treatment-by-visit and Baseline MG-ADL score-by-visit as fixed effects; study participants were added as random effects in the model.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CFB, change from Baseline; LSM, least squares mean; mITT, modified intent-to-treat; MMRM, mixed model repeated measure; QMG, Quantitative Myasthenia Gravis.

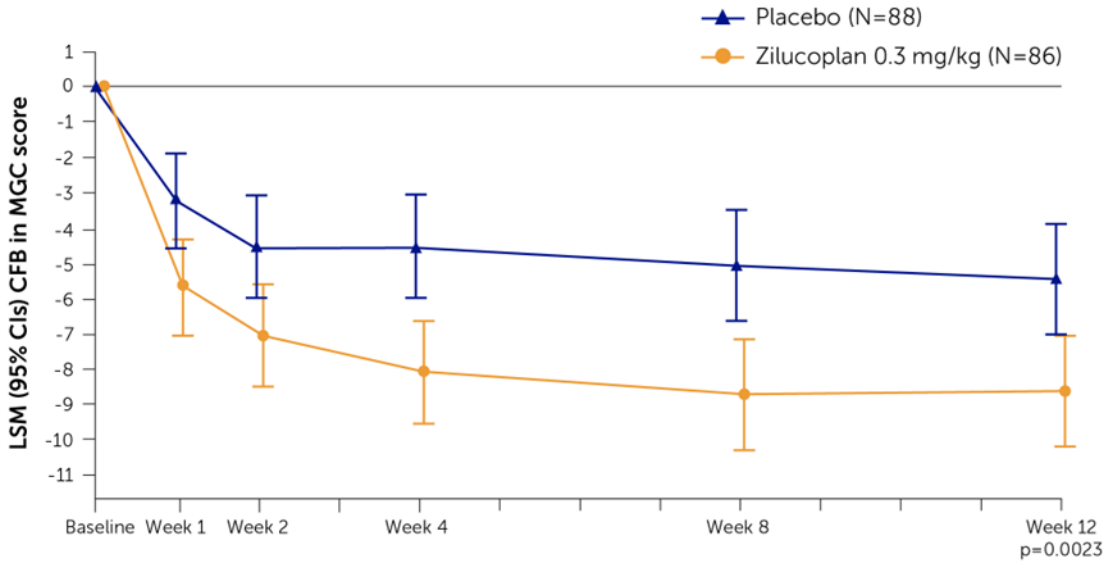
CFB to Week 12 in the MG Composite (MGC) score

The MGC is a 10-item scale that has been used to measure the clinical status of patients with MG, both in the practice setting and in clinical studies, in order to evaluate treatment response. Higher scores in the MGC indicate more severe impairment due to the disease. A 3-point change in this assessment is considered clinically meaningful.

A greater improvement was seen from Baseline to Week 12 in MGC score in the zilucoplan treatment group compared with the placebo group (MMRM ANCOVA; LS mean CFB −8.62 vs −5.42), with a statistically significant LS mean difference of −3.20 (SE: 1.03; p=0.0023; 95% CI: −5.24, −1.16), indicating clinically meaningful improvements in the severity of MG (Figure 9).

There was a rapid onset of action in the zilucoplan 0.3 mg/kg treatment group, based on separation from placebo, in the change from Baseline in MGC score using MMRM ANCOVA. This separation started at Week 1 and increased through Week 4 with stabilisation thereafter; this effect was maintained through Week 12. At each visit after Baseline, the 95% CI for the LS mean difference in MGC score between the zilucoplan 0.3 mg/kg and the placebo treatment groups did not include 0. Additionally, no fluctuation of the placebo effect was observed for the change from Baseline in MGC score using MMRM ANCOVA.

Figure 9. LS mean change from Baseline to Week 12 in MGC score (mITT population [MMRM ANCOVA])



The MGC score ranges from 0–50; higher scores indicate more severe disability. A decrease from Baseline indicated improvement. Week 12 p-value was derived by a MMRM ANCOVA model (based on imputed data following to treatment failure) using an unstructured correlation matrix with treatment, Baseline MG-ADL score, Baseline QMG score, region (North America, Europe, and East Asia) and interactions terms treatment-by-visit and Baseline MGC score-by-visit as fixed effects; study participants were added as random effects in the model.
Abbreviations: ANCOVA, analysis of covariance; CFB, change from Baseline; CI, confidence interval; LSM, least squares mean; MGC, Myasthenia Gravis Composite; mITT, modified intent-to-treat; MMRM, mixed model repeated measure; QMG, quantitative myasthenia gravis.

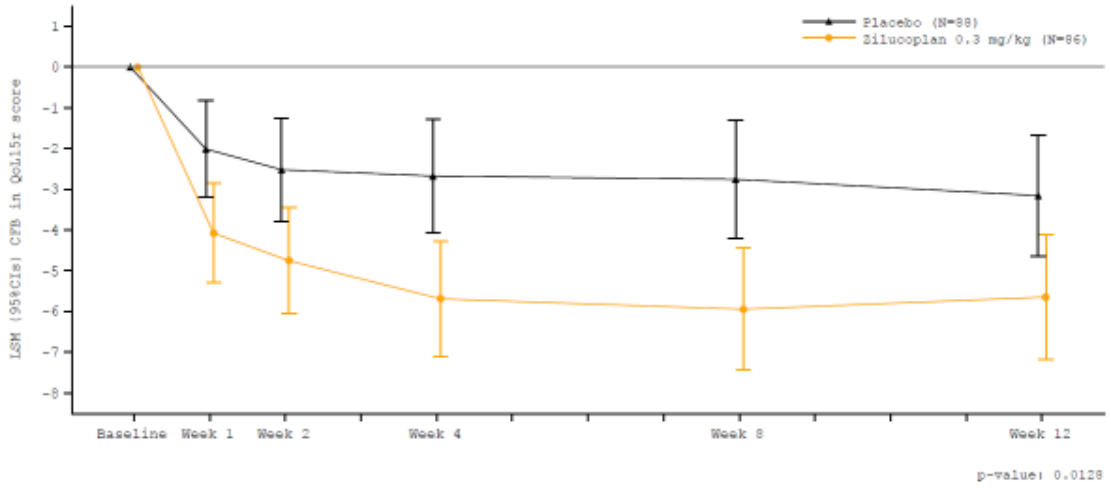
CFB to Week 12 in the MG Quality of Life 15-Item Scale (MGQoL15r) score

The MG-QoL15r is a 15-item self-administered patient-reported outcome scale that was designed to assess QoL in patients with MG. Higher scores indicate more severe impact of the disease on aspects of the patient's life. A threshold for clinical meaningfulness has not been established for MG-QoL15r score.

The LS mean change from Baseline to Week 12 in MG-QoL15r score using MMRM ANCOVA was −5.65 in the zilucoplan 0.3 mg/kg treatment group and −3.16 in the placebo treatment group. A statistically significant improvement from Baseline to Week 12 in MG-QoL15r score using MMRM ANCOVA was observed in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group, with an LS mean difference of −2.49 (p=0.0128) (Figure 10).

There was a rapid onset of action in the zilucoplan 0.3 mg/kg treatment group, based on separation from placebo, in the LS mean change from Baseline in MG-QoL15r score using MMRM ANCOVA. This separation started at Week 1 and increased through Week 4 with stabilisation thereafter; this effect was maintained through Week 12. At each visit after Baseline, the 95% CI for the LS mean difference in MG-QoL15r score between the zilucoplan 0.3 mg/kg and the placebo treatment groups did not include 0. Additionally, no fluctuation of the placebo effect was observed for the change from Baseline in MG-QoL15r score using MMRM ANCOVA.

Figure 10. LS Mean change from Baseline to Week 12 in MG-QoL15r score (mITT population [MMRM ANCOVA])



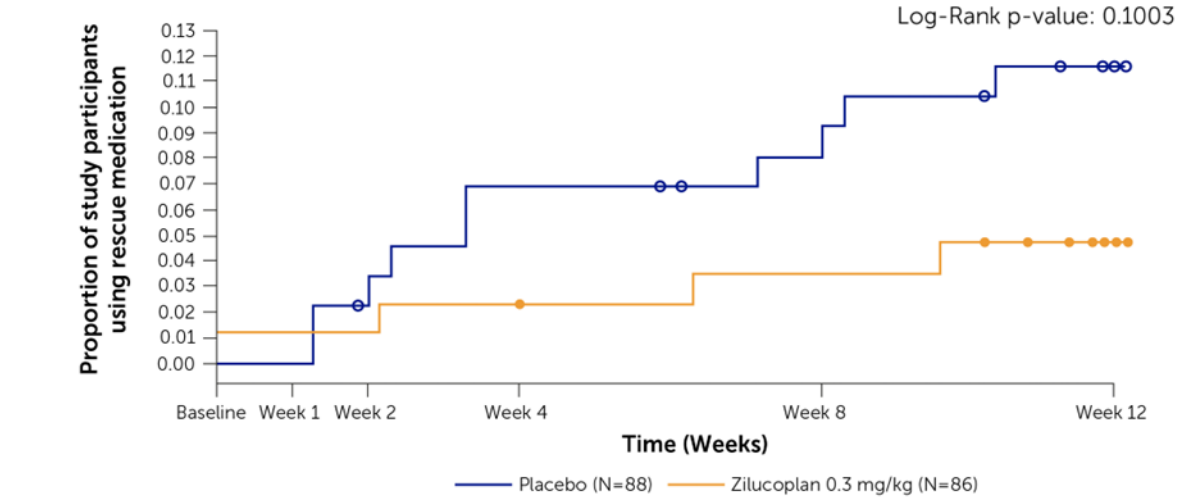
The MG-QoL15r score ranged from 0 to 30; higher score indicated more severe impact on study participants' quality of life. A decrease from Baseline indicated improvement.
Week 12 p-value was derived by a MMRM ANCOVA model (based on imputed data following to treatment failure) using an unstructured correlation matrix with treatment, Baseline MG-ADL score, Baseline QMG score, region (North America, Europe, and East Asia) and interactions terms treatment-by-visit and Baseline QMG score-by-visit as fixed effects; study participants were added as random effects in the model.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CFB, change from Baseline; LSM, least squares mean; MG-QoL15r, Myasthenia Gravis-Quality of Life 15r; mITT, modified Intent-to-Treat; MMRM, mixed model repeated measure.

Other secondary efficacy outcomes

Time to receipt of rescue therapy over 12-week treatment period

A numerically lower proportion of patients receiving zilucoplan treatment required rescue therapy compared with placebo over the course of the RAISE study (Figure 11). At Week 12, the cumulative proportion of patients requiring rescue therapy was only 5% (n=4/86) in the zilucoplan treatment group, compared with 12% (n=10/88) in the placebo group. This difference favoured zilucoplan numerically (time to event model; p=0.1003). The numerical improvement with zilucoplan was first observed by Week 2, and this separation between zilucoplan and placebo in the need for rescue therapy was maintained through Week 12.

Figure 11. Kaplan-Meier plot of time to receipt of rescue therapy



Number of Participants at Risk:

Zilucoplan 0.3mg/kg:	86	85	85	83	82	66
Placebo:	88	88	84	81	77	59

Time to receipt of rescue therapy over the 12-week Treatment Period (in days) was defined as: date of first rescue therapy use – date of first IMP + 1. Circles represent censored study participants. If a patient received rescue therapy, efficacy endpoints that occurred after rescue therapy were censored and treated as missing data for the primary efficacy analysis.
Abbreviations: IMP, investigational medicinal product; mITT, modified Intent-to-Treat.

Proportion of patients achieving minimal symptom expression (MSE) at Week 12, defined as MG-ADL of 0 or 1 without rescue therapy

A numerically greater proportion of patients treated with zilucoplan in RAISE achieved MSE, defined as an MG-ADL score of 0 or 1, compared with those treated with placebo at each timepoint over the duration of the study. These patients became free, or nearly free of their MG symptoms. In the main analysis using logistic regression (mITT population), at Week 12, 14.0% of those treated with zilucoplan became free or nearly free of MG symptoms, compared with 5.8% of patients treated with placebo (p=0.0885; OR: 2.608; 95% CI: 0.866, 7.860).

Proportion of patients achieving a ≥3 point reduction in MG-ADL score at Week 12 without rescue therapy

Zilucoplan met the MG-ADL responder rate secondary endpoint within RAISE. A significantly greater proportion of patients in the zilucoplan treatment group were MG-ADL responders (demonstrating a ≥3-point improvement [1 point more than minimal clinically important difference [MCID]) at Week 12 without rescue therapy, compared with placebo. In the main analysis using logistic regression (mITT population), 73.1% of those in the zilucoplan treatment group vs 46.1% in the placebo group were MG-ADL responders at Week 12 (p<0.001; 95% CI: 1.662, 6.101; OR: 3.184). At all time points, the zilucoplan treatment group had a numerically greater proportion of MG-ADL responders.

Proportion of patients achieving a ≥5 point reduction in QMG score at Week 12 without rescue therapy

There was a significant difference in the proportion of patients that were QMG responders, defined as ≥5-point improvement (MCID is 3 points), in the zilucoplan group compared with the placebo treatment group (logistic regression [mITT]: 58.0% vs 33.0%, respectively; p=0.0012; OR: 2.87; 95% CI: 1.518, 5.409).

B.2.6.1.3 Exploratory endpoints

Minimal Manifestation Status per Myasthenia Gravis Foundation of America Post -Intervention Status

The Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) is designed to assess the clinical state of patients with gMG after they have received treatment. MGFA-PIS was an exploratory endpoint in RAISE. At Week 12, the proportions of study participants with MGFA-PIS of pharmacological remission (PR) and minimal manifestation status (MMS) were slightly higher in the zilucoplan 0.3 mg/kg treatment group (2.6% and 28.2%, respectively) compared with the placebo treatment group (0.0% and 19.3%, respectively), as shown in Table 21.

Table 21. Patient status according to MGFA-PIS at Week 12

Response	Placebo, n=88 (n=83 at 12 Weeks)	Zilucoplan 0.3 mg/kg, n=86 (n=78 at 12 Weeks)
MGFA-PIS (n, %)		
PR†	[redacted]	[redacted]
MMS‡	[redacted]	[redacted]
Neither	[redacted]	[redacted]
Change in status as compared with baseline (n, %)		
Improved	[redacted]	[redacted]
Unchanged	[redacted]	[redacted]
Worse	[redacted]	[redacted]
Exacerbation	[redacted]	[redacted]
Died of MG	[redacted]	[redacted]

†Pharmacologic Remission: Participant has no symptoms or signs of MG since previous visit and continues to take therapy for MG. Participants taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness. ‡Minimal manifestation: Participant has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognises that some participants who otherwise meet the definition of Pharmacologic Remission do have weakness that is only detectable by careful examination.
Abbreviations: MG: myasthenia gravis; MGFA-PIS: Myasthenia Gravis Foundation of America Post-Intervention Status; MMS: Minimal Manifestation Status; PR: Pharmacological Remission.

CFB to Week 12 in Work Productivity and Activity Impairment Questionnaire

The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) assesses absenteeism and presenteeism associated with health conditions; higher scores indicate a greater impairment in work activity, and reduced productivity. The endpoints of the survey are converted to and expressed as impairment percentages, where higher numbers indicate a greater impairment and reduced productivity.

The mean WPAI-SHP scores were generally similar between treatment groups at Baseline. At Week 12, no difference in WPAI:SHP scores based on LS mean difference was observed between the zilucoplan 0.3 mg/kg treatment group and the placebo treatment group for proportion of time missed to problem (−3.30; 95% CI: −17.94, 11.35), proportion of impairment while working due to problem (−11.89; 95% CI: −25.81, 2.03), proportion of overall work impairment due to problem (−12.83; 95% CI: −27.80, 2.14), and proportion of activity impairment due to problem (−2.13; 95% CI: −13.95, 9.68).

CFB to Week 12 in EQ-5D-5L

At Week 12, the proportion of study participants the zilucoplan 0.3 mg/kg and placebo treatment groups who reported no problems for the following EQ-5D-5L response dimensions were as follows: mobility (36.6% and 32.5%, respectively) self-care (50.0% and 42.2%, respectively), usual activities (30.5% and 19.3%, respectively), pain/discomfort (35.4% and 36.1%, respectively), and anxiety/depression (47.6% and 37.3%, respectively).

For the EQ-5D-5L visual analogue scale (VAS), an increase in score indicates improvement. The mean Baseline EQ-5D-5L VAS scores were similar in the zilucoplan 0.3 mg/kg (57.4) and placebo (52.9) treatment groups. Consistently greater mean increases from Baseline in EQ-5D-5L VAS score were observed in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group as early as Week 1 (7.49 vs 5.70, respectively) and were maintained through Week 12 (8.97 vs 5.81, respectively).

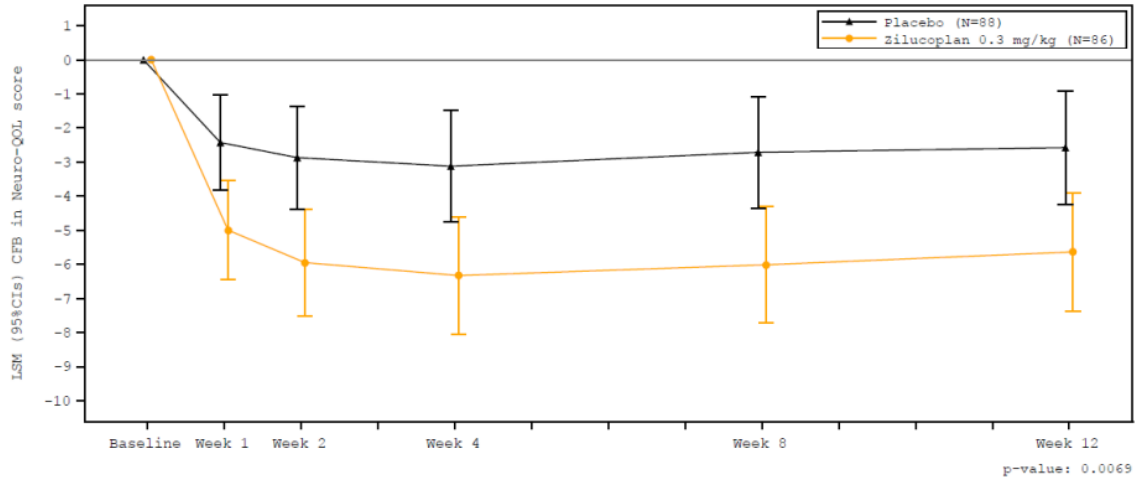
CFB in Neuro-QoL Short Form Fatigue score

The LS mean change from Baseline over time in Neuro-QoL Short Form fatigue scale is presented for the mITT Population in Figure 12.

For the Neuro-QoL Short Form fatigue scale, higher scores indicate a greater level of fatigue. There was a rapid onset of action in the zilucoplan 0.3 mg/kg treatment group, based on separation from placebo, in the LS mean change from Baseline in Neuro-QoL Short Form fatigue scale using MMRM ANCOVA. This separation started at Week 1 and increased through Week 4 with stabilisation thereafter; this effect was maintained through Week 12. Additionally, no fluctuation of the placebo effect was observed for the LS mean change from Baseline in Neuro-QOL Short Form fatigue scale using MMRM ANCOVA. Consistently greater LS mean decreases from Baseline in Neuro-QOL Short Form fatigue scale scores were observed in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group as early as Week 1 (−5.00 vs −2.43, respectively) and were maintained through Week 12 (−5.64 vs −2.57, respectively). At Week 12, the LS mean difference between the zilucoplan 0.3 mg/kg and placebo treatment groups numerically favoured zilucoplan, (−3.06 [nominal p=0.0069]).

At RAISE baseline, the fatigue severity of most patients was moderate or severe (n=66 [78.6%]), whilst at Week 60 (RAISE-XT), most patients had mild or no fatigue (n=55 [65.5%], demonstrating meaningful improvements in fatigue severity (see Section B.2.6.2.4) (154).

Figure 12. Change from Baseline to Week 12 Neuro-QoL Short Form fatigue scale (mITT population)



Abbreviations: CFB, change from Baseline; CI, confidence interval; LSM, least squares mean; mITT, modified Intent-to-Treat; Neuro-QOL, Quality of Life in Neurological Disorders.

Change from Baseline in Subscores

The changes from baseline to Week 12 in MG-ADL, QMG, and MGC subscores for the mITT population presented show high variability within subscores. Due to this variability, median values are presented below to show the overall trends within the subscores. Mean values are presented in Table 22.

The ocular, bulbar, respiratory and limb/axial subscores for the zilucoplan 0.3 mg/kg treatment group showed greater median reductions (improvements) from Baseline to Week 12 compared with placebo across the MG-ADL, QMG and MGC assessments:

- For the ocular subscore, treatment with zilucoplan 0.3mg/kg demonstrated a greater median change from Baseline to Week 12 improvement compared with placebo across the MG-ADL, QMG, and MGC assessments (for MG-QoL15r, median change from Baseline for the ocular subscore was 0.00 at Week 12 for both treatment groups):
    - MG-ADL: -1.00 vs 0.00, respectively
    - QMG: -2.00 vs -1.00, respectively
    - MGC: -2.00 vs -1.00, respectively
- For the bulbar subscore, treatment with zilucoplan 0.3mg/kg demonstrated a greater median change from Baseline to Week 12 improvement compared with placebo across the MG-ADL, MG-QoL15r, and MGC assessments (for QMG, the median change from Baseline to Week 12 for the bulbar subscore was -1.00 for both treatment groups; however, the placebo treatment group only reached this level at Week 12):
    - MG-ADL: -2.00 vs -1.00, respectively
    - MGC: -2.00 vs -1.00, respectively
    - MG-QoL15r: -1.00 vs 0.00, respectively

- For the limb/axial subscore, treatment with zilucoplan 0.3mg/kg demonstrated a greater median change from Baseline to Week 12 improvement compared with placebo across the MG-ADL, QMG, and MGC assessments (for MG-QoL15r, the median change from Baseline for the limb/axial subscore was 0.00 at Week 12 for both treatment groups):
    - MG-ADL: -1.00 vs 0.00, respectively
    - QMG: -3.00 vs -1.00, respectively
    - MGC: -2.00 vs -1.00, respectively

For the respiratory subscore across the MG-ADL, QMG, and MGC assessments, the median change from Baseline to Week 12 was 0.00 for both the zilucoplan 0.3mg/kg and placebo treatment groups. The MG-QoL15r does not include a respiratory subscore.

Mean change from baseline to Week 12 for MG-ADL, QMG, and MGC is presented in Table 22. Mean change from baseline to Week 12 in MG-QoL15r sub scores (ocular, bulbar, limb/axial) are presented for the mITT population in Table 23.

Table 22. Changes from Baseline to Week 12 in MG-ADL, QMG, and MGC subscores

Change from Baseline to Week 12, mean (min, max)						
Item	**MG-ADL†**		**QMG‡**		**MGC§**	
	Placebo (n=88)	**Zilucoplan (n=86)**	**Placebo (n=88)**	**Zilucoplan (n=86)**	**Placebo (n=88)**	**Zilucoplan (n=86)**
Ocular subscore	−0.84 (−5.0, 3.0)	−1.44 (−6.0, 3.0)	−1.24 (−9.0, 3.0)	−1.98 (−7.0, 2.0)	−1.37 (−10.0, 3.0)	−2.16 (−8.0, 2.0)
Bulbar subscore	−1.08 (−6.0, 3.0)	−1.77 (−6.0, 3.0)	−0.86 (−4.0, 3.0)	−1.23 (−5.0, 2.0)	−1.08 (−6.0, 3.0)	−1.77 (−6.0, 3.0)
Respiratory subscore	−0.22 (−2.0, 1.0)	−0.33 (−2.0, 1.0)	−0.11 (−2.0, 2.0)	−0.24 (−3.0, 1.0)	−0.23 (−2.0, 1.0)	−0.28 (−1.0, 1.0)
Limb/axial subscore	−0.71 (−5.0, 2.0)	−1.15 (−4.0, 2.0)	−1.21 (−10.0, 3.0)	−2.87 (−9.0, 3.0)	−1.55 (−5.0, 2.0)	−1.83 (−6.0, 4.0)

†Functions are grouped as follows: Ocular (double vision and eyelid droop); Bulbar (talking, chewing, and swallowing); Respiratory (breathing); and Limb/Axial (impairment of ability to brush teeth or comb hair and impairment of ability to arise from a chair).
‡Functions are grouped as follows: Ocular (double vision, ptosis, and facial muscle); Bulbar (swallowing and speech following counting aloud from 1–50); Respiratory (forced vital capacity); and Limb/Axial (right arm outstretched, left arm outstretched, right hand grip, left hand grip, head, lifted, right leg outstretched, and left leg outstretched).
§Functions are grouped as follows: Ocular (ptosis, double vision, and eye closure); Bulbar (talking, chewing, and swallowing); Respiratory (breathing); and Limb/Axial (neck flexion or extension, shoulder abduction, and hip flexion).
Abbreviations: MG-ADL, Myasthenia Gravis-Activities of Daily Living; MGC, Myasthenia Gravis Composite; QMG, Quantitative Myasthenia Gravis.

Table 23. Changes from RAISE Baseline to Week 12 in MG-QoL15r sub scores

Item	Change from Baseline to Week 12, mean (min, max)	
	Placebo (n=88)	Zilucoplan (n=86)
Ocular sub score	−0.30 (−2.0, 1.0)	−0.44 (−2.0, 1.0)
Bulbar sub score	−0.55 (−3.0, 2.0)	−0.90 (−4.0, 3.0)
Limb/axial sub score	−0.31 (−4.0, 2.0)	−0.73 (−4.0, 2.0)

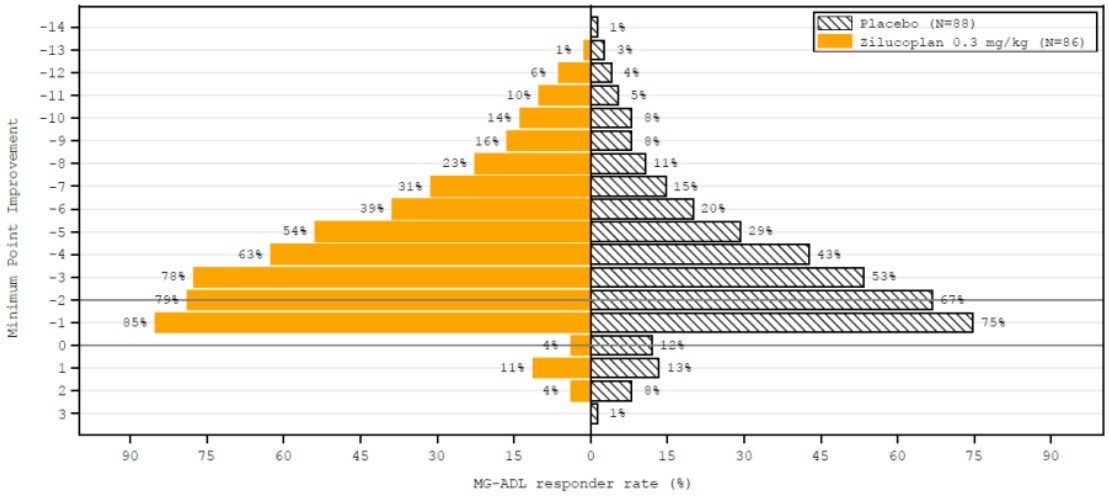
Functions are grouped as follows: Ocular (I have trouble using my eyes because of my myasthenia gravis); Bulbar (I have trouble eating because of my myasthenia gravis and I have difficulty speaking due to my myasthenia gravis); and Limb/Axial (I have trouble walking due to my myasthenia gravis and I have trouble performing my personal grooming needs because of myasthenia gravis).
Abbreviations: MG-QoL15r: Myasthenia Gravis Quality of Life 15 Item Scale-Revised; max: maximum; min: minimum.

Responder analyses for changes from baseline without rescue therapy (mITT population)

MG-ADL score

At Week 12, the proportion of participants who showed an improvement in MG-ADL score without rescue therapy was higher in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group across the minimum improvement thresholds of −1 to −12 (Figure 13).

Figure 13. Responder analysis for changes in MG-ADL at Week 12 (mITT)



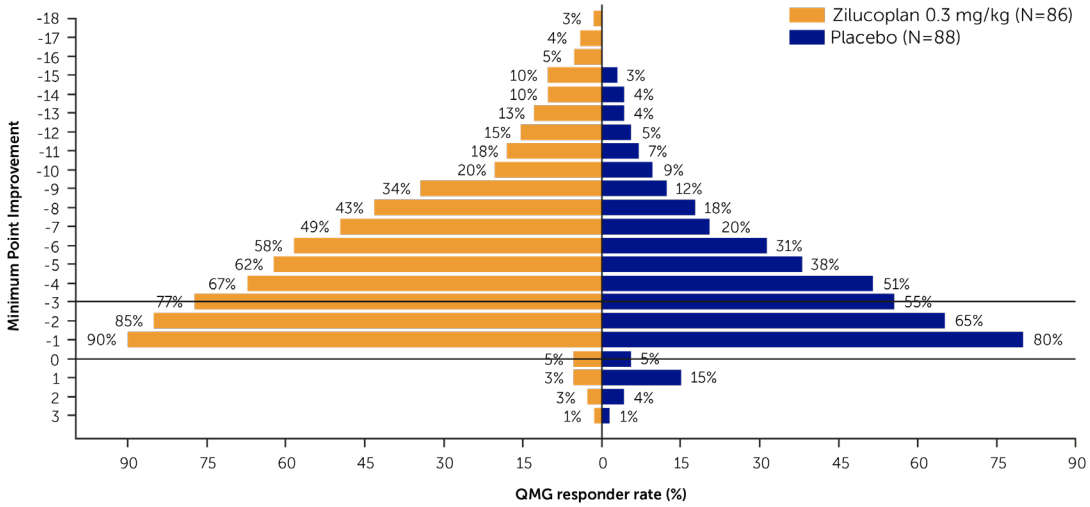
Abbreviations: mITT, modified Intent-to-Treat; MG-ADL, Myasthenia Gravis-Activities of Daily Living.

The median time to a 2-point improvement in MG-ADL response was numerically shorter in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group (9.0 days [95% CI: 8, 15] vs 14.0 days [95% CI: 9, 15], nominal p=0.1354). When evaluated for a 3-point improvement in MG-ADL, the median time was shorter in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group (15.0 days [95% CI: 9, 18] vs 29.0 days [95% CI: 15, 57], nominal p=0.0012).

QMG score

At Week 12, the proportion of participants who showed an improvement in QMG score without rescue therapy was overall higher in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group across the minimum improvement thresholds of −1 to −18 (Figure 14).

Figure 14. Responder analysis for change in QMG score at Week 12 (mITT)



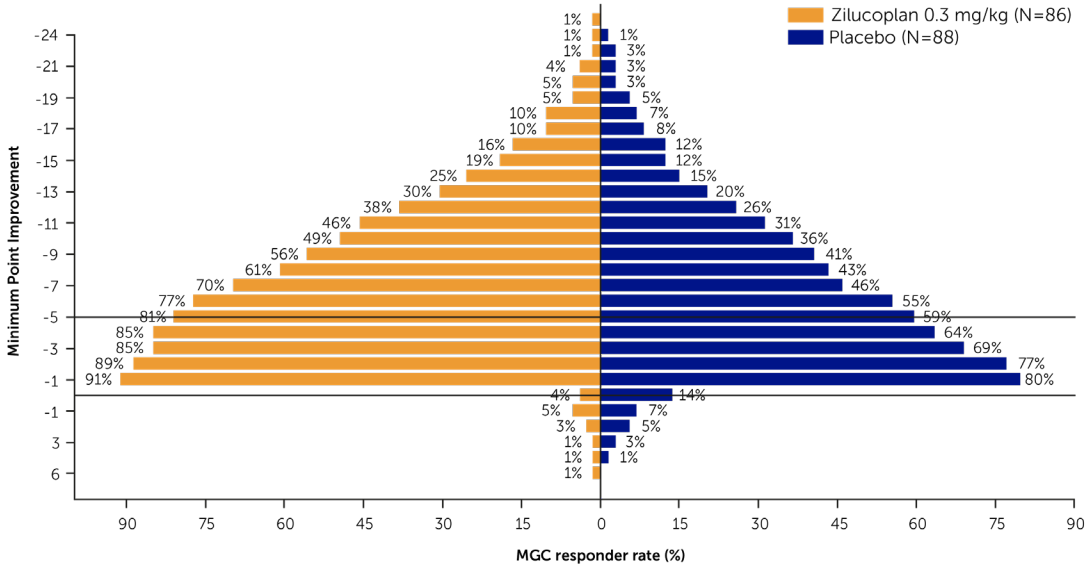
Participants who received rescue medication are classified as non-responders after the first rescue medication administration.
Abbreviations: mITT, modified intent-to-treat; QMG, Quantitative Myasthenia Gravis.

The median time to a 3-point improvement in QMG score was shorter in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group (9.0 days [95% CI: 8, 15] vs 16.0 days [95% CI: 15, 55], nominal p=0.0031). This trend was also in favour of the zilucoplan 0.3 mg/kg treatment group for a 5-point improvement in QMG score (16.0 days [95% CI: 15, 29] vs 86.0 days [95% CI: 57, not calculated], nominal p<0.001).

MGC score

At Week 12, the proportion of participants who showed an improvement in MGC score without rescue therapy was higher in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group across the minimum improvement thresholds of −1 to −18 and from −25 to −30 (Figure 15). The proportions between improvement thresholds of −19 to −24 were similar between the treatment groups and involved 1 to 4 study participants per treatment group.

Figure 15. Responder analysis for changes in MGC at Week 12 (mITT)

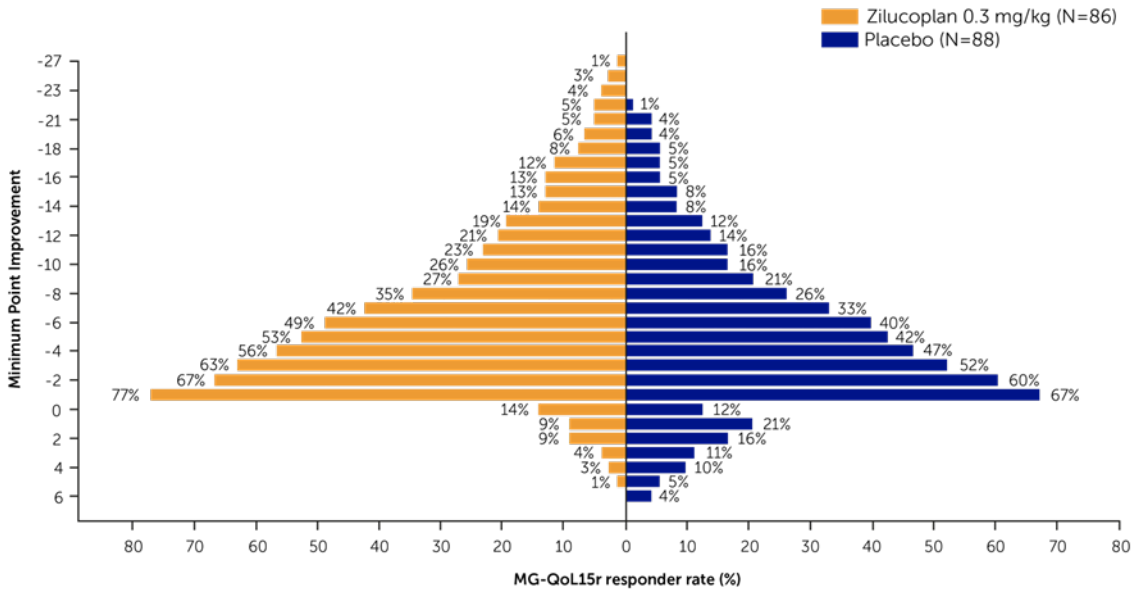


Higher MGC scores indicate more severe impairment due to gMG.
Abbreviations: MGC, Myasthenia Gravis Composite; mITT, modified intent-to-treat.

MG-QoL15r

A greater proportion of patients treated with 0.3mg/kg zilucoplan showed an improvement in MG-QoL15r (without rescue therapy) at Week 12, compared with those in the placebo group, regardless of the minimum improvement threshold applied (ranging from improvements of −1 to −27) (Figure 16).

Figure 16. Responder analysis for change in MG-QoLr score at Week 12 (mITT population)



The total MG-QoLr score ranges from 0–30, with higher scores showing more severe impact on the patient's QoL. A decrease from Baseline indicates improvement. Baseline is defined as last available value prior to the first injection of IMP in the Treatment Period, or if missing, the Screening value. Percentages are based on the number of participants with available information at the corresponding time point. Data collected after a participant has used rescue therapy are censored and treated as missing.

Abbreviations: IMP, investigational medicinal product; MG-QoL15R, Myasthenia Gravis Quality of Life 15 Item Scale–Revised; mITT, modified intent-to-treat; QoL, quality of life.

B.2.6.1.4 Efficacy conclusions for RAISE

The results of RAISE demonstrate that zilucoplan is associated with consistently greater improvements from baseline to Week 12 in MG-ADL, QMG and MGC scores (primary and secondary endpoints) compared with placebo, with a fast onset of action.

In addition, a numerically lower proportion of patients receiving zilucoplan treatment required rescue therapy compared with placebo over the course of the RAISE study, suggesting that zilucoplan reduces the risk of exacerbation of symptoms or myasthenic crisis. At Week 12, the cumulative proportion of patients requiring rescue therapy was only 5% (n=4/86) in the zilucoplan treatment group, compared with 12% (n=10/88) in the placebo group.

Zilucoplan is a once-daily subcutaneous injection that can be self-administered at home (releasing capacity to the NHS by avoiding visits to specialist treatment centres) and requires no new infrastructure or capital investment for its incorporation in the NHS. In addition to the clinical benefits demonstrated in RAISE, it is estimated that the availability of zilucoplan for patients with gMG is associated with both humanistic benefits for patients (related to symptom reduction and being able to receive care at home – please see Section B.2.6.2.3 for data on patients' positive experience and satisfaction with self-injection) and reduced burden to the NHS (see Section B.3 for the cost effectiveness of zilucoplan for patients with gMG).

Primary endpoint

- Treatment with zilucoplan 0.3 mg/kg resulted in significant reductions in CFB to Week 12 MG-ADL scores compared with placebo (−4.39 vs −2.30, respectively). This difference was considered clinically meaningful, with a significant LS mean difference of −2.09 ($p<0.001$)
- Zilucoplan demonstrated a rapid onset of action. Treatment effect with zilucoplan 0.3 mg/kg was observed from Week 1 and increased through Week 4 with stabilisation thereafter to Week 12

Key secondary endpoints

- The zilucoplan 0.3 mg/kg treatment group had significant reductions compared with the placebo treatment group for the secondary efficacy endpoints of improvement from Baseline to Week 12 in QMG score (LS mean difference of −2.94 [$p<0.001$]), MGC score (LS mean difference of −3.20 [$p=0.0023$]), and MG-QoL15r score (LS mean difference of −2.49 [$p=0.0128$])
- For QMG, MGC, and MG-QoL15r, zilucoplan 0.3 mg/kg had a rapid onset of action, with treatment effect observed from Week 1 which increased through Week 4 with stabilisation thereafter; this effect was maintained through Week 12, with a similar pattern as for MG-ADL

Other secondary endpoints

- The cumulative proportion of study participants receiving rescue therapy by Week 12 was lower in the zilucoplan 0.3 mg/kg treatment group (Day 84: 4 study participants [5%]) compared with the placebo treatment group (Day 84: 10 study participants [12%] p=0.1003)
- The percentage of study participants achieving MSE at Week 12 was higher in the zilucoplan 0.3 mg/kg treatment group (14.0%) compared with the placebo treatment group (5.8%) (p=0.0885)

Exploratory endpoint

- The proportions of study participants with MGFA-PIS of PR and minimal manifestations were higher in the zilucoplan 0.3 mg/kg treatment group (2.6% and 28.2%, respectively) compared with the placebo treatment group (0% and 19.3%, respectively)
- Consistently greater LS mean reductions from baseline in Neuro-QOL Short Form fatigue scale scores were observed in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group as early as Week 1 (−5.00 vs −2.43, respectively) that continued through Week 12 (−5.64 vs −2.57, respectively). At Week 12, the LS mean difference between the zilucoplan 0.3 mg/kg and placebo treatment groups favoured zilucoplan (−3.06 [nominal p=0.0069])
- At Week 12, the proportion of study participants who showed an improvement in MG-ADL, QMG, MG-QOL15, and MGC scores without rescue therapy was higher in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group. For MG-ADL and QMG, the median time to a clinically meaningful response (2-point and 3-point improvements from Baseline, respectively) was shorter in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group; time to response was shorter in the zilucoplan 0.3 mg/kg treatment group for a 3-point improvement in MG-ADL score (15.0 days [nominal p=0.0012]) and for 3-point and 5-point improvements in QMG score (9.0 days [nominal p=0.0031] and 16.0 days [nominal p<0.001, respectively])

Overall, zilucoplan demonstrated clinically meaningful and significant improvements for the primary efficacy endpoint and key secondary endpoints. When the primary and secondary efficacy endpoints were analysed using additional analysis sets, alternative missing data assumptions, and additional analysis methods, all results were consistent with the main primary and secondary efficacy analyses. These results suggest that zilucoplan delivers improved clinical outcomes compared with current standard of care.

B.2.6.2 *Study RAISE-XT*

B.2.6.2.1 Primary outcome

The primary endpoint was the long-term safety and tolerability of zilucoplan in patients with gMG who participated in a parent zilucoplan trial (either Phase III RAISE or Phase II MG0009). The incidence of TEAEs was evaluated and the results are detailed in Section B.2.10.1.2. The safety profile of zilucoplan within RAISE-XT was consistent with findings from the RAISE study, demonstrating favourable long-term safety and tolerability.

B.2.6.2.2 Secondary efficacy outcome

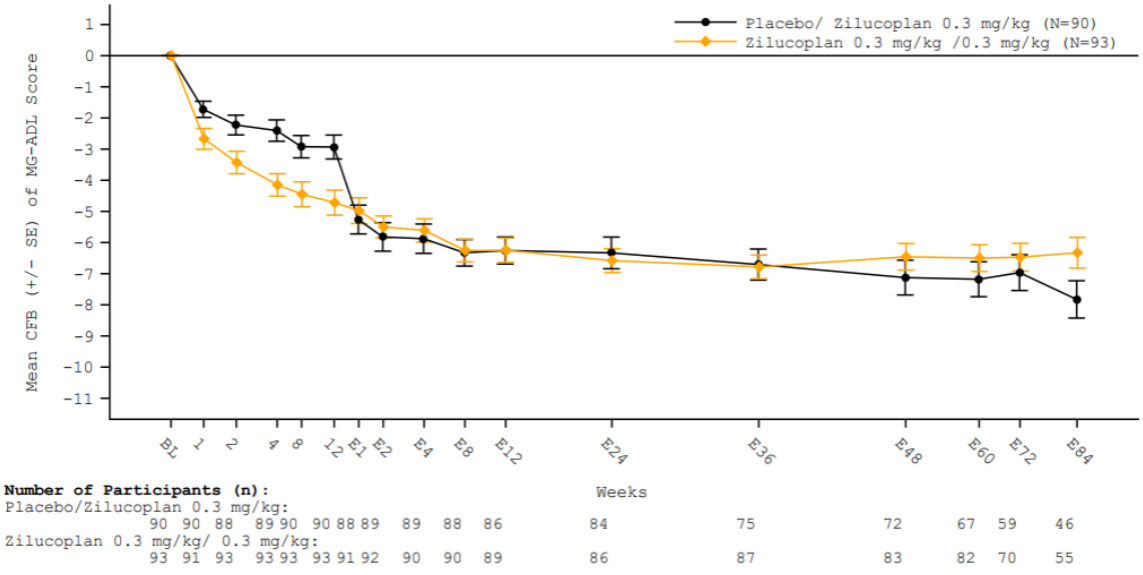
Secondary efficacy endpoints included CFB to Week 12 in MG-ADL, QMG, MGC, MG-QoL15r score, and the use of rescue therapy.

CFB to Week E84 in MG-ADL

At Week extension (E)12 (24 weeks total treatment), patients in the zilucoplan 0.3/zilucoplan 0.3 mg/kg group (received zilucoplan in both the parent study and in RAISE-XT) experienced a mean reduction (SD) in MG-ADL score from parent study baseline of [redacted] which was sustained up to Week E84 (96 weeks total). In the placebo/zilucoplan 0.3 mg/kg group (received placebo in the parent study and zilucoplan in RAISE-XT), patients experienced a mean (SD) CFB in MG-ADL score from parent study of [redacted] at Week E12. MG-ADL scores improved at Week E1 after the first week of zilucoplan dosing. This improvement in MG-ADL score continued up to Week E12 [redacted] and was sustained up to Week E84 (Figure 17) (155).

In the zilucoplan 0.3/zilucoplan 0.3 mg/kg, the LS mean difference between Week 12 of RAISE and Week E12 of RAISE-XT was [redacted] In comparison, the LS mean difference between Week 12 and Week E12 in the placebo/zilucoplan 0.3 mg/kg group was [redacted]

Figure 17: Change from parent study Baseline to RAISE-XT in MG-ADL score to Week E84 (mITT population)



The double-blind portion of the study refers to pooled data from the Phase II study and RAISE.
The MG-ADL total score ranges from 0–24, with a higher score indicating more severe symptoms of gMG. A

decrease from baseline indicates improvement. Baseline was defined as the last available assessment before first administration in the ‘parent study’ (RAISE).
Abbreviations: BL, baseline; CFB, change from baseline; E, extension; MG-ADL, myasthenia gravis activities of daily living; mITT, modified intent-to-treat; OLE, open-label extension; SE, standard error.
Source: RAISE-XT TFL, May 2023 data cut (155).

CFB to Week E84 in QMG score

In RAISE-XT, patients experienced a sustained reduction in QMG score vs parent study baseline at Week E12 (~8 points in both treatment arms), indicating zilucoplan sustained efficacy in reducing MG disease severity and improving signs of muscle weakness among patients.

The mean (SD) CFB in QMG score from parent study in the zilucoplan 0.3/zilucoplan 0.3 mg/kg group decreased from Week E1 [redacted] to Week E12 [redacted] and was maintained up to Week E84. In the placebo/zilucoplan 0.3 mg/kg group, the mean (SD) CFB decreased rapidly from Week 12 (−3.51 [4.11]) to Week E1 [redacted] once zilucoplan dosing was initiated; improvements continued to Week E12 [redacted] and Week E84 (Figure 18) (155).

Compared with Week 12 of the parent study, the LS mean (95% CI) change at Week E12 in the zilucoplan 0.3/zilucoplan 0.3 mg/kg and placebo/zilucoplan 0.3 mg/kg groups were [redacted] respectively, showing the continued benefit of zilucoplan treatment.

Figure 18: Change from parent study Baseline to RAISE-XT in QMG score to Week E84 (mITT population)

The total score was the sum of the individual scores (ranged 0–39) with a higher score indicating more severe disability. Baseline was defined as the last available assessment before first administration in the 'double-blind study' or ‘RAISE study'. A decrease from baseline indicates improvement.
Abbreviations: BL, baseline; CFB, change from baseline; E, extension; mITT, modified intent-to-treat; OLE, open-label extension; QMG, quantitative myasthenia gravis; SE, standard error.
Source: RAISE-XT TFL, [redacted] (155).

CFB to Week E84 in MGC score

In RAISE-XT, patients experienced a sustained improvement in MGC score through Week E84, indicating zilucoplan efficacy in reducing MG disease severity and reducing the impact of MG on patient QoL and daily activities.

The zilucoplan 0.3/zilucoplan 0.3 mg/kg group experienced a mean (SD) CFB in MGC score of [redacted] at Week E1, with a further decrease through Week E12 [redacted] which was maintained through Week. Similarly, the mean (SD) CFB in the placebo/zilucoplan 0.3 mg/kg group decreased from Week 12 (−6.73 [6.44]) to Week E1 [redacted], once zilucoplan dosing was initiated, and continued to decrease up to Week E12 [redacted]. The reduction in score was maintained up to Week E84 (Figure 19) (155).

Figure 19: Change from parent study Baseline to RAISE-XT in MGC score to Week E84 (mITT population)

The total score is the sum of the ten individual scores (ranged 0–50) with a higher score indicating more severe disability. A decrease from baseline indicates improvement. Baseline was defined as the last available assessment before first administration in the 'double-blind study' or ‘RAISE study’.
Abbreviations: BL, baseline; CFB, change from baseline; E, extension; MGC, myasthenia gravis composite; mITT, modified intent-to-treat; OLE, open-label extension; SE, standard error.
Source: RAISE-XT TFL, [redacted].(155).

CFB to Week E84 in MG-QoL15r score

Patients receiving zilucoplan in the RAISE-XT study experience sustained improvements in QoL, based on the disease-specific instrument MQ-QoL15r.

In the zilucoplan 0.3/zilucoplan 0.3 mg/kg group, the mean (SD) CFB in MG-QoL15r score decreased (improved) from Week E1 [redacted] the improvement was maintained up to Week E84 (Figure 20). Similarly, in the placebo/zilucoplan 0.3 mg/kg group, the mean (SD) CFB decreased rapidly from Week 12 (−3.88 [6.36]) to Week E1 [redacted] once zilucoplan dosing was initiated, and continued to decrease up to Week E12 [redacted] The decrease in score was maintained up to Week E84 (Figure 20) (155).

The LS mean (95% CI) differences between Week E12 and Week 12 in the zilucoplan 0.3/zilucoplan 0.3 mg/kg and placebo/zilucoplan 0.3 mg/kg groups were [redacted], respectively, showing the continued benefit of zilucoplan treatment.

Figure 20: Change from RAISE Baseline to Week E84 in MG-QoL15r score (mITT population)

The total MG-QoL15r score ranges 0–30, with higher scores showing more severe impact on the patient QoL. A decrease from baseline indicates improvement. Baseline was defined as the last available assessment before first administration in the 'double-blind study' or 'RAISE study'
Abbreviations: CFB, change from baseline; E, extension; MG-QoL15r, myasthenia gravis quality of life 15 item scale revised; mITT, modified intent-to-treat; OLE, open-label extension; SE, standard error.
Source: RAISE-XT TFL, [redacted](155).

Use of rescue therapy

As of the [redacted] data cut-off, [redacted] and [redacted] patients in the zilucoplan 0.3/zilucoplan 0.3 mg/kg and placebo/zilucoplan 0.3 mg/kg groups, respectively, required rescue therapy (with IVIg or PLEX).

The overall incidence rate of rescue therapy for both cohorts was [redacted]events per 100 patient-years. Patients who switched from placebo to zilucoplan experienced a decrease in rescue therapy use during RAISE-XT ([redacted]events per 100 patient-years) compared with the double-blind period of RAISE (78.16 events per 100 patient-years), indicating a reduced need for rescue therapy with zilucoplan treatment.

As of the [redacted]data cut (672 days from RAISE-XT baseline), [redacted]. Time to first receipt of rescue therapy over the full treatment period is presented in Figure 21 (48). Zilucoplan reduced the incidence of rescue therapy compared with placebo in a post-hoc analysis of patients who received zilucoplan in RAISE and RAISE-XT (see Section B.2.6.2.4, Figure 26).

Figure 21. Time to first receipt of rescue therapy for patients who received zilucoplan in RAISE-XT

Source: RAISE-XT CSR, May 2023 data cut (48).

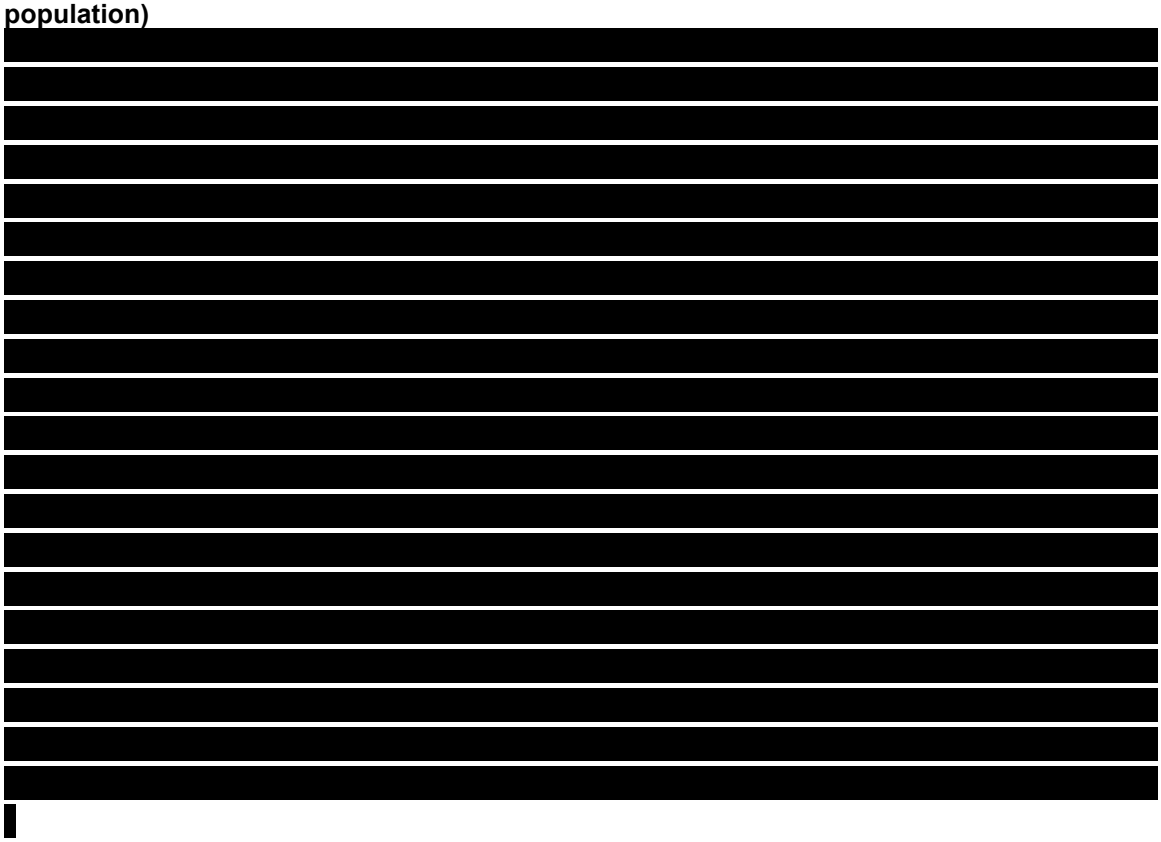
B.2.6.2.3 Exploratory efficacy endpoints

The exploratory efficacy endpoints included MMS per MGFA-PIS class, CFB to Week E12 in WPAI:SHP, EQ-5D-5L, and Neuro-QoL short form fatigue scores, and responder analyses for MG-ADL score, MSE achievement, and QMG score on the absence of rescue therapy.

MMS per MGFA-PIS

At Week E1, the proportion of patients with MGFA-PIS and MMS were slightly higher in the zilucoplan 0.3/zilucoplan 0.3 mg/kg group (respectively) compared with the placebo/zilucoplan 0.3 mg/kg group respectively). In the zilucoplan 0.3/zilucoplan 0.3 mg/kg group the proportion of patients was at Week E12 and at Week E48, while in the placebo/zilucoplan 0.3 mg/kg group the proportions of patients with MMS were at Week E12 and E48, respectively (152). At Week E84 (Figure 22), the proportion of patients with MGFA-PIS and MMS was respectively, for the zilucoplan 0.3/zilucoplan 0.3 mg/kg group compared with (respectively for the placebo/zilucoplan 0.3 mg/kg group (48).

Figure 22. Achievement of MMS per MGFA-PIS to Week E84 without rescue therapy (mITT population)



Abbreviations: E, extension; MGFA-PIS, Myasthenia Gravis Foundation of America Post-intervention Status, MMS, minimal manifestation status; mITT, modified intention to treat.
Source: RAISE-XT CSR, [redacted] data cut (48).

CFB to Week E12 in WPAI:SHP

Patients receiving zilucoplan in RAISE-XT experienced improvements productivity and employment over 48 weeks. Change from baseline in WPAI:SHP scores to Week E12 and E48 are summarised in Table 24

Table 24. Change from baseline in WPAI:SHP scores for patients who received zilucoplan in RAISE-XT

CFB in WPAI:SHP				
	Week E12		Week E48	
	Placebo/zilucoplan 0.3 mg/kg	Zilucoplan 0.3/zilucoplan 0.3 mg/kg	Placebo/zilucoplan 0.3 mg/kg	Zilucoplan 0.3/zilucoplan 0.3 mg/kg
Proportion of work time missed due to problem	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of impairment while working due to problem	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of overall work impairment due to problem	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of activity impairment due to problem	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; E, extension; WPAI: SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.
Source: RAISE-XT TFL, [redacted] data cut (155).

CFB to Week E12 and E84 in EQ-5D-5L scores

The EQ-5D-5L scores in RAISE-XT demonstrate the durable response with zilucoplan treatment, in terms of maintenance and improvement in patient QoL and health status. At Baseline, [redacted] of patients in the zilucoplan 0.3/zilucoplan 0.3 mg/kg group and reported no problems in the EQ-5D-5L domains for mobility, self-care, and usual activities, respectively, which was maintained up to Week E84 (Figure 23). Patients in the placebo/zilucoplan 0.3 mg/kg group experienced improvements in the above EQ-5D-5L after receiving treatment with zilucoplan in RAISE-XT. The proportion of patients reporting no problems in the mobility, self-care and usual activities domains increased as follows from Baseline to Week E12: mobility ([redacted]self-care ([redacted] and usual activities ([redacted]which was maintained up to Week E84 (Figure 23) (48).

Overall, participants maintained or improved their mobility, self-care and usual activities up to Week E84 (Figure 23).

Figure 23. EQ-5D-5L scores by visit for patients who received zilucoplan in RAISE-XT

Abbreviations: E, extension; EQ-5D-5L, EuropeanQoL-5 dimensions.
Source: RAISE-XT CSR, [redacted] data cut (48).

CFB to Week E12 and E96 in Neuro-QoL Short Form fatigue scale

Patients in the zilucoplan 0.3/zilucoplan 0.3 mg/kg and the placebo/zilucoplan 0.3 mg/kg treatment groups made improvements in the Neuro-QoL Fatigue Short Form from Baseline to Week E12 of [redacted], respectively. Scores improved from [redacted] in the zilucoplan 0.3/zilucoplan 0.3 mg/kg group, and from [redacted]in the placebo/zilucoplan 0.3 mg/kg group. These changes were maintained up to Week E48 in both the zilucoplan 0.3/zilucoplan 0.3 mg/kg group and the placebo/zilucoplan 0.3 mg/kg group, with scores of [redacted]respectively, which continued up to Week E84 (Figure 24) (48).

Figure 24. RAISE-XT CFB to Week 96 in Neuro-QoL Short Form Fatigue Scale score

Abbreviations: CFB change from baseline; E, extension; Neuro-QoL, Quality of Life in Neurological Disorders; SE, standard error.
Source: RAISE-XT CSR, May 2023 data cut (48).

MG-ADL responder rate without rescue therapy

A responder was defined as a participant achieving ≥3 points improvement (decrease) from Baseline in MG-ADL score (clinically meaningful change). In RAISE-XT, most patients achieved a clinically meaningful change in MG-ADL score without rescue therapy (Table 25). The responder rate in the zilucoplan 0.3/zilucoplan 0.3 mg/kg group improved from [redacted] at parent study Week 12 [redacted]at Week E12 and was maintained up to Week E84 ([redacted]In the placebo/zilucoplan 0.3 mg/kg group, the MG-ADL responder rate at Week 12 ([redacted]increased to [redacted]at Week E12 after initiation of zilucoplan dosing and was maintained up to Week E84 ([redacted](48).

Table 25. MG-ADL responder rates without rescue therapy for patients who received zilucoplan

Responders (%)	Placebo/zilucoplan 0.3 mg/kg (n=90)	Zilucoplan 0.3/zilucoplan 0.3 mg/kg (n=93)
Week E12	81.9	84.5
Week E48	87.9	90.4
Week E84	92.5	84.4

Abbreviations: E, extension; MG-ADL, myasthenia gravis activities of daily living.
Source: RAISE-XT CSR, [redacted]data cut (48).

QMG responder rate without rescue therapy

A responder was defined as a participant achieving ≥5 points improvement (decrease) from Baseline in QMG score. In RAISE-XT, most patients achieved a clinically meaningful change in QMG score without rescue therapy. In the zilucoplan 0.3/zilucoplan 0.3 mg/kg group, the QMG responder rate at Week 12 (59.8%) increased at Week E12 [redacted]and was maintained up to Week E84 ([redacted] (Table 26).

In the placebo/zilucoplan 0.3 mg/kg group, the QMG responder rate at Week 12 (37.1%) increased to [redacted] at Week E1, after the first week of zilucoplan dosing, and to [redacted] at Week E12. The responder rate was maintained up to Week E84 ([redacted] (Table 26) (48).

Table 26. QMG responder rates without rescue therapy for patients who received zilucoplan

Responders (%)	Placebo/zilucoplan 0.3 mg/kg (n=90)	Zilucoplan 0.3/zilucoplan 0.3 mg/kg (n=93)
Week E12	[redacted]	[redacted]
Week E48	[redacted]	[redacted]
Week E84	[redacted]	[redacted]

Abbreviations: E, extension; QMG, quantitative myasthenia gravis.
Source: RAISE-XT CSR, [redacted] data cut (48).

MSE achievement without rescue therapy

Minimal symptom expression was defined as an MG-ADL score of 0 or 1 in the absence of rescue therapy. In RAISE-XT, the MSE responder rate increased compared with RAISE baseline in all patients receiving zilucoplan (Table 27). In the zilucoplan 0.3/zilucoplan 0.3 mg/kg group, the MSE responder rate at Week 12 (19.4%) increased to [redacted] at Week E12 and was maintained through Week E84 [redacted]

In the placebo/zilucoplan 0.3 mg/kg treatment group, the MSE responder rate at Week 12 (7.8%) increased rapidly at Week E1 ([redacted] after initiation of zilucoplan dosing. A further increase was observed at Week E12 ([redacted] which was maintained through Week E84 ([redacted] (48).

Table 27. MSE achievement without rescue therapy for patients who received zilucoplan

Responders (%)	Placebo/zilucoplan 0.3 mg/kg (n=90)	Zilucoplan 0.3/zilucoplan 0.3 mg/kg (n=93)
Week E12	[redacted]	[redacted]
Week E48	[redacted]	[redacted]
Week E84	[redacted]	[redacted]

Abbreviations: E, extension; MSE, minimal symptom expression.
Source: RAISE-XT CSR, May 2023 data cut (48).

Post-injection Self-Injection Assessment Questionnaire (SIAQ) (US only)

Scores ≥8 and <9, and >9 indicate high and very high satisfaction, respectively.

At the first (n=63) and second (n=52) assessments of post-injection SIAQ, median (min, max) domain scores remained stable and were as follows for feelings about injections domain score ([redacted], respectively), self-image domain score [redacted] respectively), self-confidence domain score [redacted] and [redacted] respectively),

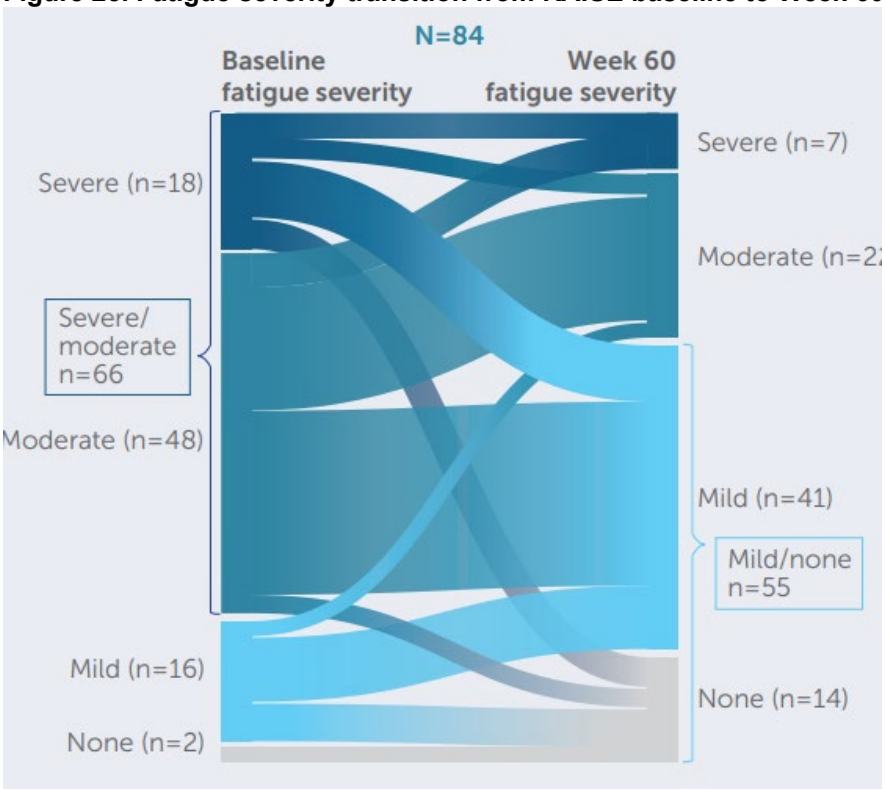
injection-site reactions domain score ([redacted] and [redacted], respectively), ease of use domain score [redacted] respectively), and satisfaction with self-injection domain score [redacted] respectively).

B.2.6.2.4 Post hoc analyses

Fatigue severity

At RAISE baseline, the fatigue severity of most patients was moderate or severe (n=66 [78.6%]), whilst at Week 60, most patients had mild or no fatigue (n=55 [65.5%], demonstrating meaningful improvements in fatigue severity (154) (Figure 25).

Figure 25. Fatigue severity transition from RAISE baseline to Week 60



The analysis set includes patients from RAISE and RAISE-XT who were included in the RAISE mITT population and had available Neuro-QoL Short Form fatigue data at RAISE baseline and Week 60. The fatigue severity level thresholds for T-scores were defined a
Source: Post-hoc analysis of data from RAISE and RAISE-XT (154).

Incidence of rescue therapy

Zilucoplan reduced the incidence of rescue therapy compared with placebo in a post-hoc analysis of patients who received zilucoplan in RAISE and RAISE-XT (Figure 26).

Figure 26. Incidence of rescue therapy in RAISE and RAISE-XT

Abbreviations: OLE, open-label extension; PBO, placebo; ZLP, zilucoplan.
Source: UCB post-hoc analysis (156).

B.2.6.2.5 Efficacy conclusions for RAISE-XT

Primary endpoint

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

Secondary endpoints

All patients who received zilucoplan 0.3 mg/kg in RAISE-XT experienced improvements in the signs and symptoms of disease activity and QoL, as measured by MG-ADL, QMG, MGC, and MG-QoL15r. Patients continued to improve further through Week E12, which was maintained through Week E84 (data cut), demonstrating long-term benefits of treating MG with zilucoplan.

SIAQ (exploratory endpoint)

The SIAQ results indicated that study participants had a positive experience with self-injection and were satisfied at both time points.

B.2.7 *Subgroup analysis*

Subgroup analyses performed in RAISE and RAISE-XT are listed below.

Subgroup analyses were preformed to evaluate the efficacy of zilucoplan in patients stratified to specific disease characteristics. Subgroup analyses indicated that zilucoplan has the potential to be a convenient, self-administered treatment for the management of gMG, irrespective of patient and disease characteristics including disease severity, disease duration and type of prior and current treatments. Results for the subgroup analyses considered in the economic model and relevant to this submission (patients refractory to treatment) are presented in Appendix E.

An additional post-hoc analysis was performed to identify the effect of zilucoplan on the CS dose required by patients during the RAISE studies (47) (see Section B.2.7.5).

B.2.7.1 *Methodology*

The primary and secondary efficacy endpoints and TEAEs and were analysed for the following subgroups in both RAISE and RAISE-XT. Subgroups were the same in both trials, with the exception of the 'By timing of the Week 12 Visit relative to COVID-19 pandemic periods (prior/during/post)' subgroup, which was not included in RAISE-XT.

- Race (Asian, Black or African American, White, Other/Mixed)
- Age (<65 years/≥ 65 years)
- Gender (male/female)
- Duration of disease at Baseline (<median/ ≥median)
- MGFA disease class at Baseline (Class II [IIa, IIb], III [IIIa, IIIb], or IV [IVa or IVb])
- Chronic kidney disease stages: normal renal function (eGFR ≥90 mL/min/1.73 m^2), mild (eGFR 60 to 89 mL/min/1.73 m^2 [CKD stage 2]), moderate (eGFR 30 to 59 mL/min/1.73m^2 [CKD stage 3]), severe (eGFR 15 to 29 mL/min/1.73 m^2 [CKD stage 4]), and renal insufficiency end stage renal disease (eGFR <15 mL/min/1.73 m^2)
- gMG refractory status (yes/no)

Additionally, the primary and secondary efficacy endpoints were analysed for the following pre-planned subgroups:

- Baseline MG-ADL (≤9/≥10)
- Baseline QMG (≤17/≥18)
- Region (North America, Europe, and East Asia)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight in kg (<43, 43 to 56, 56 to <77, 56 to <150, ≥150)
- BMI in kg/m^2 (<18.5, 18.5 to <25, ≥25 to <30, ≥30 to <40, ≥40)
- Ever had a crisis (dichotomous yes/no class variable)
- Prior thymectomy (dichotomous yes/no class variable)
- Prior steroid therapy (dichotomous yes/no class variable)
- Steroid therapy taken at Baseline (dichotomous yes/no class variable)
- Prior immunosuppressive therapy (nonsteroidal) (dichotomous yes/no class variable)
- Immunosuppressive therapy (nonsteroidal) (dichotomous yes/no class variable)
- Prior history of IVIg, SCIg or PLEX (dichotomous yes/no class variable)

- Diagnosed with thymoma
- By timing of study participants enrolment relative to COVID-19 pandemic periods (prior/during/post)

B.2.7.2 *Participant characteristics*

The subgroup considered in the economic model and relevant to this submission (as defined in the Decision Problem form) is patients who are treatment refractory, as per the definition used in the RAISE RCT. In RAISE and RAISE-XT, a study participant was considered gMG refractory if they had treatment for at least 1 year with two or more of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, other ISTs, or history of treatment with at least one of these therapies for ≥1 year, and required chronic PLEX, IVIg, or SCIg at least every 3 months for the 12 months prior to enrolment. To manage this patient cohort, clinicians currently consider chronic use of IVIg (38, 157).

B.2.7.3 *Statistical information*

All subgroup analyses were descriptive and no statistical testing of treatment-by-subgroup interactions, nor statistical testing of treatment effects within subgroups, was carried out.

B.2.7.4 *Results*

RAISE

Change from Baseline to Week 12 in MG-ADL, QMG, MGC, MG-QoL15r for patients who were refractory to treatment is presented in Table 28, Table 29, Table 30 and Table 31, respectively.

Table 28. Subgroup analysis of change from Baseline to Week 12 in MG-ADL (mITT population)

Subgroup	Placebo, n=88		Zilucoplan 0.3 mg/kg, n=86	
	n	Mean CfB (SD)	n	Mean CfB (SD)
MG refractory				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CfB, change from baseline; MG, myasthenia gravis; mITT, modified intention to treat; SD, standard deviation.

Table 29. Subgroup analysis of change from Baseline to Week 12 in QMG (mITT population)

Subgroup	Placebo, n=88		Zilucoplan 0.3 mg/kg, n=86	
	n	Mean CfB (SD)	n	Mean CfB (SD)
MG refractory				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CfB, change from baseline; MG, myasthenia gravis; mITT, modified intention to treat; SD, standard deviation.

Table 30. Subgroup analysis of change from Baseline to Week 12 in MGC (mITT Population)

Subgroup	Placebo, n=88		Zilucoplan 0.3 mg/kg, n=86	
	n	Mean CfB (SD)	n	Mean CfB (SD)
MG refractory				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CfB, change from baseline; MG, myasthenia gravis; mITT, modified intention to treat; SD, standard deviation.

Table 31. Subgroup analysis of change from Baseline to Week 12 in MG-QoL15r (mITT Population)

Subgroup	Placebo, n=88		Zilucoplan 0.3 mg/kg, n=86	
	n	Mean CfB (SD)	n	Mean CfB (SD)
MG refractory				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CfB, change from baseline; MG, myasthenia gravis; mITT, modified intention to treat; SD, standard deviation.

RAISE-XT

Change from Baseline to Week 12 in MG-ADL, QMG, MGC, MG-QoL15r for patients who were refractory to treatment is presented in Table 32, Table 33, Table 34, and Table 35, respectively.

Table 32. Subgroup analysis of change from MG0011 Baseline to Week E12 in MG-ADL (mITT population)

Subgroup	Placebo, n=90		Zilucoplan 0.3 mg/kg, n=92	
	n	Mean CfB (SD)	n	Mean CfB (SD)
MG refractory				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CfB, change from baseline; MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; mITT, modified intention to treat; SD, standard deviation.

Table 33. Subgroup analysis of change from MG0011 Baseline to Week E12 in QMG (mITT population)

Subgroup	Placebo, n=90		Zilucoplan 0.3 mg/kg, n=92	
	n	Mean CfB (SD)	n	Mean CfB (SD)
MG refractory				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CfB, change from baseline; MG, myasthenia gravis; mITT, modified intention to treat; QMG, quantitative myasthenia gravis; SD, standard deviation.

Table 34. Subgroup analysis of change from MG0011 Baseline to Week E12 in MGC (mITT population)

Subgroup	Placebo, n=90		Zilucoplan 0.3 mg/kg, n=92	
	n	Mean CfB (SD)	n	Mean CfB (SD)
MG refractory				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CfB, change from baseline; MG, myasthenia gravis; mITT, modified intention to treat; MGC, myasthenia gravis composite; SD, standard deviation.

Table 35. Subgroup analysis of change from MG0011 Baseline to Week E12 in MG-QoL15r (mITT Population)

Subgroup	Placebo, n=90		Zilucoplan 0.3 mg/kg, n=92	
	n	Mean CfB (SD)	n	Mean CfB (SD)
MG refractory				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CfB, change from baseline; MG, myasthenia gravis; MGQoL, myasthenia gravis quality of life; mITT, modified intention to treat; MGC, myasthenia gravis composite; SD, standard deviation.

B.2.7.5 *Post hoc analysis*

An additional post-hoc analysis was performed to identify the effect of zilucoplan on the CS dose required by patients during the RAISE studies (47). Treatment discontinuations and dose reductions/increases were analysed on four subgroups:

- Patients who reduced their CS dose at any time (i.e., first time they reduce)
- Patients who did not reduce their CS dose at any time
- Patients who reduced their CS dose observed at Week E48
- Patients who did not reduce their CS dose observed at Week E48

B.2.7.5.1 Results

Post hoc analysis of patients in RAISE-XT

At week E48, [redacted] of patients in the zilucoplan 0.3/zilucoplan 0.3 mg/kg arm in RIASE-XT discontinued or reduced their CS dose compared with baseline. Of patients in the placebo/ zilucoplan 0.3 mg/kg arm, [redacted] discontinued or reduced their CS dose compared with baseline.

Of patients who were on a high dose of CS (≥10 mg) at baseline, [redacted] in the zilucoplan 0.3/zilucoplan 0.3 mg/kg arm had a dose reduction by Week E48.

The proportion of patients with refractory gMG among the four subgroups (patients who reduced their CS dose at any time, patients who did not reduce their CS dose at any time, patients who reduced their CS dose observed at Week E48 and patients who did not reduce their CS dose observed at Week E48) is presented in Table 36.

Table 36. Refractory status by subgroup in patients who received zilucoplan in RAISE-XT

	Reduced CS at any time		Did not reduce any time		Reduced CS at Week E48		Did not reduce at Week E48		Overall population	
	Placebo/zilucoplan 0.3 mg/kg (n=19)	Zilucoplan 0.3/zilucoplan 0.3 mg/kg (n=22)	Placebo/zilucoplan 0.3 mg/kg (n=65)	Zilucoplan 0.3/zilucoplan 0.3 mg/kg (n=60)	Placebo/zilucoplan 0.3 mg/kg (n=10)	Zilucoplan 0.3/zilucoplan 0.3 mg/kg (n=13)	Placebo/zilucoplan 0.3 mg/kg (n=74)	Zilucoplan 0.3/zilucoplan 0.3 mg/kg (n=69)	Placebo/zilucoplan 0.3 mg/kg (n=84)	Zilucoplan 0.3/zilucoplan 0.3 mg/kg (n=82)
Refractory n, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS, corticosteroids.
Source: UCB 2023, data on file (47).

B.2.8 *Meta-analysis*

Per the decision problem (Section B.1.1), the key comparators for zilucoplan are efgartigimod, IVIg and PLEX. In the absence of direct head-to-head trial data between comparators (specified in the NICE scope) a network meta-analysis (NMA) was conducted to estimate the comparative efficacy between these treatments. Please see Section B.2.9 for details.

An NMA can provide relative measures of effect for all relevant comparators in the absence of direct evidence and is most suitable when there are multiple-arm trials included within networks. An NMA was preferred to a pairwise meta-analysis, as it allowed all available and relevant evidence to be included and more precise treatment effects to be calculated. In addition, the results from the NMA will feed into the economic model to provide the relevant cost-effectiveness of zilucoplan against relevant comparators.

A recently published meta-analysis of randomised and placebo-controlled trials of innovative therapies in MG (efgartigimod, rituximab, ravulizumab, rozanolixizumab, zilucoplan, eculizumab, and rituximab) (158), reports results that are consistent with the de novo analysis presented in Section B.2.9.

B.2.9 *Indirect and mixed treatment comparisons*

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

B.2.9.1.1 Trials used to inform the analysis

In total, 47 studies (all RCTs) qualified for inclusion from the clinical SLR. Of these, 33 were excluded due to interventions not being of interest, resulting in the inclusion of 14 studies in the analysis (Table 37). One study (Howard 2013 (159)) compared eculizumab with placebo and presented crossover data at 32 weeks; data before the crossover period at Week 16 are also available, and these were utilised in the NMA.

Table 37: Criteria used in the trial selection process

Trial	Primary publication – author (year)	Trial phase	Intervention	Comparator
ADAPT	Howard et al, 2021 (160)	Phase III	Efgartigimod	Placebo
CHAMPION MG	Vu et al, 2021 (161)	Phase III	Ravulizumab	Placebo
MycarinG	Bril et al, 2022 (162)	Phase III	Rozanolixizumab (7 or 10 mg/kg)	Placebo
RAISE	Howard et al, 2022 (163)	Phase III	Zilucoplan (0.3 mg/kg)	Placebo
REGAIN	Howard et al, 2017 (164)	Phase III	Eculizumab	Placebo
Piehl 2022	Piehl et al, 2022 (131)	Phase III	Rituximab	Placebo
BeatMG	Nowak et al, 2021 (165)	Phase II	Rituximab	Placebo
Howard 2013	Howard et al, 2013 (159)	Phase II	Eculizumab	Placebo
Bril 2021	Bril et al, 2021 (166)	Phase II	Rozanolixizumab	Placebo
Howard 2019	Howard et al, 2019 (167)	Phase II	Efgartigimod	Placebo
Howard 2020	Howard et al, 2020 (168)	Phase II	Zilucoplan (0.3 mg/kg)†	Placebo
NCT02473952	NCT02473952 (169)	Phase II	IVIg	Placebo
Wolfe 2002	Wolfe et al, 2002 (170)	Phase II	IVIg	Placebo
Zinman 2007	Zinman et al, 2007 (171)	Phase II	IVIg	Placebo

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

B.2.9.1.2 Studies excluded from the analysis

Of the 33 studies excluded from the feasibility assessment, 11 studies did not have any outcomes of interest, 18 studies did not have any interventions of interest, two studies were not connected to the network, one study had study cross-over study design and one study was Phase IV with outcomes reported at Week 2 (Table 38).

Table 38: List of trials ineligible for inclusion in indirect comparisons

Study name	Interventions	Rationale for exclusion
Gamez 2019	IVIg vs placebo	No outcomes of interest
Hewett 2018	Belimumab vs placebo	Intervention not of interest
Zhou 2017	Tacrolimus vs placebo	Intervention not of interest
Pasnoor 2016	Methotrexate vs placebo	Intervention not of interest
Zhang 2014	DFPP + Methyl prednisolone vs Methyl prednisolone	Intervention not of interest
Qi 2013	Methylprednisolone pulse therapy + pyridostigmine vs Methylprednisolone pulse therapy + pyridostigmine	No outcomes of interest
Kohler 2011	PLEX vs immunoadsorption	No outcomes of interest
Soliven 2009	Terbutaline vs placebo	Cross-over study design
Sanders 2008	MMF vs placebo	Intervention not of interest
Gajdos 2005	(IVIg 1 g/kg vs IVIg 2 g/kg)	No outcomes of interest
Gajdos 1994	PLEX vs IVIg	No outcomes of interest
Gajdos 1993	Azathioprine vs Prednisone	No outcomes of interest
NCT-02565576	CFZ533 vs placebo	Intervention not of interest
Liu 2010	DFPP vs Immunoadsorption vs IVIg	Intervention not of interest
Muscle Study Group 2008	MMF vs Placebo	Intervention not of interest
De 2002	Cyclophosphamide vs Placebo	No outcomes of interest
Palace 1998	Azathioprine vs Placebo	No outcomes of interest
Bromberg 1997	Azathioprine vs Prednisone	No outcomes of interest
Gajdos 1997	PLEX vs IVIg	No outcomes of interest
Tindall 1993	Cyclosporine vs Placebo	Intervention not of interest
Tindall 1987	Cyclosporine vs Placebo	Intervention not of interest
Sharshar 2021	Prednisone - Azathioprine slow tapering vs Prednisone - Azathioprine rapid tapering	Not connected with the overall network
Wolfe 2016	Thymectomy vs Prednisone	Intervention not of interest

Study name	Interventions	Rationale for exclusion
Barth 2011	IVIg vs PLEX	Phase IV study with outcomes reported at 2 weeks
Heckmann 2011	Methotrexate vs Azathioprine	Not connected with the overall network
Tackenberg 2018	Seasonal influenza vaccine vs placebo	Intervention not of interest
NCT03772587	Nipocalimab vs Placebo	Intervention not of interest
NCT03304054	Amifampridine Phosphate vs Placebo	Intervention not of interest
Zhao 2021	Batoclimab vs Placebo	Intervention not of interest
Benatar 2021	Batoclimab vs Placebo	Intervention not of interest
Di 2022	Prednisone+MTX vs MTX	Intervention not of interest
EuCT2019-003383-47	Mezagitamab vs Placebo	Intervention not of interest
Bril 2023	IGIV-C vs Placebo	No outcomes of interest

Abbreviations: IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; PLEX, plasma exchange.

B.2.9.2 *Methods and outcomes of included studies*

B.2.9.2.1 Rationale for choice of outcome measure and scale

An overview of the outcomes considered of relevance, analysed, and included in the NMA are described in Table 39. The table also shows the primary and sensitivity analyses conducted.

Table 39: Description of network meta-analyses conducted

Subject	Analysis Type	Trial Phase included	Endpoint	Justification
MG-ADL Responders	Primary analysis*	Phase III	≥3 point improvement in MG-ADL response at study endpoint	≥3 point improvement in MG-ADL response was the most commonly assessed definition of this outcome across the included trials
	Sensitivity 1 analysis*	Phase II & III		

Abbreviations: MG-ADL, myasthenia gravis activities of daily living.

B.2.9.2.2 Participants included

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

B.2.9.3 *Methods of analysis and presentation of results*

B.2.9.3.1 Methodology

All analyses were performed in a Bayesian framework and involved a model with parameters, data, and a likelihood distribution and prior distributions. Where results of the RCTs formed part of one evidence network and were deemed sufficiently similar for each population of interest, they were synthesised by means of NMAs by outcome of interest.

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

Model Selection

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

Equation 1: Deviance information criterion

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

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

Evaluation of inconsistency

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

Binary outcomes

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

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

Continuous outcomes

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

Prior distributions

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

Software

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

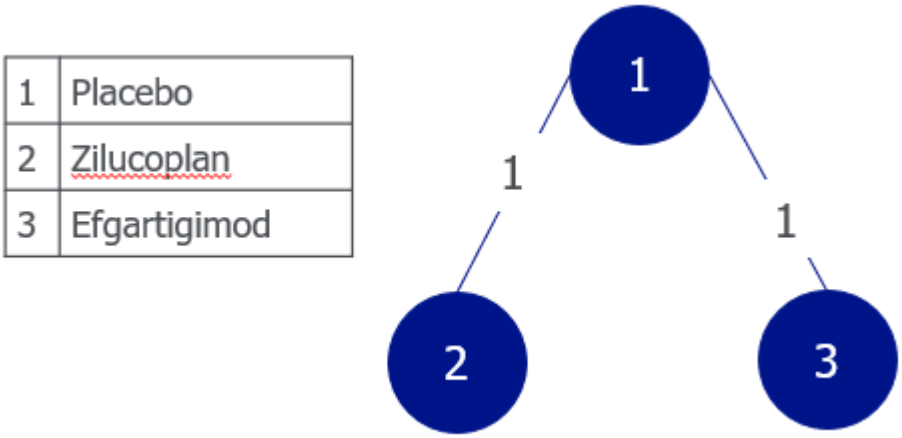
B.2.9.4 *Results*

B.2.9.4.1 Primary analysis

MG-ADL responders

In the primary analysis in the treatments of interest – zilucoplan, placebo, and efgartigimod, two Phase III trials that reported on MG-ADL ≥3 point improvement were included (Figure 27). Interventions assessed in these trials include the following: zilucoplan, ravulizumab, rozanolixizumab, eculizumab, and efgartigimod. The modelled probability of response is presented in Table 40.

Figure 27: MG-ADL response evidence network – primary analysis (Phase III trials that provided data on the ≥3 point improvement definition)



Abbreviations: MG-ADL, myasthenia gravis activities of daily living.

Table 40: MG-ADL probability of response - primary analysis (Phase III trials that provided data on the ≥3 point improvement definition)

Intervention	Mean	SE
Placebo	0.36	0.05
Zilucoplan	0.63	0.09
Efgartigimod	0.72	0.08

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

Results from the analysis showed a statistically significant improvement in response for all interventions compared with placebo. No statistically significant difference in response was observed between zilucoplan and efgartigimod.

B.2.9.4.2 Choice of model

Please see Section B.2.9.3.1.

B.2.9.4.3 Heterogeneity and inconsistency

Heterogeneity could not be estimated. There was heterogeneity in the placebo response observed across trials for the MG-ADL response outcomes. Notably, the observed responses in the placebo arms for MG-ADL were higher in the RAISE (zilucoplan) and Howard 2020 (zilucoplan) trials compared with the other trials. These differences could have influenced the results of the NMA. The placebo response or baseline risk, which represents unmeasured but significant patient-level characteristics, may act as a treatment effect modifier and contribute to heterogeneity in the NMA. While efforts were made to use consistent outcome definitions, it was not possible to control for other differences. Therefore, caution should be exercised when interpreting the results of responder outcomes.

B.2.10 *Adverse reactions*

Zilucoplan as an add-on to SOC was associated with a favourable safety profile and was generally well tolerated by patients with gMG, with the majority of TEAEs categorised as mild or moderate in severity

- In RAISE:
  - The mean (SD) duration of exposure to zilucoplan was 81.9 (11.0) days and 81.1 (13.0) days for the placebo group
  - The majority of TEAEs were mild or moderate in severity
  - The incidence of TEAEs was higher in the zilucoplan treatment group compared with placebo (n=66/86 [76.7%] vs n=62/88 [70.5%], respectively), and the incidence of severe TEAEs (n=10/86 [11.6%] vs n=11/88 [12.5%]) was comparable between the zilucoplan and placebo treatment groups, respectively
  - The incidence of TEAEs resulting in permanent withdrawal from IMP was similar in the zilucoplan 0.3 mg/kg treatment group (4 study participants [4.7%]) and placebo treatment group (2 study participants [2.3%])
  - In total, two study participants died during the trial period, including one study participant each in the zilucoplan 0.3 mg/kg (1.2%) and the placebo treatment group (1.1%); none of the TEAEs were considered treatment-related (as determined by the Investigator)
- The safety profile of zilucoplan in RAISE-XT was consistent with findings in the RAISE Phase III study, with no new safety signals observed, demonstrating long-term safety and tolerability up to 96 weeks with zilucoplan 0.3 mg/kg

B.2.10.1 *Studies reported in section 2.2*

Safety evidence for zilucoplan in the population of interest for this submission is provided by the RAISE study and the OLE phase, RAISE-XT [redacted]
Key safety outcomes for both studies are presented in Sections B.2.10.1.1 and B.2.10.1.2 and, respectively.

B.2.10.1.1 RAISE safety outcomes

Exposure

The mean (SD) duration of exposure to zilucoplan was 81.9 (11.0) days and 81.1 (13.0) days for the placebo group (Table 41). The majority of study participants received investigational medicinal product (IMP) for ≥84 days (63 study participants [73.3%] who received zilucoplan 0.3 mg/kg and 57 study participants [64.8%] who received placebo). At Week 12, total exposure was 19.8 participant-years for the zilucoplan 0.3 mg/kg treatment group and 20.0 participant-years for the placebo treatment group.

Table 41. Summary of exposure (SS)

	Placebo n=88	Zilucoplan n=86
Exposure (days)		
n	88	86
Mean (SD)	81.1 (13.0)	81.9 (11.0)
Participant-years exposure	20.0	19.8

Abbreviations: SD, standard deviation; SS, safety set.

Adverse events

The majority of TEAEs were mild or moderate in severity (Table 42). The incidence of TEAEs was higher in the zilucoplan treatment group compared with placebo (n=66/86 [76.7%] vs n=62/88 [70.5%], respectively), and the incidence of severe TEAEs (n=10/86 [11.6%] vs n=11/88 [12.5%]) was comparable between the zilucoplan and placebo treatment groups, respectively. The incidence of treatment-related TEAEs (as determined by the Investigator) was higher in the zilucoplan 0.3 mg/kg treatment group (28 study participants [32.6%]) compared with the placebo treatment group (22 study participants [25.0%]), and the incidence of serious TEAEs was similar in the zilucoplan 0.3 mg/kg treatment group (11 study participants [12.8%]) and placebo treatment group (13 study participants [14.8%]).

Table 42: Overall summary of TEAEs (SS)

Adverse events	Placebo (n=88) n (%)	Zilucoplan 0.3 mg/kg (n=86) n (%)
Any TEAE	62 (70.5)	66 (76.7)
Mild	29 (33.0)	36 (41.9)
Moderate	22 (25.0)	20 (23.3)
SAE	13 (14.8)	11 (12.8)
TEAEs resulting in permanent withdrawal from zilucoplan treatment	2 (2.3)	4 (4.7)
Treatment-related TEAEs	22 (25.0)	28 (32.6)
Severe TEAEs	11 (12.5)	10 (11.6)
All deaths (number of study participants with AEs leading to death)	1	1
Deaths (TEAEs leading to death)	1 (1.1)	1 (1.2)

Abbreviations: AE, adverse event; SAE, serious adverse event; SS, safety set; TEAE, treatment-emergent adverse event.

The incidence of TEAEs resulting in permanent withdrawal from IMP was similar in the zilucoplan 0.3 mg/kg treatment group (4 study participants [4.7%]) and placebo treatment group (2 study participants [2.3%]). In total, two study participants died during the trial period, including one study participant (1.2%) in the zilucoplan 0.3 mg/kg treatment

group who had serious TEAEs of COVID-19 and COVID-19 pneumonia leading to death, and one study participant (1.1%) in the placebo treatment group who had a serious TEAE leading to death of cerebral haemorrhage; none of the TEAEs were considered treatment-related (as determined by the Investigator) and the TEAEs of COVID-19 and cerebral haemorrhage resulted in permanent withdrawal from IMP.

Adverse events of special interest

TEAEs of special interest are summarised in Table 43. The incidence of TEAEs of interest was higher in the zilucoplan 0.3 mg/kg treatment group (41 study participants [47.7%]) compared with the placebo treatment group (29 study participants [33.0%]).

Table 43. Summary of TEAEs of interest (SS)

Adverse events	Placebo (n=88) n (%)	Zilucoplan 0.3 mg/kg (n=86) n (%)
Any TEAE of interest	29 (33)	41 (47.7)
Infections	16 (18.2)	23 (26.7)
Serious	4 (4.5)	4 (4.7)
Injection site reactions	13 (14.8)	23 (26.7)
Serious	0	0
Hypersensitivity	8 (9.1)	8 (9.3)
Serious	0	1 (1.2)
Hepatic events	1 (1.1)	3 (3.5)
Serious	0	0
Malignancies	1 (1.1)	1 (1.2)
Serious	1 (1.1)	1 (1.2)

Abbreviations: SS, safety set; TEAE, treatment-emergent adverse event;

Safety conclusions for RAISE

The incidence of TEAEs was higher in the zilucoplan 0.3 mg/kg treatment group (66 study participants [76.7%]) compared with the placebo treatment group (62 study participants [70.5%]), however, the incidence of serious TEAEs was similar between the two study groups (11 [12.8%] patients who received zilucoplan 0.3mg/kg group and 13 [14.8%] patients who received placebo). Overall, treatment with zilucoplan 0.3 mg/kg was associated with a favourable safety profile and was well tolerated in study participants with gMG.

B.2.10.1.2 RAISE-XT safety outcomes

Exposure

At the [redacted] cut-off date, total exposure to zilucoplan was [redacted] patient-years of exposure. Mean (SD) duration of exposure to zilucoplan was [redacted] days for study participants who received either zilucoplan 0.3 mg/kg or 0.1 mg/kg in RAISE-XT. Table 44 summarises zilucoplan exposure for all treatment groups, but only results for

the zilucoplan 0.3 mg/kg-to-zilucoplan 0.3 mg/kg and placebo-to-zilucoplan 0.3 mg/kg groups are discussed. The number of patients in the other treatment groups were too small to draw any meaningful conclusions when comparing safety data between the treatment groups (Table 44).

Table 44. Summary of exposure to zilucoplan (SS)

	Placebo/ zilucoplan 0.1/0.3 mg/kg	Placebo/zilucoplan 0.3 mg/kg	Zilucoplan 0.1/0.1/ 0.3 mg/kg	Zilucoplan 0.3/ 0.3 mg/kg	All zilucoplan groups
Exposure (days)					
N	[redacted]	[redacted]	[redacted]	[redacted]	200
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	761.1 (458.1)
Duration of exposure (PEY)	[redacted]	[redacted]	[redacted]	[redacted]	321.4

Abbreviations: PEY, participant-exposure years; SD, standard deviation; SS, safety set.
Source: RAISE-XT CSR, [redacted] (48).

Adverse events

The summary of TEAEs is presented in Table 45 and Table 45. At the [redacted] data cut, TEAEs were reported in [redacted] patients who received zilucoplan. The overall incidence of TEAEs was similar between the zilucoplan 0.3/0.3 mg/kg treatment group [redacted] and the placebo/zilucoplan 0.3 mg/kg treatment group (n=[redacted] In total [redacted] patients died in the study: [redacted] had a TEAE leading to death, and [redacted] had a fatal post-treatment AE.

Table 45: Overall summary of TEAEs (SS)

Adverse events	Placebo/ zilucoplan 0.3 mg/kg N=90 n (%)	Zilucoplan 0.3/ 0.3 mg/kg N=93 n (%)	All Zilucoplan groups N=200 n (%)
Any TEAE	[redacted]	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]	[redacted]
TEAEs resulting in permanent withdrawal from zilucoplan	[redacted]	[redacted]	[redacted]
Treatment-related TEAEs	[redacted]	[redacted]	[redacted]
Severe TEAEs	[redacted]	[redacted]	[redacted]
Deaths (TEAEs leading to death)	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; SS, safety set; TEAE, treatment-emergent adverse event.
Source: RAISE-XT CSR, [redacted] data cut (48).

Treatment-related TEAEs

Injection site bruising was the most common treatment-related TEAE (Table 46).

Table 46. Treatment-related TEAEs reported in ≥2% of patients (SS)

Treatment-related TEAE	Placebo/ zilucoplan 0.3 mg/kg N=90 n (%)	Zilucoplan 0.3/ 0.3 mg/kg N=93 n (%)	All Zilucoplan groups N=200 n (%)
Total	[redacted]	[redacted]	[redacted]
Injection site bruising	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Injection site nodule	[redacted]	[redacted]	[redacted]
Injection site rash	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; SS, safety set; TEAE, treatment-emergent adverse event.
Source: RAISE-XT CSR, [redacted] (48).

Serious TEAEs

Overall, as of the cut-off date, serious TEAEs were reported in [redacted] participants who received zilucoplan (Table 47). The most common serious TEAE was worsening of MG, reported in 9.0% of patients who received zilucoplan.

Overall, treatment-related serious TEAEs were reported in [redacted] study participants (2.0%). In the zilucoplan 0.3 mg/kg / 0.3 mg/kg group, treatment-related serious TEAEs were reported in [redacted] participants, with [redacted] event each of oesophagitis and injection site infection (occurred on the right inner thigh, which is not a recommended injection site).In the zilucoplan 0.1 mg/kg / 0.1 mg/kg / 0.3 mg/kg group [redacted] participant reported a treatment-related serious TEAE of colonic abscess. In the placebo / zilucoplan 0.3 mg/kg group, [redacted] participant reported a treatment-related serious TEAE of headache.

Table 47. Serious TEAEs reported in ≥1% of patients (SS)

TEAE	Placebo/ zilucoplan 0.3 mg/kg N=90 n (%)	Zilucoplan 0.3/ 0.3 mg/kg N=93 n (%)	All Zilucoplan groups N=200 n (%)
Total	[redacted]	[redacted]	[redacted]
Myasthenia gravis	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]

TEAE	Placebo/ zilucoplan 0.3 mg/kg N=90 n (%)	Zilucoplan 0.3/ 0.3 mg/kg N=93 n (%)	All Zilucoplan groups N=200 n (%)
Cellulitis	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
Cholecystitis	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]	[redacted]
Large intestine polyp	[redacted]	[redacted]	[redacted]
Myasthenia gravis crisis	[redacted]	[redacted]	[redacted]
Pancreas infection	[redacted]	[redacted]	[redacted]
Post-procedural complication	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Staphylococcal bacteraemia	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]

Abbreviations: SS, safety set; TEAE, treatment-emergent adverse event.
RAISE-XT CSR, [redacted] (48).

Adverse events of special interest

Treatment-emergent AEs of special interest are summarised, by event category and seriousness, in Table 48. The incidence of TEAEs of interest was similar in the zilucoplan 0.3/0.3 mg/kg [redacted] and placebo/zilucoplan 0.3 mg/kg [redacted]%]). In the overall zilucoplan group, TEAEs of interest were most frequently reported in the event categories of infections ([redacted] and infection site reaction [redacted]

Table 48. Summary of TEAEs of interest (SS)

Adverse events	Placebo/ zilucoplan 0.3 mg/kg N=90 n (%)	Zilucoplan 0.3/0.3 mg/kg N=93 n (%)	All Zilucoplan groups N=200 n (%)
Any TEAE of interest	[redacted]	[redacted]	[redacted]
Infections	[redacted]	[redacted]	[redacted]
Serious	[redacted]	[redacted]	[redacted]

Adverse events	Placebo/ zilucoplan 0.3 mg/kg N=90 n (%)	Zilucoplan 0.3/0.3 mg/kg N=93 n (%)	All Zilucoplan groups N=200 n (%)
Injection site reactions	[redacted]	[redacted]	[redacted]
Serious	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]
Serious	[redacted]	[redacted]	[redacted]
Malignancies	[redacted]	[redacted]	[redacted]
Serious	[redacted]	[redacted]	[redacted]
Hepatic events	[redacted]	[redacted]	[redacted]
Serious	[redacted]	[redacted]	[redacted]

Abbreviations: SS, safety set; TEAE, treatment-emergent adverse event.
RAISE-XT CSR, May 2023 data cut (48).

Any TEAE resulting in permanent withdrawal from RAISE-XT

Of all patients who received zilucoplan in RAISE-XT, 9.5% had a TEAE that resulted in permanent withdrawal from treatment (Table 49).

Table 49. TEAEs resulting in permanent withdrawal from zilucoplan treatment

Adverse events	Placebo/ zilucoplan 0.3 mg/kg N=90 n (%)	Zilucoplan 0.3/0.3 mg/kg N=93 n (%)	All Zilucoplan groups N=200 n (%)
Total	[redacted]	[redacted]	[redacted]
MG	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]
Dacryocystitis	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Endocarditis candida	[redacted]	[redacted]	[redacted]
Flatulence	[redacted]	[redacted]	[redacted]
Head injury	[redacted]	[redacted]	[redacted]
Injection site bruising	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]
Injection site rash	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]
MG crisis	[redacted]	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]	[redacted]
Scleroderma	[redacted]	[redacted]	[redacted]

Abbreviations: MG, myasthenia gravis; TEAE, treatment-emergent adverse event.
RAISE-XT CSR, [redacted] data cut (48).

Safety conclusions for RAISE-XT

The safety profile of zilucoplan in RAISE-XT was consistent with findings in the RAISE Phase III study, with no new safety signals observed, demonstrating long-term safety and tolerability up to [redacted] with zilucoplan.

B.2.10.2 *Additional studies*

The clinical systematic review, detailed in Section B.2.1, also included adverse events, and did not identify any additional studies.

B.2.10.3 *Safety overview*

Zilucoplan as an add-on to SOC was associated with a favourable safety profile and was generally well tolerated by patients with gMG, with the majority of TEAEs categorised as mild or moderate in severity. In the RAISE study, the incidence of TEAE was higher in the zilucoplan 0.3 mg/kg treatment group (66 study participants [76.7%]) compared with the placebo treatment group (62 study participants [70.5%]), however, the incidence of serious TEAEs was similar between the two study groups (11 [12.8%] patients who received zilucoplan 0.3mg/kg group and 13 [14.8%] patients who received placebo. The proportion of patients who had dose reductions or temporarily discontinued the study drug due to TEAEs was similar between the zilucoplan and placebo groups, and less than 5% of patients in the zilucoplan group discontinued treatment due to a TEAE. TEAEs leading to death occurred in one patient each from the zilucoplan 3mg/kg (1.2%) and placebo (1.1%) groups.

The safety profile of zilucoplan in RAISE-XT was consistent with findings in the RAISE Phase III study, with no new safety signals observed, demonstrating long-term safety and tolerability [redacted] with zilucoplan 0.3 mg/kg.

B.2.11 *Ongoing studies*

RAISE-XT (see Section B.2) is ongoing and is expected to complete in 2026.

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

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

B.2.12.1.1 Summary of efficacy evidence

Patients with gMG who received zilucoplan as an add-on to SOC in the RAISE study achieved a significant reduction (improvement) in MG-ADL scores vs placebo, therefore meeting the primary endpoint of the trial. Zilucoplan 0.3 mg/kg was associated with a significantly higher CFB to Week 12 MG-ADL scores compared with placebo (−4.39 vs −2.30, respectively [p<0.001]), demonstrating that zilucoplan improves the daily lives of patients with gMG. Zilucoplan may also reduce the need for CSs and the associated side effects (47), as well as the need for rescue therapy (with IVIg or PLEX). Reducing the need for rescue therapy may lead to reduced medical resource utilisation costs associated with managing exacerbations.

Secondary and exploratory endpoints also demonstrate the clinical benefits of zilucoplan as an add-on to SOC treatments for patients with gMG, as well as its rapid onset of action. A treatment effect in the zilucoplan 0.3 mg/kg treatment group was observed from as early as Week 1 and increased through Week 4, with stabilisation thereafter to Week 12. The fast onset of action of zilucoplan will provide clinical benefits for patients with refractory gMG, who cycle through different ISTs without achieving symptom control, and are at risk of myasthenic exacerbation and crisis whilst they wait for treatment effect (34, 46).

Zilucoplan decreased disease severity in patients from the RAISE study, demonstrated by a statistically significant and clinically meaningful reduction from baseline in QMG and MGC scores of 2.94 and 3.20 respectively, compared with SOC alone. A numerically lower proportion of patients receiving zilucoplan treatment (5% [n=4/86]) required rescue therapy compared with placebo (12% [n=10/88]) over the course of the RAISE study, suggesting that zilucoplan reduces the risk of exacerbation of symptoms or myasthenic crisis. In addition, a numerically greater proportion of patients treated with zilucoplan achieved MSE, defined as an MG-ADL score of 0 or 1, compared with those treated with placebo at each timepoint. These patients became either free or nearly free of their MG symptoms.

A statistically significant improvement from Baseline to Week 12 in MG-QoL15r score was observed in the zilucoplan 0.3 mg/kg treatment group compared with the placebo treatment group (p=0.0128) indicating benefit of zilucoplan on the QoL of patients with gMG.

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

RAISE-XT

All patients who received zilucoplan 0.3 mg/kg in RAISE-XT continued to experience improvements in the signs and symptoms of gMG and in QoL throughout the extension phase (up to Week E84 [redacted]), demonstrating long-term benefits of zilucoplan as an add-on to standard therapies for patients with MG. Patients also had reduced need for CSs compared with at baseline (47).

B.2.12.1.2 Summary of safety evidence

Zilucoplan as an add-on to SOC was associated with a favourable safety profile and was generally well tolerated by patients with gMG, with the majority of TEAEs categorised as mild or moderate in severity. Serious TEAEs occurred in 11 [12.8%] patients who received zilucoplan 0.3 mg/kg group and 13 [14.8%] patients who received placebo. The proportion of patients who had dose reductions or temporarily discontinued the study drug due to TEAEs was similar between the zilucoplan and placebo groups, and less than 5% of patients in the zilucoplan group discontinued treatment due to a TEAE. TEAEs leading to death occurred in one patient each from the zilucoplan 0.3 mg/kg (1.2%) and placebo (1.1%) groups.

RAISE-XT

The safety profile of zilucoplan in RAISE-XT was consistent with findings in the RAISE study, with no new safety signals observed, demonstrating the long-term safety and tolerability [redacted]0.3 mg/kg.

B.2.12.1.3 Conclusions

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

Zilucoplan as an add-on treatment to SOC for patients with gMG is associated with significant improvements in the symptoms of disease activity and QoL, as measured by MG-ADL, QMG, MGC, and MG-QoL15r, with a fast onset of action, and sustained clinical benefit [redacted] Zilucoplan may also reduce the need for CSs and the associated side effects, as well as the need for rescue therapy (with IVIg or PLEX) (47).

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

B.2.12.2.1 Strengths of the evidence base

The efficacy and safety of zilucoplan up to 12 weeks has been extensively studied through the RAISE clinical trial programme. RAISE is a robustly designed, global, -double-blind, randomised, placebo-controlled trial which includes a population that closely reflects the real-world patient population eligible for treatment with zilucoplan.

- The programme contained 200 patients with gMG. This is a key strength of the clinical evidence base, especially considering that gMG is a rare disease, making it difficult to recruit patients
- The study population at enrolment was representative of a broad range of real-world gMG patients and was well-balanced between the two treatment groups, with respect to the key demographic and disease-specific variables
- Efficacy data for the primary and secondary endpoints are supported by sensitivity- and subgroup analyses. When the primary and secondary efficacy endpoints were analysed using additional analysis sets, alternative missing data assumptions, and an additional analysis method, results were consistent with the main primary and secondary efficacy analyses
- Outcomes that accurately reflect the impact on gMG on QoL (for example fatigue) were captured by the clinical and economic evaluations of zilucoplan
- The RAISE study addresses the decision problem (see Section B.1.1, Table 1):
    - The patient population included in the trial is in line with the final NICE scope, including 88 patients (50.6% of randomised patients) who were refractory to treatment. A pre-specified sub-group analysis was conducted on the cohort specified in this submission (refractory patients), with similar outcomes to the broad population
    - The key outcomes outlined in the NICE scope were evaluated in the RAISE study and included in this submission
    - In the RAISE trial, zilucoplan is compared with placebo (plus SoC). This is in line with established clinical practice in the UK, where there are currently no targeted treatments specifically approved for gMG and non-specific immunosuppression with ISTs is used for the management of gMG

Long-term effectiveness and safety of zilucoplan are demonstrated in the ongoing extension study, RAISE-XT:

- As of the interim clinical cut-off date of [redacted] had enrolled in the RAISE-XT study. Assuming study participants remain in this study for an average of [redacted] years, it is expected that this study will provide evidence for approximately [redacted] patient-years of zilucoplan exposure
- Data are available for up to [redacted] of zilucoplan treatment in RAISE-XT ([redacted] in addition to the 12week randomised placebo-control phase (RAISE)

B.2.12.2.2 Potential limitations

This submission is for patients with refractory gMG. However, the evidence base for zilucoplan (the RAISE clinical study) includes 86 (49.4%) patients with non-refractory gMG at baseline. Subgroup analyses were conducted on the population of interest to the submission (on the 50.6% of patients with refractory gMG), with similar outcomes to the broad population, and enabled robust -cost-effectiveness analyses.

As zilucoplan is a subcutaneous injection that can be self-administered at home, patients will be required to learn how to administer zilucoplan, with the help of specialist MG clinicians and nurses. There are no data to suggest compliance issues related to self-administration if zilucoplan.

B.3. Cost effectiveness

Summary

- A state transition Markov model was developed in Excel to evaluate the cost-effectiveness of zilucoplan as a treatment for adult patients with gMG from the perspective of the UK NHS/PSS. This structure captures the chronic nature of gMG and the variability in symptom severity experienced by gMG patients.
- The base case compared zilucoplan with efgartigimod, IVIg/SCIg, and plasma exchange in adult patients utilising the RAISE trial as the source of clinical characteristics.
- Base case deterministic ICERs for zilucoplan compared with efgartigimod, IVIg/SCIg, and plasma exchange are [redacted] and [redacted], respectively.
- The model predicts discounted QALY differences of 0.0294 in comparison with efgartigimod, 0.0986 in comparison with IVIg/SCIg, and 0.1077 in comparison with plasma exchange

B.3.1 *Published cost-effectiveness studies*

B.3.1.1 *Identification of studies*

A systematic literature review (SLR) was conducted (finalised in October 2023) to identify relevant economic evidence of treatments for patients with gMG relevant to the decision problem.

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

The review identified twelve studies containing economic evaluations, two were HTA appraisals. However, none of these economic evaluations were considered relevant for the economic analysis. Identification of resource use and cost data from the published literature relevant to the decision problem is described in Section B.3.5.1

B.3.2 *Economic analysis*

At present, there are no existing NICE technology appraisals providing guidance for medicines indicated for gMG. As the SLR did not identify any previous economic evaluation that compared zilucoplan to standard therapies in a UK setting, a *de novo* economic model was built in Microsoft® Excel to address the decision problem. The main features of the economic analysis are outlined in Table 51.

B.3.2.1 *Patient population*

Zilbrysq® (zilucoplan) is expected to receive MHRA authorisation in [redacted]. The anticipated label is 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. The cost-effectiveness analysis presented considers adults with AChR-Ab+ refractory gMG, per the clinical indication under review. UK clinical experts identified the sub-group of patients with sub-optimal response to treatments earlier in the pathway to be a significant burden to the system. The baseline population in the model therefore comprises only those patients who are uncontrolled on high-dose CSs and NSISTs. The baseline characteristics of these patients are explained in greater detail in Section B.3.3.1.1.

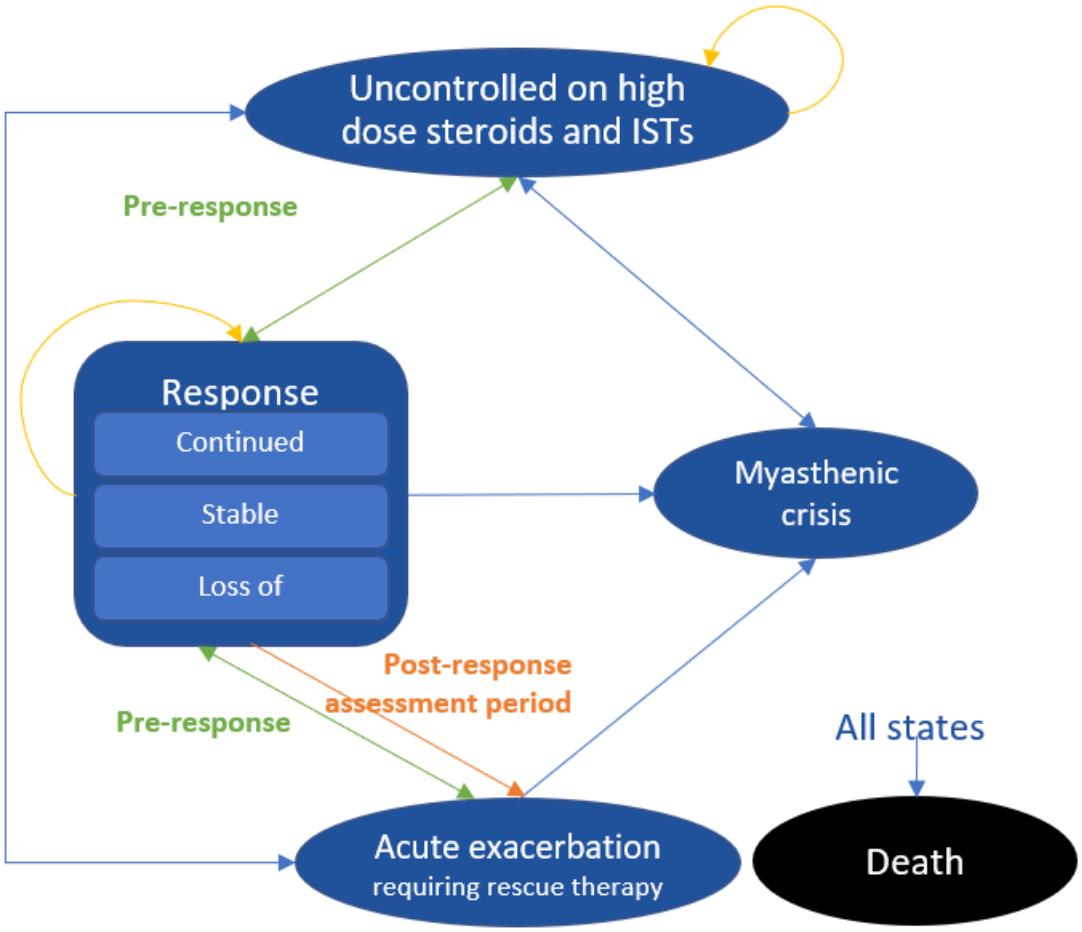
B.3.2.2 *Model structure*

A *de novo* cost-effectiveness model was developed to evaluate the cost-effectiveness of zilucoplan as an add-on to standard therapy for the treatment of adult patients with AChR antibody-positive refractory gMG who are uncontrolled on high-dose CSs and ISTs. Recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision-Making task force were followed to ensure the proposed model structure (172):

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

A Markov model was selected to illustrate the progression through seven different health states, encompassing patients on high-dose steroids and ISTs, which models their response to treatment and associated rates of exacerbation and myasthenic crisis. It captures the chronic nature of refractory gMG and incorporates the variability in symptom severity experienced by gMG patients throughout their lives. Cycle lengths are 2-weeks, providing a compromise between capturing the rapid transition of patients between key health states and the lack of long-term efficacy data, also meaning that a half-cycle correction isn't required. The model structure also allows for simplifying assumptions to be made about the long-term effects of treatments. The model structure is presented in Figure 29.

Figure 28. Model structure



The objective of the economic model is to estimate the cost-effectiveness of zilucoplan in patients with AChR-Ab+ refractory generalised myasthenia gravis. MG-ADL data collected in RAISE is used to model treatment response and associated exacerbations and myasthenic crises.

MG-ADL is an 8-item patient-reported outcome measure assessing MG symptoms and functional activities related to activities of daily living and producing a total score ranging from 0 to 24, where higher scores indicate greater severity of symptoms. A score of 6 or more is indicative of moderate to severe disease.

All patients enter the model in the 'Uncontrolled on high dose steroids and ISTs' health state, with a baseline MG-ADL score equal to the average baseline score reported in RAISE for refractory patients [redacted] Patients who meet the treatment response criteria (a decrease of ≥3 in MG-ADL score) transition to the 'response' health state at the response assessment timepoint (which differed by treatment and is shown in Table 53). At this point, patients separate into one of the three response sub-groups (continued, loss or stable response) defined in Table 50. In the pre-response assessment period, the model assumes that all responders report the same MG-ADL score equivalent to stable response until the response assessment time-point.

Within each health state (except death), patients are at risk of 'exacerbation', 'crisis' or 'death'. The model considers the impact of acute exacerbations and crises that require

hospitalisations on costs and HRQoL, and the impact of the chronic use of corticosteroids on mortality, HRQoL and costs.

B.3.2.3 *Health states*

The model is structured around seven mutually exclusive health states, described in Table 50.

Table 50. Health states included in the model

Health state	Definition
Uncontrolled on high dose steroids and ISTs	Patients with MG who do not achieve an adequate response or are intolerant to conventional treatment.
Continued (improved) response	A minimum of 3-point reduction from baseline (responder rate) in MG-ADL total score after time of response assessment AND ongoing improvement in MG-ADL score compared with baseline after time of response assessment.
Stable response	A minimum of 3-point reduction from baseline (responder rate) in MG-ADL total score at time of response assessment AND no change in MG-ADL score after time of response assessment.
Loss of response	A minimum of 3-point reduction from baseline (responder rate) in MG-ADL total score at time of response assessment AND an increase (worsening) in MG-ADL score after time of response assessment, with a return to the baseline MG-ADL score
Exacerbation	New worsening of symptoms reported by the patient accompanied by at least one of the following: • New weakness quantified by the medical research council (MRC) muscle power grade as 4 or less in more than one muscle group in more than one limb • Dysarthria with nasal or incomprehensible speech • Dysphagia associated with daily coughing and choking • Any exacerbation that had required hospital admission • Worsening of symptoms that prompted the neurologist to use PLEX or IVIg as a rescue therapy
Myasthenic crisis	Exacerbation requiring intubation
Death	Death health state

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

B.3.2.4 *Perspective*

Analyses were conducted from the perspective of the National Health Service (NHS) and of the Personal Social Services (PSS) in England, as per NICE guidance (173).

B.3.2.5 *Time horizon and model cycle length*

Myasthenia gravis is a chronic, lifelong, life-limiting condition requiring extensive care and treatment throughout the patient's lifetime. NICE guidance states that model time horizons should be long enough to capture all benefits of the treatment (174); therefore, a lifetime time horizon was applied to the model. The longer time horizon was applicable due to the

chronic nature of the condition, including the ongoing medical management required to address the symptoms of the disease. The lifetime time horizon captures all relevant costs and health outcomes associated with gMG and the respective treatments. The time horizon reflects the relatively early age of diagnosis for patients with MG, with the average age of diagnosis from the RAISE trial being 43.75 years.

The model applies a 2-week cycle length, which was considered by clinicians to be sufficient to account for the time patients may spend recovering from a worsening of symptoms, e.g. exacerbation or myasthenic crisis (175). Half-cycle correction was not implemented in the model, because a 2-week cycle length is short enough to capture the rapid transition of patients between key health states, and because there is a lack of long-term efficacy data.

B.3.2.6 *Discounting*

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

B.3.2.7 *Features of the model*

Features of the model are presented in Table 51.

Table 51: Features of the economic analysis

Factor	Chosen values	Justification
Model type	Markov	
Perspective	NHS and PSS	As per NICE reference case
Time horizon	Lifetime	As per NICE reference case (174). As gMG is a lifelong, life-limiting condition, a lifetime time horizon is required to capture all benefits of treatment.
Model cycle length	2 weeks	Considered short enough to capture changes in health and tolerability
Discounting	3.5% for costs and QALYs	In line with the NICE reference case
Type of economic analysis	Cost-utility analysis	As per NICE reference case
Source of efficacy	Change in MG-ADL score was the primary endpoint in the RAISE trial and predictor of HRQoL. Change in MG-ADL for comparators is informed by an NMA.	
Source of utilities	Utility values were derived from a repeated measures regression model of UK crosswalk utilities from RAISE (176). For this model, treatment arms were pooled.	As per NICE reference case, EQ-5D utilities were collected from the relevant population in the RAISE study. Literature values were used for ‘crisis’ and scenarios where data from the study population are not available
Source of costs	Pack costs were obtained from the BNF (177-185), or published list price for efgartigimod (129). Administration costs were sourced	As per NICE reference case

	from the NHS Schedule of Reference Costs 2020/2021 (186) or Personal Social Services Research Unit Costs (187).	

Abbreviations: BNF, British National Formulary; gMG, generalised myasthenia gravis; HRQoL, health-related quality of life; NHS, National Health Service; UK, United Kingdom.

B.3.2.8 *Intervention technology and comparators*

The intervention examined is:

- Zilucoplan, administered once daily via subcutaneous injection, in combination with standard care therapies.

The comparative treatments included in the analysis were identified through a targeted literature review and validated by UK clinical experts:

- Efgartigimod (subject to ongoing NICE technology appraisal)
- Chronic IVIg/subcutaneous immunoglobulin (SCIg)
- Chronic Plasma exchange (PLEX)

It's important to note that this list encompasses treatments that may be utilised in clinical practice but are either not approved for this particular indication or are not suitable for the specified patient population.

B.3.2.8.1 Intervention

The intervention in the analysis is zilucoplan 32.4 mg solution for injection in pre-filled syringe, self-administered once daily by subcutaneous injection in addition to standard of care therapies, as per the anticipated approved posology in the EU product label. Health-state transitions for patients receiving zilucoplan in the model are based on the zilucoplan arm from RAISE, as well as the RAISE-XT open-label extension study (in which all patients received zilucoplan).

B.3.2.8.2 Comparators

Based on literature review results, also validated by UK clinical experts, the comparators in the model are:

- Efgartigimod (subject to NICE guidance),
- Maintenance treatment with Ig (IV/SC)
- Maintenance treatment with PLEX

This aligns with the expected clinical pathway in England and Wales. Although rituximab can be used for patients with refractory disease, expert clinical opinion sought and recent publication by the AWTTC has suggested rituximab could be more effective when used as a first-line treatment for newly-diagnosed seropositive gMG with steroids, based on emerging clinical evidence (128). In addition, clinicians advise that rituximab is not very effective in refractory MG. Therefore, as rituximab is expected to be used earlier in the

pathway than zilucoplan, it was not considered a relevant comparator in the economic evaluation.

B.3.3 *Clinical parameters and variable*

The RAISE trial (Section B.2.6) and NMA (Section B.2.9) were the key data sources used to inform the clinical model inputs. Data from the 12-week double-blind phase of RAISE provide evidence to demonstrate the efficacy of zilucoplan in addition to SoC in the management of gMG. The RAISE-XT open-label extension provides an additional 60 weeks' evidence for patients receiving zilucoplan, including patients who switched from the placebo arm of the RAISE trial.

B.3.3.1.1 Baseline patient characteristics

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

To help confirm the population of the model is generalisable to England and Wales, cohort characteristics were obtained from the baseline characteristics of the refractory patients included in the RAISE trial and validated by UK clinical experts. The experts considered the overall baseline characteristics from the refractory sub-group from the RAISE trial reflects the patient population that would be treated with zilucoplan in England and Wales.

Table 52. Baseline model cohort characteristics

Characteristic	Model input
Mean age, years	[redacted]
Female, %	[redacted]
Mean weight, kg	[redacted]
Mean MG-ADL	[redacted]
Baseline BMI (kg/m^2)	[redacted]
Mean BSA (m^2)	[redacted]
Mean EQ-5D score at baseline	[redacted]

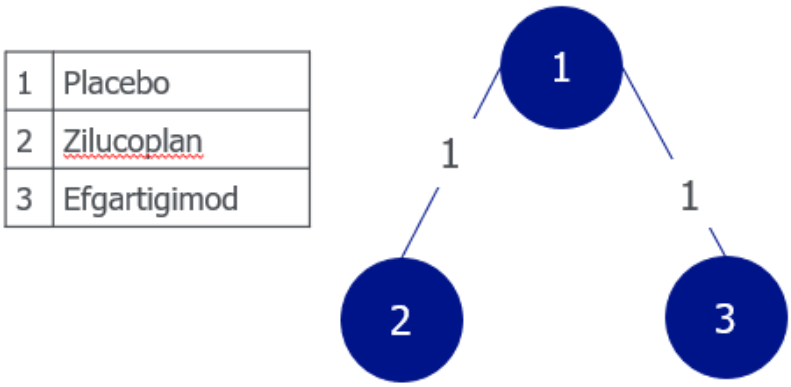
Abbreviations: BMI, body mass index; BSA, body surface area; EQ-5D, European quality of life-5 dimensions; MG-ADL, myasthenia gravis-activities of daily living.

The distribution of the simulated cohort between health states at model entry was based on baseline MG-ADL score of the AChR+ cohort in the RAISE study (n=174) (Table 13).

B.3.3.1.2 Rate of response

There were no head-to-head trials to compare zilucoplan with any of the comparators. Therefore, as recommended in the NICE process and methods guide, a network meta-analysis (NMA) was performed to evaluate the rate of response of each treatment relative to placebo, as described in Section B.2.9 (188). The rationale for the NMA is described in Section B.2.9.2. A network diagram for MG-ADL response data is shown in Figure 27.

Figure 29: MG-ADL response evidence network – primary analysis (Phase III trials that provided data on the ≥3 point improvement definition)



Abbreviatons: MG-ADL, myasthenia gravis activities of daily living.

Response in the NMA was defined as a ≥3-point improvement in a patient's MG activities of daily living (MG-ADL) score. Treatment response rates were calculated based on the odds ratio output from the NMA, applied to a referent response rate (SoC).

Firstly, ORs were converted to relative risks using the following formula due to difficulties associated with the interpretation of ORs (189):

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

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

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

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

The referent response rate was calculated as the simple average response rate across the studies used in the NMA. Odds ratios and calculated response rates used in the model are summarised in Table 53.

Response probabilities were applied up until the "Response assessment time point" (Table 53). This time point represented the period in which physicians may wait to see if a patient responds to treatment, the assumption being that if they have not responded at this point then treatment should be discontinued. Base case response timepoints were populated based on the trial endpoint associated with each of the comparators, due to limited information regarding the use of treatments in clinical practice.

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

It is worth considering that the response is assumed to be constant, but efgartigimod, which is an FcRn inhibitor, is dosed cyclically and therefore the response can wax and

wane throughout each treatment cycle, compared with zilucoplan, a complement inhibitor, which is dosed daily and therefore will inherently have a more stable response.

Table 53. Response rates and timepoints

Treatment	Odds ratio	Response rate	Source	Response timepoint used in the model (weeks)	Source
Zilucoplan	[redacted]	[redacted]	Data on file (NMA) (188)	12	Data on file (RAISE) (153)
Efgartigimod	[redacted]	[redacted]	Data on file (NMA)(188)	26	Howard et al 2021
Chronic IVIg/SCIg*	1.87	51.00%	Barth et al 2011 (190)	6	Assumption
Plasma exchange	1.42	44.17%	Barth et al 2011 (190)	6	Assumption

Abbreviations: IVIg, intravenous immunoglobulin; NMA, network meta-analysis; SCIg, subcutaneous immunoglobulin; SoC, standard of care.
*OR was not derived from ITC, it has been estimated to ensure the same calculated response rate from the literature

B.3.3.2 *Time on treatment*

Myasthenia gravis is a chronic, debilitating disease with unpredictable symptom burden; therefore, patients are expected to receive treatment for the rest of their lifetime. Zilucoplan demonstrated a rapid onset of action and sustained efficacy over the trial duration, resulting in a reduction in symptom expression as early as Week 1. Zilucoplan was well tolerated and demonstrated a good safety profile in RAISE and RAISE-XT. Due to its rapid onset of action, clinical experts noted that this will support making decisions on patients who are responding to zilucoplan, or likely to respond to zilucoplan and should continue treatment. Post response assessment period, patients who do not respond, or those who lose their initial response, are not assumed to continue to receive treatment due to lack of efficacy. Discontinuation of zilucoplan would be considered where patients have not responded to therapy or have lost response and/or for safety and tolerability issues. As the RAISE trial duration was 12 weeks, time on treatment in the model is expected to extend beyond the trial duration.

At the time of data cut ([redacted]), patients in RAISE and RAISE-XT had a maximum exposure of [redacted] and [redacted] participants remained in the study.

B.3.3.3 *Transition probabilities*

The probabilities of entering a specific health state during each cycle of the Markov model are based on the number of patients who, in the RAISE and the RAISE-XT studies, moved between health states during the pre-specified periods. The number of patients in each health state at the start and end of a period is used to estimate the transition probability matrices that are then applied over the time horizon of the analysis in the zilucoplan arm of the model. The transition matrices are calculated and applied in the model as described below and presented in Appendix M1.

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

At the outset, patients presented with a baseline MG-ADL score of [redacted], indicating a severe level of disease, posing significant treatment challenges. This was the mean MG-ADL score of refractory patients in the RAISE trial.

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

- Proportion of patients showing an initial response (Table 53, above)
- Proportion of patients showing signs of continued response (i.e. MG-ADL scores continue to fall over time)
- Proportion of patients who lose their initial treatment response (i.e. patients whose MG-ADL score initially improves, but over time their MG-ADL score starts to increase as their disease worsens)
- Proportion of patients who have a stable response (i.e. patients who experience an initial improvement in MG-ADL score, but after the response assessment their MG-ADL score remains stable)

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

Patients transition to one of the above three response health states (continued, stable, loss of response) based on a reduction ≥3 in the MG-ADL score using the odds ratios and response rates described in Section B.3.3.1.2. It was assumed that, of those patients in the response health states, [redacted] had loss of response, [redacted] had continued response, and [redacted] had stable response. The change from baseline for each health state differed.

The data pertaining to stable responders for zilucoplan and efgartigimod was extracted from the NMA. There was a lack of phase 3 trial data for IVIg and PLEX and the NMA results showed an increase (worsening) in change from baseline in MG-ADL score for IVIg (using phase 2 data); therefore, the response rate for placebo from the NMA was used as a proxy. The continued response assumes approximately [redacted] improvement vs stable response based on the difference between the CFB MG-ADL score at week 12 in RAISE (–4.79) and the lowest score reported in RAISE-XT [redacted]

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

The model attempts to account for a slow return to baseline MG-ADL score (i.e. the same as a patient who did not respond) over a period of time. In the base case, the model assumes patients return to baseline disease severity within 14 weeks of response assessment, based on the time taken for patients to return to a QMG score similar to their baseline after switching treatments in the Phase 2 eculizumab clinical trial (191), due to

immature discontinuation data from RAISE. The worsening of MG-ADL was assumed to follow a linear trend back to the baseline MG-ADL score.

The average change in MG-ADL score from baseline with different treatments is shown in Table 54. The average MG-ADL score in each health state is depicted in Figure 31.

Table 54: Average MG-ADL score change from baseline

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

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

In the uncontrolled response state, the average MG-ADL score did not change from baseline (Figure 31).

Figure 30 Average MG-ADL score for zilucoplan

[redacted]

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

B.3.3.5 *Clinical events*

Patients in any response health state had an annual rate of experiencing an exacerbation of 0.244 based on the incidence of 'any exacerbation' (mild, moderate, or severe) from Abuzinadah et al 2021 (192). The annual rate of myasthenic crisis was based on the incidence of exacerbations requiring intubation and was estimated as 0.0231 (192). For those patients in the uncontrolled health state, a relative risk of 2.67 was applied, based on the increased risk associated with patients with moderate to severe onset MG (192).

A summary of the annual event rates used in the base case of the model is presented in Table 55.

Table 55. Clinical event rates

Clinical events	Exacerbation	Myasthenic crisis	Source
Uncontrolled	0.651	0.062	Abuzinadah et al 2021 (192)
Response	0.244	0.023	

To account for patients who may experience an exacerbation, but further worsen to a myasthenic crisis, the model includes a 2-week event rate that is applied to all patients in the exacerbation health state. In the model base case, this value is 0.184, as identified from the incidence of patients receiving IVIg who required mechanical ventilatory assistance after 15 days (193). The incidence was converted to a two-weekly probability using the following formula:

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

General population background mortality was implemented for patients using the most recent National Life Tables for England (194). Patients in the myasthenic crisis health state had an increased risk of death, with 4.47% of patients in the myasthenic crisis health state dying within 2 weeks (146).

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

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

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

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

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

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

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

B.3.4 *Measurement and valuation of health effects*

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

HRQoL data were collected in the RAISE trial. EQ-5D-5L questionnaires were completed at baseline, then at Day 1, 8, 15, 29, 57, and 84.

B.3.4.2 *Mapping*

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

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

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

Electronic databases were searched on 01 May 2023 via the OVID platform using pre-determined search strategies, and included MEDLINE®, MEDLINE® In-Process, Embase, EconLit, and NHS-EED. Supplementary searches of public registries and databases, reference lists, previous HTA appraisals, and conference proceedings were performed to identify data not captured in the database search. Full details of the searches and results for HRQoL studies identified are reported in Appendix H.

In total, 95 studies reported data pertaining to humanistic burden of MG across various geographies (Table 102). Of these, 13 studies were conducted in the USA, eight each in Germany and China, seven in Japan, six in Brazil, four each in Canada, India, and Serbia, three each in Italy and Turkey, two each in Australia, Denmark, Thailand, Spain, Saudi Arabia, France, and Russia. One study each in Austria, Netherlands, Norway, Sweden, Malaysia, Poland, South Africa, and South Korea. Three studies were conducted in two countries: UK and US, Norway and Netherlands, Sweden and Estonia, and two studies were conducted in multiple countries. In the remaining eight studies, the country was not reported. The majority of studies were cross-sectional (n=48), 32 were observational, eight were surveys, five were registry-based studies, and two were case control- studies. The majority (n=47) were conducted with single centre, 31 studies did not provide this information, and 17 were multicentre studies.

Four studies reported utility values among patients with MG, assessed using EQ-5D index and SF-6D (see Table 103, Appendix H). Utilities were higher among patients in remission (0.92 [EQ-5D], 0.86 [SF-6D]) and with minimal manifestations; (0.94 [EQ-5D] and 0.83 [SF-6D]) (195). Increasing disease severity was associated with decreasing utility values as assessed by MGFA class (195, 196) .The utility value for overall MG population when assessed using EQ-5D index ranged from 0.68 (196) to 0.8 (197-199).

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

B.3.4.4 *Key differences*

In the model, the utility values are calculated based on the regression model described in Section B.3.4.6. Table 56 describes the utility values from published literature.

Table 56: Utility values from published literature

Study name	Group	n	EQ-5D Mean (SD)	SF-6D Mean (SD)
Barnett 2018	MG: with minimal manifestation	7	0.92 (0.04)	0.86 (0.14)
	MG: with pharmacologic remission	13	0.94 (0.03)	0.83 (0.07)
	MGFA class: I	52	0.89 (0.06)	0.81 (0.14)
	MGFA class: IIa	69	0.77 (0.15)	0.67 (0.13)
	MGFA class: IIb	44	0.79 (0.19)	0.68 (0.13)
	MGFA class: IIIa	25	0.58 (0.25)	0.54 (0.13)
	MGFA class: IIIb	35	0.59 (0.26)	0.56 (0.11)
	MGFA class: IVa	2	0.20 (0.17)	0.98 (0.06)
	MGFA class: IVb	7	0.60 (0.23)	0.53 (0.09)
Dewilde 2022	MG: Overall (real world sample)	610	0.689 (0.22)	
	MGFA class: I (real world sample)	83	0.817 (0.17)	
	MGFA class: II (real world sample)	162	0.766 (0.15)	
	MGFA class: III (real world sample)	226	0.648 (0.20)	
	MGFA class: IV (real world sample)	85	0.53 (0.27)	
	MGFA class: V (real world sample)	6	0.36 (0.50)	
Andersen 2021	MG overall (MG patients with no further details to patient disease characteristics)	100	0.8 (0.2)	
Mendoza 2020	MG overall (MG patients with no further details to patient disease characteristics)	124	0.8 (0.19)	

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

B.3.4.5 *Adverse reactions*

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

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

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

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

Utility values were derived from a repeated measures regression model of UK crosswalk utilities from RAISE (176). For this model, treatment arms were pooled.

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

The change in utility depended on the patient's baseline EQ-5D score, MG-ADL score, and body mass index (BMI), as described in Table 57. The regression model utilised a stepwise method for covariate selection, identifying BMI as the sole significant parameter. Consequently, BMI was incorporated into deriving the utility estimates due to its significance in the model.

Table 57. Utility equation and parameter estimates – RAISE

Parameter	Estimate	SE	P-value
Baseline EQ-5D	0.5521		
Baseline BMI, kg/m2	[redacted]	Data on file (153)	
Intercept [β0]	0.5868	0.05453	<0.0001
Coefficient of baseline EQ-5D (β1)	-0.4350	0.04150	<0.0001
Coefficient of MG-ADL score (β2)	-0.02183	0.001957	<0.0001
Coefficient of BMI (β3)	-0.00326	0.001293	0.0126

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

B.3.4.6.1 Clinical event disutilities

Exacerbations were associated with disutilities in the model, derived from patient-level data in the REGAIN trial, and reported in eculizumab's CADTH model (201), where an exacerbation was associated with a weighted average disutility of 0.20. This disutility was applied for 11.8 days, the expected duration of an exacerbation. A patient was then assumed to incur the average utility across the response and uncontrolled health states, weighted by the proportion of patients in each health state for the remaining 2.2 days of a

cycle. Following an exacerbation in the weeks prior to response assessment, patients return to one of the three response sub-groups to continue treatment and accrue costs and health outcomes associated with these patient groups accordingly. However, after the response assessment timepoint, patients who experience an exacerbation are assumed to discontinue treatment and transition to the uncontrolled health state where they accrue the costs and health outcomes associated with uncontrolled patients.

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

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

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

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

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

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

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

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

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

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

Table 58: Studies reporting resource data

Study, Year, Country	Cost year	Applicability to clinical practice in England	Resource type	Technology costs (£)
BNF 2020 (203)	2023	Completely applicable as derived from England database	IVIg (per unit cost)	6,480
NHS 2021-22 (204)	2023	Completely applicable as derived from England database	Plasma exchange (per unit cost)	11,722
Jones 2021(205)	2021	Completely applicable as derived from England database	GP visits	33
Jones 2021 (205)	2021	Completely applicable as derived from England database	Visit to other healthcare professionals	52
NHS 2021-22 (206)	2023	Completely applicable as derived from England database	Outpatient hospital visits	486
NHS 2021-22 (207)	2023	Completely applicable as derived from England database	Presenting at emergency room	278
NHS 2021-22	2023	Completely applicable as derived from England database	Hospital stay (with ICU, cost per critical care period)	11,738
NHS 2021-22 and 2017-18 (208) †	2023	Completely applicable as derived from England database	Hospital stay (no ICU, cost per day)	595

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

B.3.5.2 *Appropriateness of NHS Ref costs/PbR tariffs*

Unit costs were applied to resource use estimates, based on the latest values reported in the NHS reference costs and the PSSRU (187) in the UK.

B.3.5.3 *Clinical expert assessment of applicability of cost and healthcare resource use values*

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

B.3.5.4 *Intervention and comparators' costs and resource use*

B.3.5.4.1 Treatment costs

Zilucoplan is a once-daily self-administered subcutaneous injection. Total drug acquisition costs are calculated for all patients remaining alive in each arm of the model, based on net price. Zilucoplan costs are applied to all patients remaining on treatment in the zilucoplan arm. Patients receiving zilucoplan are assumed to receive SoC therapies as background treatment. Costs for these treatments are therefore applied to all surviving patients in both model arms throughout the modelled time horizon. The weighted list price per mg used in the model, based on the assumption that all treatment vial sizes were used equally, and the source for costs and posology, are shown below in Table 59. The mean treatment cost for zilucoplan and comparators is presented in Table 60. Where more than one formulation of a treatment was available, the mean price across all formulations of that treatment was used as the average per-cycle cost.

When calculating dosing and associated costs for treatments administered using mg/kg dosing, the model uses a standard parametric mean patient body weight. In the base case, the model assumes vials are not allowed to be shared across patients; therefore, wastage is recorded in the model, although there is an option to exclude such costs.

Table 59. Costs of treatments used in the model

Treatment	Weighted list price per mg (£)	Cost source	Posology	Posology source
Zilucoplan	[redacted]	Assumption	• <56 kg: 16.6 mg • ≥56 kg <77 kg: 23.0 mg • ≥77 kg: 32.4 mg Daily administration	Assumption Assumed launch posology
Efgartigimod	16.42	Product information	10mg/kg weekly administrations	Pasnoor et al 2016

Treatment	Weighted list price per mg (£)	Cost source	Posology	Posology source
IVIg/SCIg	0.07	BNF (177)	1,000 mg/kg, Q3W	NCT02473952 (209)
PLEX	2,587.45	BNF	Administered over 5 days Q4W	Expert opinion

Abbreviations: BNF, British National Formulary; CSs, corticosteroids; IVIg, intravenous immunoglobulin; Q3W, every 3 weeks; SCIg, subcutaneous immunoglobulin

Table 60. Mean drug acquisition cost for zilucoplan and comparators

Comparator	Cost in first and second model cycle (£)	Cost in subsequent model cycles (£)	Example annual cost (£)
Zilucoplan (based on net price)	[redacted]	[redacted]	[redacted]
Efgartigimod	26,279	26,279	262,789
IVIg/SCIg	3,898	3,898	101,684
PLEX	12,937†	5,861‡	153,597

Abbreviations: IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SCIg, subcutaneous immunoglobulin.
† In the model, the cost is applied as £6,468.5 to cycle one and two. ‡ Since PLEX is dosed every 4 weeks, the cost was applied to every two-weekly cycle as half of the NHS unit cost from 2021-2022 (204).

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

B.3.5.4.2 Administration costs

Administration costs per administration are shown in Table 61. Costs for zilucoplan were applied to the first cycle only, as the model assumes all subsequent administrations will be self-administered by the patient. Administration costs as applied to the model are presented in Table 62. The administration costs for PLEX were conservatively assumed to be equal to the subcutaneous administration cost.

Table 61. Administration costs

Administration route	Unit cost per treatment cycle (£)	Reference
IV administration	195.74 (initial administration)	NHS collection of costs WF01B (210)
	184.23 (subsequent administrations)	NHS collection of costs WF01A (210)
SC administration	41.00	Nurse time: 60 minutes, Band 5 hospital-based nurse (211)
Oral administration	0	Assumption

Abbreviations: IV, intravenous; NHS, National Health Service; SC, subcutaneous.

Table 62. Administration costs as implemented in the model

Administration route	Unit cost per treatment cycle (£)
Zilucoplan†	41.00
Efgartigimod	195.74
IVIg/SCIg	195.74
PLEX	41.00

Abbreviations: IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin; SOC, standard of care.
†Costs were applied as one-off costs associated with the cost of training patients to self-inject the treatment in future model cycles. The healthcare system was assumed not to incur any costs for self-injections in subsequent cycles.

B.3.5.5 *Health-state costs and resource use*

Annual resource use associated with patients with gMG in the 'Uncontrolled on high dose ISTs' and 'Response' health states were sourced from the literature (Table 63) and validated with UK clinical experts. Additionally, clinical event costs show the one-off costs patients incur as they transition through the 'Exacerbation' and 'Myasthenic crisis' health states(201). Unit costs were sourced from the Personal Social Services Research Unit(211), national schedule of NHS costs(210), and BNF(177).

Table 63. Health state resource use and unit costs

Resource	Costs		Health state			
			Uncontrolled	Response	Exacerbation	Myasthenic crisis
	Unit costs	Cost source	Frequency of resource use (192, 212) and length of stay (213)	Frequency of resource use (192, 212) and length of stay (213)	Frequency of resource use (192, 212) and length of stay (213)	Frequency of resource use (192, 212) and length of stay (213)
Health state resource use (all treatments except IVIG and PLEX)						
GP visits (211)	£33	Per surgery consultation lasting 9.22 minutes (214).	13.62	9.53	0.82	0.06
Visit to other Healthcare Professionals (211)	£52	Hospital based scientific and professional staff. Band 6 - physiotherapists/OTs. Cost per working hour (214).	11.47	6.89	0.58	0.32
Outpatient hospital visits (210)	£486	Outpatient care. Consultant led. Neurology Service. WF02A - Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up. (215)	7.10	4.77	0.75	0.50
Presenting at ER (210)	£278	Weighted average of Total codes VB01Z to VB09Z - Emergency Medicine, Any Investigation with Category 1-5 Treatment. (215)	0.44	0.33	0.38	1.00
Hospital stay (with ICU, cost per critical care period) (210)	£11,738	Weighted average of total costs for HRG codes XC01Z-ZC07Z: adult critical care, 1-6 organs supported. (215)	0.13	0.07	0.03	1.00

Resource	Costs		Health state			
			Uncontrolled	Response	Exacerbation	Myasthenic crisis
	Unit costs	Cost source	Frequency of resource use (192, 212) and length of stay (213)	Frequency of resource use (192, 212) and length of stay (213)	Frequency of resource use (192, 212) and length of stay (213)	Frequency of resource use (192, 212) and length of stay (213)
Hospital stay (no ICU, cost per day) (210)	£595	National Schedule of NHS Costs Year 2021-2022, 2017-18- Divided the total non-elective long stay costs from 2021/22 by the average length of stay (days) from 2017/18 to find the unit cost per day for each HRG code (AA26C-H: Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury), then took a weighted average of the unit cost by activity for each HRG code.	1.40, length of stay: 1.19 days	0.75, length of stay: 1.19 days	0.33, length of stay: 7.50 days	1, length of stay: 15 days
Corticosteroid usage cost (216)			£7,743.00	£2,949.50		
Total costs			**£14,896.09**	**£7,390.33**	**£9,209.88**	**£24,695.63**

Resource	Costs		Health state			
			Uncontrolled	Response	Exacerbation	Myasthenic crisis
	Unit costs	Cost source	Frequency of resource use (192, 212) and length of stay (213)	Frequency of resource use (192, 212) and length of stay (213)	Frequency of resource use (192, 212) and length of stay (213)	Frequency of resource use (192, 212) and length of stay (213)
Health state resource use (IVIG and PLEX)						
Hospital stay (no ICU, cost per day) (210)	£595	National Schedule of NHS Costs Year 2021-2022, 2017-18- Divided the total non-elective long stay costs from 2021/22 by the average length of stay (days) from 2017/18 to find the unit cost per day for each HRG code (AA26C-H: Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury), then took a weighted average of the unit cost by activity for each HRG code.	1.40, length of stay: 1.19 days	0.75, length of stay: 1.19 days	0.33, length of stay: 7.50 days	0.33, length of stay: 15 days
Total cost (IVIg)			**£14,896.09**	**£7,390.33**	**£8,840.30**	**£27,689.64**
Total cost (PLEX)			**£14,896.09**	**£7,390.33**	**£14,081.96**	**£32,931.31**

Abbreviations: ER, emergency room; GP, General Practitioner; HRG, healthcare resource group; ICU, intensive care unit.

B.3.5.6 *Adverse reaction unit costs and resource use*

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

B.3.5.7 *Miscellaneous unit costs and resource use*

A one-off cost was applied to the first cycle of the model for patients receiving zilucoplan because a proportion of patients receiving zilucoplan was assumed to require a meningococcal vaccine. The base case costs and proportion of patients requiring the vaccination are outlined in Table 64.

Table 64: Meningococcal vaccine costs

	Unit cost	Proportion requiring vaccine (201)
Cost of meningococcal vaccine	£48 (217)	4.00% (201)

B.3.6 *Severity*

It is not anticipated that the treatment of zilucoplan will be applicable for any form of severity weighting.

B.3.7 *Uncertainty*

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

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

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

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

B.3.8.2 *Assumptions*

A list of the key assumptions made within the model can be found in Table 65.

Table 65: Key model assumptions

Variable	Assumption	Rationale
Cycle length	2 weeks	Considered by clinical experts a sufficient length of time to account for the time patients may spend recovering from a worsening of symptoms (e.g., exacerbation or myasthenic crisis)
Time horizon	Lifetime (52.5 years)	The longer time horizon was applicable due to the chronic nature of the condition, including the ongoing

		medical management required to address the symptoms of the disease
Population	Patients with refractory AChR antibody positive gMG	This is the population of interest for this submission and the data are within the RAISE trial
Treatment response	Treatment response rate is applied in each model cycle up until the time of response assessment. After this point it is assumed that patients in the 'Uncontrolled on high dose steroids and ISTs' will not respond and therefore discontinue treatment	This represents the time at which a healthcare professional assesses whether to continue/discontinue treatment depending on response
Loss of response	There is a linear trajectory over a number of weeks, as defined by the user, in disease worsening after a patient loses the efficacy from their initial response	Based on similar outcomes shown in eculizumab's Phase II trial after patients switch from eculizumab to placebo treatment (191)
Disease worsening	Transition from exacerbation to crisis is independent of treatment received in the model	There is no evidence to suggest that once a patient's disease has worsened that further deterioration to a myasthenic crisis is a result of the initial treatment received
	Patients in the 'Uncontrolled on high dose steroids and ISTs' health state do not experience disease worsening over time (as defined by an increase in MG-ADL score)	Patients who require a change in treatment due to lack of control on high dose steroids and ISTs do not worsen, but will maintain their current state of health, unless they specifically worsen to an exacerbation or into a myasthenic crisis. A similar assumption was suggested by clinical experts during the eculizumab CADTH submission (201).
Mortality rate	Patients experience the same risk of mortality as the general public, unless patients experience a myasthenic crisis	Based on existing literature (218)
Time on treatment	Only patients in the 'Continued response' and 'Stable response' health states receive active treatment	Patients who do not respond, or those who lose their initial response, will not continue to receive treatment due to lack of efficacy
Administration costs	There are no costs associated with the administration of oral drugs	The Healthcare Professional time required to write and fulfil a prescription is negligible and the cost of the prescription would be borne by the patient
	The administration costs associated with zilucoplan are accounted for in the first cycle of the model only*	Patients receiving zilucoplan are assumed to not incur any additional associated administration costs due to the drug being self-administered
Pre-treatment costs	The model assumes the healthcare provider bears the cost associated with vaccinating a proportion of the patient population against meningococcal meningitis	Patients receiving zilucoplan may require a meningococcal vaccine before commencing treatment, as per RAISE and REGAIN clinical trial protocols

End of life costs	End of life costs are included as a one-off cost that is borne by the healthcare provider	This represents the additional costs associated with increased resource use of terminal patients
AEs	Adverse events are not included in the base case, but there is an option in the model to include. In this case, costs and disutilities associated with treatments are captured in the first cycle of the model only	This assumes AEs are associated with the initiation of treatment only, therefore AEs are not experienced over a long period of time as long-term AEs are assumed to result in treatment discontinuation

Abbreviations: AChR; acetylcholine receptor; AE, adverse event; gMG, generalised myasthenia gravis; IST, immunosuppressive therapy; MG-ADL, myasthenia gravis-activities of daily living.

B.3.9 *Base-case results*

Table 70 presents the base case results for zilucoplan versus efgartigimod (subject to NICE appraisal), IVIg and PLEX. In patients with refractory gMG, treatment with zilucoplan results in a change in mean life years (LYs) of –0.0010, 0.0010 and 0.0017 compared with efgartigimod, IVIg/SCIg and PLEX, respectively, and incremental QALYs of 0.0294, 0.0986 and 0.1077 when compared with efgartigimod, IVIg/SCIg and PLEX, respectively. This results in ICERs of [redacted], [redacted], and [redacted] in comparison with efgartigimod, IVIg/SCIg and PLEX, respectively. The base case economic results are reported with the current PAS discount of [redacted] applied on the list price of zilucoplan.

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

The costs, QALYs, and life years gained per treatment disaggregated into health states are presented in Table 68.

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

Table 66: Base-case results (based on the PAS discount on list price of zilucoplan)

Technologies	Total			Incremental vs. zilucoplan			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Zilucoplan	[redacted]	18.4057	9.7487				
Efgartigimod	£1,226,028	18.4067	9.7193	[redacted]	-0.0010	0.0294	[redacted]
IVIg/SCIg	£635,313	18.4047	9.6501	[redacted]	0.0010	0.0986	[redacted]
PLEX	£739,131	18.4040	9.6410	[redacted]	0.0017	0.1077	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; LYG, life years gained; PAS, patient access scheme; PLEX, plasma exchange; QALYs, quality-adjusted life years; SCIg, subcutaneous immunoglobulin.

Table 67: Net monetary benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	INMB at £20,000/QALY	INMB at £30,000 /QALY
Zilucoplan	[redacted]	9.7487				
Efgartigimod	£1,226,028	9.7193	[redacted]	0.0294	[redacted]	[redacted]
IVIg/SCIg	£635,313	9.6501	[redacted]	0.0986	[redacted]	[redacted]
PLEX	£739,131	9.6410	[redacted]	0.1077	[redacted]	[redacted]

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

Table 68: Disaggregated model results

	Zilucoplan	Efgartigimod	Chronic IVIg/SCIg	PLEX
Discounted life years				
Total life years	**18.4057**	**18.4067**	**18.4047**	**18.4040**
Uncontrolled on high dose steroids & ISTs	16.0029	15.7087	16.2910	16.4972
Response	1.8729	2.1737	1.5783	1.3675
Exacerbation	0.4121	0.4078	0.4164	0.4194
Myasthenic crisis	0.1178	0.1165	0.1190	0.1199
Discounted QALYs				
Total QALYs	**9.7487**	**9.7193**	**9.6501**	**9.6410**
Uncontrolled on high dose steroids & ISTs	8.4076	8.2427	8.5688	8.6843
Response	1.2037	1.3411	0.9424	0.8166
Exacerbation	0.1319	0.1301	0.1332	0.1344
Myasthenic crisis	0.0055	0.0053	0.0056	0.0057
Discounted Costs				
Total Costs	[redacted]	**£1,226,028**	**£635,313**	**£739,131**
Treatment costs	[redacted]	£765,908	£197,578	£224,793
End of life costs	[redacted]	£1,386	£1,387	£1,387
Resource use costs	[redacted]	£458,734	£436,348	£512,952
Resource use costs by health state				
Uncontrolled on high dose steroids & ISTs	[redacted]	£233,998	£242,673	£245,744
Response	[redacted]	£16,064	£11,664	£10,106
Exacerbation	[redacted]	£109,362	£96,036	£154,099
Myasthenic crisis	[redacted]	£99,309	£85,976	£103,002

Abbreviations: IST, immunosuppressive therapy; IVIg, immunoglobulin; PLEX, plasma exchange; QALYs, quality-adjusted life years; SCIg, subcutaneous immunoglobulin.

B.3.9.2 *Clinical outcomes from the model*

The clinical outcomes assessed are the event rates in various heath states of the model, presented in Table 69.

Table 69: Summary of clinical outcomes results from model

	Zilucoplan	Efgartigimod	Chronic IVIg/SCIg	Plasma Exchange
Total	[redacted]	**23.85**	**24.17**	**24.29**
Exacerbation	[redacted]	18.54	18.80	18.89
Myasthenic crisis	[redacted]	5.30	5.38	5.40

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

B.3.10 *Exploring uncertainty*

B.3.10.1 *Probabilistic sensitivity analysis*

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

B.3.10.1.1 Inputs

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

B.3.10.1.2 Results

The base-case ICER and the PSA mean ICER are shown in Table 70.

Table 70: PSA results

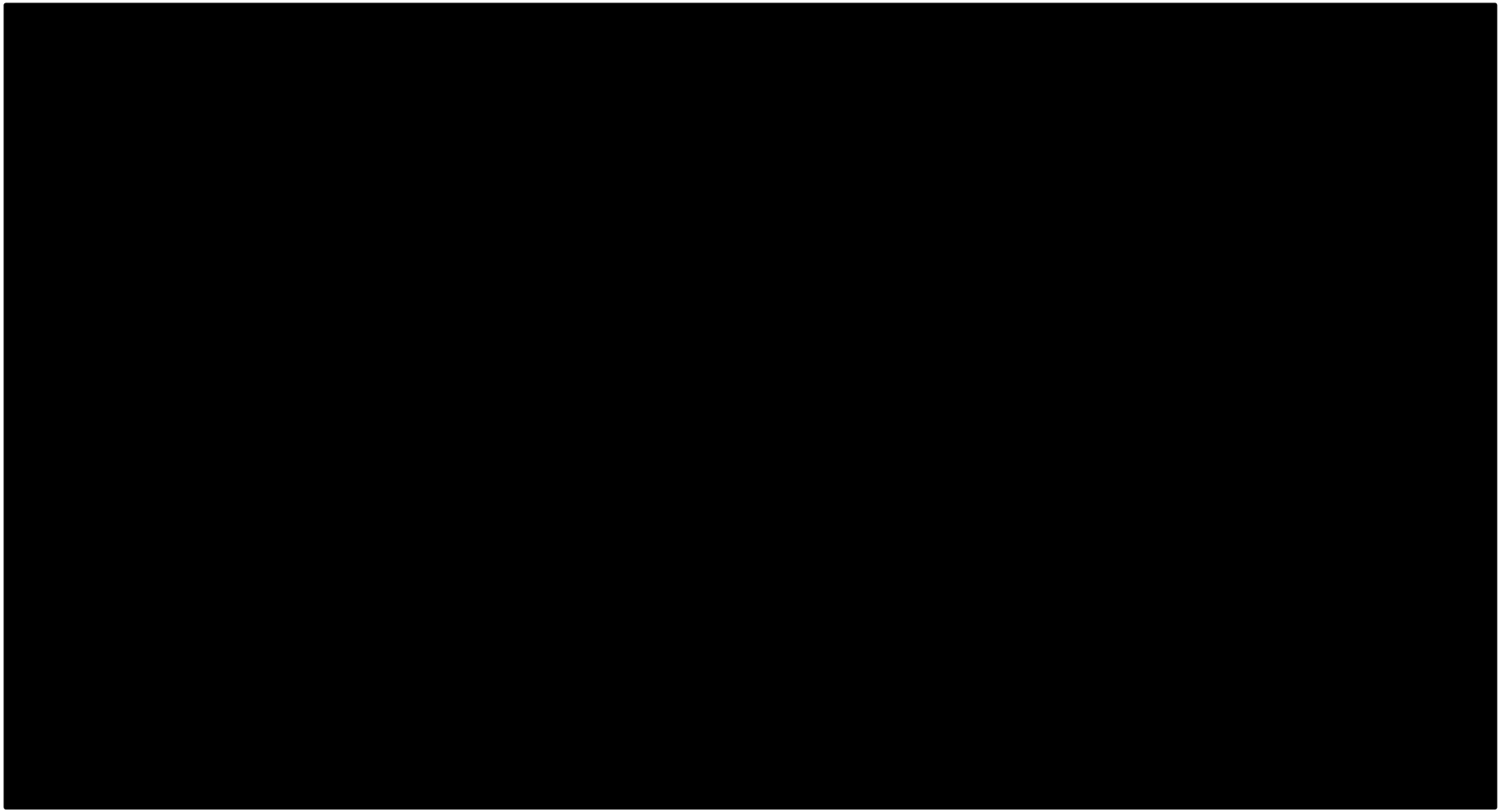
Treatment	Total		Incremental		Pairwise ICER per QALY gained
	Costs	QALYs	Costs	QALYs	
Zilucoplan	[redacted]	9.7584			
Efgartigimod	£1,121,959	9.6374	[redacted]	0.1211	[redacted]
IVIg/SCIg	£655,137	9.6005	[redacted]	0.1580	[redacted]
PLEX	£763,016	9.5918	[redacted]	0.1666	[redacted]

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

A cost-effectiveness scatterplot is shown in Figure 32. Points plotted in the north-west quadrant represent simulations in which the intervention was dominated by the comparator, i.e. the intervention incurred increased costs and provided fewer QALYs in contrast to the comparator. Points plotted in the south-east quadrant represent simulations in which the intervention was the dominant treatment, i.e. the intervention provided more benefit at a reduced cost in relative to the comparator. Points plotted in

the northeast and southwest quadrants reflect scenarios where the cost effectiveness is conditional upon the willingness-to-pay threshold.

Figure 31: Scatterplot of PSA results (Cost-effectiveness scatter plot)



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

Figure 32: Cost-effectiveness acceptability curve

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

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

Table 63 presents the variation between the base case results probabilistic sensitivity analysis results.

Table 71: Variation between base case and PSA results

	Total Costs (%)	Total QALYs (%)
Zilucoplan	9.93	0.10
Efgartigimod	-8.49	0.84
IVIg/SCIg	3.12	0.51
Plasma exchange	3.23	0.51

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

The table shows that differences between the base case and probabilistic sensitivity analysis mainly arise from different costs for different treatment arms. While the PSA doesn't include cost parameters, variations are likely propelled by healthcare resource use and effectiveness parameters.

B.3.10.2 *Deterministic sensitivity analysis*

For the DSA, model inputs were varied based on published standard errors for the respective model inputs. However, when these data were not available, a ±20% variation of the base case value was assumed conservatively. The most impactful inputs were summarised in a tornado diagram. The primary outcome considered in the DSA was the net monetary benefit (NMB) due to its stability where use of the incremental cost-effectiveness ratio (ICER) may produce extreme values and be difficult to interpret when the results fall in different quadrants of the cost-effectiveness plane. All the parameters that contributed to the DSA are outlined in Appendix N.2.

B.3.10.2.1 Results

Tornado diagrams showing the main drivers of the model are shown in Figure 34, Figure 35, and Figure 36 for the comparison vs efgartigimod, IVIg, and plasma exchange, respectively. These results are also shown in tabular form in Table 72, Table 73 and Table 74.

Figure 33: Tornado diagram for zilucoplan versus efgartigimod

Abbreviations: CFB, change from baseline; ITC, indirect treatment comparison; IVIg, immunoglobulin; PLEX, plasma exchange; MG-ADL, myasthenia gravis activities of daily living; NMB, net monetary benefit.

Table 72: Tabular results of DSA for zilucoplan versus efgartigimod based on NMB

Rank	Parameter	NMB (£) with low value	NMB (£) with high value	Difference (£)
1	Exacerbation annual event rate - responders (0.19 to 0.31)	[redacted]	[redacted]	[redacted]
2	% showing stable response - efgartigimod ([redacted])	[redacted]	[redacted]	[redacted]
3	Avg. age of population ([redacted])	[redacted]	[redacted]	[redacted]
4	Myasthenic crisis annual event rate - responders (0.01 to 0.05)	[redacted]	[redacted]	[redacted]
5	Odds ratio (ITC) - efgartigimod ([redacted])	[redacted]	[redacted]	[redacted]
6	Exacerbation annual event rate - uncontrolled (0.52 to 0.78)	[redacted]	[redacted]	[redacted]
7	Exacerbation to myasthenic crisis 2 week event rate (0.17 to 0.25)	[redacted]	[redacted]	[redacted]
8	IVIg resource use - exacerbation (0.58 to 0.87)	[redacted]	[redacted]	[redacted]

9	Baseline BMI (kg/m^2) ([redacted])	[redacted]	[redacted]	[redacted]
10	Hospital stay (with ICU, cost per critical care period) resource use - myasthenic crisis (0.80 to 1.20)	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; DSA, deterministic sensitivity analysis; ITC, indirect treatment comparison; MG-ADL, myasthenia gravis activities of daily living; NMB, net monetary benefit.

Figure 34: Tornado diagram for zilucoplan versus IVIg

Abbreviations: CFB, change from baseline; ITC, indirect treatment comparison; MG-ADL, myasthenia gravis activities of daily living; NMB, net monetary benefit; PLEX, plasma exchange.

Table 73: Tabular results of DSA for zilucoplan versus IVIg based on NMB

Rank	Parameter	NMB (£) with low value	NMB (£) with high value	Difference (£)
1	Average patient weight (kg) ( )			
2	% showing stable response - IVIg/SCIg)			
3	% showing stable response - zilucoplan ( )			
4	Odds ratio - IVIg/SCIg (1.49 to 2.24)			
5	Odds ratio (ITC) - zilucoplan ( ))			
6	IVIg resource use - exacerbation (0.58 to 0.87)			
7	Hospital stay (with ICU, cost per critical care period) resource use - myasthenic crisis (0.80 to 1.20)			
8	PLEX resource use - exacerbation (0.22 to 0.33)			
9	PLEX resource use - myasthenic crisis (0.76 to 1.14)			
10	Avg. age of population ( ))			

Abbreviations: CFB, change from baseline; DSA, deterministic sensitivity analysis; ITC, indirect treatment comparison; IVIg, immunoglobulin; PLEX, plasma exchange; MG-ADL, myasthenia gravis activities of daily living; NMB, net monetary benefit.

Figure 35: Tornado diagram for zilucoplan versus plasma exchange

Abbreviations: ICU, intensive care unit; ITC, indirect treatment comparison; IVIg, immunoglobulin; NMB, net monetary benefit; PLEX, plasma exchange.

Table 74: Tabular results of DSA for zilucoplan versus PLEX based on NMB

Rank	Parameter	NMB (£) with low value	NMB (£) with high value	Difference (£)
1	% showing stable response - plasma exchange [redacted])	[redacted]	[redacted]	[redacted]
2	Odds ratio - plasma exchange (1.14 to 1.70)	[redacted]	[redacted]	[redacted]
3	% showing stable response - zilucoplan ([redacted])	[redacted]	[redacted]	[redacted]
4	Odds ratio (ITC) - zilucoplan ([redacted])	[redacted]	[redacted]	[redacted]
5	IVIg resource use - exacerbation (0.58 to 0.87)	[redacted]	[redacted]	[redacted]
6	Exacerbation annual event rate - uncontrolled (0.52 to 0.78)	[redacted]	[redacted]	[redacted]
7	Avg. age of population ([redacted])	[redacted]	[redacted]	[redacted]
8	Hospital stay (with ICU, cost per critical care period) resource use - myasthenic crisis (0.80 to 1.20)	[redacted]	[redacted]	[redacted]
9	PLEX resource use - exacerbation (0.22 to 0.33)	[redacted]	[redacted]	[redacted]
10	PLEX resource use - myasthenic crisis (0.76 to 1.14)	[redacted]	[redacted]	[redacted]

Abbreviations: DSA, deterministic sensitivity analysis; ICU, intensive care unit; IVIg, immunoglobulin; NMB, net monetary benefit; PLEX, plasma exchange.

B.3.10.3 *Scenario analysis*

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

B.3.10.3.1 Inputs

a. Whole population weight

Since weight is the biggest driver of the ICER in the comparison vs IVIg, a scenario was conducted that used the average weight of the overall population with gMG from RAISE of 89.1 kg (compared with [redacted] kg for the refractory cohort in the base case).

b. Source of response rate data

This scenario explores the source of responders data in the model. Due to the lack of long-term MG-ADL score data for any of the comparators, a scenario analysis was conducted to analyse the impact of changing the long-term modelling assumptions in the model. Table 75 shows the data used in the base case and scenario analysis.

Table 75: Inputs for responder data scenario

	Base case: data from ITC and publications (%)	Scenario: data from clinical trial publication (%)
Zilucoplan	[redacted]	73.10
IVIg/SCIg (190)	51.00	51.00
Efgartigimod	[redacted]	73.00
Plasma exchange (190)	44.17	44.44

Abbreviations: IVIg, immunoglobulin; ITC, indirect treatment comparison; PLEX, plasma exchange; SCIg, subcutaneous immunoglobulin.

B.3.10.3.2 Results

The deterministic results associated with each scenario are presented in Table 76.

Table 76: Scenario analysis results

Model assumption	Total costs	Total QALYs	Incremental Cost	Incremental QALYs	ICER (£/QALY)
Base case					
Zilucoplan	[redacted]	9.7487			
Efgartigimod	£1,226,028	9.7193	[redacted]	0.0294	[redacted]
IVIg/SCIg	£635,313	9.6501	[redacted]	0.0986	[redacted]
PLEX	£739,131	9.6410	[redacted]	0.1077	[redacted]
Whole population weight					
Zilucoplan	[redacted]	9.7487			
Efgartigimod	£1,226,028	9.7193	[redacted]	0.0294	[redacted]
IVIg/SCIg	£644,063	9.6501	[redacted]	0.0986	[redacted]
PLEX	£739,131	9.6410	[redacted]	0.1077	[redacted]
Response rate data source: From trial publications					
Zilucoplan	[redacted]	9.7766			
Efgartigimod	£1,234,928	9.7214	[redacted]	0.0552	[redacted]
IVIg/SCIg	£635,313	9.6501	[redacted]	0.1265	[redacted]
PLEX	£740,242	9.6413	[redacted]	0.1352	[redacted]

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

B.3.11 *Subgroup analysis*

No subgroup analysis was performed.

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

The economic evaluation has attempted to encompass all conceivable benefits of zilucoplan in the QALY estimation. However, there are notable benefits of zilucoplan therapy for gMG that remain outside the scope of this evaluation. In particular, patient HRQoL was assessed using the EQ-5D instrument, which is non-disease-specific and therefore may be insensitive to the most common symptoms of MG, such as fatigue, vision impairment and hand weakness (118-120). A report by the Office of Health Economics (OHE) suggests that generic measures of HRQoL may fail to reflect what matters to patients by not capturing symptoms such as fatigue (118). In addition, the EQ-5D may miss changes to QoL when patients' symptoms and functioning are unpredictable and fluctuate over time. It is likely that widespread use of non-disease-specific instruments may lead to underrepresentation of the impact of MG on HRQoL (119, 120).

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

Furthermore, the impact of a subcutaneous administration option on patient burden/patient preference and carer quality of life, as well as health-related quality of life, is likely not accounted for in the QALY calculation.

Lastly, the economic model has not captured the full impact of gMG on carer disutility or on societal impact (productivity losses due to absenteeism). A survey of expert physicians across France, Germany, Italy, Spain, the UK, and the US reported that 38% of patients with gMG required a caregiver (14, 17, 18). In total, 25% of caregivers changed their work status or retired as a result of needing to provide care (18), which will affect both costs and QoL for the carer. Unemployment rates are higher for patients with MG than the general population or matched control groups, and higher compared with other chronic conditions (13-16). This, along with sickness absence and the resulting reduced income, will affect both cost and QoL of patients for much of their working lives, since MG is diagnosed at an early working age (51).

B.3.13 *Validation*

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

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

- Confirmed that all model inputs were correctly linked to the model engine
- Checked all cells with "IF logic" in detail, confirming that the statements provided the correct value for each condition
- Traced all links between the calculation sheets and results sheet to make sure that the proper outputs were displayed in the correct location

- Thoroughly reviewed and debugged all Visual Basic for Applications code
- Searched for common Microsoft Excel® errors (e.g.,!#REF errors, unused named ranges, broken links, links to external workbooks, copy/paste errors) and resolved them as needed
- Checked all text and formatting to ensure that there were no typographical errors or formatting irregularities

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

B.3.14 *Interpretation and conclusions of economic evidence*

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

Costs and outcomes were estimated based on the most relevant sources available in the UK including BNF and PSSRU. The results of the base case analysis indicate that the ICER for zilucoplan is [redacted] in comparison with efgartigimod with incremental costs of [redacted] and incremental QALYs of 0.0294. In comparison with IVIg/SCIg, the ICER is [redacted] with incremental costs of [redacted] and incremental QALYs of 0.0986. For the comparison versus plasma exchange, the ICER is [redacted] with incremental costs of [redacted] and incremental QALYs of 0.1077.

The model parameters with the most significant impact on the ICER, as identified from the DSA performed, included the clinical parameters and healthcare resource utilisation parameters for all the treatments.

At present, the model provides a platform for estimating the costs and health outcomes associated with the adoption of zilucoplan compared with current and upcoming therapeutics in the treatment of patients with refractory gMG who are currently uncontrolled on high dose steroids and ISTs. The model is flexible to allow the user to edit inputs and vary assumptions, which is important when uncertainty remains in the available data.

The key strength of the economic evaluation is its flexibility and scope for future expansion and enhancement; the model can accommodate a wide variety of inputs, and the key parameters of the model are user modifiable. In this analysis, the healthcare resource use

and cost parameters in the model were derived from recent sources, the majority from the UK databases. Furthermore, the mortality data were adjusted using UK life table data.

The limitations of this analysis are largely centred around the availability, or lack thereof, of long-term efficacy data for any of the comparators. Therefore, the assumptions that most responders maintain their response is uncertain past the current data cut of RAISE-XT, with scenario analyses indicating that this assumption can substantially impact the health outcomes in the model. Another limitation is that the response in the model is assumed to be constant, but efgartigimod, which is an FcRn inhibitor, is dosed cyclically and therefore the response can wax and wane throughout each treatment cycle, compared with zilucoplan, a complement inhibitor, which is dosed daily and therefore will inherently have a more stable response. This adds bias to the results in favour or efgartigimod.

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Zilucoplan for antibody positive generalised myasthenia gravis

Summary of Information for Patients (SIP)

30th November 2023

File name	Version	Contains confidential information	Date
SIP	1.0	Yes	30th November 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Generic name: zilucoplan Brand name: Confidential

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

Adult patients with acetylcholine receptor (AChR) antibody-positive generalised myasthenia gravis (gMG) that are refractory (not responding) to standard treatment, and therefore require an additional treatment on top of their standard prescribed therapies to help control their symptoms.

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

European Medicines Agency Positive opinion was granted in September 2023 from the Committee for Medicinal Products for Human Use (CHMP): https://www.ema.europa.eu/en/medicines/human/summaries-opinion/zilbrysq UK regulatory approval Approval is expected via the European Commission Decision Reliance Procedure route. Further information related to the marketing authorisation of zilucoplan can be found in the company submission, Document B, Section B.1.2.

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

MyAware are members of the MG Community (patient advocacy groups [PAGs] from across Europe), which is supported by UCB, and are attending the Rare Disease Connect in Neurology (RDCN) congress in late 2023. There are no other collaborations or financial support being provided.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

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

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

What is myasthenia gravis?

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

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

Patients experience debilitating fatigue and weakness in muscles responsible for vital functions including breathing, swallowing and mobility. Persistent fatigue is one of the most common symptoms of MG and negatively impacts daily activities – such as walking, self-care and going to work – to such an extent that employment and working hours are impacted and caregiver support is needed (3, 7-14).

Myasthenia gravis has a profound impact on the quality of life of affected people. The severe, chronic symptoms of gMG negatively impact patients' mental health and are associated with depression, fear and anxiety (15-18), particularly in those with active disease despite receiving maximal immunosuppression therapy (12, 19-23).

The symptoms of gMG are unpredictable and fluctuate in intensity. Patients can experience sudden worsening of their symptoms that requires urgent intervention to prevent life-threatening deterioration of muscle weakness and respiratory failure (known as a myasthenic crisis) (5, 24-26), which requires treatment and mechanical ventilation in an intensive care unit (24, 27-29).

Patients feel that living with gMG impacts their decision to have a family. Concerns about the effects of gMG on their ability to cope as a parent can deter patients from planning a pregnancy (18). Younger patients in particular may feel a sense of loss due to restrictions in activity and limitations in life choices (18).

How many people develop MG?

It is estimated that there are currently 19,053 people living with MG in England (30, 31). MG is more common in females (60% of patients) than males (40% of patients) (32, 33), and females are younger than males at disease onset (mean age of disease onset is 35±18 vs 45±18 years, respectively [$p<0.001$]) (34). Women are therefore exposed to the economic, social, and quality-of-life impact earlier in life and for longer than men, over more of their working lives, amounting to a greater total burden. Women face a considerable economic and social disadvantage if MG diagnosis occurs at a time in their lives when they may be building a career and/or starting a family.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

There is no formal pathway for diagnosis recommended by NICE. MG is a rare disease and therefore unfamiliar to many doctors, and an overlap in symptoms with other neurological diseases can result in an MG diagnosis being missed or delayed (4, 35).

Diagnosis is based on the signs and symptoms, neurological findings, and laboratory results, while excluding other diagnoses (29, 36, 37). The Association of British Neurology management guidelines and others recommend that MG is diagnosed through a combination of patient medical history, physical and neurological exams, autoantibody serum testing, and electrophysiological tests (35, 36, 38-40).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

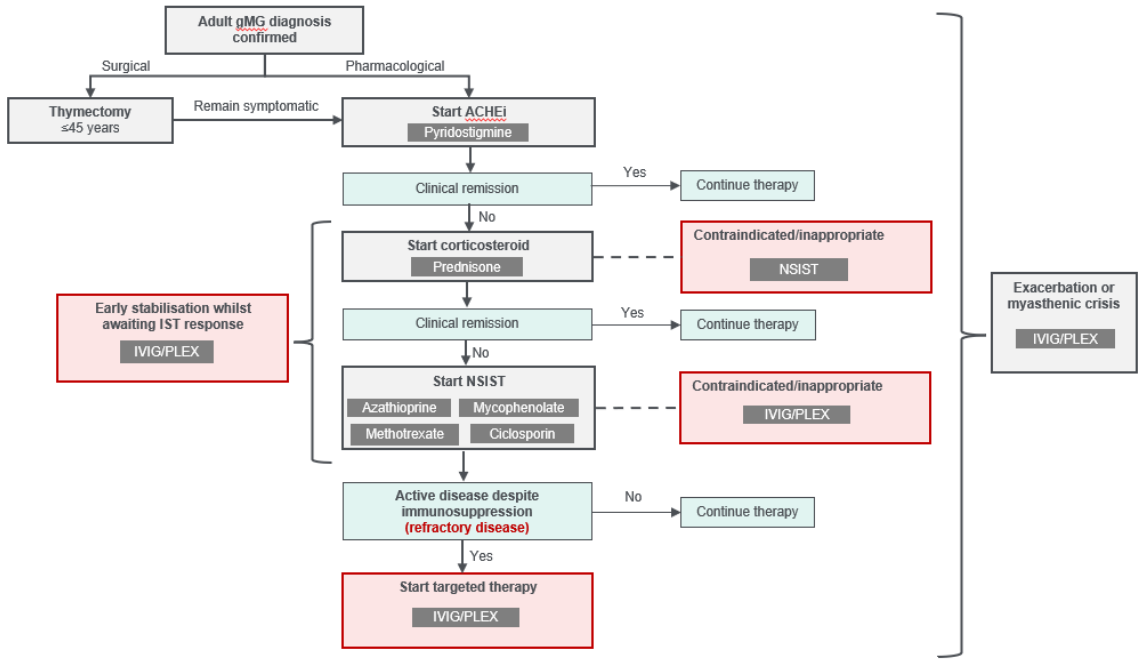
What treatments are currently available?

Treatment for people with gMG focuses on controlling symptoms and providing supportive care. There are no treatments addressing the root cause of MG, therefore current options for patients are based on non-specific suppression of the immune system (40, 41). Many of these treatments are currently not licensed for MG in the UK (including azathioprine, methotrexate, ciclosporin and rituximab) (40, 42-46). There are no completed NICE technology appraisals or guidance for gMG.

Standard of care includes cholinesterase inhibitors such as pyridostigmine (40, 42, 43) (Figure 1). If treatment with cholinesterase inhibitors is not effective or only provides short term relief, corticosteroids such as prednisolone are used (40, 42, 43). Non-steroidal immunosuppressive therapies (NSISTs) are offered in addition to steroids as current standard of care, with the aim of reducing the corticosteroid dose over time.

Patients may cycle through different immunosuppressive therapies until their symptoms are under control. For patients who continue to experience active disease despite maximal immunosuppression, intravenous immunoglobulin (IVIg) or plasma exchange (PLEX) can be used, although both are associated with limitations related to supply and treatment burden (long infusion duration which some patients have to travel long distances for), and are costly to the healthcare system and are supported by a limited evidence base (40, 42, 43, 47, 48).

Figure 1. Current treatment pathway for mild-to-severe gMG in the UK



Source: Adapted from the ABN management guidelines and validated by UK clinical expert opinion (39, 40, 43).

Why is there a need for new treatments?

Patients with active disease despite receiving maximal immunosuppressive therapy experience ongoing, burdensome symptoms, poor quality of life and are at risk of myasthenic exacerbation and crisis (12, 19-23, 27, 49-56). Given the limitations of current treatment options, there is an urgent unmet need for a novel targeted treatment to improve clinical outcomes for patients with gMG. A targeted treatment with a fast onset of action that minimises both symptom burden and the burden of therapy (for example side effects and having to travel for treatment), and reduces the risk of myasthenic exacerbations and crises, would improve quality of life for patients with gMG. Patients would also benefit from a home-based treatment which would offer more convenience and fit better into their everyday lives than current therapies, some of which require having to travel for treatment at specialist centres or hospitals.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patients with gMG experience debilitating symptoms that severely impact all aspects of their lives (18).

Patient-based evidence indicates that patients with gMG experience poor quality of life (QoL) (57-60). Factors associated with worse QoL include:

- Refractory gMG (compared with non-refractory disease)

- Severe disease (compared with less severe disease)
- Being female
- Age <40 years (compared with age >65 years)

In addition to the burden of living with symptoms of gMG, QoL is impacted by the effects of long term corticosteroid use, which is associated with high rates of depression among patients with gMG (61-63).

Of patients with gMG participating in a survey, 50% reported that their disease impacted their ability to lead a full life. Of patients with moderate to severe disease, 48% felt their ability to perform daily routines was considerably impaired by their disease (64).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Zilucoplan is a C5 complement inhibitor that inhibits a part of the immune system called the complement system, which is inappropriately activated in myasthenia gravis. Zilucoplan has a dual mechanism action as it inhibits the complement system in two ways, preventing the destruction of the neuromuscular junction that is one of the main causes of MG (65).

Zilucoplan is a once-daily subcutaneous injection that provides patients the freedom to administer in their own homes. The Phase III RAISE clinical trial met all of its primary and secondary endpoints (66). Patients who received zilucoplan in addition to standard of care experienced clinically meaningful improvements in symptoms of gMG, with improvements seen as early as one week after starting treatment. Zilucoplan had a favourable safety profile and was well tolerated, with no major safety findings.

Zilucoplan may also reduce the need for corticosteroids, which are associated with burdensome side effects. As it can be self-administered at home, zilucoplan may reduce the impact of ongoing treatment on the daily lives of patients with gMG.

It is anticipated that zilucoplan will be offered as an add-on to current standard of care for patients with refractory gMG, as these patients have an urgent unmet need for a treatment with a fast onset of action that can control symptoms and reduce the risk of myasthenic crisis.

It is estimated that zilucoplan will reduce the devastating impact of uncontrolled disease, as well as the treatment burden associated with non-specific treatments such as corticosteroids, on patients and the healthcare system, improving quality of life for patients with high unmet needs.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of

life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

The intended use for zilucoplan is as an add-on treatment to standard of care to control symptoms in patients with refractory gMG (65). There are no known reasons preventing zilucoplan being prescribed as an add-on to other gMG therapies. Based on the potential inhibitory effect of zilucoplan on complement-dependent cytotoxicity of rituximab, zilucoplan may reduce the expected pharmacodynamic effects of rituximab (65). Rituximab is not a licensed treatment for MG.

Due to its novel mechanism of action (zilucoplan specifically targets an immune system pathway called the complement system; see Section 3a), zilucoplan is expected to provide additional benefits beyond standard of care treatments, which do not provide symptom relief for some patients with gMG who have active disease despite maximal immunosuppression (67, 68).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Zilucoplan is provided as a clear solution for subcutaneous injection in a pre-filled syringe. The recommended dose is based on patient weight (Table 1) and should be administered once daily around the same time each day (65).

Table 1. Total daily dose by body weight range

Body weight	Dose†	Number of pre-filled syringes by colour
<56 kg	16.6 mg	1 (Rubine red)
≥56–<77 kg	23 mg	1 (Orange)
≥77 kg	32.4 mg	1 (Dark blue)

Source: Draft SmPC for zilucoplan (65).
†The recommended dose corresponds to approximately 0.3 mg/kg.

As a subcutaneous treatment that can be self-administered at home, zilucoplan offers more convenience and fits better into patients' everyday lives than current therapies, some of which require having to travel for treatment at specialist centres.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Phase II trial:

Name: MG0009

Locations: The US and Canada

Population: Patients age ≥18 years with acetylcholine receptor antibody positive gMG.

Key inclusion criteria:

- Diagnosis of gMG [Myasthenia Gravis Foundation of America (MGFA) Class II-IV] at Screening
- Positive serology for acetylcholine receptor (AChR) autoantibodies
- MG-ADL Score of ≥ 6 at Screening and Baseline (where a higher score means worse symptoms)
- QMG score ≥ 12 at Screening and Baseline
- No change in corticosteroid dose for at least 30 days prior to Baseline or anticipated to occur during the 12-week Treatment Period

- No change in immunosuppressive therapy, including dose, for at least 30 days prior to Baseline or anticipated to occur during the 12-week Treatment Period

Key exclusion criteria:

- Thymectomy within 12 months prior to Baseline or scheduled to occur during the 12-week treatment period
- History of meningococcal disease
- Current or recent systemic infection within 2 weeks prior to Baseline or injection requiring intravenous (IV) antibiotics within 4 weeks prior to Baseline

Study size: Number of participants = 45

Comparators: Placebo (non-active substance) + standard of care. Patients were randomised to receive either zilucoplan or a placebo in addition to their standard gMG medications.

Started: October 2017

Completed: December 2018

Study publication: https://pubmed.ncbi.nlm.nih.gov/32065623/

National Clinical Trials link: https://clinicaltrials.gov/study/NCT03315130

Phase III trial:

Name: RAISE (Safety, Tolerability, and Efficacy of Zilucoplan in Subjects with Generalized Myasthenia Gravis)

Locations: The UK, France, Germany, Italy, Japan, Norway, Poland, Spain, the US, and Canada

Population: Patients age ≥18 years with acetylcholine receptor antibody positive gMG

Key inclusion criteria: Same as for MG0009 (see above), with the addition of: MG-ADL Score of ≥ 6 at Screening and Baseline (where a higher score means worse symptoms)

Key exclusion criteria:

Same as for MG0009 (see above).

Study size: Number of participants = 174

Comparators: Placebo (non-active substance) + standard of care. Patients were randomised to receive either zilucoplan or a placebo in addition to their standard gMG medications.

Started: September 2019

Completed: December 2021

Study publication: https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(23)00080-7/fulltext

National Clinical Trials link: https://clinicaltrials.gov/ct2/show/NCT04115293

Extension trial

Name: RAISE-XT (Open-Label Extension of Zilucoplan in Subjects with Generalized Myasthenia Gravis)

Locations: The UK, France, Germany, Italy, Japan, Norway, Poland, Spain, the US, and Canada

Population: Patients age ≥18 years with acetylcholine receptor antibody positive gMG who have previously participated in a zilucoplan clinical trial (RAISE or MG0009, a Phase IIa trial)

Key inclusion criteria: Completion of a qualifying zilucoplan study

Key exclusion criteria: With the exception of a prior zilucoplan trial, participation in another concurrent clinical trial involving an experimental therapeutic intervention (participation in observational studies and/or registry studies is permitted)

Study size: Number of participants = 200

Comparators: None. All participants received zilucoplan as RAISE-XT is a single-arm, open-label extension study with no comparator treatment

Started: December 2019

Completed: RAISE-XT is ongoing, with an estimated completion date of June 2026

Study publication: https://n.neurology.org/content/100/17_Supplement_2/2948
National Clinical Trials link: https://clinicaltrials.gov/study/NCT04225871

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Zilucoplan, in addition to standard of care treatments for patients with gMG, is associated with significant improvements in the signs and symptoms of gMG disease activity and quality of life (QoL), with a fast onset of action, and sustained long-term efficacy.

RAISE, a Phase III, randomised, placebo-controlled trial, provides pivotal clinical evidence for zilucoplan as an add-on treatment to standard of care for patients with gMG. The ongoing open label extension phase of RAISE, RAISE-XT (interim results; cut-off date May 2023), demonstrates the long-term efficacy and safety of zilucoplan in this patient population.

RAISE

Zilucoplan reduces disease activity and symptom burden in patients with gMG

Section B.2.6.1.1 of the company submission

In the RAISE study, the primary efficacy endpoint (change in Myasthenia Gravis Activities of Daily Living [MG-ADL] score, which measures the symptoms of MG related to activities of daily living, from the start of the study) was met. Patients who received zilucoplan in addition to their standard treatments had a significantly greater change from baseline to Week 12 MG-ADL scores compared with the standard of care + placebo-treated group (−4.39 vs −2.30, respectively, where a reduction in score means an improvement in symptoms). This significant difference vs placebo (least squares [LS] mean difference −2.09, $p<0.001$) was also considered clinically meaningful.

Reducing disease activity and symptoms is the primary therapeutic aim of treatment for patients with gMG, and results from the RAISE trial show that zilucoplan provides a greater reduction in the symptoms of gMG, and how they interfere with daily living, compared with current standard of care treatments + placebo.

Zilucoplan may lower the risk of myasthenic exacerbation and crisis in patients with gMG

Section B.2.6.1.2 of the company submission

A numerically lower proportion of patients receiving zilucoplan treatment (5% [n=4/86]) required rescue therapy compared with placebo (12% [n=10/88]) over the course of the RAISE study, suggesting that zilucoplan reduces the risk of exacerbation of symptoms or myasthenic crisis.

Zilucoplan improves QoL for patients with gMG

Section B2.6.1.2 of the company submission

Patients who received zilucoplan in addition to their standard of care treatments experienced a significant improvement from the start of treatment to Week 12 in quality of life (measured by the MG-QoL15r survey score) compared with patients in the placebo + standard of care group ($p=0.0128$). Patients experienced an improvement in quality of life as early as Week 1 after receiving zilucoplan.

Zilucoplan reduces fatigue in patients with gMG

Section B.2.6.1.3 of the company submission

Zilucoplan was associated with a reduction in fatigue, as measured by the Neuro-QoL Fatigue scale. Patients who received zilucoplan in addition to standard of care had a significantly greater

improvement from the start of the RAISE study to Week 12, compared with patients in the placebo + standard of care group (p=0.0069).

RAISE-XT

Section B.2.6.2 of the company submission

All patients who received zilucoplan in RAISE-XT experienced improvements in the signs and symptoms of disease activity and quality of life. Patients continued to improve through Week 12 of the extension study, which was maintained through Week 84, demonstrating the long-term benefits of zilucoplan as an add-on to standard therapies for gMG.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The RAISE clinical trial demonstrated a significant improvement in the quality of life of patients who received zilucoplan in addition to standard of care treatment, compared with placebo + standard of care treatment. Patient quality of life was assessed in the RAISE trial using the:

- MGQoL15r survey (an MG-specific self-administered patient-reported outcome survey designed to assess quality of life)
- EuroQoL-5D-5L (a standardised survey for measuring generic health status, assessing the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression)
- Neuro-QoL Short Form fatigue scale (quantifies the physical, mental, and social effects experienced by patients with neurological conditions). This tool captures symptoms that are important to patients with gMG, such as fatigue.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The most frequent adverse events experienced by patients treated with zilucoplan are general disorders and administration site conditions, including injection site reactions, bruising and pain. However, overall, zilucoplan has been shown to be generally well tolerated in clinical studies to date.

During the double-blind phase of the RAISE study, zilucoplan was generally well tolerated in patients with gMG, with most side effects following treatment categorised as mild or moderate in severity. Zilucoplan continued to be well tolerated in the extension phase (RAISE-XT), with no new safety signals observed.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There are no approved treatments that specifically target the underlying abnormal immunological processes in gMG to control disease activity and symptoms in patients with active disease despite maximal immunosuppression. Treatments such as IVIg and PLEX are available for these patients, although both are associated with limitations related to availability (IVIg is in short supply in the UK (47, 69, 70)) and treatment burden, and are costly to the healthcare system (40, 42, 43, 47, 48). Therefore, there is an urgent need for a treatment with a targeted mechanism of action (see Section 3k) to control symptoms and reduce the burden of gMG on patients and their families.

The clinical benefits of zilucoplan, demonstrated in the RAISE study (and its open-label extension, RAISE-XT) help address these unmet needs for patients with gMG who continue to experience disease activity despite maximal immunosuppression. These patients experience chronic, ongoing symptoms that interfere with daily living and reduce their quality of life (25, 47, 49, 69-75). In addition, patients with ongoing symptoms have a high treatment burden related to cycling through different therapies with little or no relief from their symptoms. Patients whose symptoms are not controlled live with the risk of myasthenic exacerbation and crisis (27, 49-56).

The primary outcome in the RAISE study (change in MG symptoms [measured by MG-ADL] to Week 12) and other key outcomes assessed in this trial are expected to translate into clinical benefits to patients in real-world practice, including:

- Improvements in signs and symptoms of gMG, and how they interfere with activities of daily living
- Improvements in quality of life
- Reduction in fatigue
- Potential to reduce the risk of myasthenic exacerbation and crisis
- Sustained efficacy and tolerability in the long-term (open-label interim results)

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The most common side effect reported by patients who received zilucoplan during the Phase III trial RAISE was injection site bruising. Bruising was mild or moderate in severity and was linked to discontinuation of zilucoplan in one patient only.

Due to its mechanism of action, zilucoplan may increase susceptibility to infections with *Neisseria meningitidis*. As a precautionary measure, all patients must be vaccinated against meningococcal infections, at least 2 weeks prior to the start of treatment. If treatment needs to start less than 2 weeks after vaccination against meningococcal infections, the patient must receive appropriate prophylactic antibiotic treatment until 2 weeks after the first vaccination dose. Meningococcal vaccines reduce but do not completely eliminate the risk of meningococcal infections (65).

As zilucoplan is a subcutaneous injection that can be self-administered at home, UCB will provide support to healthcare professionals and patients via our patient support programme to learn and practice how to administer zilucoplan, with the help of specialist MG clinicians and nurses. There are no data to suggest compliance issues related to self-administration of zilucoplan.

Zilucoplan is a daily subcutaneous injection, so has a higher injection frequency than IVIg or PLEX. However, the convenience of rapid at-home self-administration versus multiple lengthy hospital intravenous infusions serves to mitigate this.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

- What is the structure of the model? Explain how the model reflects the experience of having the condition over time.

The RAISE clinical trial used a patient-reported outcome measure called the myasthenia gravis activities of daily living scale (MG-ADL), which assesses patients' speech, swallowing, beathing and ability to perform tasks such as brushing hair or teeth and standing up from a chair. The MG-ADL scores collected in the RAISE clinical study were used to reflect the experience of patients with refractory gMG in the health economic model.

The model estimated the impact of zilucoplan compared with a new targeted treatment, efgartigimod (subject to NICE evaluation), as well as current therapies (IVIg and PLEX) on patients' clinical outcomes and quality of life, using a measure called quality-adjusted life years (QALYs), which combines both aspects. The use of NHS resources is also modelled.

- Describe briefly which trial outcomes feed into the economic model. If trial data used for a certain length of time followed by extrapolation, please note how long the trial data was used for and briefly how the data has been extrapolated.

The clinical effectiveness of zilucoplan was modelled using MG-ADL data reported from the RAISE study.

Primary clinical inputs used in the health economic model (Chapter in Company Submission)
Improvement in MG-ADL score compared with baseline (the start of the trial) (B.3.3)
Annual rate of experiencing an exacerbation or crisis (B.3.3.2.2)

Modelling how much a treatment improves quality of life

- How is the treatment modelled to change a person's quality of life compared with the treatments already in use? This should include after stopping treatment if relevant. For example, say if the treatment improves quality of life because of improving symptoms or decreases quality of life because of side effects.

The impact of the treatment on symptoms and quality of life of patients with gMG in the RAISE study, compared with standard treatments, is the primary measure of treatment impact in the health economic model. Treatment is stopped if symptoms start to deteriorate, and all patients are assumed to be 'uncontrolled' when they stop treatment. Zilucoplan was found to improve quality of life more than efgartigimod, IVIg and PLEX.

- Which quality of life measure(s) did you use to estimate a person's quality of life over time and on treatments? Are there any aspects of the condition or its treatments affecting quality of life which may not have been fully captured by the methods used to estimate quality of life?

A quality-of-life measure called the EuroQoL-5D (EQ-5D) was used to measure the effect of treatment on patient quality of life.

As gMG is a relapsing and remitting rare disease, collecting robust quality-of-life data can be challenging. Furthermore, EQ-5D is a generic measure of health-related quality-of-life (rather than being specific to gMG), and so may not fully capture all relevant aspects of gMG that impact quality of life, such as fatigue, vision impairment, and hand weakness. A quality-adjusted life year (QALY) calculation based on EQ-5D data may not capture all the health-related benefits of zilucoplan treatment specific to patients and carers. The impact of a subcutaneous administration option on patient burden/patient preference and carer quality of life is also unlikely to be captured in the QALY calculation.

Modelling how the costs of treatment differ with the new treatment

- Does the medicine lead to any cost implications (positive or negative) for the health service (e.g., drug costs, number of days in hospital)?

Based on the company's economic analysis, zilucoplan as a treatment for patients with gMG is considered to offer value for money, representing a cost-effective use of NHS resources.

Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g., where it is given or the monitoring that is needed)?

Zilucoplan is a once-daily injection that can be self-administered at home. This may minimise the treatment burden and effect on patients' lives compared with other treatments administered intravenously (efgartigimod, IVIg and PLEX), which can only be given in hospital and often require a hospital stay. This will also be beneficial to the health service in terms of cost and clinician/nurse time, and will free up space on infusion suites.

Uncertainty

- Are there any key assumptions you have made in your model about the medicine's benefits or costs because of lack of data?

As gMG is a rare disease, there is a lack of clinical data, particularly long-term efficacy data. Therefore, assumptions are applied in the health economic model, including:

- Uncontrolled patients do not experience disease worsening over time (as defined by an increase in MG-ADL score)
- The likelihood of an exacerbation worsening and becoming a crisis is not related to which treatment a patient is receiving
- Unless in crisis, gMG patients have the same overall risk of death as the general population
- Patients who do not respond or lose their initial response do not continue to receive treatment

- Adverse events are not included because there were no side effects during the clinical trial that were judged to be serious that were experienced by 5% of patients or more.
    - Did you test using alternative assumptions or data in your model? Which had the largest effect on your cost effectiveness estimates?

The parameter with the largest effect on the results of the comparison with efgartigimod was the annual rate of exacerbations in patients who had responded to treatment. The parameter affecting the comparison vs IVIg the most was average patient weight, and the parameter affecting the comparison vs PLEX the most was the percentage of patients showing a stable response with PLEX. A scenario was tested using the average patient weight of the whole gMG cohort from RAISE rather than just the refractory patients; this didn't change the cost-effectiveness conclusions.

- What is the modelled benefit in overall survival, quality adjusted life years and the incremental cost effectiveness ratio?

Based on the model, zilucoplan provides more quality-adjusted life years (a measure of how well a treatment improves a patient's life) compared with efgartigimod, IVIg and PLEX.

- Are there any benefits or disadvantages of the treatment not captured in the modelling?

The impact of a treatment that can be self-administered at home on patient and carer quality of life is unlikely to be captured (e.g. impact on employment for patient and caregivers, cost of travel to hospital for treatment). The model also doesn't include the burden on caregivers or the impact of gMG on a patient's or caregiver's ability to work.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

The availability of zilucoplan will be a step forward in the treatment of gMG, as when licensed it will specifically target the abnormal immunological processes in gMG.

Unlike current standard of care treatments, which are based on non-specific suppression of the immune system instead of targeting the root cause of MG (40, 41), zilucoplan targets the complement pathway of the immune system to prevent self-antibodies from impairing communication between nerves and muscles.

Zilucoplan has been shown to minimise the symptom burden for patients with gMG who have active disease despite maximal immunosuppression, for whom there is an urgent unmet need for a treatment to control symptoms and to reduce the risk of myasthenic exacerbation and crisis.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

There is health inequality between males and females in terms of the burden of MG. As females are younger than males at disease onset (34), women are exposed to the negative impacts (economic, social, and quality of life) earlier in life and for longer than men, over more of their working life, amounting to a greater total burden. Women face a significant economic and social

disadvantage if MG diagnosis occurs at a time in their lives when they may be building their careers and/or starting a family. Woman of childbearing age face contraindications to therapy during pregnancy and lactation and may face a difficult choice between starting a family and managing symptoms of MG (18).

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

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's project information and documents, Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]: https://www.nice.org.uk/guidance/indevelopment/gid-ta11096
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf
- NHS page for myasthenia gravis: https://www.nhs.uk/conditions/myasthenia-gravis/
- Myaware, a UK charity solely dedicated to the support, care and advocacy of people affected by myasthenias: https://www.myaware.org/
- Muscular Dystrophy UK, the leading charity for over 60 muscle wasting and weakening conditions, including myasthenia gravis: https://www.musculardystrophyuk.org/conditions/myasthenia-gravis
- UCB's clinical studies index for zilucoplan: https://www.ucb.com/clinical-studies/Clinical-studies-index/Zilucoplan-RA101495

4b) Glossary of terms

A

Adverse event/Side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe

B

Crisis: see myasthenic crisis

Clinical trial: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study (76)

D

E

Exacerbation: see myasthenic exacerbation

EMA (European Medicines Agency): The regulatory body that evaluates, approves, and supervises medicines throughout the European Union (76)

F

G

HRQoL (health-related quality of life): An individual's perception of the impact of health status on quality of life (77)

HTA (Health Technology Assessment) (organisations): Organisations that make recommendations groups regarding the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones.

I

J

K

L

M

Myasthenic crisis: a life-threatening deterioration of muscle weakness and respiratory failure requiring treatment in an intensive care unit with mechanical ventilation and hospitalisation.

Myasthenic exacerbation: a sudden worsening of symptoms that requires urgent intervention to prevent a myasthenic crisis.

N

O

P

QALY (quality-adjusted life-year): A way of measuring how well medical treatments lengthen and/or improve patients' lives (78)

Quality of life: The overall enjoyment of life. Many clinical trials assess it to measure aspects of an individual's sense of wellbeing and ability to carry out activities of daily living (76)

R

Refractory: When a patient experiences symptoms despite receiving treatment. In the RAISE trial, this was defined as patients on treatment for ≥1 year with ≥2 of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, other ISTs, or history of treatment with ≥1 of these therapies for ≥1 year, and required chronic PLEX, IVIg, or SCIg at least every 3 months for the 12 months prior to enrolment.

S

Subcutaneous: Under the skin (76)

Symptom: A physical or mental problem that a person experiences that may indicate a disease or condition. Symptoms cannot be seen and do not show up on medical tests. Some examples of symptoms are fatigue, nausea, and pain (76)

T

U

V

W
X
Y
Z

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Clarification questions

January 2024

File name	Version	Contains confidential information	Date
	1.0	Yes	17th January 2024

Section A: Clarification on effectiveness data

Literature searches

A1. In the company submission (CS) please explain why plasma exchange (PLEX) is stated as an exclusion criterion in the systematic literature review (SLR) (CS Table 7), but is listed as a comparator in the decision problem (CS Table 1) and in the additional "targeted literature review" that was carried out to identify intravenous immunoglobulin (IVIG) and PLEX data for the economic model (CS section B.3.2.8).

Plasma exchange (PLEX) was initially excluded from the global systematic literature review (SLR) after early advice was sought from a key opinion leader (KOL) that it would not be used as a chronic treatment. However, the literature review conducted in 2021 identified the "International consensus guidance for management of myasthenia gravis" (1), which describes chronic intravenous immunoglobulin (IVIg)/PLEX as a treatment for refractory patients.

Subsequently, United Kingdom (UK) expert elicitation was sought from leading clinicians from Oxford, London and the South of England with experience in treating patients with refractory myasthenia gravis (MG). PLEX is used chronically as a maintenance therapy in England as confirmed by clinical experts. Therefore, PLEX is a relevant comparator in the decision problem.

A2. Please give details of the search strategy, results, and selection process, including a list of the excluded studies and their reasons for exclusion, for the "targeted literature review" (CS section B.3.2.8).

Apologies, the term 'targeted literature review' is misleading here. Desk research was conducted in the initial stages of the global model development (2020) to identify an initial list of treatments, alongside searches for other aspects of the PICOS criteria to populate the model specification document. As such, there was not a formal search strategy or selection process at the time, given its preliminary nature. This research was largely focussed on the 'International consensus guidance for management of myasthenia gravis (1)', which were selected because they were

the most recent and were not country specific, which fitted the objectives for the development of a global model. Other treatment guidelines reviewed included:

- Association of British Neurologists, Sussman et al. 2015
- Treatment strategies for myasthenia gravis: An update, Diaz-Manera 2012
- China guidelines for the diagnosis and treatment of MG, Li et al. 2016
- Treatment of MG, Maggi and Mantegazza 2011
- Guidelines of the German Neurological Society, Melzer et al 2016

There is a paucity of clinical and real-world evidence available for how patients with refractory MG are treated in England. The company has gone to considerable lengths to collect data on the use of IVIg. The company requested anonymised data from the National Immunoglobulin Database (which captures National Health Service [NHS] use of IV/subcutaneous immunoglobulin [SCIg] in MG [n=666 patients with MG]) (2), but this was denied by NHS England. In addition, the company explored data from individual centre databases in England but none are available that would significantly reduce uncertainty.

RAISE trial

A3. PRIORITY QUESTION. Please provide the baseline demographic and disease characteristics for the refractory subgroup of patients in the RAISE trial, for the same characteristics as reported for the whole trial population in CS Tables 12 and 13.

Baseline demographics and disease characteristics for the refractory cohort of RAISE are presented in Table 1 and Table 2, respectively.

Table 1. Baseline demographics of patients enrolled in the RAISE study

MG0010 RAISE	Refractory patients (n=88)	All study patients (n=174)
Age (years)†		
Mean (SD)	[redacted]	53.0 (15.1)
Median	[redacted]	55.0
Min, max	[redacted]	19, 75
Age group, n (%)‡		
≤18 years	[redacted]	0
19–64 years	[redacted]	126 (72.4)
≥65 years	[redacted]	48 (27.6)

MG0010 RAISE	Refractory patients (n=88)	All study patients (n=174)
Sex n (%)		
Female	[redacted]	99 (56.9)
Race, n (%)		
American Indian or Alaska Native	[redacted]	1 (0.6)
Asian	[redacted]	21 (12.1)
Black	[redacted]	13 (7.5)
Native Hawaiian or other Pacific Islander	[redacted]	0
White	[redacted]	128 (73.6)
Other/Mixed	[redacted]	0
Missing	[redacted]	11 (6.3)
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	12 (6.9)
Not Hispanic or Latino	[redacted]	151 (86.8)
Missing	[redacted]	11 (6.0)
Region, n (%)		
East Asia	[redacted]	16 (9.2)
Europe	[redacted]	67 (38.5)
North America	[redacted]	91 (52.3)
BMI (kg/m^2)		
Mean (SD)	[redacted]	31.0 (7.63)
Median	[redacted]	30.0
Min, max	[redacted]	16, 54

Abbreviations: BMI, body mass index; gMG, generalised myasthenia gravis; MG, myasthenia gravis; SD, standard deviation.
†Age was calculated as: year informed consent signed – year of birth; ‡Clinicaltrials.gov age categories.
Source: RAISE CSR supplementary tables, (refractory cohort). Table 14.1.3.1.1 (3).

Table 2. Baseline disease characteristics of patients enrolled in the RAISE study

MG0010 RAISE	Refractory patients (n=88)	All study patients (n=174)
MGFA class at screening, n (%)		
Class II	[redacted]	49 (28.2)
Class III	[redacted]	117 (67.2)
Class IV	[redacted]	8 (4.6)
Age at disease onset, years		
Mean (SD)	[redacted]	43.8 (18.0)
Median	[redacted]	44.0
Min, max	[redacted]	9.0, 73.0
Missing	[redacted]	43.8 (18.0)
Duration of disease, years		
Mean (SD)	[redacted]	9.2 (9.9)
Median	[redacted]	5.00
Min, max	[redacted]	0.1, 51.9
Symptoms at onset, n (%)		
Ocular	[redacted]	62 (35.6)
Generalised	[redacted]	112 (64.4)
Prior thymectomy, n (%)	[redacted]	82 (47.1)
Prior MG crisis, n (%)	[redacted]	57 (32.8)
Missing	[redacted]	-
Time since most recent crisis (months)†		
Mean (SD)	[redacted]	73.9 (100.5)
Median	[redacted]	26.9
Min, max	[redacted]	1.4, 469.8
Missing	[redacted]	-
Baseline MG-ADL score		
Mean (SD)	[redacted]	10.6 (3.0)
Median	[redacted]	10.0
Min, max	[redacted]	6, 19
Baseline QMG score		
Mean (SD)	[redacted]	19.1 (4.1)
Median	[redacted]	18.0
Min, max	[redacted]	12, 36

Abbreviations: BMI, body mass index; gMG, generalised myasthenia gravis; IVIG, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; QMG, quantitative myasthenia gravis; SCIG, subcutaneous immunoglobulin; SD, standard deviation.

†Time since most recent crisis (months) was calculated as: (Date of Study Day 1–Date of crisis)/(365.25/12).

Source: RAISE CSR supplementary tables (refractory cohort) Table 14.1.3.1.1 (3).

A4. CS Table 10 reports that 4 patients discontinued from each of the RAISE trial arms. Were any of these discontinuations from the refractory subgroup?

In total, three of the eight patients who discontinued from the trial were from the refractory subgroup (Table 3).

Table 3. Discontinuation for refractory patients in the RAISE study

MG0010 RAISE	Placebo (n=44)	Zilucoplan 0.3mg/kg (n=44)
Discontinued n, (%)	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]

Source: RAISE CSR supplementary tables. Table 14.1.1.5.1.1 (4).

A5. PRIORITY QUESTION. The company submission is for the purpose of evaluating the clinical efficacy and cost-effectiveness of zilucoplan for a refractory generalised myasthenia gravis (MG) population. The only outcomes reported for the refractory population are change from baseline to Week 12 for MG-ADL, QMG, MGL and MG-QoL.

a) Please provide results for the outcome 'time to clinically meaningful improvement', as specified in the decision problem addressed by the company in CS Table 1, for the refractory subgroup.

Please see Table 4 below.

Table 4. Time to MG-ADL response for refractory patients in the RAISE study (mITT)

MG0010 RAISE	Placebo (n=44)	Zilucoplan 0.3mg/kg (n=44)
Median time (days)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
% censored	[redacted]	[redacted]
p-value	[redacted]	

Abbreviations: CI, confidence interval; MG-ADL, Myasthenia Gravis-Activities of Daily Living; mITT, modified intent to treat.
Source: RAISE CSR supplementary tables (refractory cohort) Table 14.2.6.13.1 (3).

b) Please report the 'number of hospitalisations', as specified in the decision problem addressed by the company in CS Table 1, for the refractory subgroup. And for the whole trial population for context.

Please see Table 5 below. The RAISE trial only captured hospitalisations resulting from TEAEs.

Table 5. TEAEs resulting in hospitalisation for patients in the RAISE study

MG0010 RAISE	Total patient cohort		Refractory cohort	
	Placebo (n=88)	Zilucoplan 0.3mg/kg (n=86)	Placebo (n=44)	Zilucoplan 0.3mg/kg (n=44)
TEAE resulting in hospitalisation, n, (%) [#]†	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE, treatment-emergent adverse event.
† The number of individual occurrences of the TEAE in that category.
Source: RAISE CSR supplementary tables (refractory cohort) Table 14.3.2.1.0.1 (3).

c) Please provide the MG-ADL and QMG responder rates for the refractory subgroup.

Myasthenia gravis activities of daily living (MG-ADL) and quantitative myasthenia gravis (QMG) responder rates for the refractory subgroup in the RAISE study are presented in Table 6 and Table 7, respectively.

Table 6. MG-ADL responder rates (at least 3-point improvement) for the refractory subgroup in the RAISE study

Subgroup category	Placebo (n=88) n/ NSub (%)	Zilucoplan 0.3mg/kg (n=86) n/ NSub (%)
MG Refractory		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Abbreviations: MG, myasthenia gravis; MG-ADL, myasthenia gravis-activities of daily living; NSub, number of subjects with available information at the timepoint.
Source: RAISE CSR, supplementary tables Table 14.2.6.4 (5).

Table 7. QMG responder rates (at least 5-point improvement) for the refractory subgroup in the RAISE study

Subgroup category	Placebo (n=88) n/ NSub (%)	Zilucoplan 0.3mg/kg (n=86) n/ NSub (%)
MG Refractory		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Abbreviations: MG, myasthenia gravis; NSub, number of subjects with available information at the timepoint; QMG, quantitative myasthenia gravis.
Source: RAISE CSR, supplementary tables, Table 14.2.7.4 (5).

A6. In CS section B.2.6.1 the sample size is reported for the whole RAISE trial population for each outcome, consistent with a mITT analysis. For each outcome reported in CS section B.2.6.1, please clarify how many data were missing and imputed for each outcome to achieve the mITT analysis.

In the primary analysis, a mixed model for repeated measures (MMRM) regression was used. For data occurring after intercurrent events (rescue, death or myasthenic crisis), imputation was based on the worse of baseline or last score from the time of the intercurrent event. All other missing data was imputed via maximum likelihood estimation within the MMRM model. With this method, all available data is utilised and the missing values are assumed to be missing at random. This assumption was tested with a tipping point analysis and shown not to be influential to the results.

The summary of missing data are provided for MG-ADL, QMG, MGC and MG-QoL15r in Table 8, Table 9, Table 10 and Table 11, respectively.

Table 8. Summary of MG-ADL score missing values overall and by visit analysis set (mITT)

Category	Placebo (n=88) n (%)	Zilucoplan 0.3mg/kg (n=86) n (%)
Participants with no ICEs during the study n, (%)	[redacted]	[redacted]
Participants with ICEs during the study n, (%)	[redacted]	[redacted]
Use of rescue therapy (IVIG or PLEX or eculizumab) prior to Week 12 (ICE1) n, (%)	[redacted]	[redacted]
Any Death or Myasthenic Crisis (ICE2) n, (%)	[redacted]	[redacted]
Monotonic missing of MG-ADL Score (ICE3) n, (%)		[redacted]

Abbreviations: ICE, intercurrent event; IVIg, intravenous immunoglobulin; MG-ADL, myasthenia gravis-activities of daily living; mITT, modified intention to treat; PLEX, plasma exchange.
Source: RAISE CSR, supplementary tables Table 14.2.1.5 (5).

Table 9. Summary of QMG score missing values overall and by visit analysis set (mITT)

Category	Placebo (n=88) n (%)	Zilucoplan 0.3mg/kg (n=86) n (%)
Participants with no ICEs during the study	[redacted]	[redacted]
Participants with ICEs during the study	[redacted]	[redacted]
Use of rescue therapy (IVIG or PLEX or eculizumab) prior to Week 12 (ICE1)	[redacted]	[redacted]
Any Death or Myasthenic Crisis (ICE2)	[redacted]	[redacted]
Monotonic missing of MG-ADL Score (ICE3)	[redacted]	[redacted]

Abbreviations: ICE, intercurrent event; IVIg, intravenous immunoglobulin; QMG, quantitative myasthenia gravis; mITT, modified intention to treat; PLEX, plasma exchange.
Source: RAISE CSR, supplementary tables, Table 14.2.2.5 (5).

Table 10. Summary of MGC score missing values overall and by visit analysis set (mITT)

Category	Placebo (n=88) n (%)	Zilucoplan 0.3mg/kg (n=86) n (%)
Participants with no ICEs during the study	[redacted]	[redacted]
Participants with ICEs during the study	[redacted]	[redacted]
Use of rescue therapy (IVIG or PLEX or eculizumab) prior to Week 12 (ICE1)	[redacted]	[redacted]
Any Death or Myasthenic Crisis (ICE2)	[redacted]	[redacted]
Monotonic missing of MG-ADL Score (ICE3)	[redacted]	[redacted]

Abbreviations: ICE, intercurrent event; IVIg, intravenous immunoglobulin; MGC, myasthenia gravis composite; mITT, modified intention to treat; PLEX, plasma exchange.
Source: RAISE CSR, supplementary tables, Table 14.2.3.5 (5).

Table 11. Summary of MG-QoL15r Score Missing Values Overall and by Visit Analysis Set (mITT)

Category	Placebo (n=88) n (%)	Zilucoplan 0.3mg/kg (n=86) n (%)
Participants with no ICEs during the study	[redacted]	[redacted]
Participants with ICEs during the study	[redacted]	[redacted]
Use of rescue therapy (IVIG or PLEX or eculizumab) prior to Week 12 (ICE1)	[redacted]	[redacted]
Any Death or Myasthenic Crisis (ICE2)	[redacted]	[redacted]
Monotonic missing of MG-ADL Score (ICE3)	[redacted]	[redacted]

Abbreviations: ICE, intercurrent event; IVIg, intravenous immunoglobulin; MG-QoL15r, myasthenia gravis-quality of life 15 item scale; mITT, modified intention to treat; PLEX, plasma exchange.
Source: RAISE CSR, supplementary tables, Table 14.2.4.5 (5).

Safety

A7. Please explain why the company did not include safety results from the MG0009 study and its extension in the CS.

Results from MG0009 were not included in the company submission as it was a Phase 2a trial and did not inform the economic model (6). Patients completing MG0009 were able to continue in the RAISE-XT extension study, therefore the safety extension results would be captured in this study (described in Section B2.10.1.2 of the company submission).

For completeness, a summary of safety data (adverse events [AEs], deaths, and discontinuation rates) from MG0009 is presented in this section. An overall summary of study medication duration and participant-years of time at risk during the main and extension periods of the study is presented for the zilucoplan safety population in Table 12.

Table 12. Overall summary of study medication duration and participant-years of time at risk – main and extension periods of MG0009 (ZLP safety population)

Parameter Statistic	**ZLP 0.1mg/kg/day (N=22) Before switch to 0.3mg/kg/day (N=22)**	**ZLP 0.1mg/kg/day (N=22) After switch to 0.3mg/kg/day (N=21)**	**ZLP 0.3mg/kg/day (N=21)**	**ZLP 0.1mg/kg/day + 0.3mg/kg/day (N=43)**
Study medication duration (days)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Total study medication duration (participant-years)	[redacted]	[redacted]	[redacted]	[redacted]
Total time at risk (participant-years)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; max, maximum; min, minimum; SD, standard deviation; ZLP, zilucoplan.
Note: Study medication duration (days) was defined as the final dose date – first dose date + 1 where first dose was the first dose of active treatment and final dose date was taken as the day the participant either discontinued or completed the study. For participants in the ZLP 0.1mg/kg treatment group, the final dose date before switching to ZLP 0.3mg/kg was the day prior to the participant first taking the ZLP 0.3mg/kg dose.
Note: Total medication duration (participant-years) in a study period is the sum of all study medication duration (in days) divided by 365.25.

Note: Total study medication duration was a subset of total time at risk excluding non-treated periods.
Note: Total time at risk was the sum of the duration of exposure derived as follows: [(min(Date of Final dose + 40 days, Last contact) – Date of First Dose+1)] / 365.25 where final dose date was taken as the day the participant either discontinued or completed the study or the final dose date before switch to ZLP 0.3mg/kg.
Note: Participants administered placebo during the main period switched to ZLP 0.3/0.1mg/kg during the open-label extension period of the study. Participants administered with ZLP 0.1mg/kg during the extension period, switched to ZLP 0.3 mg/kg during the extension period of the study after Protocol Version 3.0.
Source: MG0009 CSR (6).

Adverse events

An overall summary of treatment-emergent adverse events (TEAEs) during the main and extension periods of the study is presented for study participants for the zilucoplan safety population in Table 13.

Table 13. Overall summary of TEAEs before or after dose switch – main and extension periods of MG0009 (ZLP safety population)

AE category	ZLP 0.1mg/kg/day (N=22) Before switch to 0.3mg/kg/day (N=22) 23.94 participant-years n (%) [#]	ZLP 0.1mg/kg/day (N=22) After switch to 0.3mg/kg/day (N=21) 15.63 participant-years n (%) [#]	ZLP 0.3mg/kg/day (N=21) 32.33 participant-years n (%) [#]	ZLP 0.1mg/kg/day + 0.3mg/kg/day (N=43) 69.61 participant years n (%) [#]
Any TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any Grade 2 or greater TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any Grade 3 or greater TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any Grade 4 or greater TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any Grade 2 or greater treatment-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any Grade 3 or greater treatment-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any Grade 4 or greater treatment-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]

AE category	ZLP 0.1mg/kg/day (N=22) Before switch to 0.3mg/kg/day (N=22) 23.94 participant-years n (%) [#]	ZLP 0.1mg/kg/day (N=22) After switch to 0.3mg/kg/day (N=21) 15.63 participant-years n (%) [#]	ZLP 0.3mg/kg/day (N=21) 32.33 participant-years n (%) [#]	ZLP 0.1mg/kg/day + 0.3mg/kg/day (N=43) 69.61 participant years n (%) [#]
Any serious TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any treatment-related serious TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs with outcome of death	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CSR, clinical study report; TEAE, treatment-emergent adverse events; ZLP, zilucoplan.
Note: For each treatment group and for each AE category, study participants were included only once, even if they reported multiple AEs in that category. Treatment-emergence was defined as an AE that occurred after a treatment start date or an AE that increased in severity after treatment start date.
Note: Included AEs occurring while the study participant was receiving active treatment in the main or extension periods of the study.
Note: Data for study participants who received placebo in the main period and ZLP in the extension period were combined with data for study participants who received ZLP in both the main and extension periods.
Note: The ZLP 0.3mg/kg/day treatment column only contains TEAEs occurring for study participants who were randomised to the ZLP 0.3mg/kg/day dose group in the main or extension periods of the study. It does not include TEAEs that occurred for study participants randomised to the ZLP 0.1mg/kg/day dose group in the main and extension periods of the study after they switched to the ZLP 0.3mg/kg/day dose group in the extension period of the study.
Data source: MG0009 CSR (6).

A summary of treatment-related TEAEs (as determined by the Investigator) in ≥2 study participants in any zilucoplan treatment group during the main and extension periods of the study is presented for the zilucoplan safety population in Table 14.

Table 14. Overall summary of treatment-related TEAEs (as determined by the Investigator) in ≥2 study participants in any ZLP treatment group –main and extension periods of MG0009 (ZLP safety population)

MedDRA V24.0 SOC PT	ZLP 0.1mg/kg/day (N=22) Before switch to 0.3mg/kg/day (N=22) 23.94 participant-years n (%) [#]	ZLP 0.1mg/kg/day (N=22) After switch to 0.3mg/kg/day (N=21) 15.63 participant-years n (%) [#]	ZLP 0.3mg/kg/day (N=21) 32.33 participant-years n (%) [#]	ZLP 0.1mg/kg/day + 0.3mg/kg/day (N=43) 69.61 participant years n (%) [#]
Any treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[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: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, System Organ Class; TEAE, treatment emergent adverse event; ZLP, zilucoplan

Note: [#]=number of events

Note: The study participants were assigned to the treatment group which they received that dose at the highest frequency.

Note: For each treatment group and for each category, study participants were included only once, even if they reported multiple events in that category. Treatment-emergence was defined as an AE that occurred after a treatment start date or an AE that increased in severity after treatment start date.

Note: Included AEs occurring while the study participant was receiving active treatment in the main or extension periods of the study.

Note: The ZLP 0.3mg/kg/day treatment column only contains TEAEs occurring for study participants who were randomised to the ZLP 0.3mg/kg/day dose group in the main or extension periods of the study. It does not include TEAEs that occurred for study participants randomized to the ZLP 0.1mg/kg/day dose group in the main and extension periods of the study after they switched to the ZLP 0.3mg/kg/day dose group in the extension period of the study.

Data source: MG0009 CSR (6).

Deaths

No deaths occurred during the main period of the study.

During the extension period of the study, [redacted] in the zilucoplan 0.3mg/kg/day dose group. No deaths due to TEAEs were considered treatment-related by the Investigator.

Additional information is provided below for the study participant who had [redacted]

At screening, study participant 023-017 in the zilucoplan 0.3mg/kg/day dose group throughout the study was 69 years old, male, and weighed 149kg with a body mass index (BMI) of 43.54kg/m^2. The study participant [redacted] during the extension period of the study. The events occurred 188 days after investigative medicinal product (IMP) initiation. The final dose of study drug was taken on 02 Nov 2018; the final visit date prior to the study participant's death was on 16 Oct 2018. An autopsy was not performed. Per the Investigator, the diagnosis [redacted] was associated with the study participant's history of poorly controlled diabetes and prominent vasculopathy.

Discontinuation due to AEs

[redacted] discontinued during the extension period of the study due [redacted]. In addition [redacted].

A8. The FDA review (section 7.7.1) reports a pancreatic safety signal due to a delayed effect of pancreatic adverse events seen in the extension studies. Please provide results from RAISE-XT and from the Phase II extension study for the following adverse events: pancreatitis, pancreatic/cyst/pseudocyst, infected pancreatic cyst/pseudocyst, pancreatic cancer, and serum lipase elevations.

See Table 15 below for pancreatic events from the RAISE-XT (MG0011) and Phase 2 (MG0009) studies.

Table 15. Key characteristics of pancreatic events

Study at onset of event/ Study participant ID/Age (years)/Gender	Event	Days since first ZLP dose at onset	Serious/ Severity/ Investigator causality	Action Taken/ Outcome	Baseline Amylase/ Lipase	Key risk factors and relevant concomitant medications	Likely aetiology
MG0009 025-035 59 M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MG0009 038-010 59 M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MG0009 041-008 76 M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MG0011 022-022 64 M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study at onset of event/ Study participant ID/Age (years)/Gender	Event	Days since first ZLP dose at onset	Serious/ Severity/ Investigator causality	Action Taken/ Outcome	Baseline Amylase/ Lipase	Key risk factors and relevant concomitant medications	Likely aetiology
MG0011 047-047 62 M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MG0011 131-034 67 M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MG0011 143-091 56 M	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERCP, Endoscopic retrograde cholangiopancreatography; ZLP, zilucoplan.

[redacted]

[b] The exact time-to-onset from the first ZLP dose is unknown; In ISS 120-Day SU Listing 6.2, it is computed as 1 day as only the year of the pancreatic event was reported
Source: MG0011 and MG0009 CSRs.

Network meta-analyses (NMAs)

A9. The NMA report ("UCB_Report for NMA_Updated Analysis_V2.0 - first draft - 1st part") states that the systematic literature review (SLR) for the NMAs is reported in a separate document. Please provide the full SLR report.

The SLR report is provided with this document. UCB would also like to highlight the correct NMA technical report (MG-ADL_UCB_Report for NMA_Updated Analysis_V1.1_Jan 10.docx). This document includes data for some treatments that are out of scope for this appraisal (rozanolixizumab, eculizumab, ravulizumab) and thus only in-scope comparators are referenced in the company submission and this response document.

A10. PRIORITY QUESTION: To clarify and account for population heterogeneity in the NMAs:

(a) Please provide a tabulation of the trial baseline characteristics, for those characteristics listed in CS Tables 12 and 13 where available, for each of the zilucoplan, efgartigimod, IVIG and rituximab trials included in the NMA analyses. Where data are available, please also provide a tabular comparison of the baseline characteristics for refractory populations or subgroups of the trials (refractory as defined in the CS and RAISE trial).

There was no prespecified refractory population in any of the trials for the relevant comparators, therefore data were not available for inclusion in the NMA. As data from refractory patients were available from the zilucoplan trials, these were included in the NMA. Below are all baseline characteristics available from the trials or publications for zilucoplan, efgartigimod, IVIg and rituximab.

<u>Baseline characteristics from the efgartigimod trials included in the NMA</u>

Baseline demographics and disease characteristics from the Phase 3 efgartigimod trial (ADAPT, Howard et al, 2021 (7)) included in the NMA are presented in Table 16 and Table 17, respectively.

Baseline demographics and disease characteristics from the Phase 2 efgartigimod trial (Howard et al, 2019 (8)) included in the NMA are presented in Table 18 and Table 19, respectively.

Table 16. Baseline demographics of AChr-Ab+ patients enrolled in the Phase 3 efgartigimod trial, ADAPT

ADAPT Howard et al, 2021	All study participants (n=167)	AChR-Ab+ patients	
		Placebo (n=64)	Efgartigimod (n=65)
Age (years)			
Mean (SD)	47.0 (14.7)	49.2 (15·5)	44.7 (15.0)
Sex n (%)			
Female	118 (70.7)	40 (62.5)	46 (70.8)
Race, n (%)			
Asian	16 (9.6)	4 (6.3)	7 (10.8)
Black/African American	6 (3.6)	3 (4.7)	1 (1.5)
White	141 (84.4)	56 (87.5)	54 (83·1)

Abbreviations: SD, standard deviation.
Source: Howard et al, 2021 (7).

Table 17. Baseline disease characteristics of patients enrolled in the Phase 3 efgartigimod trial, ADAPT

ADAPT Howard et al, 2021	All study participants (n=167)	AChR-Ab+ patients	
		Placebo (n=64)	Efgartigimod (n=65)
MGFA class at screening, n (%)			
Class II	65 (38.9)	25 (39.1)	28 (43.1)
Class III	96 (57.5)	36 (56.3)	35 (53.8)
Class IV	6 (3.6)	3 (4.7)	2 (3.1)
Duration of disease, years			
Mean (SD)	9.5 (8.4)	8.9 (8.2)	9.7 (8.3)
Prior thymectomy, n (%)	95 (56.9)	30 (46.9)	45 (69.2)
Baseline MG-ADL score			
Mean (SD)	9.0 (2.5)	8.6 (2.1)	9.0 (2.5)
Baseline QMG score			
Mean (SD)	15.9 (4.8)	15.2 (4.4)	16.0 (5.1)
Baseline MGC score			
Mean (SD)	18.5 (5.8)	18.1 (5.2)	18.6 (6.1)
Baseline MG-QoL15r score			
Mean (SD)	16.4 (6.0)	16.6 (5.5)	15.7 (6.3)

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15r, Myasthenia Gravis Quality-of-Life Revised Scale; QMG, quantitative myasthenia gravis; SD, standard deviation.
Source: Howard et al, 2021 (7).

Table 18. Baseline demographics of patients enrolled in the Phase 2 efgartigimod trial (ITT)

Howard et al, 2019	Placebo (n=12)	Efgartigimod (n=12)	Total (n=24)
Age (years)	43.5 +/- 19.3	55.3 +/- 13.6	49.4 +/-17.4
Sex n (%)			
Female	8 (66.7)	7 (58.3)	15 (62.5)
Race, n (%)			
Asian	0 (0)	1 (8.3)	1 (4.2)
Black/African American	1 (8.3)	0 (0)	1 (4.2)
White	11 (91.7)	11 (91.7)	22 (91.7)

Abbreviations: ITT, intention to treat; MG, myasthenia gravis; SD, standard deviation.
Source: Howard et al, 2019 (8).

Table 19. Baseline disease characteristics of patients enrolled in the Phase 2 efgartigimod trial (ITT)

Howard et al, 2019	Placebo (n=12)	Efgartigimod (n=12)	Total (n=24)
MGFA class at screening, n (%)			
Class II	7 (58.4)	6 (50.0)	13 (54.2)
Class III	4 (33.3)	6 (50.0)	10 (41.7)
Class IV	1 (8.3)	0 (0)	1 (4.2)
MG duration (years)	13.3 +/- 11.2	8.2 +/-9	10.8 +/-10.3
Baseline scores			
QMG	11.8 +/-5.4	14.5 +/-6.3	13.2 +/-5.9
MG-ADL	8.0+/-2.2	8.0+/-3.0	8.0+/-2.6
MGC	14.5 +/-4.5	16.7 +/-8.7	15.6 +/-6.9
MG-QoL15r	14.5 +/-6.1	19.7 +/-5.7	17.1 +/-6.4

Abbreviations: ITT, intention to treat; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis activities of daily living; MGFA, Myasthenia Gravis Foundation of America; MGC, Myasthenia Gravis composite; MG-QoL15r, Myasthenia Gravis quality of life.
Source: Howard et al, 2019 (8).

Baseline characteristics from the rituximab trials included in the NMA

Baseline demographics and disease characteristics from the Phase 3 rituximab trial (RINOMAX, Piehl et al, 2022 (9)) included in the NMA are presented in Table 20 and Table 21, respectively.

Baseline demographics and disease characteristics from the Phase 2 rituximab trial (BeatMG, Nowak et al, 2021 (10)) included in the NMA are presented in Table 22 and Table 23, respectively.

Table 20. Baseline demographics of patients enrolled in the Phase 3 rituximab trial

RINOMAX Piehl et al, 2022	Rituximab (n=25)	Placebo (n=22)
Age at inclusion, mean (SD), y	67.4 (13.4)	58 (18.6)
Sex n (%)		
Female	7 (28.0)	7 (31.8)
BMI, mean (SD)	27.5 (3.7)	27.6 (5.7)

Abbreviations: BMI, body mass index; SD, standard deviation.
Source: Piehl et al, 2022 (9).

Table 21. Baseline disease characteristics of patients enrolled in the Phase 3 rituximab trial

RINOMAX Piehl et al, 2022	Rituximab (n=25)	Placebo (n=22)
MGFA class at baseline, n (%)		
Class 2a	2 (11.8)	3 (17.6)
Class 2b	7 (41.2)	3 (17.6)
Class 3a	1 (5.9)	1 (5.9)
Class 3b	7 (41.2)	10 (58.8)
Time since onset of generalised myasthenia gravis (days), mean (SD)	132.4 (91.5)	143.0 (93.3)
Baseline scores, mean (SD)		
QMG	9.4 (4.5)	9.3 (4.2)
MG-ADL	5.1 (3.2)	4.5 (2.7)
MG-QoL	20.1 (11.0)	22.2 (12.8)

Abbreviations: MG-ADL, Myasthenia Gravis activities of daily living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL, Myasthenia Gravis quality of life.
Source: Piehl et al, 2022 (9).

Table 22. Baseline demographics of patients enrolled in the Phase 2 rituximab trial, BeatMG

BeatMG Nowark et al, 2021	Total (n=52)	Rituxumab (n=25)	Placebo (n=27)
Age at enrollment, y	55.1 (17.1)	53.2 (17.5)	56.8 (17)
Age at diagnosis, y	49.6 (18.7)	46.6 (18.7)	52.4 ()
Sex n (%)			
Female	23 (44.2)	11 (44)	12 (44.4)
Race/ethnicity, n (%)			
Asian	1 (1.9)	0 (0)	1 (3.7)
African American	11 (21.2)	2 (8)	9 (33.3)
Hispanic	5 (9.6)	3 (12)	2 (3.7)
Non-Hispanic	35 (67.3)	20 (80)	15 (55.6)

Abbreviations: SD, standard deviation.
Source: Nowark et al, 2021 (10).

Table 23. Baseline disease characteristics of patients enrolled in the Phase 2 rituximab trial, BeatMG

BeatMG Nowark et al, 2021	Total (n=52)	Rituxumab (n=25)	Placebo (n=27)
MGFA class at screening, n (%)			
Class I	1 (1.9)	0 (0)	1 (3.7)
Class II	31 (59.6)	15 (60)	16 (59.3)
Class III	18 (34.6)	9 (36)	9 (33.3)
Class IV	2 (3.9)	1 (4)	1 (3.7)
Baseline scores, mean (SD)			
MGC	9.8 (5.2)	11.1 (6.1)	8.5 (4.0)
QMG	10.1 (4.5)	11.0 (5.1)	9.2 (3.9)
MG-ADL	4.9 (3.6)	5.8 (3.6)	4.0 (3.4)
MG-QoL	20.1 (12.5)	22.7 (14.1)	17.7 (10.6)
MSE	8/50 (16)	1/24 (4.2)	7/26 (26.9)

Abbreviations: MGC, Myasthenia Gravis Composite; MG-ADL, Myasthenia Gravis activities of daily living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL, Myasthenia Gravis quality of life; MSE, minimal symptom expression.
Source: Nowark et al, 2021 (10).

Baseline characteristics from the zilucoplan trials included in the NMA

Baseline demographics and disease characteristics from the Phase 3 zilucoplan trial (RAISE, Howard et al, 2022 (11)) included in the NMA are presented in Table 24 and Table 25, respectively.

Baseline demographics and disease characteristics from the Phase 2 zilucoplan trial (Howard et al, 2020 (12)) included in the NMA are presented in Table 26 and Table 27, respectively.

Table 24. Baseline demographics of patients enrolled in the Phase 3 zilucoplan trial, RAISE

RAISE Howard et al, 2022	All study participants (n=174)	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)	All refractory study participants (n=88)
Age (years)†				
Mean (SD)	53.0 (15.1)	53.3 (15.7)	52.6 (14.6)	[redacted]
Median	55.0	55.5	54.5	[redacted]
Min, max	19, 75	19, 75	21, 75	[redacted]
Age group, n (%)‡				
≤18 years	0	0	0	[redacted]
19–64 years	126 (72.4)	62 (70.5)	64 (74.4)	[redacted]
≥65 years	48 (27.6)	26 (29.5)	22 (25.6)	[redacted]

RAISE Howard et al, 2022	All study participants (n=174)	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)	All refractory study participants (n=88)
Sex n (%)				
Female	99 (56.9)	47 (53.4)	52 (60.5)	[redacted]
Race, n (%)				
American Indian or Alaska Native	1 (0.6)	1 (1.1)	0	[redacted]
Asian	21 (12.1)	14 (15.9)	7 (8.1)	[redacted]
Black	13 (7.5)	7 (8.0)	6 (7.0)	[redacted]
Native Hawaiian or other Pacific Islander	0	0	0	[redacted]
White	128 (73.6)	62 (70.5)	66 (76.7)	[redacted]
Other/Mixed	0	0	0	[redacted]
Missing	11 (6.3)	4 (4.5)	7 (8.1)	[redacted]
Ethnicity, n (%)				
Hispanic or Latino	12 (6.9)	5 (5.7)	7 (8.1)	[redacted]
Not Hispanic or Latino	151 (86.8)	79 (89.8)	72 (83.7)	[redacted]
Missing	11 (6.3)	4 (4.5)	7 (8.1)	[redacted]
Region, n (%)				
East Asia	16 (9.2)	9 (10.2)	7 (8.1)	[redacted]
Europe	67 (38.5)	33 (37.5)	34 (39.5)	[redacted]
North America	91 (52.3)	46 (52.3)	45 (52.3)	[redacted]
BMI in kg/m^2 or weight in kg				
Mean (SD)	BMI in kg/m^2 31.0 (7.63)	BMI in kg/m^2 30.5 (8.02)	BMI in kg/m^2 31.4 (7.22)	[redacted]
Median	30.0	29.0	30.5	[redacted]
Min, max	16, 54	16, 54	19, 50	[redacted]

Abbreviations: BMI, body mass index; SD, standard deviation.
†Age was calculated as: year informed consent signed – year of birth; ‡Clinicaltrials.gov age categories.
Source: Howard et al, 2022 (11) and RAISE CSR supplementary tables, (refractory cohort) (3).

Table 25. Baseline disease characteristics of patients enrolled in the Phase 3 zilucoplan trial, RAISE

RAISE Howard et al, 2022	All study participants (n=174)	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)	All refractory study participants (n=88)
MGFA class at screening, n (%)				
Class II	49 (28.2)	27 (30.7)	22 (25.6)	[redacted]
Class III	117 (67.2)	57 (64.8)	60 (69.8)	[redacted]
Class IV	8 (4.6)	4 (4.5)	4 (4.7)	[redacted]
Age at disease onset, years				
Mean (SD)	43.8 (18.0)	44.0 (18.7)	43.5 (17.4)	[redacted]
Median	44.0	44.5	43.0	[redacted]
Min, max	9.0, 73.0	9.0, 73.0	13.0, 73.0	[redacted]
Missing	0	0	0	[redacted]
Duration of disease, years				
Mean (SD)	9.2 (9.9)	9.0 (10.4)	9.3 (9.5)	[redacted]
Median	5.00	4.75	5.55	[redacted]
Min, max	0.1, 51.9	0.2, 51.9	0.1, 42.3	[redacted]
Symptoms at onset, n (%)				
Ocular	62 (35.6)	34 (38.6)	28 (32.6)	[redacted]
Generalised	112 (64.4)	54 (61.4)	58 (67.4)	[redacted]
Prior thymectomy, n (%)	82 (47.1)	37 (42.0)	45 (52.3)	[redacted]
Prior MG crisis, n (%)	57 (32.8)	29 (33.0)	28 (32.6)	[redacted]
Missing	0	0	0	[redacted]
Time since most recent crisis (months)†				
Mean (SD)	73.9 (100.5)	72.3 (109.8)	75.6 (91.8)	[redacted]
Median	26.9	22.0	39.0	[redacted]
Min, max	1.4, 469.8	1.4, 469.8	1.4, 277.6	[redacted]
Missing				[redacted]
Baseline MG-ADL score				
Mean (SD)	10.6 (3.0)	10.9 (3.4)	10.3 (2.5)	[redacted]
Median	10.0	10.5	10.0	[redacted]
Min, max	6, 19	6, 19	6, 16	[redacted]
Baseline MG-ADL score, n (%)				
≤9	66 (37.9)	33 (37.5)	33 (38.4)	[redacted]
≥10	108 (62.1)	55 (62.5)	53 (61.6)	[redacted]
Baseline QMG score				
Mean (SD)	19.1 (4.1)	19.4 (4.5)	18.7 (3.6)	[redacted]
Median	18.0	18.5	18.0	[redacted]

RAISE Howard et al, 2022	All study participants (n=174)	Placebo (n=88)	Zilucoplan 0.3 mg/kg (n=86)	All refractory study participants (n=88)
Min, max	12, 36	13, 36	12, 31	[redacted]
Baseline QMG score, n (%)				
≤17	76 (43.7)	38 (43.2)	38 (44.2)	[redacted]
≥18	98 (56.3)	50 (56.8)	48 (55.8)	[redacted]

Abbreviations: MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; QMG, quantitative myasthenia gravis; SD, standard deviation.
†Time since most recent crisis (months) was calculated as: (Date of Study Day 1–Date of crisis)/(365.25/12).
Source: Howard et al, 2022 (11) and RAISE CSR supplementary tables, (refractory cohort) (3).

Table 26. Baseline demographics of patients enrolled in the Phase 2 zilucoplan trial

Howard et al, 2020	Placebo (n=15)	Zilucoplan 0.1 mg/kg (n=15)	Zilucoplan 0.3 mg/kg (n=14)
Age (years)			
Mean (SD)	48.4 (15.7)	45.5 (15.7)	54.6 (15.5)
Sex n (%)			
Female	11 (73.3)	8 (53.3)	4 (28.6)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	1 (6.7)	0	1 (7.1)
Black/African American	2 (13.3)	2 (13.3)	2 (14.3)
Native Hawaiian or other Pacific Islander	0	0	0
White	12 (80.0)	13 (86.7)	11 (78.6)
Other/Mixed	0	0	0
Missing	0	0	0
Region, n (%)			
East Asia	0	0	0
Europe	0	0	0
North America	15 (100)	15 (100)	14 (100)
Weight (kg)			
Mean (SD)	85.3 (21.44)	93.7 (24.72)	110.9 (30.79)
BMI (kg/m^2)			
Mean (SD)	30.9 (7.39)	32.8 (6.55)	36.0 (8.24)

Abbreviations: BMI, body mass index; SD, standard deviation.
†Clinicaltrials.gov age categories.
Source: Howard et al, 2020 (12).

Table 27. Baseline disease characteristics of patients enrolled in the Phase 2 zilucoplan trial

Howard et al, 2020	Placebo (n=15)	Zilucoplan 0.1 mg/kg (n=15)	Zilucoplan 0.3 mg/kg (n=14)
MGFA class at screening, n (%)			
Class II	7 (46.7)	5 (33.3)	5 (35.7)
Class III	8 (53.3)	10 (66.7)	5 (35.7)
Class IV	0	0	4 (28.6)
Age at disease onset, years			
Mean (SD)	40.3 (17.79)	37.3 (16.04)	46.9 (19.48)
Duration of disease, years			
Mean (SD)	6.3 (0.1-20.9)	6.5 (1.6-24.1)	5.3 (0.5-26.0)
Prior thymectomy, n (%)	5 (33.3)	8 (53.3)	7 (50.0)
Prior MG crisis requiring intubation, n (%)	3 (20.0)	4 (26.7)	2 (14.3)
Baseline MG-ADL score			
Mean (SD)	8.8 (3.6)	6.9 (3.3)	7.6 (2.6)
Baseline QMG score			
Mean (SD)	18.7 (4.0)	18.7 (4.0)	19.1 (5.1)
Baseline MGC score			
Mean (SD)	18.7 (5.7)	14.5 (6.3)	14.6 (6.3)
Baseline MG-QoL15r score			
Mean (SD)	15.9 (7.4)	19.1 (5.0)	16.5 (7.3)

Abbreviations: MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15r, Myasthenia Gravis Quality-of-Life Revised Scale; QMG, quantitative myasthenia gravis; SD, standard deviation.
Source: Howard et al, 2020 (12).

Baseline characteristics from the IVIG trials included in the NMA

Baseline demographics and disease characteristics from the Phase 2 IVIG trial (Wolfe et al, 2002 (13)) included in the NMA are presented in Table 28 and Table 29, respectively.

Table 28. Baseline demographics of patients enrolled in the Phase 2 IVIG Wolfe 2002 trial

Wolfe et al, 2002	IVIG (n=6)	Placebo (n=9)
Age (mean, years)	46.0	37.8
Sex distribution	p>0.45	
Ethnicity distribution	p>0.45	

Abbreviations: IVIG, intravenous immunoglobulin.
Source: Wolfe et al, 2002 (13).

Table 29. Baseline disease characteristics of patients enrolled in the Phase 2 IVIG Wolfe 2002 trial

Wolfe et al, 2002	IVIG (n=6)	Placebo (n=9)
Baseline MG-ADL score		
Mean (SD)	5.3 (3.8)	6.0 (3.8)
Baseline QMG score		
Mean (SD)	8.5 (1.8)	11.3 (5.6)

Abbreviations: IVIG, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis; SD, standard deviation.
Source: Wolfe et al, 2002 (13).

(b) Please identify any heterogeneity among these trials' baseline characteristics that could influence interpretation of the NMA results.

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

In terms of disease characteristics, the IVIg study had a mean baseline MG-ADL score of 5.3 (13); which is below the inclusion criteria for the RAISE study (a score of ≥6, with mean baseline MG-ADL of 10.6 ITT/10.7 refractory). This indicates a less severe population in the IVIg study (13). Furthermore, the results of the IVIg study (13) do not align with the results of other studies: the nine placebo patients had a greater mean (SD) MG-ADL change from baseline of –2.6 (2) compared with the six active comparator/IVIg patients' change of –0.3 (2.4).

For the rituximab trials, similar heterogeneity is present. The RINOMAX (rituximab) study was conducted in patients with early onset MG (disease duration of approximately 4.5 months) compared with RAISE (mean duration of disease at baseline was 9.2 years). The other included rituximab study, the Phase 2 BeatMG study had a baseline disease duration of 5.5 years (calculated by: age at baseline – age at diagnosis). Both rituximab studies had a lower baseline MG-ADL of around 5. As in the IVIg study (13), this indicates a less severe population.

There are differences in trial design between the zilucoplan and efgartigimod studies. Zilucoplan is administered once daily, whereas efgartigimod is dosed cyclically. This

means the timepoint of the analysis is influential on the results for a cyclical treatment; with week 12 ±2 week analyses showing the return to baseline between cycles; whereas the zilucoplan treatment effect is maintained once achieved.

Although baseline characteristics were comparable, the efgartigimod trials had lower entry criteria in terms of MG-ADL score at baseline than the zilucoplan trials (≥5 vs ≥6, respectively), as well as a different definition of response (reduction of ≥2 vs ≥3 in MG-ADL score, respectively). The NMA used a 3-point change as the definition and the data from the ADAPT study (7). In addition, patients received different background therapies and different treatment strategies across the studies. The IVIg trial used in the NMA is not representative of chronic use of IVIg and has the additional limitations of being a small Phase 2 study.

The ratio of refractory vs non-refractory patients, and the outcomes, is unclear in the comparator studies. There is also heterogeneity in the response assessment timepoint between the trials, therefore a sensitivity analysis was performed using the primary endpoint timepoint of the included study, in addition to a week 12±2 weeks analysis- which aligns with the primary endpoint in the RAISE study.

(c) If heterogeneity is present in the trials' baseline characteristics, please use statistical approaches to account for this, e.g. sensitivity analysis, matching-adjusted indirect comparison (MAIC), or simulated treatment comparison (STC), as appropriate, for comparisons of zilucoplan against efgartigimod, IVIG and rituximab. If using any matching or weighting method, please justify the baseline characteristics matched on or weighted and report all statistics required for interpretating the analysis (including model fit, the distribution of weights, effective sample sizes, the post-adjustment baseline characteristics, and the statistical code).

There are limitations with conducting a MAIC due to heterogeneity in reporting across the trials. For example, differences in the response assessment timepoint, inclusion/exclusion criteria and response criteria across the zilucoplan and comparator trials cannot be adjusted by a MAIC. In addition, there are limited studies available for the comparison, especially in rituximab and IVIg, and small sample sizes. The relatively small number of patients in the RAISE study might reduce the effective sample size after adjustment, which may affect the robustness of the

results, especially if only considering the refractory subgroup for analysis. A small sample size is often a limitation of studies in rare diseases such as MG.

Scenario analyses have been performed to test the assumptions and outcomes, varying the studies included (from Phase 3 only to both Phase 2 and Phase 3 studies) and changing the timepoint of the change from baseline MG-ADL analysis.

Including Phase 2 studies for MG-ADL responders, as per scenario analysis 1, does not change the outcomes. [redacted] the results rank the treatments in the same order vs placebo (Table 30).

Table 30. MG-ADL probability of response scenario analysis 1 (Analysis with both Phase 3 and Phase 2 trials)

Intervention	Mean (SE)
Placebo	[redacted]
Zilucoplan	[redacted]
Efgartigimod	[redacted]

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; SE, standard error.
Source: NMA, January 2024 (14).

For MG-ADL change from baseline, the primary analysis aligns with the zilucoplan primary endpoint timepoint (12 weeks ± 2 weeks) and scenario analysis 1 includes Phase 2 studies that report at this timepoint. Similar to the primary analysis, zilucoplan has the highest change from baseline numerically- although this is not unexpected due to the cyclical nature of FcRn treatment. Efgartigimod is not significantly better than placebo, assumed to be caused by the waning effect of treatment at week 12± 2.

Scenario analysis 2 includes results at week 12± 2 for Phase 2 and 3 studies if available, and if not, the primary endpoint was used. This analysis might introduce unnecessary heterogeneity by using this approach to timepoints; but the results are consistent with the primary analysis.

Scenario analysis 3 considers only Phase 3 studies and includes data from all studies from their primary endpoint timepoint only. This analysis allowed the inclusion of rituximab from the RINOMAX study (which did not show a significant difference to placebo). At the primary endpoint timepoint, [redacted]

[redacted]

(Table 31).

Table 31: Modelled treatment outcomes for mean change from baseline in MG-ADL score – scenario analysis 3 (Analysis at time at which primary endpoint with Phase 3 trial only)

Intervention	Mean (SE)
Placebo	[redacted]
Rituximab	[redacted]
Zilucoplan	[redacted]
Efgartigimod	[redacted]

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; SE, standard error.
Source: NMA, January 2024 (14).

Scenario analysis 4 builds on scenario analysis 3 by including Phase 2 studies that reported MG-ADL change from baseline at the primary endpoint timepoint. This analysis allowed the inclusion of IVIg into the network. Results suggest IVIg performed worse than placebo, with a non-significant disease worsening. The heterogeneity makes this result difficult to interpret, as it is unlikely that IVIg is truly worse than placebo, but the company concludes that there is no more robust evidence base to include IVIg in this analysis. In addition, two UK clinicians consulted since the submission both were not surprised with the result that patients receiving IVIg experienced a worsening of disease overall. The other results are consistent with scenario 3.

Scenario analysis 5 considered an earlier timepoint of 4 weeks, using Phase 2 and 3 studies. IVIg was eligible for inclusion, but neither the BeatMG nor RINOMAX studies reported outcomes at week 4 (rituximab usually takes longer than 4 weeks to demonstrate effect). In the ADAPT study, efgartigimod showed the greatest change from baseline at week 4, with treatment effect waning until week 10. The results of this scenario align with the prior scenarios, with the targeted treatments significantly better than placebo, but with limited differences between them (Table 32).

Table 32: Modelled treatment outcomes for mean change from baseline in MG-ADL score – scenario analysis 5 (analysis at the most commonly reported timepoint (week 4))

Intervention	Mean
IVIg	[redacted]
Placebo	[redacted]
Zilucoplan	[redacted]
Efgartigimod	[redacted]

Abbreviations: IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; SE, standard error.
Source: NMA, January 2024 (14).

The results of the company's NMA are supported by the independent published NMA of innovative treatments for MG (15), which showed that there was no significant difference between complement inhibitors and anti-FcRn treatments when assessing at primary endpoint timepoint, and that all targeted treatments were associated with a significantly greater improvement in MG-ADL and QMG vs placebo (standard of care), but rituximab did not significantly improve MG-ADL or QMG scores compared with placebo (15).

A11. PRIORITY QUESTION The network meta-analyses (as reported in "UCB_Report for NMA_Updated Analysis_V2.0 - first draft - 1st part") appear to contain a mix of refractory and non-refractory populations.

(a) Please clarify whether the populations of the trials of efgartigimod, IVIG, and rituximab included in the NMAs align with the definition of refractory as used in the RAISE trial and with the company's intended positioning of zilucoplan and, if not, how the populations differ from the refractory population as defined in the RAISE trial and CS.

Intent-to-treat (ITT) populations were used for the comparator trials, as the comparator trials did not include refractory patients as a specific subgroup. The efgartigimod trial ADAPT included 63% refractory patients (16), but refractory was not included as a subgroup for endpoint analysis, nor was a definition of 'refractory' provided in the study publication (7). Refractory patients were not included as a subgroup in the rituximab or IVIg trials (13).

(b) To investigate the influence of the trial population definition on NMA results, please investigate the feasibility of conducting NMAs, or other ITC analyses as appropriate, that are limited solely to refractory patients, i.e.

including the refractory subgroup of the RAISE trial and any other refractory trial populations or subgroups. Please conduct and report any analyses that are feasible.

An NMA or indirect treatment comparison (ITC) limited to refractory patients would not be feasible due to a lack of data for refractory patients from clinical trials in comparator treatments. However, an NMA scenario analysis was performed using refractory data for zilucoplan, with data from ITT populations for other the comparator trials (as refractory was not included as a specific subgroup for comparators). This provides similar outcomes as with the ITT population treatment with zilucoplan, albeit with a slight numerical advantage for zilucoplan. Modelled treatment outcomes are presented below in Table 33 and Table 34 (14).

Table 33. Modelled mean change from baseline in MG-ADL score for stable responders, using refractory data for zilucoplan

Intervention	Mean (SE)
Zilucoplan	[redacted]
Efgartigimod	[redacted]
Placebo	[redacted]

Abbreviations: MG-ADL, myasthenia gravis-activities of daily living.
Source: NMA, January 2024 (14).

Table 34. Modelled response rate using refractory data for zilucoplan

Intervention	Response rate
Zilucoplan	[redacted]
Efgartigimod	[redacted]

Source: NMA, January 2024 (14).

(c) If it is not feasible to limit an NMA or other ITC approach entirely to a refractory population, please conduct a sensitivity analysis for each of the primary NMAs reported in "UCB_Report for NMA_Updated Analysis_V2.0 - first draft - 1st part" that includes as much data from refractory populations or subgroups as possible.

A sensitivity analysis was conducted using the refractory data from the RAISE study with ITT data for the other comparators (whose trials did not include refractory as a specific subgroup) as presented above in A10(b) (17).

A12. Please explain why 3 patients are missing from the zilucoplan arm and 4 patients are missing from the placebo arm of the RAISE trial in the NMA analysis for QMG responders (NMA report part 1 section 5.2.2) ("UCB_Report

for NMA_Updated Analysis_V2.0 - first draft - 1st part"). Were these patients in the refractory subgroup?

Only MG-ADL outcomes were presented, therefore the QMG responder analysis was not part of the company submission, nor included in the modelling. In addition, this document was a first draft and UCB has since updated the analysis and are considering the MG-ADL outcomes only as this is what is used in the economic model. Please see MG-ADL_UCB_Report for NMA_Updated Analysis_V1.1_Jan 10.docx for the technical report of the NMAs included in the company submission.

However, to answer the question of the three missing observations in the zilucoplan arm, one was refractory and two were non-refractory. Of the four missing observations in the placebo arm, three were refractory and one was non-refractory.

A13. To ensure consistency of comparisons and enable any effects of outcome definitions on the NMA results to be considered, please repeat the NMAs for the MG-ADL responder outcome using the MG-ADL responder definition of a ≥2 point improvement in MG-ADL score, to align with the ADAPT trial outcome definition.

The performance of MG-ADL was analysed in a multicentre scale validation study and concluded that a 2-point improvement in MG-ADL indicates clinical improvement (18). In the RAISE trial, not only did the changes in score meet the defined threshold for clinical meaningfulness with zilucoplan, nearly three-quarters of patients in the zilucoplan group improved beyond the clinically meaningful threshold for MG-ADL score (i.e. a reduction of at least 3 points from baseline). The definition from RAISE is a stricter criterion for response and therefore a tougher test for zilucoplan.

However, the company has performed this analysis as requested, please see below.

Table 35. Response rates using a 2-point improvement in MG-ADL for responder

Intervention	Response rate
Zilucoplan	[redacted]
Efgartigimod	[redacted]

Abbreviations: MG-ADL, myasthenia gravis activities of daily living.
Source: NMA, January 2024 (14).

The company would like to highlight that RAISE is powered for responders at a 3-point change in MG-ADL score and the marginally non-significant result likely

represents the high number of placebo responders who experienced a 2-point change. Further investigation into this result highlights a potential source of bias in the data. This analysis used the responder analysis in Figure 3 from Howard 2023 (11), where no imputation was done; data collected after a participant used rescue therapy are censored and treated as missing. A sensitivity analysis using data where participants who received rescue medication are classified as non-responders after the first rescue medication administration was performed to derive an accurate responder rate, and results are presented below (Table 36).

Table 36: Response rate using a 2-point improvement threshold in MG-ADL: Sensitivity analysis using data where patients receiving rescue medication are classified as non-responders

Intervention	Response rate
Zilucoplan	[redacted]
Efgartigimod	[redacted]

Abbreviations: MG-ADL, myasthenia gravis activities of daily living.
Source: NMA, January 2024 (14).

A14. Please provide the WinBUGS / R code used for the NMAs.

This have been provided separately with this document.

A15. Please explain how the NMA results should be interpreted given that the placebo response varied between the included trials. If possible, please use a baseline risk model or other approach to investigate and account for the differences in placebo responses.

We acknowledge that there was heterogeneity in the placebo response observed across trials in the NMA (for example, the observed response in the placebo arms was higher in the RAISE trial compared to the other comparator trials), which may impact the results of the NMA.

It is possible that the placebo effect was more pronounced for the zilucoplan trials because it is a once-daily injection vs cyclical dosing in other treatments and is therefore administered more frequently during the trials than the comparator treatments. In addition, differences in SoC treatments across the trials could have contributed to the variation in the placebo responses observed across the trials.

Despite differences in the placebo response across the trials included in the NMA, all new targeted therapies are significantly more efficacious than standard of care

(corticosteroids and/or NSISTs)/placebo and with no significant differences between zilucoplan and efgartigimod. At week 12±2 weeks, efgartigimod was no longer significantly better than placebo, whilst response with zilucoplan maintains a consistent response. The cyclical administration of efgartigimod adds complexity into the NMA, as the response is not maintained across timepoints.

The results with IVIg and rituximab have greater uncertainty due to limited randomised controlled trial data and small sample sizes, but in the NMA they are not proven to be better than standard of care (14, 15). These results are supported by the independent published network meta-analysis of innovative treatments in MG by Sacca et al, 2023, which showed that there was no significant difference between complement inhibitors and anti-FcRn treatments and that all targeted treatments were associated with a significantly greater improvement in MG-ADL and QMG vs placebo (standard of care), but rituximab did not significantly improve MG-ADL or QMG scores compared with placebo (15).

Other methodologies such as meta-regression and a baseline risk model were considered, however due to the limited number of studies and datapoints the Bayesian NMA methodology was preferred as the most robust approach.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY QUESTION. The NICE scope specifies that standard of care (SoC) is a relevant comparator and SoC has also been included as a comparator in previous technology appraisals for generalised MG. Therefore, please provide a version of the economic model that includes SoC as a comparator. If you disagree that IVIG, PLEX and rituximab should be considered as part of SoC then please provide options to compare SoC with and without these therapies.

All patients with refractory gMG are assumed in the model to be receiving acetylcholinesterase inhibitors (AChEi), corticosteroids, and non-steroidal immunosuppressant therapies (NSISTs). It is assumed that the doses of AChEi and NSISTs are equal in both treatment arms in the model. There is evidence of a reduction in corticosteroid dose in patients receiving zilucoplan; therefore, the cost of corticosteroids differs between treatment arms. The data on the effects of corticosteroid treatment on quality of life or mortality is currently not sufficiently robust to include in the economic model; therefore, conservatively, only costs were included.

Rituximab is not a relevant comparator for zilucoplan, as it is anticipated that zilucoplan will be used earlier in the treatment pathway for gMG than rituximab. Clinical opinion is that rituximab is not effective in refractory patients or in patients who are AChR-Ab+, and the limited data from the NMA highlights that it is not significantly better than placebo. In addition rituximab does not have marketing authorisation for MG in the UK, and the budget impact analysis received from NHS England states that rituximab would be used after zilucoplan. Therefore, standard of care in refractory patients who have active disease despite maximal immunosuppression is chronic IVIg/SCIg or chronic PLEX, meaning that these are the only relevant comparators for zilucoplan. In addition, the definition of ‘refractory’ in the RAISE trial was ‘having received treatment for at least 1 year with two or more of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for gMG, other ISTs, or history of treatment with at least one of these therapies for ≥1 year, and required chronic PLEX, IVIg, or SCIg at least every

3 months for the 12 months prior to enrolment'. This means that patients in the RAISE study are considered refractory after receiving rituximab, and need further treatment, defined in the second point as regular Ig or PLEX.

B2. CS Section B.3.3.4 (page 124) states "There was a lack of Phase 3 trial data for IVIG and PLEX and the NMA results showed an increase (worsening) in change from baseline in MG-ADL score for IVIG (using Phase 2 data); therefore, the response rate for placebo from the NMA was used as a proxy." However, CS Table 53 and the Excel model Sheet!Response state that the odds ratios (ORs) were back-calculated to obtain the same response rates for IVIG and PLEX as obtained from the study by Barth et al.

(a) Please explain this discrepancy.

There is an error in the statement "There was a lack of Phase 3 trial data for IVIG and PLEX and the NMA results showed an increase (worsening) in change from baseline in MG-ADL score for IVIG (using Phase 2 data); therefore, the response rate for placebo from the NMA was used as a proxy." The correct statement would be "There was a lack of Phase 3 trial data for IVIG and PLEX and the NMA results showed an increase (worsening) in change from baseline in MG-ADL score for IVIG (using Phase 2 data); therefore, the change from baseline for stable responders for placebo from the NMA was used as a proxy."

The rate of response for IVIg and PLEX were taken from the study by Barth et al (51% and 57%, respectively) (19). These response rates were converted into odds ratios using the average placebo response rates across studies in the NMA as the referent response rate [redacted] This calculation was conducted to ensure alignment across the calculation of response for each comparator in the model and to avoid having different calculation chains for different treatments in the model, i.e. they all use odds ratios instead of the model having a mix of some treatments using odds ratios while some treatments use absolute response rates for calculations.

Placebo data from the NMA were used as a proxy for the change from baseline in MG-ADL score for IVIg and PLEX [redacted] for stable response).

(b) Please explain the calculation of ORs for IVIG and PLEX.

As stated above, the odds ratios for IVIg and PLEX were back-calculated using the response rates reported in Barth et al (51% and 57%, respectively (19)) and the referent response rate [redacted] The goal seek functionality within Excel was used to back-calculate the ORs, using the appropriate form of the following equation programmed within the model: treatment response rate = referent response rate * odds ratio/ ((1-referrent response rate) + (referent response rate * odds ratio)).

(c) The EAG understand, from the company's correspondence with NICE, that CS section B.2.9.4 was updated to clarify the source of IVIG inputs to the economic model (although this was not provided to the EAG). Please could the company provide this update?

Please see the responses to parts (a) and (b) of this question to clarify the source of the IVIg responder and change from baseline inputs.

(d) The EAG understand, from the company's correspondence with NICE, that the company identified an error in the PLEX input to the economic model which they intended to investigate and resolve in a clarification response. Please could the company provide this?

Based on Barth et al, 2011, the response rate for PLEX is 57% (19). The odds ratio is back-calculated from this response rate as described above, i.e., [redacted] The company will update this in the model and submit the updated model.

B3. PRIORITY QUESTION. The CS reports in several sections that the company received clinical advice from experts and the company provided reports of expert engagement ("MG patient needs exploration", "Zilucoplan SMC clinician interviews"). The number of experts who provided information, their geographic locations, type of institution (e.g. general or specialist care centre), and any potential conflicts are unclear. Please provide this information for all instances in the CS where expert opinion is reported.

"Zilucoplan SMC clinician interviews" was included in error. Reference 156 should read "UCB. Data on file. Zilucoplan post hoc OLE analysis: Tapering of corticosteroids; Incidence rate of rescue therapy" (20).

See below a table with a list of experts who provided information, their geographic locations and type of institution. UCB will also provide declarations from the experts as a separate attachment.

Name	Hospital	Type of Institution	Conflict of interest
Dr Channa Hewamadduma	Sheffield NHS	Specialist Neurologist Centre	See attachment
Dr Saiju Jacob	Birmingham NHS	Specialist Neurologist Centre	See attachment
Dr Ashwin Pinto	Southampton NHS	Specialist Neurologist Centre	See attachment
Dr Maria Isabel Leite	Oxford NHS	Specialist Neurologist Centre	See attachment

B4. The CS states that the model considers the impact of the chronic use of corticosteroids on mortality, HRQoL and costs. However, the Parameters sheet in the Excel model and CS Appendix M only list corticosteroid costs. Please clarify how the effects of corticosteroids on HRQoL and mortality are incorporated within the model.

In the model, only the costs related to corticosteroids were considered in the Resource Use sheet cell E18 and G18; the impact of corticosteroid on health-related quality of life (HRQoL) and mortality was not considered.

B5. CS Table 53 indicates that the response timepoint used for efgartigimod is 26 weeks whereas the Excel model (Sheet!Resposne) specifies 10 weeks. Please explain this discrepancy.

This was a typographical error in the submission document. The response assessment timepoint for efgartigimod is 10 weeks.

B6. PRIORITY QUESTION. According to CS Section B.3.3.4, the economic model assumes that, of those patients in the response health states, [redacted] had loss of response, [redacted] had continued response and [redacted] had stable response. Please provide the rationale for this assumption.

This was derived from expert clinical opinion. There were two key opinion leaders who were interviewed, one from the UK on 3rd March 2022 (a consultant neurologist at an NHS teaching hospital) and one from Canada on 10th March 2022, to provide input on the model structure and assumptions. Further to this, the assumptions were further validated with UK clinicians who supported the assumptions.

B7. The economic base case assumes that patients return to baseline disease severity within 14 weeks of response assessment. This assumption is based on return to baseline QMG score in a Phase 2 eculizumab trial. However, we note that the RAISE-XT study has longer-term data, to 60 weeks. Please provide information on how long patients took to return to their baseline disease severity after discontinuing zilucoplan in RAISE-XT.

It is not possible to assess return to baseline after discontinuation from RAISE-XT, as patients were not followed after discontinuation in this trial. In addition, even if the data were available for zilucoplan, patients discontinuing may receive rescue therapy or change their base medication (e.g. a higher dose of corticosteroids), which could affect the results. Given the lack of available data, the published Phase 2 study in eculizumab was the only source to use for this input. This is not expected to significantly impact the results as the same duration has been used for all comparators. In addition, clinical expert opinion received since the submission is that patients would take around 6 months to return to baseline after a loss of response, so 14 weeks is proposed as a conservative assumption.

B8. CS Table 54 provides estimates of stable response for each treatment. Please explain how these were obtained.

Thank you for highlighting this. The response rates for stable response included in the company submission and the original submitted model were obtained from the company NMA performed in March 2023. However, subsequently there was found to be an error in how efgartigimod was incorporated (the whole study N was used as denominator, as opposed to the AChR+ patients that were reported in Howard 2021

(7)), and therefore an updated NMA was completed in November 2023 (14). Unfortunately, there was an error in that the November NMA report was provided but the response rates were not updated in the model, which was due to time constraints with preparing the submission for November 30th. The different values for each version of the NMA are shown in Table 37. These values are from the primary analysis MG-ADL change from baseline network which uses a week 12±2 week response timepoint; where the effect of efgartigimod is returning towards baseline after the end of a cycle.

Table 37: Change in MG-ADL score obtained from previous draft versions of the NMA

Treatment	March 2023 value	November 2023 value
Zilucoplan	[redacted]	[redacted]
Efgartigimod	[redacted]	[redacted]
IVIg/SCIg	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

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

The correct NMA report that should have been submitted with the company submission, as explained in the response to question A9, provides the change from baseline in MG-ADL scores as shown in Table 38. These values are from the scenario analysis 3 MG-ADL change from baseline network which includes data at the study primary endpoint timepoint; and therefore represents the peak treatment effect for efgartigimod, taken from week 4.

Table 38. Change in MG-ADL score in the correct version of the NMA

Treatment	ITT population	Refractory data for zilucoplan
Zilucoplan	[redacted]	[redacted]
Efgartigimod	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

Abbreviations: ITT, intent to treat; MG-ADL, myasthenia gravis activities of daily living; NMA, network meta-analysis.
Source: NMA, January 2024 (14).

B9. PRIORITY QUESTION. CS Section B.3.3.5 reports that the model includes a 2-week event rate of 0.184 applied to all patients in the exacerbation health

state who may worsen to myasthenic crisis. However, in the Excel model Sheet!Clinical events cell F12, the 2-week event rate is reported as 0.211.

a) Please explain this inconsistency in the 2-week event rate. Which is the correct value?

Please see response to part b).

b) In the following equation reported in the CS, what is the source of the estimate 0.1954?

The Gajdos et al. 2005 study outlines a trial conducted in patients with gMG who experienced acute exacerbations (21). There was a cumulative incidence of patients who required mechanical ventilation (assumed proxy for myasthenic crisis) of 19.54 after 15 days. Therefore, this value was taken as the probability of a patient in exacerbation worsening to a myasthenic crisis within 15 days. As this was reported within a 15-day period (21), a minor adjustment was made in the calculations to ensure the probability aligned with the 14-day cycles in the model.

The negative sign in the equation was a typographical error, the updated equation is presented below.

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

The error that led to the calculation of 0.211 was caused by dividing the number of patients who experienced mechanical ventilation by the sample size before being applied to the equation above (i.e. =1-(EXP(LN(1-(**19.54/87**))/(15/14))) = 0.211).

The cumulative incidence value should be considered the proportion of people who develop the outcome of interest during a specified block of time (21). Therefore, it is understood this should already account for the sample size. Ultimately, 0.184 is the correct value to be used in the model.

B10. PRIORITY QUESTION. CS Table 65 states "Adverse events are not included in the base case, but there is an option in the model to include". The

EAG are unable to find the switch in the model to include adverse events (AEs).

a) Please clarify the functionality within the excel model to include the AEs.

The functionality exists within the model to include AE costs if a percentage is added to the 'AdverseEvents' sheet. This is set to zero for the base case analysis. Apologies for the misunderstanding – there is no 'switch' in the model to include a set percentage of AEs.

b) Please conduct a scenario analysis including the AEs with an incidence of ≥2% at Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or above in the RAISE trial.

For zilucoplan, the only AE that is CTCAE Grade ≥3 with an incidence of ≥2% in the zilucoplan arm is 'myasthenia gravis', which is already incorporated into the overall modelling within the exacerbation and crisis health states (Table 39). There also aren't the equivalent data available for the comparators, since the trial publications don't list AEs that are Grade ≥3. Therefore, we are unable to provide the scenario requested. However, it is expected that there would be a higher risk of AEs of Grade ≥3 such as venous failure and thrombosis associated with long-term use IVIg and PLEX administration (compared with zilucoplan) (22-25).

Grade ≥3 AEs for zilucoplan are shown in Table 39.

Table 39. Grade ≥3 AEs for zilucoplan

Any severe TEAE (CTCAE Grade ≥3)	**Zilucoplan 0.3 mg/kg N=86 N (%) [#]**
Any severe TEAE	[redacted]
Blood and lymphatic system disorders	
Anaemia	[redacted]
Leukopenia	[redacted]
Gastrointestinal disorders	
Gastrointestinal and abdominal pains	[redacted]
Odynophagia	[redacted]
Aphthous ulcer	[redacted]

Mouth ulceration	[redacted]
Infections and infestations	
Oesophageal candidiasis	[redacted]
Oral candidiasis	[redacted]
COVID-19	[redacted]
COVID-19 pneumonia	[redacted]
Pneumonia	[redacted]
Sepsis	[redacted]
Tonsillitis	[redacted]
Investigations	
Amylase increased	[redacted]
Lipase increased	[redacted]
Weight decreased	[redacted]
Musculoskeletal and connective tissue disorders	
Muscle spasms	[redacted]
Nervous system disorders	
Myasthenia gravis	[redacted]
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	[redacted]
Pulmonary embolism	[redacted]
Vascular disorders	
Deep vein thrombosis	[redacted]

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
Source: RAISE CSR supplementary tables. Table 14.3.5.1 (26).

Adverse event data from published efgartigimod studies are presented in Table 40, and those for IVIg and PLEX are presented in Table 41.

Table 40. AEs from efgartigimod studies

AE	Study name	Treatment	N	n (%)
Any severity	Howard 2021	Efgartigimod	84	65 (77)
		Placebo	83	70 (84)
Arthralgia	Howard 2019	Efgartigimod IV 10 mg/kg + SOC	-	2 (16.7)
		Placebo + SOC	12	0
Nasopharyngitis	Howard 2021	Efgartigimod	84	10 (11.9)

		Placebo	83	15 (18.1)
Upper respiratory tract infection	Howard 2021	Efgartigimod	84	8 (9.5)
		Placebo	83	4 (4.8)
Diarrhoea	Howard 2021	Efgartigimod	84	6 (7.1)
		Placebo	83	9 (11)
Nausea	Howard 2021	Efgartigimod	84	7 (8.3)
		Placebo	83	9 (11)
Headache	Howard 2021	Efgartigimod	84	24 (28.6)
		Placebo	83	23 (27.8)

Abbreviations: AE, adverse event; SOC, standard of care; IV, intravenous.

Table 41. AEs from IVIg and PLEX studies

AE	Study name	Treatment	N	n (%)
Any severity	Gajdos 1997	PLEX	41	8 (19.5)
		IVIg	46	1 (2.2)
	Kohler 2011	Immunoadsorption + background therapy	32	11 (34.3)
		PLEX + background therapy	30	23 (76.6)
	Liu 2010	DFPP	15	3 (20)
		Immunoadsorption	10	4 (40)
		IVIg	15	1 (6.7)
Arthralgia	NCT02473952	IVIg-C 2g/kg→1 g/kg q3w + background therapy	30	2 (6.7)
		Placebo + background therapy	32	0
Pneumonia	Barth 2011	IVIg 1g/kg/day for 2 days	41	1 (2.4)
		PLEX (5 procedures every 2nd day)	43	0
Nausea	Barth 2011	IVIg 1g/kg/day for 2 days	41	7 (17.1)
		PLEX (5 procedures every 2nd day)	43	0
	Gajdos 1997	PLEX	41	1 (2.4)
		IVIg	46	0
Headache	Zinman 2007	IVIg	24	18 (75.0)

		Placebo	27	5 (18.5)
	Wolfe 2002	IVIg	6	2 (33.3)
	Gajdos 1997	PLEX	41	0
		IVIg	46	1 (2.2)

Abbreviations: AE, adverse event; IVIg, intravenous immunoglobulin; NMA, network meta-analysis; PLEX, plasma exchange.

The adverse events presented in the IVIg and PLEX SmPCs are shown in Table 42 and Table 43, respectively.

Table 42. Adverse reactions presented in the IVIg (Nanogram) SmPC

MedDRA System Organ Class	Adverse reaction	Frequency per patient	Frequency per infusion
Blood and lymphatic system disorders	Leukopenia, neutropenia	Uncommon	Rare
Immune system disorders	Hypersensitivity reactions	Common	Uncommon
Nervous system disorders	Migraine	Uncommon	Rare
	Headache	Common	Uncommon
	Dizziness	Uncommon	Rare
Cardiac disorders	Palpitations, Tachycardia	Uncommon	Rare
Vascular disorders	Hypertension, hypotension	Uncommon	Rare
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Uncommon	Rare
Gastrointestinal disorders	Diarrhoea	Uncommon	Rare
	Nausea	Common	Uncommon
Skin and subcutaneous tissue disorders	Skin disorders (rash, erythema, urticaria, pruritus, blister, exfoliation)	Common	Uncommon
	Hyperhidrosis	Uncommon	Rare
Musculoskeletal and connective tissue disorders	Back pain, neck pain, myalgia	Common	Uncommon
General disorders and administration site conditions	Malaise (fatigue, chills, pyrexia, influenza like illness)	Common	Uncommon

Abbreviations: IVIg, intravenous immunoglobulin; SmpC, summary of product characteristics.
Source: Nanogram SmPC (27).

Table 43. Adverse reactions presented in the PLEX (LG-Octaplas) SmpC

MedDRA System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)

Blood and lymphatic system disorders				Haemolytic anaemia, haemorrhagic diathesis
Immune system disorders		Anaphylactoid reaction	Hypersensitivity	Anaphylactic shock, anaphylactic reaction
Psychiatric disorders				Anxiety, agitation, restlessness
Nervous system disorders		Hypoesthesia		Dizziness, paraesthesia
Cardiac disorders				Cardiac arrest, arrhythmia, tachycardia
Vascular disorders				Thromboembolism (LLT), hypotension, hypertension, circulatory collapse, flushing
Respiratory, thoracic and mediastinal disorders		Hypoxia		Respiratory failure, pulmonary haemorrhage, bronchospasm, pulmonary oedema, dyspnoea, respiratory disorder
Gastrointestinal disorders		Vomiting, nausea		Abdominal pain
Skin and subcutaneous tissue disorders	Urticaria pruritus			Rash (erythematous), hyperhidrosis
Musculoskeletal and connective tissue disorders				Back pain
General disorders and administration site conditions		Pyrexia		Chest pain, chest discomfort, chills, localised oedema, malaise, application site reaction
Investigations				Antibody test positive, oxygen saturation decreased
Injury, poisoning and procedural complications				Transfusion-related circulatory overload, citrate toxicity, haemolytic transfusion reaction

Abbreviations: PLEX, plasma exchange; SmpC, summary of product characteristics.

Source: LG-Octaplas SmPC (28).

B11. CS Table 68 reports that end-of-life costs are [redacted] whereas the model uses the value of £3,785 (Sheet!ResourceUse cell C41). Please explain this inconsistency and clarify which value is correct.

Table 68 reports the discounted disaggregated results (output) for the end-of-life cost, i.e., [redacted], while 'Sheet!ResourceUse cell C41' is the input value of end-of-life cost, i.e. £3,785.

This difference is because not all patients die within the time horizon of the model, and therefore discounting applies until the end of the time horizon.

In the DetailedResults sheet cell C7, when the "Discounted" checkbox is unticked, i.e. undiscounted results are presented, then the end-of-life cost is [redacted].

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Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Myaware and Muscular Dystrophy UK (MDUK)
3. Job title or position	Research and Partnerships Officer and Director of Care, Communications and Support
4a. Brief description of the organisation (including who funds it). How many members does it have?	Myaware is the only charity in the UK dedicated solely to the care and support of people affected by myasthenia gravis. Founded in 1968, we are working hard to raise awareness of myasthenia gravis, provide support for people with myasthenia gravis and their families, whilst offering advice and tips for living with the condition. There are currently around 3000 active members of myaware, all of whom have full access to a wide range of support services and events including our specialist benefits advisor and telephone or Skype counsellor. Myaware has a long history of working with patients with myasthenia. Before covid this entailed regular face to face meetings, and since Covid regular quarterly zoom meetings. Myaware also host three closed Facebook pages in which living with MG is discussed daily. We also fund the research that brings us closer to finding a cure as well as funding specialists nurses and advisors. We campaign for better medical services for people with myasthenia gravis and work to inform medical professionals. Muscular Dystrophy UK (MDUK) is the leading charity for over 60 muscle wasting and weakening conditions. For over 60 years, we've been building our community of individuals living with muscle-wasting or weakening conditions, families and carers, scientists, health professionals, supporters, volunteers, and donors. Making advances that would have been unthinkable just ten years ago. We share expert advice and support people to live well now. We fund groundbreaking research to understand the different conditions better and lead us to new treatments. We work with the NHS towards universal access to specialist healthcare. And we campaign for people's rights, better understanding, accessibility, and access to treatments. Collaboration lies at the heart of our work and as such this submission has been collated together jointly between MDUK and Myaware.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Myaware has received funding from UCB totalling £334.78 to cover the cost of accommodation associated with attendance of the MG: Connects meeting in Manchester.

	Muscular Dystrophy UK has not received funding from UCB Pharma in the past 12 months. Muscular Dystrophy UK received £9,600.00 from comparator treatment company Pfizer Ltd in March 2023 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 are due to receive from the comparator treatment company Alexion £2,750 (plus VAT) for sponsorship of the myasthenia gravis session of its 2023/24 virtual seminar series. Muscular Dystrophy UK have received the following funding from comparator treatment company Roche. • £5,500.00 on 23 January 2023 for sponsorship of the MDUK Translational Research Conference 2023. Not ongoing. • £720.00 from Roche on 17 April 2023 for participation in its SMA Adult Activation Advisory Board. Not ongoing. • £1,710.83 in June 2023 towards pass, accommodation and travel costs associated with MDUK attendance of the European Paediatric Neurology Society congress. Not ongoing. • £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 has been pledged for 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. • £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.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No links to the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gathered information through the following avenues: - A patient survey on the impact of living with Myasthenia Gravis where we had 551 respondents. - A focus group to gather feedback on living with the condition and current treatments which was attended by 21 people living with Myasthenia Gravis. The focus group was aimed particularly at understanding what it is like to live with the condition and insight into current treatments. - Published evidence on disease burden and media case studies/published reports. - A patient survey for those currently being treated with Zilucoplan focused on their experiences. We had 6 respondents. We liaised with the two UK trial sites for the treatment (Oxford and Sheffield) who between them reported that they have 17 participating patients, so this is a high proportion of UK patients with direct experience of the treatment.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Myasthenia Gravis (MG) is an autoimmune condition that can affect anyone, old or young and of any gender. People with MG have characteristically fatigable muscles and the harder they try, the weaker they get. They are often strongest in the mornings and get weaker throughout the day. The course of the disease is extremely variable, between individuals and individual people with myasthenia can vary considerably from day to day. Some days are better than others; for no "apparent" reason. Life threatening "myasthenic crisis" can happen suddenly, requiring hospitalisation, and necessitating lifesaving treatment. Our survey revealed MG has a physical, emotional, and financial impact on individuals and their families: **Physical Impact** The first signs of MG often are: droopy eyelids and possibly double vision, tiredness and weakness in the neck arms and legs. It is common that people find their faces are affected, this means smiling, making facial expressions, or chewing may become difficult. The symptoms often evolve into difficulty swallowing and breathing. In addition, some peoples' speech can be difficult, especially if they have been talking for a long time, they may realise their speech has started to sound different, possibly slurred. As the day goes on, some people find they are getting weaker, and they may need a rest. Pushing yourself to do things, like walk and talk, may make this even worse. From our survey, one respondent told us: "*I am unable to do the majority of the things I used to do due to my extreme weakness, breathlessness and fatigue. I have had to reduce my working hours. I can't do much around the house or garden fatigued most of time and really weak physically*." Another told us: "*Constant double vision, poor balance, cannot drive, some bad days, poor bladder control, need to know nearest toilets. I have been refused service as restaurant owners think I am drunk and have commented on my eyes, been asked to leave*." Further, 40% of respondents were admitted to hospital within the first year of their diagnosis, of which 15% landed in intensive care mainly for close monitoring. **Emotional impact**

	Almost seven in ten (68%) respondents said having MG has had a negative impact on their social life and increased feelings of anxiety, with one respondent telling us: *"I've had myasthenia for 60 years and I thought I could manage it very well. What I have found is I have become very suspicious of people. I didn't go out beforehand. So many letters from the NHS made me feel extremely vulnerable and now when I go shopping I look at which is the shortest queue and I'm quite suspicious of people. And that is so unlike me. But now I want to withdraw from people."* Another respondent told us: "*Due to fatigue and embarrassment with my slurry speech, I don't feel comfortable going out too much. I also can't walk for long durations and am unable to walk long distances which has changed me as a person with regards to feeling comfortable going out with friends and even leaving the house unless necessary*." These feelings are only further exacerbated due to the unpredictability of their symptoms which can be difficult to explain to others, with 27% of respondents finding it difficult to talk about their condition with their community. One example is: "*Because I appear well and bubbly, it feels like I'm creating a problem where none is apparent. It is difficult to explain to people how you can be all right one minute and then extremely fatigued the next. People look at me and see a "normal" person and are quite surprised when I reveal I have a disability and have never heard of or understand MG*". This emotionally impacts not only the individual, but also their families, with 50% of respondents stating that their condition has negatively impacted their family's mental health. For example, respondents told us the following: "*Being diagnosed at a young age this has been stressful for my family, especially my parents seeing me unwell and admitted to hospital numerous times and in intensive care. Caused them worry and stress which continues any time I am unwell*." "*Having your mother in hospital when doing A level exams and starting University without support is difficult*."

	"*…hit my partner very hard as she saw me at the most life-threatening stages through which I passed completely unaware*." Further, the impact of living with MG on mental health has been exacerbated by the pandemic. Members who have been shielding for a significant amount of time, due to the medications used to treat/manage MG, have suffered from extreme isolation. There has also been a knock-on effect in terms of consultation and face-to-face interaction with specialists. There has been an increased feeling of vulnerability in the community. For example, one attendee in our focus group told us: "*I was diagnosed 5-6 years before COVID. What I found was things take longer to compute and I had to think about things a lot more, which has an invisible effect on your mental health. It makes you more tired. With COVID you are reminded all the times of the dangers out there, which had an impact. The impact of MG on my mental health is the constant awareness of it and it is grinding you down and you have to think about the things that you do and say, and I find it tiring*." Another told us about the sense of visibility the pandemic has put on their condition: "*Shielding has led to the exposure of medical history due to work-from-home schemes. First time people found out you had a medical condition, making you stand out and encourage feelings of resentment. Having the vaccine improved my mental health by allowing more freedom from isolation and shielding. However, I was made to feel vulnerable by wearing masks at the office*." **Financial Impact** Over a third (37%) of respondents have had to stop working or change roles due to their condition. This was mainly due to fatigue, breathing challenges, vision problems, voice becoming slurred, inability to focus, unable to drive to and from work (when remote working not possible). Similarly, 37% also stated their condition had negatively impacted them financially, with many needing to change to part time working. However, some respondents told us that the hardest part was the limbo before receiving their diagnosis, where they had to take time off work due to illness resulting in loss of salary and found themselves unable to explain to employers what additional support they may need or to arrange a working pattern that suits them better.

	One respondent told us: "*Having a job paying £30,000 then having to go on benefits which only pays a pittance meant I had to cash in my private pensions and now being in a low paid job due to having to find work that fits around my MG*" For those in employment, there was a consensus in our focus group that employers are relatively understanding and generous with time and resources for employees with MG. However, MG has been seen by members as holding back their careers. For example, attendees have been wary of changing their careers or looking for better opportunities in their profession, which has limited their career progression. This is because they don't know if their new employer will be as supportive as their previous one. For example, one attendee told us: "*One of the worst things I found when I was working was (that) some days I'm good and some days I'm bad. And people will say to you 'well you don't look ill'. If you have a broken leg, it's broken until it heals. MG isn't like that*." Another attendee told us: "*I had a very encouraging employer and they helped me a lot. They supported me, I had regular reviews. They did know about MG. Even within the health service though they didn't have an in-depth understanding of it. I had regular reviews and eventually with their support I realised I had to take early retirement. Which is where my problems started as I was initially refused the ill-health pension. I went to my doctor, and he told me this was the system, people get refused and [they] don't `fight back. [But] He wrote a great report with the support of my employer and managed to get me accepted for the ill-health pension*." However, despite reports of support from employers being common amongst attendees, there was also evidence of a lack of awareness and response from occupational health representatives. "*My employer (university) is incredibly generous. Occupational health not so much. They have to assess me every year even though myasthenia is not going to go away. It really has affected my career choices. I have a supportive employer, so I don't dare change jobs in case I end up somewhere where my employer doesn't understand. I was headhunted while I was being diagnosed but had to turn down a lucrative and exciting prospect. It's accepting the fact that I won't be looking for a change of employer of job for a long time. Career progression has slowed down massively, so myasthenia will affect my finances at some point."*

	A lot of work is still required to create policies and pathways for managing myasthenia in the workplace, and these have yet to come to fruition in the occupational health sector. Another attendee commented: "*Occupational health – the first assessment I had they basically said to me that I should meet my employer halfway and go part-time. It felt like they just dismissed me. There is a lot of identity tied to work and it is really shaken up when there is a diagnosis and extra hoops to jump through*." A lack of understanding in terms of capability or the ever-evolving nature of myasthenia has left patients feeling unsupported and misunderstood, which in turn has affected career prospects and the desire to advance for fear of not receiving support universally. This has had a knock-on effect on their families, with 30% stating their condition has negatively impacted their family financially who rely on both salaries to pay for mortgage and costs of living. Additionally, having MG has led to additional costs for adaptations. For example, one respondent told us they had to purchase various electrical appliances to maintain the individual's independence such as purchasing a specific kettle as they can't lift their current kettle because they are too weak. **The experience of carers** In the appraisal process for a separate myasthenia gravis treatment, efgartigimod, we put forward strong testimony showing the benefit caregivers provide to patients with gMG and of the impact that being a caregiver can have. The substantial caregiver burden of gMG arises from both physical, emotional and financial impact caused by symptoms experienced by gMG patients. Firstly, the physical impact of gMG such as difficulties with swallowing, vision, speech, breathing, and mobility, as well as extreme fatigue mean that patients often require help with eating or mobility, both of which a regular caregiver is required to support. To assist in preparing our submission to the first stage of the efgartigimod appraisal, myaware conducted a patient survey on the impact of living with myasthenia gravis that received 551 responses. The survey found that 50% of patients with gMG believe that their symptoms have negatively impacted their family's mental health. Carers of people with gMG may experience anxiety and depression due to their caregiving responsibilities or worry about the patient's health.

	Finally, the financial impact of gMG contributes to the caregiver burden. In the survey, 30% of gMG patients stated their condition has negatively impacted their family financially. Carers for gMG patients often become responsible for upholding the family finances which is significant given that they may also have to reduce or stop working due to their responsibilities. To assist in preparing our submission to the second stage of the efgartigimod appraisal myaware conducted a survey of 156 members to further explore the impact of gMG on caregivers. The survey asked members of myaware to describe their experience of receiving care – specifically support or assistance from family, partners, or friends as a result of living with gMG. Of those receiving this care, 82% receive carer support from family all week. A time investment of this scale does not align with the statement that gMG does not have a substantial effect on carers. In addition, requiring care all week suggests these respondents are not able to be independent. When asked to respond to the statement "*The support I receive from family, a partner, or friends positively impacts me*" 80% of respondents strongly agreed, with a further 17% agreeing. This in itself emphasises the importance of these carers to gMG patients. In response to the statement "*Supporting me has an impact on my family members, partner, or friends who do so*" 72% strongly agreed with this, with a further 22% agreeing. This suggests that, contrary to the EAG's view and the company submission, that gMG has a substantial effect on carers. Finally we wanted to provide some quotes from our survey respondents which in our opinion underlines the dependency on carers and the effect gMG has on them. "My *husband has been my carer since diagnosis. He gave up work to care for me full-time. It is both physically and mentally demanding. When our two children were young, he also had a greater share of childcare because of my MG. Now they are grown, they both contribute to my care, helping with chores and shopping. My MG has an effect on the whole family, and we make extra efforts to ensure we stay positive and loving to each other*." *"Caring for me is a big job, its pretty much a full time job as my symptoms never go away. We never know when muscle weakness will strike next, so we are always on high alert. My partner has completely changed his life to give me love, care and support. It's a very debilitating condition not only for the patient but also for those around*

	us. Its not just a case of a bit of looking after, its intense and every part of our lives is governed by the high demands of MG." In addition, one of our respondents was a carer of their husband with gMG and had the following to say: "*I have had to give up a well-paid full-time job in order to care for my husband. His is very unsteady and cannot walk more than a few paces. Without me help he would find it almost impossible to get out of bed. The house is also full of mobility aids so feels cluttered and we can no longer sleep in the same bedroom due to him needing a hospital bed and walking frame which would not fit into our room even if we changed the kingsize bed for a single. I find it depressing that we can no longer do the things we used to enjoy like fell walking every weekend and scuba diving I find life really depressing now but do not mention this as I know he feels bad enough being reliant on me without worrying about me too*." Separate to the evidence set-out above, Muscular Dystrophy UK supported research conducted by the Research Institute for Disabled Consumers (RIDC) that recruited 21 carers of people with a diagnosis of gMG. In line with NICE's definition of a carer, participants confirmed that they supported a family member, partner or friend with needs that resulted from living with gMG. The research was conducted between 13 June 2023 and 21 June 2023 through one-to-one in-depth telephone interviews. Participants were asked to what extent their responsibilities around caring for someone with generalised myasthenia gravis effects their quality of life on a scale of 1-5, where 1 is not at all affected and 5 is extremely significantly affected. The average score given was 3.4 and no one gave a score of 1 (three people gave a score of 2; nine people gave a score of 3; six people gave a score of 4; three people gave a score of 5). Participants were asked in which aspect of daily living (if any) they experienced any impact due to caring for someone with generalised myasthenia gravis. Participants could select more than one option. None said that it had no impact. • 19 people (90%) said it impacted their ability to undertake their usual activities such as personal shopping/ hobbies • 16 people (76%) said it impacted their mobility/ ability to move around • 14 people (67%) said it caused anxiety/depression • 11 people (52%) said it impacted their personal care e.g. washing/dressing • 5 people (24%) said it caused them pain/discomfort

	Asked about the impact that caring for someone with generalised myasthenia gravis has on specific activities (participants could select more than one option); • 21 people (100%) said their social life • 19 people (90%) said working/studying • 18 people (86%) said sleeping • 8 people (38%) said eating Comments relating to the impact on social life included; *"You can't do anything social or working. I like music and the cinema and you cannot go to music or jazz clubs. You can't socialise."* *"My social life is affected, and I cannot hang out as much as I want to. I can't be free and be outdoors as much as I would like to."* *"Social life and dating are impossible. No sports or any other things like you could do before. You try to do them, but you get a call and then you have to go home."* *"It becomes very difficult as I have no time for leisure anymore. My personal life is tough as my caring takes a whole lot of time and I do not have much sleep."* *"Getting to leisure and recreational activities. I love sport but I have to limit the time I spend outside as the person I am caring for may need me at any time. [It alters] the way I would live otherwise."* *"I was able to crochet more before care giving. My hobby was too time consuming so I am unable to continue doing what I like. I have had to stop."* In terms of the impact of caring for someone with generalised myasthenia gravis on employment, only two participants (10%) in the research were not employed; eight (38%) were employed part-time; seven (33%) were employed full-time; three (14%) were self-employed; and one (5%) was employed but on long-term medical leave. Nine participants (43%) said they worked less hours as a result of their responsibilities as a care giver. *"My part-time job is online as you cannot be taken away physically from the person you are taking care of. Some days he cannot move his body."*

	"I can't commute because my dad is more important." *"Mostly at work I get called home. It is really stressful. I have no peace of mind. I can get called at any time."* In terms of the impact of caring for someone with generalised myasthenia gravis on studying, comments from participants included; *"I would love to further my education but I can only do a little online study. Taking care of your relation takes up your time and is paramount."* *"Academics are online but there is no social element for you to do some interaction. You can get the qualifications online but it is not the same experience."* Five participants (24%) in the research stated that being a carer for someone with generalised myasthenia gravis caused them pain or discomfort, with comments including; *"The stress sometimes and always being active it gets very stressful and heavy on my lower back."* *"Lifting her with my legs. Helping her stand and communicating with her for a long time is tiring. Standing for a long time to communicate and support her."* *"In terms of pain I am constantly having to be up all of the time and being on my feet and moving around has caused mild pain and feeling lightheaded due to a lack of sleep."* 14 participants (67%) said that they experienced anxiety and/or depression as a result of caring for someone with generalised myasthenia gravis. 8 of these 14 (57%) said this was to a mild extent; 4 of these 14 (29%) said that it was to a moderate extent; and 2 of these 14 (14%) said that this was to a severe extent. *"At times I feel down because this is someone I love so much and having to watch her go through such problems can be disheartening and I feel down and bad and I wish I could prevent that but it is beyond me. At times I feel it is my fault."*

	"Generally being a carer is difficult because sometimes we have no choice. You have to make huge sacrifices. You cannot achieve your dreams. You cannot maintain relationships or friendships and cannot travel around." *I fell into depression. I had a lot in life I liked to do. Being stuck makes me think a whole lot. I am not getting paid, and I feel that my life is wasting away, and I think too much, and it doesn't get better. Sometimes it is okay and then there is another crisis. I do not want to lose him, but I am scared, and I am stuck. I can't overreact and I have to be gentle and can't show my own side and my own feelings. I can't make him feel that he is making my life pause. No one is there to talk to, and you feel like sometimes social media makes things harder. I see other people doing a whole lot of stuff [such as] working or starting a family. It is really hard."* *"Sometimes I look forward to when my care giving role comes to an end and I can get on with my life. Doing the same thig over and over again sometimes I think about the end of life and is this what life is about. It gives me anxiety."* *"You have no control of the situation. You just worry because if you had your way you would have your loved one fully well and you could return to your normal life."* *"My life turned all of a sudden and I can't get a grip on it at the moment."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	People with MG are on a range of different treatments, which creates two main difficulties: (1) managing the different timings within their day-to-day activities and (2) getting the dosage right between balancing the side effects of steroids and managing MG symptoms. Overall, our focus group showed there are a lot of problems with the management of steroid intake, particularly with prednisolone. Attendees would largely like to reduce their dose but fear the impact of this on their MG. Following a stringent routine for medication intake is incredibly taxing, as the process must be consistent to achieve the most relief from MG symptoms. Ordering prescriptions has no clear sensible system either and demands a lot of time and careful coordination from patients. There is a constant feeling of being dictated by medication and 'living at the mercy of a clock'. Lots of medications must be ordered and collected at alternate times, further contributing to the burden of managing myasthenia. Access to more expensive treatments feels like it is being withheld in place of cheaper options. **<u>Scheduling treatments</u>** In our focus group, there was a lot of frustration at how an individual's treatment schedule inhibits day to day activities. For example, people with MG must consistently be aware of what food they are consuming, and at what time of the day to ensure it doesn't impact their treatments. As a result, socialising where food is involved is very challenging with their meals needing to be regulated to be in time with their medications which feels restrictive for them and the people they are eating with. Further, accessing their treatments is inconsistent with ordering all medications at the same time. One respondent told us: "*It's not just about remembering to take medication in a sort of order, but the ordering itself. Every medication has a different place it can be prescribed from, and the ordering all takes different times*." **<u>Side effects and opinion on steroids and steroid sparing agents</u>** A lot of people with MG are on steroids to reduce inflammation by reducing the production of the autoantibodies that are attacking the neuromuscular system, this is achieved by 'damping down' the activity of the body's immune system. However, getting the dose right to reduce the risk of side effects but to still manage the MG symptoms is tricky and causes a lot of stress for this community. We particularly heard: "*The medication I was put on to start with controlled my symptoms. I saw a consultant a month later who thought he found some weakness in one of my arms. The protocol was to increase prednisolone. My intuition was that it had been more down to being unable to eat for alternative reasons. The increase to steroid did not help*

	physically but stressed me mentally. I explained this to him and he was very good. It's a risky business when you want to trust your own intuition about your body even when it goes against what a consultant is recommending." Side effects from non-steroidal immunosuppressants such as Azathioprine have also been reported by respondents, with one saying: "*I did have to come off Azathioprine as it impacted my blood, liver and kidney functions*."

8. Is there an unmet need for patients with this condition?	People with MG struggle to balance their treatments with symptom management and undertaking their day-to-day activities such as work and socialising. As we have demonstrated this has negatively impacted their mental health as well, which clearly shows the need for new treatments to reduce this burden of care. The accessibility to new treatments is an additional problem for people with MG. Sometimes it can feel like the cost to NHS outweighs a beneficial outcome to them. As spoken by an attendee: "*I have hated prednisolone since the day they put me on it. I was convinced it was not making a difference. I was on 60 mg and have had to fight for a reduction. I'm now on 3 mg but also taking a cocktail of others. Then there is the side effects of the medication you take to reduce the side effects of prednisolone. I've found even the most empathetic of doctors find IVIG is too expensive. Rituximab really changed my life, and I would like another round of it but there is a feeling that it is being held back because of the expense. I just wonder why it feels like sometimes the doctors don't listen to you, don't fiddle with medications that do work. I knew Rituximab wouldn't be immediately effective, but after 6 months it was like magic. I was feeling so much better I felt I was in remission*." In addition, there appears to be a reluctance to deviate from treatments that work in favour of trying alternative approaches that might give an improved result. One attendee said: "*My GP will not prescribe me mycophenolate, so I have to get it prescribed by my consultant at the hospital and have to make a long car journey. GP is happy to prescribe 100 mg of prednisolone. GPs don't seem to have necessarily as much comfort with immunosuppressive agents which makes life harder sometimes*." People with myasthenia who are taking immunosuppressive drugs are at high risk of being severely affected by infections, such as Covid19. Their immune systems are "dampened down" and so cannot respond effectively to opportunist infections.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Myasthenia gravis, is an autoimmune diseases caused by autoantibodies to components of the neuromuscular junction. Antibodies to the acetylcholine receptor are found in over 80% of patents, with a smaller number of other patients having detectable antibodies to other neuromuscular proteins such as MuSK. Myasthenia is a difficult to control chronic disease. Many patients may have myasthenic crisis brought on by infection, stress and other causes both known and unknown. Zilucoplan is a very new drug for the treatment for patients with autoimmune diseases which is particularly pertinent to our members who have the autoimmune form of disorder myasthenia gravis. This drug is different to many of the other new drugs currently in the pipeline such as Efgartigimod or Ravulizumab as it is macrocyclic peptide complement C5 inhibitor and not a monoclonal antibody. It works by attaching to and blocking the C5 complement protein. By blocking the complement cascade the drug will prevent the destructive action of the anti-acetylcholine receptor (AChR) antibodies on the acetylcholine receptors present on the neuromuscular junction of the muscle. It is the action of the complement cascade that causes the destruction of the neuromuscular junction, resulting in the muscle weakness, especially in the chest muscles that can be life threatening. By acting on the complement cascade, Zilucoplan should bring symptomatic relief to all autoimmune patients with anti-AChR mediated myasthenia gravis. However it will not be used for the patients (<20%) with muscle-specific kinase mediated myasthenia (MuSK-MG) as this is not mediated by the complement system, but by a direct effect on the MuSK protein itself. Although the symptoms of a proportion of patients can be controlled using a range of drugs including steroid and steroid replacement drugs, patients with myasthenia, do not like taking steroids. They are worried about the medical side effects of steroids including low resistance to infections, weight gain, possible onset of other disorders (diabetes, osteoporosis), and sleep and mood problems including depression. Reducing dosage brings on the fear and possibility of a loss of control of their symptoms and an increase possibility of myasthenic crisis. Some patients can have their symptoms controlled by steroids, however the symptoms in a significant proportion of patients are hard to control, and these patients face a prolonged period on steroids with the danger of the many known medical side effects of long-time steroid usage and are prone to “myasthenic crisis”, when their condition may suddenly become severe and life threatening. There are several major advantages of Zilucoplan over steroids and the other new drugs that are being developed. 1. Zilucoplan, can be self-administered (after minimal training) and given as a single daily injection. The monoclonal drugs in development require infusion, with trips to hospital

	2. So far, no serious side effects have been reported, unlike the long-term use of steroids. 3. Zilucoplan is a peptide, which will make it cheap to make and easy to store, making the drug cheaper than many alternative drugs and so it is potentially likely to be used more widely and benefit more patients, than the costly monoclonal antibody derived drugs. Many of our members spend their life fearing a myasthenic crisis that could warrant a hospital stay or worse. In a significant minority of patients with myasthenia the symptoms are not well controlled, and these patients are continuously seriously and chronically unwell. This new treatment may certainly offer the possibility of a superior prognosis in patients in which current treatments are ineffective or partially effective. We were able to survey patients who had taken part in the RAISE trial for Zilucoplan and had 6 respondents. All had been taking Zilucoplan for a period between 2-3 years. When asked to describe the benefits of receiving Zilucoplan have been, one patient said: "*This treatment has been absolutely lifechanging. This is as close to feeling like "Normal" as I have ever felt. The symptomatic improvement since starting Zilucoplan was almost instantaneous - significant improvement in all my symptoms within 48hrs. I was able to walk for miles without fear of falling and very minimal weakness - I haven't been able to do that for nearly 20 years. It has changed my life in a very significant way for the better. I am able to socialise, travel, climb stairs safely. Reduction in fatigue and improved muscular strength and tone*." Another patient described a resurgence in their independence and goals for the future, stating: "*I've transitioned from being chair bound and dependent on my parents to wash and dress me to leading a normal life, being completely independent, exercising daily and pursuing my A-Levels*"

	Some also described the effect Zilucoplan has had on their ability to complete what are often considered to be basic tasks: "*Before zilucoplan, I was having major difficulties in speaking, chewing, smiling, walking, doing sports. Now I can do all of that (some parts - like smiling - are still not ideal but much better from what it used to be). I don't have difficulties with speaking or chewing at all anymore and it's great. Don't have double-vision at all anymore*." 83% of respondents reported no negative side effects when taking Zilucoplan, and between the two patients who did report negative side effects both stated they were unsure whether these could be attributed to Zilucoplan (an increase in colds, poorer aftereffects when consuming alcohol). Finally, one respondent commented on the effect their gMG has on their family on how Zilucoplan has helped: "*Before Zilucoplan I was beginning to feel that I was a burden to my family and unable to socialise and take part in normal life. This has now all changed and while I am still aware that I still have MG, I feel that I can now manage it and lead a near-normal life again*." Four patients with experience of Zilucoplan also shared their assessment of its impact on their life when we were seeking nominees for patient experts in the appraisal. One commented that: *"My quality of life has been transformed since being part of Raise XT from December 2020. There are no side effects, it is so easy to administer at home and my life is now highly predictable. I had experienced terrible side effects while on prednisolone such as diabetes, glaucoma, weight gain and mood changes. IVIG and plasmapheresis had worked but the effects were not long lasting so it was difficult to make medium term plans without having to risk cancelling at short notice. Since being on Zilucoplan I have been able to restart playing competitive hockey and enjoying sports again."*

	Another shared: *"Zilucoplan was the first clinical trial I was offered to join, and was the most impactful treatment I have ever received since diagnosis. Prior to zilucoplan, I was admitted into hospital for plasma exchange for a minimum of 7 days 1 – 2 times a year, with frequent medicines review and additional IVIG as a rescue therapy. Since Zilucoplan, I have had no hospital stays, and was able to reduce one of my core medications within 4 weeks of starting the trial."* A third patient shared that: *"I was diagnosed with myasthenia gravis towards the end of 2002. Post a thymectomy in early 2003 I completely crashed and ended up on a ventilator under anesthethic for 11 days. It took four months to leave hospital and a further two before they removed the tracheotomy. I was told I had brittle myasthenia. It was advised I should receive regular IvIg as I kept crashing in the months that followed. I was also given a cocktail of other drugs to keep me stable. Fast forward to 2015 and I crashed really badly. Drugs were changed and I had to take steroids again where I put on a staggering 50kg. Today, after being on the trial for two years the only myasthenia drug I have is zilucoplan. I have been feeling so much better and I have lost 30kg so far thanks to finally coming of steroids in January this year. Zilucoplan has changed my life. I'm so so grateful for the opportunity to test this drug."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The most likely clinical disadvantage of this drug (and other related complement-cascade interfering drugs, both peptide and monoclonal antibody), is its non-selective mode of action. Blocking the complement cascade can affect the protection of the body from pathogens. In certain cases it may lay the patient open to infection. However, this is true of other forms of immunosuppressive drugs too, and so the patient will be need to be monitored and be aware of this possibility. The nature of Zilucoplan, means it will work on a large and significant majority of myasthenic patients, but unlike, for example Efgartigimod, it will not work on forms of myasthenia that are not mediated by the complement system such as MuSK-MG. In addition, three different mechanisms of potential antibody action have been postulated for autoimmune myasthenia gravis, namely 1) activation of the complement cascade 2) direct block of the AChR and 3) and bivalent cross-linkage of adjacent AChR causing an increase in internalisation and receptor loss. The part that each mechanism plays in the disease varies from patient to patient. It may be the case that the drug may not be as effective in some patients as in others The drug will be self-administered, and this should be an advantage as long as sufficient training is given, to avoid possible infections The cost of the drug, although cheaper than similar monoclonal antibody drugs, will be higher than steroids and some other immunosuppressive drugs. Our members appreciate the cost is higher than the day-to-day cost of tablets, but suggest that long-term steroid usage is not cheap and leads to other medical problems, such as obesity, heart problems and diabetes, which are themselves debilitating and costly to treat.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As previously mentioned, there is a small number of myasthenia patients who present MuSK antibodies rather than AChR. This may make treatment through Ravulizumab ineffective given its mode-of-action in complement pathway interference.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Myasthenia is a very variable and fluctuating disorder. Gender-based differences in MG onset change based on age, with early onset MG being more common in women while men tend to present with MG between the ages of 40-70. With this in mind, there are some gender and ethnicity predispositions, but these are irrelevant to the treatment the patient receives. The needs of particular treatment regimes in individual patients will be administered as to their personal needs at the time, by their own physician and is independent of gender or ethnicity.

Other issues

13. Are there any other issues that you would like the committee to consider?	Nothing else to add.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Myasthenia Gravis (MG) is a chronic, incurable disease which significantly impacts the lives of patients and their carers. This impact can be felt physically, emotionally, socially, and financially. • The medication burden which currently exists for myasthenia patient takes a distinct toll on patients, who often feel they are living their lives 'by a clock' and constantly monitoring their own symptoms. The number of medications taken by patients, and their off-target effects, results in side effects that have a overwhelmingly negative effect and these result in a poor overall quality of life. Steroids such as Prednisolone raise concerns about potentially extensive and irreversible side effects. And finding the right balance between dose strength and side effects can result in a loss of control of symptoms, which can be costly to the NHS. • MG can affect anyone of any gender and at any age. The primary symptom of muscle fatigue worsens as the day progresses. Myasthenic crisis, where swallowing and breathing difficulties presist, can be a fatal if not intervened. • Zilucoplan targets the complement pathway, making it a more targeted therapeutic than what is currently available. The RAISE trial has shown it to be effective and well tolerated, and the testimony provided by patients in this submission emphasise the positive effect it has had on their lives, and the lives of their families. • For a significant minority of MG patients, standard treatments are not able to control their symptoms. These refractory patients are without a sustainable way to manage their MG, and targeted therapies such as Zilucoplan may be able to provide a solution to this problem.

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Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists' mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	N/A
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	N/A

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Treatment aim in autoimmune myasthenia gravis is to resolve the symptoms causes by neuromuscular junction transmission failure/ impairment caused by the pathogenic antibodies: AChR and MuSK. This means resolution of fatiguable ptosis, diplopia (ocular manifestations), facial, bulbar and limb weakness (generalised MG) and reversal of any diaphragmatic weakness (neuromuscular respiratory failure). Complete symptom resolution is the ultimate aim but is not currently attainable in all patients within the current treatment paradigm. Between 50-80% have ongoing symptoms despite treatment with corticosteroids, steroid sparing agents and 20% have resistant and significantly disabling disease. Rituximab, IVIg and PLEX are used to manage treatment resistant cases. In addition, side effects of existing therapies (particularly steroids) can significantly increase the risk of comorbidities and quality of life.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Complete symptom resolution is the ultimate aim, as delineated above. There are a range of patient outcome scales recognised as useful in the monitoring of disease activity. These scales are used in clinical practice and in the clinical trial setting. MG-ADL (Myasthenia Gravis – Activities of Daily living) score QMG (Quantitative Myasthenia Gravis) score MGC (Myasthenia Gravis Composite) score MG-QOL15r (Myasthenia Gravis Quality of Life 15-item revised) score However, these scores are focused on direct MG symptoms and do not fully take into account treatment side effects and the impact of hospital attendance or sub-optimally controlled disease on lifestyle or employability.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. A significant proportion of patients with autoimmune MG remain symptomatic or have undesirable side effects, despite optimised treatment according to the current therapeutic algorithm. Corticosteroids followed by maintenance with steroid sparing agents: 50% symptom resolution But often tolerance issues limit use of these steroid sparing agents (azathioprine, Methotrexate, mycophenolate) Rituximab is licenced for ACHR and MuSK Ab positive MG refractory to first line treatments but is less effective in ACHR positive disease than MuSK positive cases, which represent a small proportion of the UK population. Resistent cases are treated with supplementary IVIg or PLEX which are immunomodulatory and require regular hospital attendance, expensive therapeutics (IVIg= £70/g, - usual maintenance IVIg dose= 1g/kg) or specialist staffing and equipment for PLEX. Cyclophosphamide is rarely used and carries significant adverse risk (renal and bone marrow toxicity, bladder oncogenicity). Therefore patients and healthcare professionals would benefit from alternative therapeutic options which may address both treatment resistant disease and existing drug tolerance issues. An important factor is the impact on QOL that dependence on hospital based treatments creates. Subcutaneous treatment options, delivered at home may address these issues.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The first line of medical treatment is with pyridostigmine, corticosteroids and steroid sparing agents. In those resistant to or intolerant or these treatments with frequent relapses with MG crisis or precipitous severe presentations the following additional treatment options exist - Thymectomy - IVIg or PLEX for significant bulbar or neuromuscular respiratory manifestations (MG crisis) In the past year Efgartigimod (FcRn inhibitor) has been made available to patients with refractory MG via the EAMS scheme
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Sussman J, Farrugia ME, Maddison P*, et al* Myasthenia gravis: Association of British Neurologists' management guidelines *Practical Neurology* 2015;**15:**199-206.

	Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults) NHS England Reference: 170084P Version 2
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The care pathway is well defined within Neurology as a specialty and summarised by the Association of British Neurologists guidelines published in 2015. This applies across the UK and beyond. However, the care of patients with refractory disease is less well defined and subspecialist myasthenia regional centres have developed since the availability of rituximab. It is in this setting where there is less consensus and the use of as required or regular maintenance IVIg or PLEX or alternative immunosuppressive agents (such as cyclophosphamide) is used for refractory, severe or frequently relapsing cases. There is also a need for additional treatments in those with particular contraindication to first line therapeutic options (such as MG in pregnancy). An evolving and complex cohort of MG patients are those developing MG in the context of cancer treatment with immune checkpoint inhibitors: triple M syndrome. There is no existing consensus guidance on the management of these patients.
9c. What impact would the technology have on the current pathway of care?	Data from clinical trials on zilucoplan (C5 complement inhibitor) is very promising with impressive impact on MG-ADL, QMG, MGC and MG-QoL-15r reflecting meaningful improvement in MG symptoms on a range of validated clinical scores. Importantly this change was measurable promptly on MG-ADL and QMG (within a week) and sustained at 12 weeks. The drug was well tolerated with similar adverse events profile to the placebo arm and importantly is a subcutaneously delivered treatment. Therefore this suggests Zilucoplan as an effective, tolerable treatment for antibody positive MG. The question is where is to be placed in the treatment algorithm. It has not been tested in MG crisis and is immunomodulatory but does not induce remission according to current data and on the basis of its mechanism of action. We would consider its role to be in patients refractory to or intolerant of first line therapies, as an alternative to rituximab (but head to head comparison has not been made). It may have a particular role in either the treatment of MG crisis or in those with refractory disease dependent on alternative immunomodulatory treatments such as IVIg or PLEX (of which numbers are small but disease, treatment and financial burden to the NHS is high). The benefit of a SC therapy deliverable at home by the patient should be acknowledged here. The need for pre-treatment vaccination may limit its use in the ITU or precipitous MG presentations.
10. Will the technology be used (or is it already used) in the same way as current	As described above there are a number of points in the current treatment algorithm where zilucoplan may be utilised. The application will depend on individual patient and disease characteristics.

care in NHS clinical practice?	The duration of its use should be considered before its incorporation into guidelines, its use as a rescue therapy in severe or refractory cases may be relevant. Its potential role and placement in therapeutic guidelines must take into account other new and promising therapies for MG: FcRN inhibitors (efgartigimod and rozanoloxizumab). New patient cohorts (triple M syndrome precipitated by immune checkpoint inhibitor therapies in cancer) may present a particularly relevant subgroup for these novel molecules.
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The introduction of new, molecule specific therapies for use in complex or refractory cases of a rare disease should ideally be managed by subspecialists with significant experience in and knowledge of complex myasthenia care. There are regional myastheniologist- consultant neurologists throughout the UK and our recommendation that the use of these drugs should be via these specialist centres. This will allow definitive diagnosis, consideration of all alternative therapies, appropriate and controlled application of these drugs in a setting which would facilitate close documentation of clinical response as well as recording of rare or unexpected complications. This regional specialist centre network already exists for the use of rituximab in MG as per NICE commissioning guidelines.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Appropriate support to regional specialist centres would be sensible. This could be through MG clinical nurse specialists/clinical care co-ordinators who could support consultants in patient screening, clinical outcome monitoring and collection of information on tolerance. An acknowledgement of consultant time should be included, introducing any novel therapy requires time to facilitate local set up with pharmacy, clinical care structure, patient information, consent and out of hospital support. These element of introducing a new clinical therapeutic in a relapsing-remitting inflammatory neurological disease should be considered.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, if we consider the impression improvement across a broad range of MG specific clinical outcome scores this drug has the potential for major impact on patients and their lives and lifestyle, as well as a significant reduction on inpatient care burden and cost of treatment (IVIg and PLEX) for refractory or frequently relapsing patients.

11a. Do you expect the technology to increase length of life more than current care?	There is a small mortality rate associated with MG (>1%) and this drug might impact that, but the patient numbers of direct MG mortality are so small it is unlikely that this metric is the most meaningful one. Measurement of MG specific outcome measures and their improvement in individuals treated with the drug would be a better measure of its efficacy. Its broader impact could be measured in reduction of hospital admission days, increase in days in employment, a reduction in use of alternative treatments (IVIg, PLEX), reduction in mean corticosteroid dose (and its associated adverse effects in the long term).
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, through the resolution of symptoms, the reduction in number of relapses and associated hospital admissions, the reduction in days on ITU/ requiring ventilation. The stabilisation of disease activity and facilitation of independence and re-engagement of employment are all very likely outcomes of the introduction of this medication into the MG therapeutic arsenal. Given the complement inhibitory role, additional vaccinations and antibiotics may need to be given to minimise the risk of meningococcal meningitis. This can affect the QoL.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Myasthenia can affect all ages, both sexes but vary in severity and treatment response across this spectrum. It is the individual's disease characteristics and cormobidities that will influence treatment choice . There are no specific groups that I would consider this drug for above the general population of those with AChR positive myasthenia gravis.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical	The main difference is the subcutaneous delivery of this drug. This may allow self-administration outside the hospital and reduce hospital admission, and associated health care and consumable use associated with alternative treatments for refractory disease (IVIg or PLEX). However this does require appropriate patient training in safe administration techniques, storage and disposal of consumables, with appropriate out of hospital support for queries and issues which might

requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	arise as well as a responsive model of specialist care to facilitate this. Pre-treatment vaccination will be required.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Clinical monitoring with disease specific validated outcome measures (as listed above) should be used to assess clinical efficacy, other helpful markers include reduction of corticosteroid dose, reduction in number of severe relapses/ MG crisis requiring hospital admission in a year, reduction in number of ITU days/ hospital days/ rescue treatments with IVIg or PLEX. Lack of meaningful clinical response should lead to consideration of discontinuation. Appropriate follow up to document and adverse reactions and a clear plan for management should be in place. Duration of treatment should be discussed in the context of where this drug is placed in the treatment algorithm for MG. Its immunomodulatory (and not suppressing mechanism of action) should be taken into account. So should consideration of efficacy, safety and financial implications of alternative options
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Impact of reduction in corticosteroid dose on patient well being and QOL is difficult to measure but a well documented adverse effect of current MG treatment regimens, is particularly onerous on those with refractory disease. Lifestyle, personal cost and employability impact of frequent relapses and needing to attend hospital for assessment or treatment is another limitation patients with difficult to control MG deal with which is not always measured / easily measurable.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, the mechanism of action of this drug is innovative in the interruption of the end stage of the complement pathway which we know has a major role to play in the impairment of neuromuscular junction transmission which is the hallmark of autoimmune myasthenia as a disease. The impressive improvement across a range of disease specific clinical outcome measures demonstrated this effectively. In those patients with ongoing myasthenia symptoms, or frequently relapsing disease the addition of a novel and highly effective therapy is very promising. The cost of new therapeutics and the place of this particular drug within the current treatment algorithm will require careful consideration and must acknowledge how we might place other novel molecular specific therapies coming on to the MG horizon. We suggest zilucoplan could be considered in a similar position to where rituximab in placed currently, as an alternative to rituximab or if rituximab treatment is ineffective: 1. MG patients, who demonstrate active disease despite treatment with maximal immunosuppression: This includes maximal dose of corticosteroids and at least 2 trials of a steroid-sparing immunosuppressant (for example azathioprine, mycophenolate mofetil, methotrexate, ciclosporin or tacrolimus) for an adequate period of time, in an adequate dose. 2. MG patients with crisis: MG patients, with frequent hospital admissions due to MG crisis or significant MG relapses (despite adequate oral immunosuppression) who require regular treatment with IVIg or

	plasmapheresis, as well as continuing treatment with high doses of corticosteroids and other steroid sparing immunosuppression, to achieve stabilisation of symptoms. 3. MG patients with frequent significant relapses: Patients in whom corticosteroids are relatively contraindicated (e.g. poorly controlled diabetes, morbid obesity, psychiatric issues), and where stabilisation from steroid sparing immunosuppression may be insufficient or delayed. 4. MG patients in whom oral immunosuppression is complicated by significant side effects: for example, steroid-related side effects, or in whom comorbidities such as diabetes limits the use of high-dose steroids, or patients demonstrating intolerance to various steroid-sparing immunosuppressant; also MG patients who experience multiple and serious infections from oral immunosuppression, and are therefore unable to tolerate oral immunosuppression and where their MG remains active and uncontrolled. 5. Patients whose disease at onset is "explosive", who are unresponsive to conventional rescue treatments such as plasmapheresis or intravenous immunoglobulin, and whose bulbar and respiratory functions are not responding in a timely fashion to high doses of corticosteroids and rescue treatments, and who are unable to wean from ventilatory support in a critical care setting. 6. There should be a lower threshold to consider the drug in MuSK antibody positive MG patients with bulbar disease (which characterises this form of the condition), responding poorly to IVIg or plasmapheresis, or who demonstrate poor tolerability to immunosuppression.

	The evidence for efficacy in MG crisis is lacking, however early introduction of molecule specific drugs as an alternative to high and prolonged doses of corticosteroids is worth considering. Where there is rapid onset of action, there is likely to be benefit in this setting
16a. Is the technology a 'step-change' in the management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, the unmet need is those who remain symptomatic despite maximal treatment according to current treatment options. It should also reduce the impact on life and lifestyle on those who require frequent hospital admissions and onerous or high risk treatments to maintain symptom control
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	With pre-treatment vaccination against encapsulated bacteria (meningococcal vaccination) this was a well tolerated and low risk in the trial setting

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials placed zilcoplan as a medication to use in clinically severe AChR antibody positive generalised MG (MGFA II-IV, MG-ADL score of at least 6 and a QMG score of at least 12). In UK clinical

	practice one would expect these patients to received pyridostigmine, corticosteroids and most likely IVIg or PLEX (+/- thymectomy). The opportunity to utilise a molecule specific, subcutaneously delivered, rapidly effective and safe drug in this setting would be a welcome addition to the current options.
18a. If not, how could the results be extrapolated to the UK setting?	Clinical trials could easily be extrapolated to the UK clinical setting if appropriate diagnostic and clinical grading requirements were met. It is
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The rapidity and magnitude of improvement was impressive as shown in the primary end point and all secondary endpoints (all reliable and valid disease specific clinical outcome scores which are already utilised by neurologist in the management and monitoring of patients with MG in the UK. The improvement was sustained at 12 weeks, but measurable at 1 week. Tolerance was very reassuring.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	This is a very difficult question to answer in the context of what this molecule does and the pathological mechanism of AChR antibody positive generalised MG. This is a highly specific complement inhibitor with reduces the pathogenicity of the ACHR molecule which characterises and effects the disease mechanism of interruption of neuromuscular transmission. It is very encouraging and impressive that zilcuplan has meaningful clinical effect but it has a short-lived effect, requires daily dosing and is more likely to have a role in short term management of severe disease or MG crisis. Longterm immunosuppressing agents are likely to be required after remission induction with zilucoplan.

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	I am not aware of any further published data beyond that from clinical trials

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to specialist centres. Although regional myasthenia expertise should be available throughout the UK. People with disabilities cannot always access centres easily.
21b. Consider whether these issues are different from issues with current care and why.	With the evolution of molecule specific and novel therapies which require sub-specialist approval those who previous accessed their myasthenia care via their local DGH neurologists will need to travel to specialist centres of access novel drugs. If we are applying these criteria to those with more symptomatic, resistant and disabling disease this need to travel to access care and therapeutics and its impact on the individual in need should be taken into account.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Meaningful and prompt clinical impact in patients with clinical significant disease • Well tolerated and easy to administer – potential for self-administration at home/ out of hospital • Promising option for patients resistant to or intolerant off current first line therapeutic options • Promising lifestyle and financial benefits to those dependent on onerous maintenance therapies such as in hospital IVIg or PLEX • Potential application in novel/ evolving disease subgroups: checkpoint inhibitor precipitated MG (triple M syndrome)

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Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with this condition or caring for a patient with this condition. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **10 June.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with myasthenia gravis

Table 1 About you, myasthenia gravis, current treatments and equality

1. Your name	Abby Mabil
2. Are you (please tick all that apply)	☒ A patient with myasthenia gravis ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with myasthenia gravis ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Myaware & Muscular Dystrophy UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with myasthenia gravis? **If you are a carer (for someone with myasthenia gravis) please share your experience of caring for them**	At 19years old and a student at university, I experienced a number of debilitating eye symptoms – double vision with a drooping eyelid. It was a long process until I was finally diagnosed with ocular myasthenia gravis around when I was 22yrs old. It was a long process (3 years) between onset of symptoms to diagnosis which had a huge impact on my life as a young adult Due to mg, I had to quit university after 2 years as I was unable to continue my studies. I experienced a brief period of remission whilst I was pregnant with my daughter (aged 24), but after her birth, my symptoms returned into full blown generalised myasthenia gravis. This presented as weakness in my neck, arms, legs, foot & ankle. It also affected my speech and swallowing at times. I was unable to properly care for myself or my daughter, requiring twice daily carers visits and support from adult social services. I had to move into the living room as I was unable to manage the stairs in my home. This had a significant and detrimental impact on my mental health. The sudden loss of independence and struggle to accept my disability. Over the years, I have also required support from talking therapies and mental heath services due to depression and anxiety, caused to some extent by my diagnosis. I was referred to Oxford Hospitals as my previous trust were unable to get my symptoms under control and I should be moved under a specialist consultant. For a number of years, I worked my way through a number of medicines and therapies to try managing my symptoms. I never managed full remission and

	almost accepted that I will always live with some level of disability for the rest of my life. I was able to return to full time work by the age of 26years, however that was supported with additional funding through PIP and a blue badge as my mobility was still affected. I have been fortunate to work with supportive employers that helped me manage my condition and demonstrate some relative flexibility to support me staying within the workforce. It did however have a long term detrimental effect in career progression, as I still had no university degree qualifications, and the roles I was suitable for were limited due to my inability to travel too far or on public transport for work. Whilst well enough to work, my life (any my daughters) was still severely limited due to the myasthenia gravis. The fatigue meant most evening and weekends were for recovery to ensure I was ready to go again the next week. My daughter, by the age of 7/8 was registered as a young carer and had dedicated support to ensure she could go out and enjoy extracurricular activities, when I was unable to do so. Following several falls, one of the most serious was down a flight of stairs, causing a serious wound to the back of my head, I was moved by the council into a ground floor flat on medical grounds. I grew incredibly anxious about walking outside on uneven surfaces, and would avoid going out if I was unsure I could park close to the site or had to walk a distance without anywhere to sit and take a break. Adult social services conducted an assessment and provided a number of tools and adaptions to try to maintain by independence and safety at home. I found this process very distressing, as it further cemented the idea that I wouldn't ever feel well again.

	Slowly over the years, my world became very small. I didn't really socialise, most of my adult contact came through work. Due to weakness in my hands, I lost the ability to knit or type for any real length of time. I struggled with most self-care tasks – doing my own hair was particularly upsetting to me as I had been braiding and styling my own hair since I was 13yrs old. I once got into a bath after a long day, and was so weak, I was unable to get myself out. I had to call out the emergency services and sat in a bath for over 6 hours before the ambulance could attend to get me out. I did not have a bath for a very long time after that incident. Whilst the mestinon was a tried and tested medication, it came with side effects which meant I hand to be very mindful of timing and ensure I had access to it at all times. These (not inconspicuous) brown bottles were everywhere in my home, car, work lockers. I couldn't be spontaneous with my activities as I was controlled by my medication schedule. Plasma exchange (prior to zilucoplan) was probably the most effective treatment. Prior to the trial, I was probably an inpatient for 7 days in Oxford up to twice a year. The effects of plasma exchange were variable and often rather short lasting. When I was offered the chance of participating and commencing in this clinical trial in November 2020, I jumped at it. I am so grateful, because my life changed for the better almost immediately.
7a. What do you think of the current treatments and care available for myasthenia gravis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. I think there are lots of current treatments for mg, but for some (like the immunosuppressants) it takes a very long time for impact to be felt, if it works at all. Trying to find the right combination of medications that specifically work for me/the individual can be laborious and time intensive. Also quite demoralising at times when improvement is slow and/or limited.

	The treatments I was offered prior to zilucoplan; • Mestinon • Azathioprine • Prednisolone • Mycophenolate • IVIG • Plasma exchange 7b. I know and feel very fortunate that I was able to have access to clinical specialists and a treatment centre that offer all of these options. I think now my view is these previous treatments (for me) are rather "old fashioned" as there has been a real expansion in drugs and interventions to treat MG than ever before. I am also aware that people respond very differently to the drugs, so I am aware when I share my experience on some of the drugs I've tried with others living with mg, that it is a personal one, and not everyone will have the same response.
8. If there are disadvantages for patients of current NHS treatments for myasthenia gravis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Some side effects of the medication below; • Mestinon – moderate gastrointestinal side effects. Sometimes severe enough for bladder and bowel incontinence. • Azathioprine – excessive nausea and fatigue • Prednisolone – significant detrimental effect on my mental and physical health leading to a severe mental health crisis and weight gain. • Mycophenolate – no significant side effects, however constant and routine blood monitoring required, which was difficult to schedule around work and childcare commitments. • IVIG – limited benefit experienced but required a lot of travel and I have poor veins which made daily access difficult. Often required inpatient stay

	• Plasma exchange – required 7day inpatient stay due to requiring femoral vein access. Overall, with all the different treatments, I never reached a level of remission or feeling of “wellness” that I was aware was possible since starting this trial. The impact of the inpatient stays was detrimental not only to my mental health, but also that of my daughter. Having to find childcare that could facilitate my daughter getting to school with overnight stays was difficult and also very expensive. When I was unable to drive, the NHS would have to provide patient transport from my home to hospital (circa 50miles) to facilitate my inpatient stay. I was unable to be spontaneous with my activities/schedules as they revolved around my medication timetable. I never reached a level of remission, which meant I was reliant on disability benefits for a number of years as well. Whilst I was fortunate that MG allowed me to have a medical exemption certificate for my medications – there were times that I was taking up to 4/5 different drugs multiple times a day to manage my mg. It would have put an additional financial burden on me if I had to fund these medications personally.
9a. If there are advantages of zilucoplan over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability	9a. I simply cannot overstate what a positive impact zilucoplan has had on my life. I was not aware that I could feel so well on a treatment.

to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does zilucoplan help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	• The speed of improvement on zilucoplan. I participated in the double-blind study and was evident by the 2nd dose (48hrs) a significant improvement in my physical symptoms. • Allowed me to continue with work and take on roles within other regions (requiring travel) that was not possible before. • My relationship with my daughter has improved now she no longer has to provide caring role for me. She is able to live her life as a normal teenager now. • Being able to have an active social life with friends and family. • Reduced anxiety – I am not worried about falling over, but also know I can get myself up if I did. • Braiding hair/knitting – enabling me to participate in creative hobbies and self-care actions I had to stop for years due to myasthenia gravis. • No inpatient hospital stays since I started the trial. • No longer dependant on disability benefits. • Ability to exercise – I was able to walk for miles without incident and improve my mental and physical health during lockdown and beyond. • No side effects at all from the medication. 9b. Significant and rapid improvement of my physical symptoms, because this had the most profound impact on my quality of life and supports several of the other benefits mentioned above. 9c. Zilucoplan has overcome most listed disadvantages I raised in question 8, aside from; • Routine blood testing (however this is now every 6 months) • Travel to hospital monthly as part of the trial.

10. If there are disadvantages of zilucoplan over current treatments on the NHS please describe these. For example, are there any risks with zilucoplan. If you are concerned about any potential side effects you have heard about, please describe them and explain why	Compared to previous treatments I have received for MG, there have been zero side effects since starting zilucoplan. I cannot identify any disadvantage of zilucoplan over the current treatments I have listed above.
11. Are there any groups of patients who might benefit more from zilucoplan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	As I am required to self-inject, I imagine it could pose a difficulty for individuals with limited dexterity in their hands? I believe this would really benefit patients like myself, who have struggled to achieve a level of remission despite trying various medications. Possibly patients that end up requiring more invasive therapeutics like plasma exchange. Patients that cannot tolerate steroids.
12. Are there any potential equality issues that should be taken into account when considering myasthenia gravis and zilucoplan? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Whilst not directly a protected characteristic, I think its important to note the socioeconomic status of patients with MG. People from a BAME backgrounds/disabled/women (esp. with caring responsibilities) are more likely to be in lower paid roles, or unable to have the flexibility and finances to attend frequent hospital appointments. Frequent inpatient stays, hospital appointments and poorly controlled MG has had a significant impact on my educational progression and career path to date. I am not sure how we ensure equity of access to this drug for some of the issues I described above. Possibly if zilucoplan can be prescribed and dispensed in primary care, that could support accessibility?

No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The positive impact on my (and my daughters) quality of life is truly life changing since starting this trial.
- I have not had a single inpatient stay or requirement of any recue therapies since starting the trial.
- I am no longer dependant on any disability benefits or require social service or mental health support to maintain independent living.
- The significant benefits I have gained though participating in the trial has allowed my career to blossom and accept opportunities and roles I would not have been physically and mentally strong enough to pursue due to my level of disability.
- I am most thankful that my daughter now has the mother I feel she truly deserves.

Thank you for your time.

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Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with this condition or caring for a patient with this condition. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with myasthenia gravis

Table 1 About you, myasthenia gravis, current treatments and equality

1. Your name	Gary Mahon
2. Are you (please tick all that apply)	☒ A patient with myasthenia gravis ? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with myasthenia gravis ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Muscular Dystrophy UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with myasthenia gravis? **If you are a carer (for someone with myasthenia gravis) please share your experience of caring for them**	I was diagnosed with MG in summer 2015, initially as ocular MG which then generalised a year later. At its worst, I had double vision, droopy eyelids, had difficulty swallowing, difficulty breathing, couldn't hold up my head, had difficulty walking and had to lie in bed most of the time. It felt like my whole life had in essence stopped since I could barely work, couldn't socialise and playing sport (a large part of my life) was impossible. I had become a burden on my family and my confidence was gone. The symptoms seemed to vary in severity for no apparent reason.
7a. What do you think of the current treatments and care available for myasthenia gravis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The NHS have been great and I was lucky to be diagnosed within about a month of developing the first symptoms. My care team have aways been accessible and easy to interact with whenever any changes to my symptoms occurred. I have been offered many treatments over the years. All of the currently available treatments have significant limitations. Although they reduce the symptoms of MG, they are never completely gone and the treatments all have significant side effects. Many of the treatments mean that MG is not just my illness but the burden is also shared by my whole family.
8. If there are disadvantages for patients of current NHS treatments for myasthenia gravis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Pyridostigmine gives some relief but doesn't take away the symptoms and causes severe craps and stomach issues. I still take these tablets before doing any very physical activities. Prednisolone also helps but comes with terrible side-effects and caused me to put on weight (especially around my face), gave me steroid-induced diabetes, glaucoma and mood changes. It also meant I had to take other pills to counteract these symptoms which I found difficult to keep on top of and further hospital visits to check bone density and eye health. I would never take steroids again.

	When my MG got really bad I had plasma exchange which meant being driven to the hospital by my wife for 5 days and the treatments made me extremely tired. Although they were highly effective in eliminating symptoms, the benefits only lasted a few weeks. This meant I could not commit to any projects at work, since I had no confidence that the MG symptoms would not recur at some critical time. Similarly, IVIg meant hospital visits and although it worked well, it made me extremely tired while being treated and the benefits only lasted about 4 weeks before my symptoms returned. This meant I could not commit to any social or work activities for fear of letting people down at short notice. I was lucky that in my case this coincided with lockdown during covid so I could get plenty of rest and worked reduced hours.
9a. If there are advantages of zilucoplan over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does zilucoplan help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	It works better than anything else I've tried. I've been taking Zilucoplan since November 2020 as part of Raise XT and it has been transformational for me. I can now do most of the things that I used to do before MG, although I know I do still have MG and must pace myself. I am now back to working full time as Managing Director and senior consultant at a small engineering technical consultancy business, which I find intellectually challenging and rewarding. Also, I can now play sports again both competitively and socially, which has always been a major part of my life. I also can contribute fully to family life again, including helping with care of others. Zilucoplan is very easy to self-administer and because it is taken daily there are no dips when my symptoms return. This also means I am able to keep my strength levels high since there are no periods when I am unable to be physically active. Also, there are no adverse side effects. The major advantage is being able to live a fulfilling life again at work, socially and with my family. There are no side effects, it can be administered at home and makes me nearly symptom-free. It's amazing!
10. If there are disadvantages of zilucoplan over current treatments on the NHS please describe these.	I'm not aware of anything that is negative about zilucoplan as a treatment.

For example, are there any risks with zilucoplan. If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from zilucoplan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Not enough experience to comment.
12. Are there any potential equality issues that should be taken into account when considering myasthenia gravis and zilucoplan? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Not enough experience to comment.
13. Are there any other issues that you would like the committee to consider?	None.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Living with myasthenia gravis has affected my ability to function in all aspects of my life: work, social, family.
- Currently available treatments all have limitation either due to severe side effects or time-limited benefits.
- Zilucoplan effectively makes me symptom-free and enable me to live a fulfilling life again.
- It’s easy to administer and there are no side effects.
- Click or tap here to enter text.

Thank you for your time.

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

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

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Fay Chinnery, Research Fellow, Health Economics Lois Woods, Senior Research Assistant, Evidence Synthesis and Information Specialist Neelam Kalita, Senior Research Fellow, Health Economics David Alexander Scott, Principal Research Fellow, Statistics Asyl Hawa, Research Fellow, Health Economics Geoff Frampton, Principal Research Fellow, Evidence Synthesis
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Date completed	16th February 2024 (corrected version 7th June 2024)

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Dr Pablo Garcia-Reitboeck, Consultant Neurologist, St George's University Hospitals NHS Foundation Trust, & Honorary Senior Lecturer, St George's University of London.

We also thank Joanna Picot, Southampton Health Technology Assessments Centre (SHTAC), for reading and commenting on a draft of this report for quality assurance.

Declared competing interests of the authors and advisors

The authors, Dr Garcia-Reitboeck and Dr Huda declare that they have no conflicts of interest.

Dr Burke received funding from UCB Pharma (manufacturer of zilucoplan) for travel and accommodation to attend their sponsored Rare Disease Connect meeting in Berlin (December 2023) and Madrid (December 2022) although UCB Pharma had no input into the meeting and none of the new myasthenia gravis therapies were discussed. Dr Burke has had regular contact with Argenx (manufacturer of efgartigimod), having prescribed efgartigimod on the Early Access to Medicines (EAMS) scheme; and has discussed experiences using efgartigimod as part of the National Myasthenia Special Interest Group.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Fay Chinnery critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Lois Woods critically appraised the clinical effectiveness systematic review and drafted the report; Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Scott critically appraised the indirect treatment comparisons and drafted the report; Asyl Hawa critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Geoff Frampton critically appraised the clinical effectiveness systematic review and indirect treatment comparisons, drafted the report and is the project co-ordinator and guarantor.

Confidential information (CON) is redacted

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LIST OF ABBREVIATIONS

ABN	Association of British Neurologists
AE	Adverse event
AChE	Acetylcholinesterase
AChR	Acetylcholine receptor
AIC	Academic in confidence
ANCOVA	Analysis of covariance
BNF	British National Formulary
CFB	Change from baseline
CFS	Covid-19 Free Set
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DSU	Decision Support Unit
EAG	External Assessment Group
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
FDA	Federal Drugs Agency (US)
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
Ig	Immunoglobulin
IPD	Individual patient level data
ISTs	Immunosuppressive therapies

ITT	Intent to treat
IVIg	Intravenous immunoglobulin
MAIC	Matching-adjusted indirect comparison
MCID	Minimum Clinically Important Difference
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite score
MGFA	Myasthenia Gravis Foundation of America
MG-QoL15r	Myasthenia Gravis Quality of Life 15-item scale revised
mITT	Modified intent to treat
MMRM	Mixed model repeated measures
MSE	Minimum symptom expression
MuSK	Muscle specific tyrosine kinase
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMJ	Neuromuscular junction
NR	Not reported
PLEX	Plasma exchange
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QMG	Quantitative Myasthenia Gravis scale
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SAE	Serious adverse event
SCIg	Subcutaneous immunoglobulin
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of Care
TA	Technology appraisal
TEAE	Treatment-emergent adverse event

TSD	Technical Support Document
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's Key Issues

Table 1 List of the Key Issues identified by the EAG

Issue number	Summary of the issue	Report sections
1	Exclusion of standard of care as a comparator	2.3 / 4.2.4 / 6
2	Uncertain relevance of the clinical efficacy evidence to patients with refractory generalised myasthenia gravis	2.3 / 3.2.1.2.2 / 3.3.2
3	Uncertainty in network meta-analysis results	3.4.1 / 3.4.4
4	Treatment response rates	4.2.6.1
5	Response timepoint for all treatments	4.2.8.1
6	Resource use for chronic IVIg and PLEX therapy	4.2.8.1 / 4.2.8.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are listed in section 1.7 and their cumulative effect on the company's base case ICER is shown in Table 3.. We discuss these differences in section 1.3 and section 1.5.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

In their response to the Clarification Questions, the company updated their model. The company's revised base case deterministic cost-effectiveness results for zilucoplan compared with efgartigimod, intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) and plasma exchange (PLEX) are shown in Table 2. Zilucoplan provides an increase of 0.165 QALYs at an additional cost [redacted] compared with IVIg/SCIg and provides an increase of 0.180 QALYs at an additional cost [redacted] compared with standard of care (which is a basket of therapies: corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, and pyridostigmine), respectively. Zilucoplan [redacted]

The EAG requested the company to provide a version of the model that included standard of care as a comparator, with an option to include IVIg and PLEX within the standard of care arm (Clarification Question B1). The company did not provide this analysis, so we have created a standard of care arm using the functionality within the company's model. Using the company's revised base case, comparing zilucoplan with standard of care (the basket of therapies that includes corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, and pyridostigmine; and excludes IVIg and PLEX) results in an ICER of [redacted] per QALY (Table 2). The EAG note that the company did not include the cost of standard of care treatments (corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine) within the costs for the targeted therapies (zilucoplan, efgartigimod, IVIg/SCIg and PLEX).

Table 2 Company updated base case results for zilucoplan, pairwise results, including PAS

Technologies	Total		Incremental vs. zilucoplan		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Zilucoplan	[redacted]	9.81	-	-	-
Efgartigimod	£1,224,683	9.80	[redacted]	0.016	[redacted]
IVIg/SCIg	£628,862	9.65	[redacted]	0.165	[redacted]
SoC (excl. IVIg and PLEX)[a]	£469,374	9.64	[redacted]	0.180	[redacted]
PLEX	£783,124	9.66	[redacted]	0.158	[redacted]

Source: Company's revised base case model results
Abbreviations: Excl., excluding; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; QALYs, quality-adjusted life years; SCIg, subcutaneous immunoglobulin; SoC, standard of care
[a] Analysis conducted by the EAG on the company's base case; the SoC includes a basket of the following therapies: corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, and pyridostigmine

1.3 The Decision Problem: summary of the EAG's key issues

Issue 1 Exclusion of standard of care (SoC) as a comparator for patients with refractory generalised myasthenia gravis

Report section	Section 2.3 (Decision Problem); section 4.2.4, section 6 (economic analysis)
Description of issue and why the EAG has identified it as important	The comparators used in the company's Decision Problem and economic model are inconsistent with the NICE scope. According to the NICE scope, standard of care (SoC) includes corticosteroids and immunosuppressants with or without intravenous immunoglobulin (IVIg) or plasma exchange (PLEX), i.e., an overall 'basket' of care. However, the company have included IVIg and PLEX as separate comparators. The EAG do not consider this to appropriately reflect SoC for patients with refractory generalised MG in England, which is the population specified in the company's Decision Problem.
What alternative approach has the EAG suggested?	The EAG's three clinical experts advised us that both IVIg and PLEX are used as chronic therapies for refractory patients as part of SoC, and that practically all patients who are eligible for treatment with chronic IVIg or PLEX would receive it. Some centres use IVIg as chronic therapy for refractory patients, but other centres (with a strict protocol for IVIg use) use PLEX instead. In our economic model base case, patients in the comparator arm receive the EAG's definition of SoC: 43.8% of patients receive IVIg along with the basket of other standard treatments (corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine; proportions shown in

	Table 28); 14.6% of patients receive PLEX plus the basket of other standard treatments, and 41.6% of patients receiving only the basket of standard treatments. The data source for the proportions of patients receiving chronic IVIg and PLEX is the patient cohort in the efgartigimod Early Access to Medicine Scheme (EAMS),[1] which the EAG consider to be comparable to the patient group of interest for zilucoplan in the current appraisal. The EAG note that the proportion of patients receiving neither IVIg nor PLEX in the EAMS[1] is different to our clinical experts' opinion. We conducted scenario analyses exploring the effect of different proportions of patients receiving IVIg and PLEX treatment.
What is the expected effect on the cost-effectiveness estimates?	Using the EAG's definition of SoC as the comparator decreases the ICER from [redacted] (obtained from the company's revised model) to [redacted] per QALY for zilucoplan versus SoC.
What additional evidence or analyses might help to resolve this key issue?	Further clinical opinion to clarify the proportions of patients with refractory generalised MG in England receiving chronic IVIg and PLEX treatment, and the proportion of this patient group who would be eligible to receive chronic IVIg or PLEX but receive neither.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Uncertain relevance of the clinical efficacy evidence to patients with refractory generalised myasthenia gravis

Report section	Section 2.3 (Decision Problem); section 3.2.1.2.2 (RAISE trial population); section 3.3.2 (network meta-analysis populations)
Description of issue and why the EAG has identified it as important	The population specified in the company's Decision Problem is patients with AChR antibody-positive generalised myasthenia gravis (MG) who are refractory to prior therapies. Clinical evidence for the efficacy of zilucoplan is more limited for the refractory population than it is for the broader population specified in the NICE scope. The company's pivotal RAISE trial (zilucoplan versus placebo) includes a relatively small (44 patients per arm) pre-defined refractory subgroup making up half of the randomised trial population while the ADAPT trial of efgartigimod (a comparator in the company's Decision

	Problem) contained 63% refractory patients (although refractory was not defined in precisely the same way as in the Decision Problem). The EAG's clinical experts suggested that the overall randomised population of the RAISE trial could be broadly reflective of refractory generalised myasthenia gravis patients in England, and we note that the randomised population and refractory subgroup in the trial generally yielded [redacted] treatment effects. However, it is unclear whether such an assumption could be applied to the comparison of zilucoplan against efgartigimod which informs the economic analysis, using the proportion of patients showing improvement in MG Activities of Daily Living (MG-ADL) scores (i.e., the MG-ADL response outcome) obtained from the NMAs. Comparisons of zilucoplan against IVIg and PLEX were not feasible in NMAs for the MG-ADL response outcome; instead, the company used alternative data sources for these comparisons in their economic model which are associated with other uncertainties - see Key Issue 4).
What alternative approach has the EAG suggested?	The EAG requested the company to clarify whether the populations of the comparator trials included in NMAs align with the company's Decision Problem definition of refractory patients (Clarification Question A11). The company confirmed that only the RAISE trial included an explicitly defined subgroup of refractory patients. According to a CADTH technology assessment cited by the company in Clarification Response 11(a), 63% of patients in the ADAPT trial of efgartigimod were also "refractory", i.e. having prior exposure to ≥2 immunosuppressive therapies or treatment with ≥1 immunosuppressive therapy and requiring plasma exchange, but were not a defined subgroup (Clarification Response reference 16). The company provided an NMA scenario analysis that included the RAISE refractory subgroup and the full ADAPT trial population. However, this scenario does not address the uncertainty arising from 37% of the ADAPT trial population not being refractory. Moreover, the EAG were unable to verify whether this analysis had been conducted appropriately.
What is the expected effect on the cost-	Uncertain

effectiveness estimates?	
What additional evidence or analyses might help to resolve this key issue?	Further clinical opinion on whether the full-trial populations of the RAISE and ADAPT trials are reflective of patients with refractory generalised MG who would be seen in NHS clinical practice.

Issue 3 Uncertainty in network meta-analysis results

Report section	Sections 3.4.1 and 3.4.4
Description of issue and why the EAG has identified it as important	The company's economic analysis base case uses relative treatment effects for the MG-ADL response and the MG-ADL score change from baseline, obtained from the comparison of zilucoplan against efgartigimod in the network meta-analyses. There is uncertainty in these NMA results because of differences in the baseline population characteristics of the RAISE (zilucoplan) and ADAPT (efgartigimod) trials which were not adjusted for. Placebo response rates also differed between the trials, also not adjusted for.
What alternative approach has the EAG suggested?	The EAG requested that the company explore and, if possible, account for clinical and statistical heterogeneity in the NMAs. The company tabulated the characteristics of the trials included in the NMAs and discussed these narratively in Clarification Responses A10(a) and A10(b), respectively, but did not specify which of the trial population characteristics are effect modifiers or prognostic factors or whether these were balanced within and between the trials. The EAG believe that an anchored matching-adjusted indirect comparison (MAIC) linking the RAISE (zilucoplan) and ADAPT (efgartigimod) trials should be feasible to clarify the reliability of the NMA results and reduce uncertainty in the estimated relative treatment effects. The company stated in Clarification Response A10(c) that a MAIC would be difficult to adjust for differences in inclusion/exclusion criteria, outcome assessment timepoints and response criteria, and that sample sizes would be restrictive. The EAG disagree that these limitations would preclude a MAIC for the comparison of zilucoplan against efgartigimod; and we note that the current NMAs do not adjust for these issues.
What is the expected effect on the cost-effectiveness estimates?	This issue would not affect the EAG's current base case economic analysis which, as explained in section 4.2.6.1 does not model relative treatment effects from the NMAs, but instead uses trial-based sources of response rates for zilucoplan and efgartigimod. However, uncertainty in both

	the company's and EAG's base case economic analyses could potentially be improved by the provision of more reliable relative treatment effects for zilucoplan versus efgartigimod. The impact on the ICERs for either the company's base or an updated EAG base case is uncertain.
What additional evidence or analyses might help to resolve this key issue?	Conducting a MAIC for the RAISE and ADAPT trials, for the MG-ADL response outcome and the MG-ADL score change from baseline outcome. Alternative indirect treatment comparison approaches such as simulated treatment comparison could also be considered (e.g., depending the extent of overlap of the trial characteristics and on model fit).

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4 Treatment response rates

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	The company's base case uses odds ratios from the NMAs to estimate the response rates for zilucoplan and efgartigimod. In principle, the EAG agree with this approach. However, as described in Key Issue 3 above, the EAG are uncertain about the network meta-analysis results for the comparison of zilucoplan with efgartigimod. In addition, we are unable to verify the response rates for zilucoplan and efgartigimod used in the company's revised base case and are uncertain whether the refractory subgroup was included in the company's NMA scenario analysis or not (section 3.4.1). Response rates for IVIg and PLEX are not available from the company's NMAs for the MG-ADL response outcome. The company derive the IVIg and PLEX response rates from Barth et al.[2]: 51.00% and 57.00%, respectively. The company assume the response rate for subcutaneous immunoglobulin (SCIg) is the same as the IVIg response rate. The Barth et al. study enrolled 84 patients in Canada with moderate to severe MG. The paper does not specify if the patients had generalised MG, but the inclusion criteria defined 'moderate to severe' as "Quantitative Myasthenia

	Gravis Score (QMGS) >10.5, and worsening weakness requiring a change in treatment modality as judged by a neuromuscular expert". Two of the EAG's clinical experts explained that about 70% of patients respond to IVIg treatment and about 70% respond to PLEX treatment. We note that the definition of 'response' differs between the Barth paper and clinical expert opinion. Barth et al. define responders as patients who had a decrease in QMG score of ≥3.5 units (considered the minimum clinically important difference). An EAG clinical expert who provided a definition of 'response' uses the term 'pharmacological remission', which is a term used in the Myasthenia Gravis Foundation of America (MGFA) post-intervention status and refers to having no MG symptoms that affect daily living.
What alternative approach has the EAG suggested?	We prefer to use the response rates for zilucoplan and efgartigimod based on results from the RAISE and ADAPT trials, respectively (Table 31).This approach does not capture relative treatment effectiveness, but given the uncertainty with the NMA results, the EAG consider it appropriate and we have validated the trial response rates for zilucoplan and efgartigimod with our clinical experts. We also prefer to use the alternative response rates for IVIg and PLEX suggested by our clinical experts, because this is more reflective of UK clinical practice.
What is the expected effect on the cost-effectiveness estimates?	Using the trial response rates for zilucoplan and efgartigimod, and a response rate of 70% for IVIg and PLEX increases the ICER from [redacted] to [redacted] per QALY for zilucoplan compared with standard of care (including corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine). Comparing zilucoplan directly with IVIg, efgartigimod and PLEX: the ICER decreases from [redacted] to [redacted] per QALY for zilucoplan versus IVIg; whereas the ICERs [redacted]
What additional evidence or analyses might help to resolve this key issue?	As discussed in Issue 3, conducting a MAIC or a simulated treatment comparison may help resolve the uncertainties with the NMA and could therefore provide a more robust

	estimate of relative treatment effectiveness between zilucoplan and efgartigimod. Further clinical advice regarding response rates to IVIg and PLEX for patients with refractory generalised MG would be helpful, as well as determining clinical consensus on the definition of 'response'.

Issue 5 Using a response timepoint of three weeks for all treatments

Report section	Section 4.2.8.1
Description of issue and why the EAG has identified it as important	The treatment response timepoints in the model use the time of the primary outcome assessment from the clinical trials (Table 30). The EAG's clinical experts noted that treatment effect was seen (and maintained) after only 1-2 weeks in the zilucoplan and efgartigimod trials, and we were advised that patients are usually assessed 3-4 weeks after starting IVIg or PLEX treatment. Furthermore, one of our experts viewed assessing PLEX after 6 weeks was inappropriate, because a patient may have responded but lost response by then.
What alternative approach has the EAG suggested?	We use a response timepoint of 3 weeks for all treatments.
What is the expected effect on the cost-effectiveness estimates?	This change decreases the ICER from [redacted] to [redacted] per QALY for zilucoplan compared with standard of care.
What additional evidence or analyses might help to resolve this key issue?	Further clinical advice about the most appropriate timepoint to assess response to treatment.

Issue 6 Resource use for chronic IVIg and PLEX therapy

Report section	Section 4.2.8.1 and Section 4.2.8.3
Description of issue and why the EAG has identified it as important	Treatment costs for chronic IVIg therapy are applied every 3 weeks and treatment costs for chronic PLEX are applied every 4 weeks in the company's base case. The EAG do not believe this reflects clinical practice in England. Two of our clinical experts explained that IVIg is given every 4-8 weeks, and the third expert mentioned the interval can be extended to 12 weeks, and very rarely to 16 weeks, depending on patient response. All experts also explained that PLEX is usually administered every 4-8 weeks. In addition, we disagree with the company's assumption that PLEX administration costs are equal to subcutaneous immunoglobulin administration costs.
What alternative approach has the EAG suggested?	Based on our expert advice, we apply chronic IVIg and PLEX treatment costs every 6 weeks. We also use the NHS reference cost SA44A – Single Plasma Exchange (£910), applied every 6 weeks, for the PLEX administration cost.
What is the expected effect on the cost-effectiveness estimates?	These changes result in an ICER of [redacted] per QALY for zilucoplan compared with standard of care. Note that due to the model structure, standard of care must also be selected as the comparator to run this scenario. Consequently, this ICER represents the cumulative effect of selecting standard of care as the control arm, applying chronic IVIg and PLEX therapy costs every 6 weeks and using the SA44A administration cost every 6 weeks.
What additional evidence or analyses might help to resolve this key issue?	Further clinical opinion on how frequently patients with refractory generalised MG receive chronic IVIg and PLEX therapy.

1.6 Other issues: summary of the EAG's view

The EAG identified other issues in the cost effectiveness evidence, but we do not consider these to be key issues as they have little impact on the model results. Details are in section 1.7.

In previous technology appraisals for generalised MG there was uncertainty around the relevance of rituximab as a comparator. The EAG's clinical experts do not believe rituximab is a relevant comparator for the current technology appraisal population, because evidence

for rituximab efficacy in this patient group is lacking and the other available comparators (efgartigimod, IVIg, PLEX) are much faster acting. Furthermore, rituximab is not listed as a comparator in the NICE scope nor in the company's Decision Problem, which the EAG agree is appropriate.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG's critique of the company's model (discussed in section 5.3), we have identified several aspects of the company's base case with which we disagree. Our preferred model assumptions are:

1. Using standard of care (including IVIg and PLEX) as the comparator with 43.8% of patients receiving IVIg; 14.6% of patients receiving PLEX; 41.6% of patients receiving neither;[1] all patients receive the cheaper standard therapies (EAG report Table 25 and section 6.1). However, we acknowledge there is uncertainty regarding the proportions of IVIg and PLEX used in standard of care. We have conducted scenarios comparing zilucoplan directly to efgartigimod, IVIg and PLEX using our base case (scenarios 1-3 in Table 48 of this report).
2. Adapting the proportions of SoC therapies (4% tacrolimus, 4% cyclosporin, 4% methotrexate; 25% mycophenolate) (EAG report section 4.2.4).
3. Including standard of care costs (corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine; proportions shown in Table 27) in costs of targeted therapies (zilucoplan, efgartigimod, IVIg/SCIg, PLEX).
4. Using a 70% response rate for IVIg and PLEX and trial response rates for zilucoplan (73.1%) and efgartigimod (73.0%) (EAG report section 4.2.6.1).
5. Using the change in MG-ADL score from the RAISE trial refractory subgroup (CS Table 28) (EAG report section 4.2.6.2).
6. Using a response timepoint of three weeks for all treatments (EAG report section 4.2.6.1).
7. Chronic IVIg costs applied every 6 weeks (EAG report section 4.2.8.1).
8. Chronic PLEX administration costs applied every 6 weeks (NHS reference cost SA44A, Single Plasma Exchange) (EAG report section 4.2.8.2).
9. Chronic PLEX treatment costs applied every 6 weeks (EAG report section 4.2.8.1)
10. Increasing the duration of a myasthenic crisis to 21 days (EAG report section 4.2.8.3)
11. Increasing the resource use for time in ICU due to a myasthenic crisis to 21 days (EAG report section 4.2.8.3)

The EAG's preferred assumptions decrease the ICER for zilucoplan compared with standard of care to [redacted] per QALY (see Table 3). We conducted scenario analyses comparing

zilucoplan directly with efgartigimod, IVIg and PLEX on the EAG base case; further details on the cost-effectiveness results are in Table 47 in section 6.3 of this report.

Table 3 Cumulative change from the company base case of zilucoplan compared with standard of care using the EAG's preferred model assumptions

Scenario	Cumulative ICER £/QALY
Company revised base case (excluding IVIg and PLEX in SoC arm)	[redacted]
+ Include IVIg and PLEX in SoC: 43.8% of patients receive IVIg; 14.6% of patients receive PLEX; 41.6% of patients receive neither, but do receive the cheaper standard therapies (EAG report Table 28)	[redacted]
+ Adapting the proportions of SoC therapies (4% tacrolimus, 4% cyclosporin, 4% methotrexate; 25% mycophenolate)	[redacted]
+ Include SoC costs (corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine; proportions shown in Table 27) in targeted therapies (zilucoplan, efgartigimod, IVIg/SCIg, PLEX)	[redacted]
+ Using a response rate of 70% for both IVIg and PLEX, giving a response rate of 40.88% in our comparator arm (SoC including IVIg and PLEX), and trial response rates for zilucoplan (73.1%) and efgartigimod (73.0%)	[redacted]
+ Using the change in MG-ADL score from the RAISE trial refractory subgroup (CS Table 28)	[redacted]
+ Using a response time point of 3 weeks for all treatments (including zilucoplan)	[redacted]
+ Applying chronic IVIg costs every 6 weeks	[redacted]
+ Using the NHS reference cost SA44A – Single Plasma Exchange - applied every 6 weeks, for PLEX administration costs	[redacted]
+ Applying chronic PLEX costs every 6 weeks	[redacted]
+ Increasing the duration of a myasthenic crisis to 21 days	[redacted]
+ Increasing the resource use for time in ICU due to a myasthenic crisis to 21 days	[redacted]
EAG base case	[redacted]

[a] SoC includes IVIg and PLEX in these cumulative ICERs

ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IVIg: intravenous immunoglobulin; MG-ADL: Myasthenia Gravis Activities of Daily Living score; PLEX: plasma exchange; QALY: quality-adjusted life-year; SoC: standard of care.

The EAG did not identify any technical calculation errors in the company's economic model. However, based on our expert advice, we consider that the model may not capture the full cost of refractory generalised MG as it does not account for carers' burden and any

additional costs associated with managing patients' symptoms or complications of treatment as described in section 2.2.1.4.

For further details of the exploratory and sensitivity analyses undertaken by the EAG on our base case, see section 6.3.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from UCB Pharma on the clinical effectiveness and cost effectiveness of zilucoplan for treating generalised myasthenia gravis. It identifies the strengths and weaknesses of the CS. Three clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 15th December 2023. A response from the company via NICE was received by the EAG on 18th January 2024 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on generalised myasthenia gravis

The CS accurately describes myasthenia gravis (MG) as a chronic autoimmune disease caused by antibody-mediated destruction of the neuromuscular junction (NMJ) (CS sections B.1.3.1 and B.1.3.1.2). Approximately 80% to 90% of MG patients have autoantibodies that bind to the acetylcholine receptors (AChR) of the NMJ, about 3% to 7% have autoantibodies that bind to muscle specific tyrosine kinase (MuSK), and about 10% do not have AChR or MuSK autoantibodies detected (CS section B.1.3.1.2; NICE Scope). MG affects muscle function and control in patients and severity is classified using the Myasthenia Gravis Foundation of America (MGFA) classification, classes I-V: class I refers to ocular disease, classes II to IV refer to generalised disease involving other muscles impacting mobility, breathing, and swallowing (CS section B.1.3.1), and class V refers to myasthenic crisis requiring intubation with or without mechanical ventilation.[3]

As explained in the company's Decision Problem (see section 2.3 below), this appraisal focuses on refractory patients with AChR-antibody positive generalised MG (CS section B.1.1).

2.2.1.1 Definition of refractory MG

The Association of British Neurologists (ABN) myasthenia gravis management guidelines (2018) do not include a definition of refractory patients.[4] A variety of definitions can be found in the scientific literature, which have been summarised into five categories, each of which can stand alone, by Mantegazza and Antozzi 2018. These are: failure to respond adequately

to conventional treatment; severe or intolerable adverse effects from immunosuppressive or symptomatic therapy; inability to reduce immunosuppressive therapy without clinical relapse or need for ongoing rescue therapy e.g. intravenous immunoglobulin (IVIg) or plasma exchange (PLEX); comorbid conditions restricting use of conventional therapies; or frequent myasthenic crises even while on immunosuppressive and symptomatic therapy.[5]

The definition of refractory generalised MG in the company's Decision Problem (see Table 4) combines the various definitions from the published literature. It differs from the literature definitions in (i) referring to efgartigimod, which is not yet introduced as a treatment in mainstream clinical practice in England (currently only in the Early Access Medicines Scheme); and (ii) representing disease severity using the MG-ADL and QMG instruments without mention of frequent myasthenic crises (for explanation of these instruments see section 3.2.3). The EAG's clinical experts agreed that the definition of refractory in the company's Decision Problem is appropriate for their intended population because it defines patients with uncontrolled symptoms despite previous treatments. The company's pivotal RAISE trial definition of refractory aligns with the company's Decision Problem definition albeit with a slightly narrower definition (see section 3.2.1.1.1).

2.2.1.2 Epidemiology of refractory generalised myasthenia gravis

The company estimate that around 19,053 people are living with MG in England.[6] CS section B.1.3.1.1 states that around 15% of patients with generalised MG are refractory to standard therapy. This is consistent with the literature which reports between 5% and 20% of the generalised MG population as being refractory.[7-10] The EAG's three clinical experts also estimated the proportions of patients with generalised MG in their practices who have refractory MG to be around 5% to 10% in London; 10 to 15% in North Wales/Liverpool; and less than 20% in Southampton.

2.2.1.3 Prognostic factors for refractory patients

The EAG's clinical experts noted that refractory patients who have received maximal doses of corticosteroids and immunosuppressants are more likely to be resistant to further treatment. Refractory patients are more likely to have developed comorbidities as side effects of long-term corticosteroid use, such as obesity, diabetes, dyslipidaemia, hypertension, etc, which may influence their prognosis. However, one expert said that not all refractory patients have comorbidities, and refractory patients can be young or old. Another expert said that women with early age of MG onset and MG patients with thymoma are more

likely to be refractory. Patients with refractory disease are more likely to experience exacerbations (a sudden worsening of symptoms requiring hospitalisation) and myasthenic crises (severe muscle weakness requiring intubation and/or mechanical ventilation) (MGFA class V), and more likely to be hospitalised than those without refractory disease.[9]

2.2.1.4 Disease burden

Clinical burden of MG is discussed in CS section B.1.3.13. The 2017 Muscular Dystrophy UK re-audit of unplanned hospital admissions in patients with neuromuscular disease reported that MG was the most common reason for admission (121 admissions) amounting to 1878 hospital bed days and 30% of the intensive therapy unit bed days in a 30-month period.[11] Evidence from the UK Clinical Practice Research Datalink (CPRD) of primary care records suggests people with refractory generalised MG experience a greater treatment burden than those who are not refractory.[12] Disease severity and resource use parameters that are included in the economic model are discussed in sections 4.2.6 and 4.2.8 below. One of the EAG's clinical experts highlighted other factors that affect cost: many MG patients have to give up work, require carers and have additional costs associated with managing their symptoms (e.g. nocturnal non-invasive ventilation), or complications of treatment (e.g. cataracts, diabetes, serious inflammation of the liver, hip fracture, and stroke); some of these costs are discussed in CS section B.1.3.1.5.

2.2.2 Background information on zilucoplan

Zilucoplan (brand name Zilbrysq®) is a C5 complement inhibitor. Its mechanism of action is described in CS Table 2 and CS Figure 1. According to the Summary of Product Characteristics (SmPC), zilucoplan is indicated as an add-on to standard therapy (including corticosteroids and immunosuppressants) for the treatment of adult patients with generalised MG who are AChR-antibody positive.[13]

Patients self-inject a dose of zilucoplan once daily using a pre-filled syringe (CS Table 2). It is a home-based treatment (CS section B.1.3.3.3). The dose required depends on the patient's body weight. The pricing is £/mg for three weight-based dose groups (CS Table 2).

2.2.3 The position of zilucoplan in the treatment pathway

We briefly summarise the standard of care treatment pathway below then consider the positioning of zilucoplan within it.

2.2.3.1 Current treatment pathway

The CS describes the current treatment pathway for MG in CS section B.1.3.2.2. According to CS Figure 3, patients with generalised MG are initially treated with acetylcholinesterase

(AChE) inhibitors (usually pyridostigmine) with the addition of corticosteroids if they are not effective. Thymectomy is an option for patients under 45 years, although effectiveness may not be seen for up to a year, and if they remain symptomatic they rejoin the pharmacological treatment pathway. Non-steroidal immunosuppressive therapies (ISTs) are added to these treatments if patients are non-responsive, and/or to try to reduce the corticosteroid dose. Patients who remain with active disease despite immunosuppression are considered refractory.

Both refractory and non-refractory generalised MG patients can experience exacerbations or myasthenic crises (refractory patients experience these events more frequently) for which the treatment is IVIg or PLEX. This is usually referred to as rescue therapy to distinguish it from chronic (i.e. maintenance) use of IVIg or PLEX.

Here we focus on treatment for refractory patients. CS Figure 3 shows that if a patient has refractory disease (i.e. active disease despite immunosuppression) then they would start therapy with either IVIg or PLEX. This corresponds with IVIg or PLEX as part of inpatient management for MG patients in hospital in the ABN MG guidelines,[4] and the commissioning policy for immunoglobulin use in England which specifies the circumstances where IVIg and/or PLEX may be used chronically for refractory patients.[14] This is off-label use of IVIg and PLEX as neither are licensed for use in MG.

The EAG's three clinical experts confirmed that all refractory patients would receive either IVIg or PLEX as chronic therapy if they are eligible unless contraindicated. Contraindications for IVIg include risk of thromboembolism, stroke, and meningitis. The main contraindication to PLEX is having inaccessible veins (for the central line or cannula); the clinical experts said that very few patients would not tolerate PLEX. The decision to use either PLEX or IVIg also depends on the facilities available at a particular centre, e.g., PLEX is more usually available at larger centres as it requires an inpatient stay and usually a central line; and IVIg has had supply issues and clinicians need to apply to a local board for access. One of the EAG's three clinical experts said they are also able to offer subcutaneous immunoglobulin (SCIg) to refractory patients who are eligible for IVIg. The expert estimated that in practice no more than 10% of their patients who are eligible for IVIg currently receive SCIg instead, although this proportion could increase as SCIg has the advantage of being administered by the patient at home. The contraindications of a particular patient and the availability of facilities for PLEX at any particular treatment centre influence whether a patient initially receives IVIg or PLEX. There may be some waiting times associated with these treatments but the EAG's

three experts said that very few refractory patients who would be eligible to receive either IVIg or PLEX do not receive these.

The ABN guidelines give recommendations for the use of AChE inhibitors, non-steroidal ISTs and/or corticosteroids alongside IVIg or PLEX when used as rescue therapy for myasthenic crisis management, but not for the chronic (i.e. maintenance) use of IVIg or PLEX.[4] The EAG's clinical experts advised that refractory patients would continue to receive corticosteroids and immunosuppressants, with IVIg or PLEX used in addition. Additionally, the experts said that doses may change, for example AChE inhibitors may be reduced to confirm disease suppression is complete and corticosteroid dose would be reduced where possible to reduce steroid-related side-effects.

The EAG understand that rituximab exists as an option in the treatment pathway for refractory generalised MG in England (NHS England commissioning guidelines for use of rituximab in myasthenia gravis patients[15]), but it is not licensed for this indication, the EAG's clinical experts do not find it consistently effective, and it is not widely used. Rituximab should have been included in CS Figures 3 and 4 illustrating the treatment pathway for completeness but the EAG's clinical experts suggested that it is not a useful comparator in this appraisal due to having a substantially longer time to effect compared to zilucoplan and the other comparators (see Decision Problem section 2.3 of this report).

2.2.3.2 Position of zilucoplan in the treatment pathway

Both the SmPC[13] and the CS (CS section B.1.3.4) indicate zilucoplan as an add-on to standard therapy for the treatment of generalised MG in adult patients who are AChR-antibody positive. As noted in our critique of the company's Decision Problem (section 2.3 below), the population in the company submission, refractory generalised MG patients who are AChR-antibody positive, is narrower than the indicated population in the SmPC.

CS Figure 4 illustrates the position of zilucoplan at two points in the treatment pathway:

- When non-steroidal ISTs are contraindicated or inappropriate and IVIg or PLEX would be indicated. This is illustrated in CS Figure 4 as prior to the refractory disease stage but is consistent with the definition of refractory in the company's Decision Problem (which includes non-steroidal ISTs are contraindicated or not tolerated, the disease is uncontrolled and IVIg or PLEX are indicated).
- When refractory disease is diagnosed and IVIg or PLEX therapy is being used or considered.

CS Figure 4 does not indicate whether zilucoplan is intended as an add-on to IVIg/PLEX or if it is an alternative to IVIg/PLEX. The accompanying text in CS section B.1.3.4 discusses the results of the company's pivotal RAISE trial but does not discuss the position of zilucoplan in the pathway. The company's Decision Problem shows that IVIg and PLEX are considered comparators. In the RAISE trial, zilucoplan could be used concomitantly with IVIg and PLEX as rescue therapy if required (RAISE clinical study report (CSR) section 3.5.5.4) but IVIg and PLEX were not listed as concomitant treatments (RAISE CSR section 3.5.5.2). Therefore, we understand that zilucoplan is intended to replace the off-label use of IVIg and/or PLEX as chronic/maintenance therapy but use of zilucoplan would not affect use of IVIg or PLEX as rescue therapies.

EAG conclusion on the condition and treatment pathway

Generalised MG is accurately described in the CS. The positioning of zilucoplan, for refractory patients only, is narrower than the licensed indication in the SmPC and narrower than the eligible population in the pivotal RAISE trial. The company's definition of a refractory population is appropriate and broadly consistent with published definitions. There is lack of clarity in the company description of zilucoplan's position in the treatment pathway leading to uncertainty about relevant comparators and standard of care. However, the EAG's three clinical experts agreed that in practice very few, if any, patients eligible to receive chronic IVIg or PLEX would not receive them.

2.3 Critique of the company's definition of the Decision Problem

Table 4 below summarises the Decision Problem addressed by the company in the CS in relation to the final scope issued by NICE, and the EAG's comments on this.

The company's Decision Problem is consistent with the NICE scope with the following two exceptions, which are explained in further detail in Table 4:

- **Population: The CS focuses on a subgroup of patients with refractory generalised MG**. The population specified in the company's Decision Problem is patients with AChR antibody-positive generalised myasthenia gravis who are refractory to prior therapies. This is narrower than the population specified in the NICE scope, which is not limited to refractory patients. We have noted the uncertainty around how well the available clinical evidence reflects the refractory population of patients with generalised MG as a Key Issue for further consideration (see Key Issue 2 in section 1 above).

- **Comparator: The CS excludes standard of care (SoC) as defined in the NICE scope**. The NICE scope specifies SoC as a comparator and defines SoC to include corticosteroids and immunosuppressants with or without IVIg or PLEX. The company's Decision Problem does not include SoC as defined in this way (that is, as an overall 'basket' of care) but instead specifies IVIg and PLEX as separate individual comparators. However, the way that these therapies are modelled separately by the company is not reflective of how they would be used for refractory patients in clinical practice. The EAG conducted scenario analyses to explore different combinations of SoC therapies including IVIg and PLEX (see section 6.3 below). Uncertainty around the relevance of SoC for patients with refractory generalised MG is noted as a Key Issue for further consideration (see Key Issue 1 in section 1 above).

A further comparator, rituximab, is of potential interest for patients with refractory generalised MG and has been discussed in this context in the NICE appraisal of efgartigimod (Guidance in Development, GID-TA10986). The EAG note that rituximab is not specified as a comparator in the NICE scope or the company's Decision Problem for the current appraisal of zilucoplan and we agree that the exclusion of rituximab from the present appraisal is appropriate. The EAG's three clinical experts commented that although rituximab may have efficacy for some patients, these patients are in a difficult to identify minority and, overall, evidence for the clinical efficacy of rituximab in refractory generalised MG is lacking. The experts also noted that rituximab has a different mode of action and very slow time to onset of effect compared to IVIg, PLEX and efgartigimod. As such, the experts considered that the exclusion of rituximab as a comparator for zilucoplan is appropriate.

Table 4 Summary of the Decision Problem

	Final scope issued by NICE	Company's Decision Problem	Rationale if different from the final NICE scope	EAG comments
Population	Adults with antibody-positive generalised myasthenia gravis	Adults with refractory AChR antibody-positive generalised myasthenia gravis, if: • the disease has not responded to other systemic treatments, including pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, methotrexate and ciclosporin, or these options are contraindicated or not tolerated, and • the disease is uncontrolled, as defined by a MG-ADL of 6 or more or a QMG of 12 or more, and • an alternative option to efgartigimod (subject to NICE approval), and/or an additional therapy such as immunoglobulin	There is a high unmet need for a novel effective treatment with an acceptable safety profile in this patient population as there are currently no treatments other than chronic IVIg/PLEX, which are a burden to the patient and costly to the healthcare system. There is limited evidence available on the effectiveness of IVIg in MG, and issues with supply and access. In addition, IVIg and PLEX are used off label as they are unlicensed for the treatment of gMG. In addition, adult patients with AChR antibody-positive refractory gMG is in line with patients who clinicians are expected to prioritise. The evidence base for zilucoplan is based on a proportion of patients (50.6%)	The company's Decision Problem population, focusing on refractory patients (defined in CS Table 1), is narrower than that in the NICE scope and the marketing authorisation. The EAG's three clinical experts agreed that this population is appropriate in terms of unmet need, although the comparative clinical evidence for refractory patients is from a pre-specified subgroup in the pivotal trial (n=44 per arm). The three clinical experts also agreed that in terms of participant baseline characteristics and outcomes, the full (intention to treat, ITT) population of the pivotal trial adequately represents those patients with refractory generalised MG likely to be treated in the NHS.

		(IVIg) or plasma exchange (PLEX) is being considered, or patients are being treated chronically with IVIg/PLEX	who had refractory gMG at baseline in the pivotal phase lll trial (RAISE) and as such provides sufficient subgroup data to perform meaningful indirect comparisons or allow cost cost-effectiveness analyses in refractory MG.	The NICE scope does not specify the antibody type, but the focus on the AChR antibody-positive population is consistent with the mode of action of zilucoplan.
Intervention	Zilucoplan	Zilucoplan	Not applicable	Consistent with the NICE scope.
Comparators	• Standard of care without zilucoplan (including cortico-steroids and immunosuppressive therapies, with or without intravenous immunoglobulin or plasma exchange) • Efgartigimod (subject to NICE evaluation) • Ravulizumab (subject to NICE evaluation)	• Efgartigimod (subject to NICE evaluation) • Intravenous immunoglobulin (IVIg) and plasma exchange (PLEX)	1. Is anticipated that efgartigimod will be approved for use in refractory gMG patients (subject to NICE evaluation) 2. IVIg/PLEX (added to corticosteroids and immunosuppressants and ISTs) is the current standard of care (SoC) in patients who are refractory to treatment	The company have excluded standard of care (SoC) as defined in the NICE scope (as a 'basket' of several therapies with or without IVIg or PLEX) and instead include IVIg and PLEX as separate comparators. The EAG's three clinical experts agreed with the company's argument that IVIg and PLEX can be considered as SoC for the refractory population, noting that the number of patients who would be eligible to receive IVIg or PLEX but unable to receive at least one

				of these due to supply or tolerability issues is very small. However, the separate modelling of IVIg and PLEX by the company does not reflect their usage in clinical practice. We have noted uncertainty in the relevance of SoC as a comparator as a Key Issue for further consideration (see Key Issue 1 in section 1 above). Clinical efficacy evidence for efgartigimod is provided in network meta-analyses (NMAs). No direct or indirect comparisons of zilucoplan against IVIg or PLEX are available. Outcomes for the economic analysis for these therapies are taken from literature sources and the uncertainty around this is considered in this report. The EAG agree with the exclusion of ravulizumab as

				this therapy was withdrawn from NICE evaluation and therefore is not recommended for this indication.
Outcomes	• Improvement in MG • Time to clinically meaningful improvement • Mortality • Number of hospitalisations • Adverse effects of treatment • Health-related quality of life	• Improvement in MG (MG-ADL responder) • Time to clinically meaningful improvement • Mortality • Number of hospitalisations • Adverse effects of treatment • Health-related quality of life (in patients and carers)	Many patients with gMG require a caregiver for daily activities, which leads to reduced employment (productivity loss) and reduced QoL in those caring for gMG patients [16-18]. Therefore, carer disutility was addressed in the submission	The EAG agree that MG-ADL responder is a clinically meaningful measure of MG improvement. The CS reports all the outcomes specified in the NICE scope. Additionally, the company say that caregiver disutility was addressed in the CS. However, the company's economic model does not include caregiver disutility. CS Table 5 summarises caregiver burden by MG-ADL score but does not provide an interpretation of how this would affect cost-effectiveness conclusions.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of	No company comment provided	No company comment provided	The company do not specify their method of economic analysis in their Decision Problem form. However, their

	incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			cost-utility analysis meets the specifications of the NICE reference case (Table 26), including applying a lifetime time horizon which is appropriate for the health condition.
Subgroups	None specified	No company comment provided	No company comment provided	As noted above, the company's Decision Problem focuses on refractory patients which is a pre-specified subgroup of those included in

				the pivotal clinical efficacy trial.
Other considerations (the CS refers to these as “Special considerations including issues related to equity or equality”)	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	There is **geographic variability** in treatment availability and access to specialist centres, which introduces inequality among patients with MG in terms of access to care. The introduction of zilucoplan will improve equity of access to treatment, as access will not be restricted based on geography, and patients will be able to receive zilucoplan as a self-administered SC injection in their own homes. Treatment at home will reduce HCRU and help alleviate capacity challenges in hospitals and long waiting times in the NHS, compared with the comparators, which require in-hospital administration. In addition, the rapid onset of action of zilucoplan provides benefit to	No company comment provided	The considerations noted by the company here, apart from the subcutaneous administration of the therapy, apply to people with generalised MG and are not specific to this technology appraisal.

		patients versus currently available treatment. There is **health inequality between males and females** in terms of the burden of MG. Like other autoimmune conditions, MG is more prevalent in female patients than male, with female patients making up 60% of the MG population [19, 20]. As females are younger than males at disease onset (mean age of disease onset is 35±18 vs 45±18 years, respectively [p<0.001]) [21], they are exposed to a greater total burden throughout their lives than men, and through more of their working life.		

Source: Reproduced from CS Table 1 with EAG interpretation added.

For the refractory definition employed in the RAISE trial see section 3.2.1.1.1.

AChR, acetylcholine receptor; gMG, generalised myasthenia gravis, IST, immunosuppressant therapy, IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, MG Composite; MGQoL15r, MG Quality of Life 15-Item Scale; MSE, minimal symptom expression; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis; SC, subcutaneous; SCIg, subcutaneous immunoglobulin.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted three systematic literature reviews (SLRs):

- To identify clinical effectiveness evidence for zilucoplan, including evidence to inform the company's network meta-analyses (NMAs) (discussed in the paragraph below).
- To identify cost-effectiveness, cost, and resource use evidence (discussed in section 4.1 of this report).
- To identify health-related quality of life (HRQoL) evidence for MG (discussed in section 4.2.7.1 of this report).

The clinical effectiveness SLR is described in CS section B.2.1 and CS Appendix D, with some details relating to the NMAs in CS section B.2.9. Additionally, a confidential NMA report (in two parts) provided to the EAG on 12th December 2023 gives outline details of the SLR and a separate report of the SLR was provided in response to clarification question A9. The SLR searches were broad, and they covered from database inception up to May 2023; the EAG and our clinical experts have not identified any more recent relevant studies.

Studies were selected according to appropriate eligibility criteria outlined in Table 2 of the confidential report of the SLR (there is an inconsistency between the company documents in reporting whether PLEX studies were included or not, but this was resolved in Clarification Response A1). Following the selection process, few studies of IVIg or PLEX remained in the review which meant that no suitable studies on these therapies were available in the NMAs for outcomes which inform the economic model. The company carried out further informal searches (CS section B.3.2.8; Clarification Response A2) to identify comparator data and discovered a paucity of clinical and real-world evidence for the treatment of MG in the UK. For example, a phase IV study on PLEX, by Barth et al. 2011,[2] (CS Table 38) was excluded appropriately according to the selection criteria and later used as the only available evidence for the basis for assumptions used for IVIg and PLEX response rates in the economic model (CS Table 53).

Generally, the conduct of the SLR was appropriate and no key studies appear to have been missed. The EAG's detailed critique is provided in Appendix 9.1.

3.2 Critique of studies included in the technology appraisal

3.2.1 Included studies

Studies included in the CS that provide efficacy and safety evidence for zilucoplan are the company-sponsored completed phase III randomised controlled trial (RCT) called RAISE and an ongoing single-arm observational long-term extension study called RAISE-XT.[22-24] The RAISE trial compared zilucoplan against placebo whilst in the RAISE-XT study all patients received zilucoplan. The company's SLR also identified a company-sponsored phase II RCT that compared zilucoplan against placebo[25] but the company did not include it in their submission because it does not inform the economic model (CS section B.2.2). However, the EAG believe that the phase II study should have been included in the CS for the safety results (subsequently provided in clarification response A7), and because it is included in some of the NMAs. We therefore include it in our critique here.

3.2.1.1 Study characteristics

RAISE and RAISE-XT are described in CS section B.2.3.1; the description of the Phase II study below is based on the CSR and the trial publication by Howard et al. 2020.[25]

3.2.1.1.1 RAISE (MG0010; NCT04115293)

RAISE was a 12-week, phase III, multicentre, double-blind, placebo-controlled RCT. The trial was international, including the US, Japan, and Europe, with 2 UK sites (Oxford and Sheffield).[24] Key features are summarised in Table 5 below.

Table 5 RAISE trial study design

Study characteristic	Description
Population	Patients with AChR-antibody positive generalised MG
Key eligibility criteria	• Age 18-74 years • MGFA class II-IV • MG-ADL score ≥6 • QMG score ≥12 • Vaccinated for meningococcal infection
Pre-planned subgroup: Refractory patients	Refractory patients defined as: patients on treatment for >1 year with >2 of the following therapies: prednisone, azathioprine, mycophenolate, cyclosporine, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for generalised MG, other ISTs, or history of treatment with >1 of these therapies for >1 year, and required chronic PLEX, IVIg, or SCIg at least every 3 months for the 12 months prior to enrolment.

Sample size	Randomised population: N=174 (Zilucoplan: n=86; Placebo n=88); UK participants: n=[redacted] Refractory subgroup: N=88 (Zilucoplan: n=44; Placebo n=44); UK refractory participants: n=[redacted]
Intervention	Subcutaneous injection of 0.3 mg/kg zilucoplan as an add-on to standard of care. Permitted concomitant medications were acetylcholinesterase (AChE) inhibitors corticosteroids and non-steroidal immunosuppressant (IST) therapies.
Comparator	Subcutaneous injection of placebo as an add on to standard care.
Duration	12 weeks. Study is complete.
Primary outcome	Change from baseline in MG-ADL total score at week 12. This was also a pre-planned outcome for the refractory subgroup.
Key secondary outcomes	Change from baseline to week 12 in QMG, MGC, and MG-QoL15r scores. These were also pre-planned outcomes for the refractory subgroup.
Other outcomes	See outcomes assessment in section 3.2.3 of this report.
Source: CS sections B.2.3.1 and B.2.3.1.1, CS Table 9, trial publication.[24] AChR: acetylcholine receptor; IST: immunosuppressant therapy; IVIg: intravenous immunoglobulin; MG: myasthenia gravis; MG-ADL: Myasthenia Gravis Activities of Daily Living score; MGC: Myasthenia Gravis Composite score; MG-QoL15r: Myasthenia Gravis Quality of Life 15-item scale revised; PLEX: plasma exchange; QMG: Quantitative Myasthenia Gravis score; SCIg: subcutaneous immunoglobulin.	

The pre-planned refractory subgroup in RAISE has a slightly narrower definition of refractory MG than the definition in the company's Decision Problem. A key difference is the time stipulation in the RAISE trial definition which requires that treatments must have been tried and failed for one year whereas this requirement is not included in the Decision Problem definition. The disease was defined as uncontrolled according to the MG-ADL score (≥6) or QMG score (≥12) and if a patient required chronic PLEX, IVIg or SCIg at least every three months for the 12 months prior to enrolment. The only aspect of the Decision Problem definition that is missing from the trial definition is reference to efgartigimod which would not have been available at the trial outset. Therefore, the EAG agree that the RAISE definition of refractory is appropriate.

RAISE was an international trial, and standard of care varies from country to country. The permitted concomitant medications reflect a trial-specific standard of care incorporating AChE inhibitors, corticosteroids, and non-steroidal ISTs for both study groups and patients were expected to remain on a stable dose throughout the trial. RAISE trial participants could

only receive IVIg or PLEX as rescue therapy (RAISE CSR sections 3.5.5.2 to 3.5.5.4): participants in the refractory subgroup would therefore not continue to receive chronic (i.e. maintenance) IVIg or PLEX during the trial. In terms of trial design this would reduce confounding. In addition, censoring for receipt of rescue therapy (CS Table 18) and determining response as achievement of the outcome without rescue therapy at week 12 reduces variation in response between the two groups that would be due to the placebo group not being able to receive the comparator therapies.

3.2.1.1.2 Phase II study (MG0009; NCT03315130)

The phase II study of zilucoplan was a small (N=45) multicentre North American placebo-controlled RCT in a population with moderate to severe generalised MG. The phase II study did not have a pre-planned subgroup of refractory participants and therefore the number of refractory participants is not known. Three trial arms (n=15 in each arm) investigated two potential doses of zilucoplan (0.1 mg/kg and 0.3 mg/kg) versus placebo for 12 weeks in the 'Main portion' of the study after which, dependent on meeting eligibility criteria, participants continued into the 'Extension portion' of the study whereby participants in each of the zilucoplan groups continued to receive the same dose and participants in the placebo group were randomised 1:1 to receive either 0.1 mg/kg/day or 0.3 mg/kg/day of zilucoplan (phase II study CSR).[25] Patients who completed the 'Extension portion' of this trial were then eligible to enter the same extension study (RAISE-XT) as those who completed the RAISE trial.

3.2.1.1.3 RAISE-XT (MG0011)

RAISE-XT is an ongoing open-label, observational extension study of the 12-week RAISE and phase II RCTs. Eligibility for this study was completion of the RAISE trial or the 'Extension portion' of the phase II study. The latest CSR for RAISE-XT provided by the company is dated September 2022 and used to report patient disposition and analysis sets (CS Tables 11 and 17). A more recent [redacted] data cut, reported only in the CS, provides the number of participants enrolled and patient baseline characteristics (CS section B.2.3.1.2), clinical efficacy results (CS section B.2.6.2), and safety results (CS section B.2.10.1.2), with up to [redacted] of data for each participant.

There were [redacted] participants enrolled in RAISE-XT at the [redacted] data cut, of whom [redacted] were refractory. As in the RAISE trial, refractory patients were a pre-planned subgroup. All participants received 0.3 mg/kg of zilucoplan daily. To distinguish the assessment timepoints in RAISE-XT from those in the parent RCTs, the company prefixed the assessment times in RAISE-XT with 'E', for example week 'E12' means week 12 of the RAISE-XT study. The RAISE-XT study comprises four patient groups which differ according to their prior study

therapy, dependent on which of the zilucoplan (0.1mg or 0.3mg) or placebo arms in the RAISE and phase II RCTs the patients originated from. In this report we focus on the two groups in RAISE-XT which have greatest relevance to the present appraisal, that is, the group which had previously received 0.3mg zilucoplan and continued on this (zilucoplan 0.3mg/zilucoplan 0.3 mg; [redacted]) and the group which had previously received placebo and was switched to zilucoplan 0.3mg (placebo/zilucoplan 0.3mg; [redacted]) (CS section B.2.4.1.2).

The primary outcome is safety and tolerability of zilucoplan. All other efficacy, exploratory, and quality of life outcomes are the same as in the RAISE RCT. The same outcomes are reported for the refractory subgroup within RAISE-XT: change from baseline for MG-ADL, QMG, MGC, and MG-QoL15r – but only up to week E12 (i.e. 24 weeks of total treatment since starting the RAISE trial) (CS Table 9).

3.2.1.2 Participants' baseline characteristics in RAISE

3.2.1.2.1 All study participants

Baseline characteristics for all study participants for each trial arm are reported in CS Tables 12 and 13. CS Table 13 reports that 50.6% of participants (51% in the zilucoplan group and 50% in the placebo group)[24] in RAISE were treatment refractory according to the trial definition (Table 5 above). The RAISE trial therefore contains a larger proportion of refractory participants compared to the generalised MG population in clinical practice (5% to 20%, section 2.2.1 above). Baseline characteristics for the refractory subgroup are reported in clarification response A3; they are discussed in section 3.2.1.2.2 below.

The EAG's clinical experts viewed the participants in the trial as being generally representative of clinical practice and they confirmed that the baseline characteristics of the overall trial population reflect the relatively large proportion of refractory participants included in the trial. The experts noted the following specific points relating to generalisability of the trial population:

- **Age.** There were patients aged up to 75 years in the RAISE trial which our clinical experts did not view as being fully representative of clinical practice since they treat many patients in their 80s and 90s, explaining that most of their patients are elderly.
- **Sex.** There were proportionally more females in the trial (56.9%) than would be seen in clinical practice, but this probably reflects that the trial includes more younger participants, and females are more likely to be diagnosed earlier.

- **BMI.** Patients in the trial were generally heavier (31.0 kg/m^2 (SD 7.63)) than those the clinical experts see in clinical practice in England.
- **MGFA class, MG-ADL score, and QMG score.** A range of disease severity is represented by the MGFA class, MG-ADL and QMG scores although overall they reflect patients with more severe disease compared to those seen in clinical practice (one clinical expert said most generalised MG patients they see have an MG-ADL score of around 5).
- **Ethnicity.** Non-White populations are under-represented which is not uncommon for clinical trials; Black MG patients can have a more severe disease course.
- **Comorbidities.** Comorbidities, such as diabetes or impaired HbA1c (average blood glucose level), are not reported in the CS. NB the CSR (section 7.4.3) reports prior and concomitant diseases: [redacted] of participants had type 2 diabetes mellitus, but further details and the balance between study groups are in CSR Table 14.1.4.1 which was not provided to the EAG.

Participant baseline characteristics reported for the overall trial population were evenly balanced across both trial arms, except that the proportion of females in the zilucoplan group (60.5%) was higher than in the placebo group (53.4%) (CS section B.2.3.1.2). Additionally, the trial publication notes that there were more participants with previous thymectomy in the zilucoplan group (52%) than in the placebo group (42%).[24] Sex is not a prognostic factor but having a thymoma can predict refractory MG; however, the zilucoplan group did not have more refractory participants than the placebo group. Given the generally well-balanced population characteristics between the zilucoplan and placebo arms, we believe there is low risk of selection bias in the trial (see risk of bias, section 3.2.2 below).

3.2.1.2.2 Refractory subgroup

Baseline characteristics for the refractory subgroup compared to all study participants are reported in Tables 1 and 2 of Clarification Response A3.

Participants in the refractory subgroup were [redacted] ([redacted]) than in the mITT group (median 55 years), and there were [redacted] females in the refractory group ([redacted]) compared to the overall trial population (56.9%). Disease duration was [redacted] in the refractory subgroup ([redacted]) compared to the overall trial population (median 5.00 years). There was a [redacted] proportion of participants with prior thymectomy in the refractory subgroup ([redacted]) compared to the overall trial population (47.1%). The refractory subgroup also had a [redacted] proportion of participants who had prior MG crisis ([redacted]) compared to the overall trial population

(32.8%). Median MG-ADL score was [redacted] in the refractory subgroup and median QMG score was [redacted] in both the refractory and overall trial populations. BMI was [redacted] in the refractory subgroup (median [redacted]) than in the overall trial population (median 30 kg/m^2). Comorbidities are not reported in the baseline characteristics. According to the EAG's clinical experts, these characteristics are generally consistent with the expected characteristics of a refractory subgroup.

Refractory status was not a stratification factor at randomisation so it is not certain whether the participants in the refractory zilucoplan and refractory placebo arms would have had balanced characteristics. Participant baseline characteristics for the refractory subgroup are not reported separately by trial arm in clarification response A3 so we cannot tell if they were evenly balanced between the zilucoplan and placebo groups.

EAG conclusion on included studies

All relevant studies evaluating zilucoplan have been identified. Participant baseline characteristics were generally evenly balanced across both trial arms for the overall trial population in RAISE, with negligible potential for selection bias (see risk of bias section 3.2.2 below). The RAISE trial eligibility criterion of an MG-ADL score $\geq$6 or QMG score $\geq$12 reflects a population with more severe MG than patients with generalised MG who would be seen in NHS practice. Although only around 50% of patients in RAISE were refractory, the EAG's clinical experts believe this was sufficient for the overall (mITT) trial population of RAISE to be reasonably reflective of the characteristics of a refractory population (noting that there is no precise and universally agreed definition of refractory). The phase II study and RAISE-XT study add appropriate safety and longer-term efficacy evidence.

3.2.2 Risk of bias assessment

The company performed quality assessments of the RAISE and RAISE-XT trials using the NICE checklist for randomised controlled trials (CS Table 19) which is appropriate for RAISE but not for the non-randomised RAISE-XT study. The company answered the checklist questions but did not frame their overall conclusions as risk of bias statements. The EAG checked the company's assessments, and we provide our interpretation in terms of the risk of bias alongside the company's judgements in Appendix 9.2.

In summary, we identified most aspects of the RAISE and RAISE-XT trials to have low risk of bias but with the following exceptions:

- The RAISE-XT trial has an inherently high risk of bias due to its open-label design. The patient- and physician-reported MG-ADL, QMG, MGC, MG-QoL15r and EQ-5D outcomes involve subjective judgements by those completing the instruments that might be sensitive to knowledge of the treatment being received. Results from RAISE-XT are therefore uncertain.
- The specific way that EQ-5D is reported by the company in CS sections B.2.6.1.3 (RAISE) and B.2.6.2.3 (RAISE-XT) as the proportion of patients who have no problems in specified subscales of the EQ-5D, rather than reporting EQ-5D scores, introduces a high risk of outcome reporting bias (section 3.2.5.7). However, this has no bearing on the company's economic analysis which employs orthodox EQ-5D scores as inputs (section 4.2.7).
- In both RAISE and RAISE-XT there are some uncertainties around missing data meaning that the risk of attrition bias is unclear. In RAISE this mainly relates to whether the timing of intercurrent events differed between the trial arms (which is relevant as imputation assumptions used either the worst value from baseline or from the time of the intercurrent event), as well as some data being missing from the refractory subgroup for specific outcomes. In RAISE-XT it is unclear why the dropout rate was higher in the placebo/zilucoplan group than the zilucoplan/zilucoplan group after week E24 and whether this might have influenced the observed outcomes for MG-ADL, QMG, MCG, and MG-QoL15r (and possibly also the company's EQ-5D analysis noted above).

The CS does not discuss the phase II zilucoplan study but this is one of the studies included in the company's NMAs, for which risk of bias is considered in section 3.3.4 below.

EAG conclusion on risk of bias

The RAISE-XT study is inherently at high risk of bias due to its open-label design, meaning that outcomes from RAISE-XT are uncertain. Aside from a high risk of outcome reporting bias linked to a specific way that the company have reported EQ-5D outcomes in both RAISE and RAISE-XT (which has no bearing on the economic analysis), no other high risks of bias were identified. However, there is an unclear risk of attrition bias in both RAISE and RAISE-XT for most outcomes due to some uncertainties around missing data.

3.2.3 Outcomes assessment

The main aim of treatment for MG is to control patients' symptoms, and therefore the main clinical outcomes focus on assessment of symptoms using instruments which measure

disease symptom and severity, and health-related quality of life (HRQoL). Responders were defined as patients who achieved specified threshold changes in scores on the MG-ADL and QMG instruments, and the thresholds are clinically appropriate as they exceed the minimum clinically important difference (MCID) for these instruments (see Table 6 below).

3.2.3.1 Disease symptom and severity measures

Several measures of disease symptoms and severity and HRQoL were used in the RAISE trial and RAISE-XT study and included in the CS (see Table 6 below). Here we outline the measures used for the primary outcome, key secondary outcomes, and the EQ-5D utility measure (an exploratory outcome which informs the company's economic evaluation). Six of these outcomes are also reported for the company's network meta-analyses (see section 3.5).

Myasthenia Gravis Activities of Daily Living (MG-ADL). The MG-ADL asks eight questions about talking, chewing, swallowing, breathing, ability to brush teeth or comb hair, ability to arise from a chair, double vision, and eyelid droop. The questions are each scored 0-3, with 0 representing normal ability and 3 representing maximum impairment, giving a total score ranging from 0 to 24, with higher scores indicating greater disease severity. The MG-ADL is entirely patient-reported and relatively quick to use. The MCID is 2 points.[26, 27]

Quantitative Myasthenia Gravis scale (QMG). The QMG has 13 items that measure endurance or fatiguability, each scored 0 to 3, giving a total score ranging from 0 to 39, with higher scores indicating greater disease severity. The QMG scale is based on a physical examination requiring a dynamometer and spirometer and can take up to 25 minutes to complete, therefore it is used mostly in research rather than clinical practice. The MCID is 2 or 3 points.[27]

Myasthenia Gravis Composite score (MGC). The MGC is a 10-item scale comprised of both patient-reported outcomes (for speech, chewing, swallowing and respiratory function) and physician measured outcomes (to evaluate ocular, neck and proximal limb muscles using quantitative tests and spirometry). Items are weighted so that a maximum score for worst respiratory function is worth more points than the maximum score for worst eyelid strength. The total score ranges from 0 to 50 and higher scores indicate more severe disease. The MCID is 3 points.[28]

Myasthenia Gravis Quality of Life 15 revised version (MG-QoL15r). The MG-QoL15r has 15 items relating to mobility (9 items), symptoms (3 items), and contentment and emotional

wellbeing (3 items). Each item is scored 0 to 2, with total scores ranging from 0 to 30, and higher scores indicating worse quality of life. The MG-QoL15r has improved psychometric properties compared to the original version of the instrument (G-QoL15). However, a MCID: has not been established.[27]

EQ-5D-5L index and visual analogue scale (VAS) scores. The trial publication[24] and CS do not list EQ-5D as an outcome (CS Table 9), although the EQ-5D was a pre-specified exploratory outcome according to the CSR.[29] EQ-5D results from RAISE and RAISE-XT are reported in CS sections B.2.6.1.3 and B.2.6.2.3.

The MG-ADL, QMG and MGC are widely used instruments for assessing patients with MG and the EAG's clinical experts agreed that the outcome measures reported in the CS are appropriate. Using all these measurement instruments together gives an overview of the full range of symptoms experienced by MG patients as well as reflecting the patients' and physicians' perspectives when reporting symptoms. The CS uses clinically acceptable thresholds which for MG-ADL and QMG responses are conservative, i.e. exceeding the minimum clinically important differences.

Table 6 Main disease symptom and severity and HRQoL measures and outcomes used in the RAISE trial

Measure	Outcome	Reported for refractory subgroup?	Informs economic analysis?
MG-ADL total score	**Primary outcome:** change from baseline at week 12	Yes	Yes (section 4.2.6.2 below)
	Secondary outcome: MG-ADL response: proportion of patients achieving a ≥3 point [a] reduction in MG-ADL score without rescue therapy at week 12	Yes (clarification response A5(c))	Yes (CS section B.3.3.4)
	Secondary outcome: proportion of patients achieving MSE at week 12 (MG-ADL of 0 or 1 without rescue therapy)	No	No
QMG total score	**Key secondary outcome:** change from baseline at week 12	Yes	No

	Secondary outcome: QMG response: proportion of patients achieving a ≥5 point [b] reduction in QMG score without rescue therapy	Yes (clarification response A5(c))	
MGC score	**Key secondary outcome:** change from baseline at week 12	Yes	No
MG-QoL15r score	**Key secondary outcome:** change from baseline at week 12	Yes	No
EQ-5D-5L index score	**Exploratory outcome:** change from baseline at week 12	No	Yes (mapped to EQ-5D-3L, CS section B.3.4.2)
EQ-5D-5L VAS score	**Exploratory outcome:** change from baseline at week 12	No	No

Sources: CS sections B.2.6.1.1, B.2.6.1.2, and B.2.6.1.3.
[a] MCID for MG-ADL is a ≥2 point change, so this is a stringent outcome.
[b] MCID for QMG is a ≥3 point change, so this is a stringent outcome.
Outcomes: **Primary:** statistically powered; **Key secondary:** tested statistically and ranked to account for multiplicity; **Secondary:** tested statistically; **Exploratory:** descriptive summary.
Abbreviations: MCID: minimum clinically important difference; MG-ADL: Myasthenia Gravis Activities of Daily Living; MGC: Myasthenia Gravis Composite scale; MG-QoL15r: Myasthenia Gravis Quality of Life 15 item revised scale; MSE: minimal symptom expression; NMAs: network meta-analyses; QMG: Quantitative Myasthenia Gravis scale; VAS: visual analogue scale.

The RAISE-XT extension study reported the same outcomes as the RAISE trial (CS Table 9) for up to week E84, i.e., 96 weeks total from the RAISE baseline (CS sections B.2.6.2.1 to B.2.6.2.3). The primary outcome of RAISE-XT was long-term tolerability and safety with the primary outcome from RAISE, change from baseline in MG-ADL score, specified as a secondary outcome.

3.2.3.2 Other clinical effectiveness outcomes

The time to clinically meaningful improvement in MG is specified as an outcome of interest in the NICE scope but not reported in the CS. We have obtained results for this outcome from the RAISE CSR and company Clarification Response Table 4 (see section 3.2.5.8.1 below).

Number of hospitalisations is another outcome of interest specified in the NICE scope but not reported in the CS. Results were provided by the company in Clarification Response Table 5 and are summarised in section 3.2.6.1.4 below.

Other outcomes of potential clinical interest reported in the CS, although not specified in the NICE scope, are the time to receipt of rescue therapy over 12 weeks (summarised in section

3.2.5.8.2 below) and the proportion of patients who experienced minimal symptom expression at week 12 (summarised in section 3.2.5.8.3 below).

3.2.3.3 Safety outcomes

The CS reports a summary of all adverse events, treatment-emergent adverse events, serious adverse events, and those leading to treatment discontinuation for the 12-week RAISE RCT (CS Table 42); this was for a total of 19.8 participant years for the zilucoplan group and 20.0 participant years for the placebo group (CS section B.2.10.1.1). The open-label RAISE-XT extension study provides a further [redacted] of safety data with a total of [redacted] patient-years exposure, [redacted] data cut (CS Table 44).

EAG conclusion on the company's outcome selection

All outcomes in the NICE scope and the company Decision Problem are covered, either by the CS, CSR, or Clarification Responses. Clinical efficacy and HRQoL outcome measures used by the company are all appropriate for MG and either reflect or exceed the established minimum clinically important differences. Safety outcomes, including adverse events of special interest, are relevant and include sufficient data. Outcomes for the refractory subgroup are limited to the primary and key secondary outcomes.

3.2.4 Statistical methods of the included studies

The company used descriptive statistics to analyse the results for the refractory generalised MG population in the RAISE and RAISE-XT studies (CS sections B.2.7.3 to B.2.7.4) The EAG believe this is appropriate because it follows the study protocols for analysis of this subgroup and the subgroup is small (N=88). However, it does mean that the results for the refractory population reported in the CS have not been statistically tested and it is uncertain whether they are robust.

The results for the mITT population in RAISE were analysed using the statistical methods summarised below. No statistical testing was done for the RAISE-XT study in accordance with the study Statistical Analysis Plan (SAP) (RAISE-XT SAP section 2).

Analysis populations. In the RAISE trial, the modified Intention to Treat (mITT) population was defined as all randomised study participants who received at least one dose of zilucoplan and had at least one post-dosing MG-ADL score. This is an appropriate definition. We note that the mITT population included all randomised patients (CS Table 16) and so

does not differ from a full intention to treat analysis population (ITT). Likewise in the RAISE-XT study, all enrolled participants were included in the analysis. The safety populations in both studies were all participants who received at least one dose of zilucoplan and also included all randomised participants.

Sample size calculations. These appear to be appropriate. In the RAISE trial, the number of patients randomised (N=174, minus 8 dropouts) exceeded that required (156) to achieve the specified 94% power to detect a difference between active and placebo treatment groups for the primary outcome of MG-ADL change from baseline. It is unclear whether the MG-ADL response outcome which informs the company's economic model was sufficiently statistically powered because it was subject to different statistical testing to the primary outcome.

Methods to account for multiplicity. Multiplicity was accounted for: the RAISE trial used fixed sequential statistical testing for the primary outcome and the ranked key secondary outcomes (CS Table 18).

Analysis of outcomes. Appropriate methods, covariates, and precision of effect estimates are used: the RAISE trial used the least squares (LS) mean difference effect estimate with a mixed model repeated measure (MMRM) analysis of covariance (ANCOVA) to test the difference between the zilucoplan and placebo groups for the primary and key secondary outcomes (change from baseline to week 12 for MG-ADL, QMG, MGC and MG-QoL15r scores) (CS section B.2.6.1.1).

Handling of missing data. In both the RAISE trial and RAISE-XT study the methods for imputation, imputing non-response, and censoring appear sensible, although the quantity of missing data was not reported in the results (Clarification Response A6). For the RAISE trial, the sensitivity analyses, noted below, analysed the impact of missing data.

Sensitivity and post-hoc analyses. In the RAISE trial, comprehensive and pre-specified sensitivity analyses assessed the impact of missing data due to multiple imputation using jump to reference and tipping point analyses for the primary and key secondary outcomes. Missing data was anticipated due to the COVID-19 pandemic and the impact assessed using the COVID-19 Free Set (CFS) which was a pre-specified analysis set of participants who did not have missing data for COVID-19 reasons. Post-hoc analyses were performed to assess the effect of the study intervention on corticosteroid use, however that outcome is not in the Decision Problem of this appraisal.

EAG conclusion on study statistical methods

The statistical methods used in the RAISE and RAISE-XT studies appear to be appropriate and do not raise any concerns.

3.2.5 Efficacy results of the intervention studies

In this section the two response outcomes (for MG-ADL and QMG) are presented first, followed by the change from baseline outcomes (MG-ADL, QMG, MGC, MG-QoL15r). We summarise results for the EQ-5D in section 3.2.5.7 and results for other outcomes (time to clinically meaningful improvement, time to rescue medication and proportion experiencing minimum symptom expression) in section 3.2.5.8.

We provide results for the modified ITT analysis, as well as the company's pre-specified refractory subgroup which reflects their intended indication for zilucoplan.

3.2.5.1 MG-ADL response at week 12 in RAISE

The proportion of patients achieving a response (≥3-point improvement in the MG-ADL score without rescue therapy) at week 12 was a secondary outcome in the RAISE trial (though not-pre-specified for the refractory subgroup analysis) and is the key clinical efficacy parameter that informs the company's economic model. Note that a ≥3-point improvement in the score exceeds the minimum clinically important difference (MCID=2 points) so this is a stringent outcome.

A strong placebo effect is evident, with a response rate of 46.1% in the placebo group modified ITT analysis. Despite this, the response rate was statistically significantly higher in the zilucoplan arm than the placebo arm (Table 7). The response rates were marginally higher in the refractory subgroup than the mITT population, but this difference is subject to some uncertainty as the n/N values for the modified ITT analysis are not reported for this outcome and the placebo arm refractory subgroup had 2 missing observations.

Table 7 MG-ADL response at week 12 in the RAISE trial

Analysis	**Zilucoplan** (mITT N=86; refractory N=44)	**Placebo** (mITT N=88; refractory N=44)	**Odds ratio (95% confidence interval)**
mITT analysis, % (n/N)	73.1% (NR)	46.1% (NR)	3.18 (1.66 to 6.10); p<0.001

Refractory subgroup, % (n/N)	[redacted]	[redacted] [a]	NR
Source: CS section B.2.6.1.2 and Clarification Response Table 6. [a] [redacted] observations were missing. NR: Not reported.			

3.2.5.2 QMG response at week 12 in RAISE

The proportion of patients achieving a response (≥5-point improvement in the QMG without rescue therapy) at week 12 was a secondary outcome in the RAISE trial, although not a pre-specified outcome for the refractory subgroup. Note that a ≥5-point improvement in the score exceeds the minimum clinically important difference (MCID=3 points) so this is a stringent outcome.

A placebo effect is evident, with a QMG response rate of 33% in the placebo group modified ITT analysis. Despite this, the QMG response rate was statistically significantly higher in the zilucoplan arm than the placebo arm (Table 8). For both trial arms, the QMG response rate was slightly lower in the refractory subgroup than the mITT population.

Table 8 QMG response at week 12 in the RAISE trial

Analysis	**Zilucoplan** (mITT N=86; refractory N=44)	**Placebo** (mITT N=88; refractory N=44)	**Odds ratio (95% confidence interval)**
mITT analysis, % (n/N)	58.0% (NR)	33.0% (NR)	2.87 (1.52 to 5.40); p=0.0012
Refractory subgroup, % (n/N)	[redacted]	[redacted] [a]	NR
Source: CS section B.2.6.1.2 and Clarification Response Table 7. [a] [redacted] observations were missing. NR: Not reported.			

3.2.5.3 MG-ADL score change from baseline in RAISE and RAISE-XT

The change from baseline to week 12 was the primary outcome of the RAISE trial and the change from baseline to week E12 was a secondary outcome in the RAISE-XT study, with further assessments reported up to week E84.

3.2.5.3.1 RAISE

In the modified ITT population analysis, the MG-ADL had score decreased overall at week 12 by a clinically meaningful amount (>2.0) in both trial arms. There was a rapid onset of zilucoplan effect on the MG-ADL score within the first week (although this initial change did

not reach the MCID of 2 points) (CS Figure 7). The difference between trial arms at week 12 was statistically significant, favouring the zilucoplan arm (Table 9). The modified ITT analysis results are generally robust to the sensitivity analyses to account for missing data that were conducted (CS section 3.2.5.1).

Table 9 MG-ADL score change from baseline at week 12 in the RAISE trial

Analysis	Least squares mean (95% confidence interval) [SD]		
	Zilucoplan (mITT N=86; refractory N=44)	**Placebo** (mITT N=88; refractory N=44)	**Difference**
Primary analysis (mITT)	-4.39 (-5.28 to -3.50) (N=86)	-2.30 (-3.17 to -1.43) (N=88)	-2.09 (-3.24 to -0.95) p=0.0004
Refractory subgroup	[redacted]	[redacted] [a]	[redacted] [b]

Source: CS section B.2.6.1.1, CS Table 28 and trial publication.[24]
[a] [redacted] observations were missing.
[b] Not reported in the CS, raw difference calculated by EAG. mITT: modified intention to treat.

The change in MG-ADL score was similar for the mITT population and the refractory subgroup (Table 9), although relatively large standard deviations indicate that the subgroup results are subject to imprecision.

3.2.5.3.2 RAISE-XT

CS Figure 17 (reproduced in Figure 1 below) shows the long-term overall change in MG-ADL score up to week E84 in RAISE-XT for the modified ITT population. A [redacted] in MG-ADL score occurred when placebo patients in RAISE were switched to zilucoplan 0.3mg in RAISE-XT. Between weeks E12 and E36 of RAISE-XT, MG-ADL scores [redacted] for the zilucoplan/zilucoplan and placebo/zilucoplan groups. From week E36 onwards there was a [redacted] in scores in the placebo/zilucoplan group but not the zilucoplan/zilucoplan group, perhaps explained by the higher rate of dropouts from the placebo/zilucoplan group towards the end of the study.

Figure 1 MG-ADL score changes in the RAISE trial and RAISE-XT study

The company report the change in MG-ADL score for the refractory subgroup only for the first 12 weeks of RAISE-XT (Table 10). The change in MG-ADL score for the modified ITT population over this period appears to be [redacted] than the change observed for the refractory subgroup. However, there is statistical uncertainty in the subgroup outcome, [redacted] for the mean changes.

Table 10 Change in MG-ADL score during the first 12 weeks of RAISE-XT

Analysis	Least squares mean change from RAISE-XT baseline to week E12 (95% confidence interval) [SD]	
	Zilucoplan 0.3mg → Zilucoplan 0.3mg	Placebo → Zilucoplan 0.3mg
Primary analysis (mITT) [a]	[redacted]	[redacted]
Refractory subgroup [b]	[redacted]	[redacted]

[a] Reported as the change from week 12 of RAISE to week E12 of RAISE-XT.
[b] Reported as the change from RAISE-XT baseline to week E12 of RAISE-XT.
Sources: CS section B.2.6.2.2 (mITT analysis); CS Table 32 (subgroup analysis).

3.2.5.4 QMG score change from baseline in RAISE and RAISE-XT

The QMG score change from baseline to week 12 was a key ranked secondary outcome in the RAISE trial and the change from baseline to week E12 was a secondary outcome in the RAISE-XT study, with further assessments reported up to week E84.

3.2.5.4.1 RAISE

In the modified ITT population analysis, the QMG score decreased by a clinically meaningful amount (>3.0) in both trial arms, indicating a placebo effect. There was a rapid onset of

zilucoplan effect on the QMG score within the first week (CS Figure 8). The difference between trial arms was statistically significant, favouring the zilucoplan arm (Table 11).

Table 11 QMG score change from baseline at week 12 in the RAISE trial

Analysis	Least squares mean (95% confidence interval) [SD]		
	Zilucoplan (mITT N=86; refractory N=44)	**Placebo** (mITT N=88; refractory N=44)	**Difference**
Primary analysis (mITT)	-6.19 (-7.29 to -5.08) (N=86)	-3.25 (-4.32 to -2.17) (N=88)	-2.94 (-4.39 to -1.49); p<0.001
Refractory subgroup	[redacted]	[redacted]	[redacted] [a]

[a] Not reported in the CS; raw difference calculated by EAG.
Source: CS section B.2.6.1.2, CS Table 29 and trial publication.[24]

The change in QMG score was [redacted] the modified ITT population [redacted] the refractory subgroup, although [redacted] the subgroup results are subject to imprecision (Table 11).

3.2.5.4.2 RAISE-XT

The long-term change in QMG score up to week E84 of RAISE-XT (reported only for the mITT analysis) (Figure 2) [redacted] for the MG-ADL score. There was a [redacted] in the score when patients receiving placebo were switched to zilucoplan.

[redacted]

Figure 2 QMG score changes in the RAISE trial and RAISE-XT study

The company report the change in QMG score for the refractory subgroup only for the first 12 weeks of RAISE-XT (Table 12). The change in QMG score for the modified ITT population over this period appears to be [redacted] than the change observed for the

refractory subgroup. However, there is statistical imprecision in the subgroup outcome, [redacted] for the mean changes.

Table 12 Change in QMG score during the first 12 weeks of RAISE-XT

Analysis	Least squares mean change from RAISE-XT baseline to week E12 (95% confidence interval) [SD]	
	Zilucoplan 0.3mg → Zilucoplan 0.3mg	Placebo → Zilucoplan 0.3mg
Primary analysis (mITT) [a]	[redacted]	[redacted]
Refractory subgroup [b]	[redacted]	[redacted]

[a] Reported as the change from week 12 of RAISE to week E12 of RAISE-XT.
[b] Reported as the change from RAISE-XT baseline to week E12 of RAISE-XT.
Sources: CS section B.2.6.2.2 (mITT analysis); CS Table 33 (subgroup analysis).

3.2.5.5 MGC score change from baseline in RAISE and RAISE-XT

The MGC score change from baseline to week 12 was a key ranked secondary outcome in the RAISE trial and the change from baseline to week E12 was a secondary outcome in the RAISE-XT study, with further assessments reported up to week E84.

3.2.5.5.1 RAISE

In the modified ITT population analysis, the MGC score decreased by a clinically meaningful amount (>3.0) in both trial arms, indicating a placebo effect. There was a rapid onset of zilucoplan effect on the MGC score within the first week (CS Figure 9). The difference between trial arms was statistically significant, favouring the zilucoplan arm (Table 13).

Table 13 MGC score change from baseline at week 12 in the RAISE trial

Analysis	Least squares mean (95% confidence interval) [SD]		
	Zilucoplan (mITT N=86; refractory N=44)	Placebo (mITT N=88; refractory N=44)	Difference
Primary analysis (mITT)	-8.62 (-10.22 to -7.01) (N=86)	-5.42 (-6.98 to -3.86) (N=88)	-3.20 (-5.24 to -1.16); p=0.0023
Refractory subgroup	[redacted]	[redacted]	[redacted] [a]

[a] Not reported in the CS, raw difference calculated by EAG.
Source: CS section B.2.6.1.2, CS Table 30 and trial publication.[24]

The change in MGC score was [redacted] the modified ITT population [redacted] the refractory subgroup, although [redacted]

[redacted] the subgroup results are subject to imprecision (Table 13).

3.2.5.5.2 RAISE-XT

The change in MGC score up to week E84 of RAISE-XT (Figure 3) [redacted] for the MG-ADL and QMG scores discussed above. However, over the longer term, patients who had previously received placebo in the RAISE trial appeared to have a [redacted] decrease in the MGC score compared to those who had received zilucoplan in RAISE. This difference is notable after week E36 and appears likely to be statistically significant at week E60, with non-overlapping confidence intervals. It is unclear whether this is explained by the higher rate of dropouts from the placebo/zilucoplan group towards the end of the study. One of the EAG's clinical experts commented that they would not expect this difference based on drug mechanism of action and they were uncertain whether 'tolerance' to zilucoplan might develop after extended exposure.

[redacted]

Figure 3 MGC score changes in the RAISE trial and RAISE-XT study

The company report the change in MGC score for the refractory subgroup only for the first 12 weeks of RAISE-XT (Table 14). The change in MGC score for the modified ITT population over this period appears to be [redacted] than the change observed for the refractory subgroup. However, there is statistical imprecision in the subgroup outcome, [redacted] for the mean changes.

Table 14 Change in MGC score during the first 12 weeks of RAISE-XT

Analysis	Least squares mean change from RAISE-XT baseline to week E12 (95% confidence interval) [SD]	
	Zilucoplan 0.3mg → Zilucoplan 0.3mg	Placebo → Zilucoplan 0.3mg
Primary analysis (mITT) [a]	[redacted]	[redacted]
Refractory subgroup [b]	[redacted]	[redacted]

[a] From section 9.1.3.1.1 of the September 2022 RAISE-XT CSR (not reported in the CS).
[b] Reported as the change from RAISE-XT baseline to week E12 of RAISE-XT.
Sources: RAISE-XT CSR (mITT analysis); CS Table 34 (subgroup analysis).

3.2.5.6 MG-QoL15r score change from baseline in RAISE and RAISE-XT

The MG-QoL15r score change from baseline to week 12 was a key ranked secondary outcome in the RAISE trial and the change from baseline to week E12 was a secondary outcome in the RAISE-XT study, with further assessments reported up to week E84.

3.2.5.6.1 RAISE

In the modified ITT population analysis, the MG-QoL15r score decreased in both trial arms, indicating a placebo effect. There was a rapid onset of zilucoplan effect on the MG-QoL15r score within the first week (CS Figure 10). The difference between trial arms was statistically significant, favouring the zilucoplan arm (Table 15).

Table 15 MG-QoL15r score change from baseline at week 12 in the RAISE trial

Analysis	Least squares mean (95% confidence interval) [SD]		
	Zilucoplan (mITT N=86; refractory N=44)	**Placebo** (mITT N=88; refractory N=44)	**Difference**
Primary analysis (mITT)	-5.65 (-7.17 to -4.12) (N=86)	-3.16 (-4.65 to -1.67) (N=88)	-2.49 (-4.45 to -0.54) p=0.0128
Refractory subgroup	[redacted]	[redacted]	[redacted] [a]

[a] Not reported in the CS, raw difference calculated by EAG.
Source: CS section B.2.6.1.2, CS Table 31 and trial publication.[24]

The subgroup data provided by the company suggest that the [redacted] zilucoplan in the modified ITT analysis was [redacted] for the refractory subgroup. However, we are uncertain about the comparability of the modified ITT population and the refractory subgroup [redacted]

[redacted]

3.2.5.6.2 RAISE-XT

The change in MG-QoL15r score up to week E84 of RAISE-XT (Figure 4) [redacted] for the MG-ADL, QMG and MGC scores discussed above, except that there was [redacted] of the trajectories of the placebo/zilucoplan and zilucoplan/zilucoplan groups towards the end of the assessment period, despite the higher rate of dropout in the placebo/zilucoplan group.


[redacted]

Figure 4 MG-QoL15r score changes in the RAISE trial and RAISE-XT study

The company report the change in MG-QoL15r score for the refractory subgroup only for the first 12 weeks of RAISE-XT (Table 16). The change in MGC score for the modified ITT population over this period is [redacted] the change observed for the refractory subgroup. However, there is statistical imprecision in the subgroup outcome, [redacted] for the mean changes.

Table 16 Change in MG-QoL15r score during the first 12 weeks of RAISE-XT

Analysis	Least squares mean change from RAISE-XT baseline to week E12 (95% confidence interval) [SD]	
	Zilucoplan 0.3mg →	Placebo →

	Zilucoplan 0.3mg	Zilucoplan 0.3mg
Primary analysis (mITT) [a]	[redacted]	[redacted]
Refractory subgroup [b]	[redacted]	[redacted]

[a] Reported as the change from week 12 of RAISE to week E12 of RAISE-XT.
[b] Reported as the change from RAISE-XT baseline to week E12 of RAISE-XT.
[c] The confidence interval reported in the CS is implausible; the EAG assume that the minus symbols are missing and have inserted these.
Sources: CS section B.2.6.2.2 (mITT analysis); CS Table 35 (subgroup analysis).

3.2.5.7 EQ-5D outcomes at week 12 (exploratory outcome)

This was an exploratory outcome, not subject to any statistical testing rules. EQ-5D-L scores inform the company's economic analysis (after mapping to EQ-5D-3L).

3.2.5.7.1 RAISE

The clinical efficacy sections of the CS provide limited EQ-5D-5L results (and no comparison of EQ-5D-5L and mapped EQ-5D-3L results). CS section B.2.6.1.3 reports the proportion in the RAISE trial at week 12 who reported no problems for each of five EQ-5D-5L index subscales: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The proportions for all these subscales were higher in the zilucoplan group than the placebo group, apart from pain/discomfort. However, these results are not easy to interpret clinically as they do not relate to the original EQ-5D-5L scale, and 19.3% to 42.2% of patients in the placebo group reported no problems on these subscales. The CS reports that the EQ-5D-5L visual analogue scale (VAS) score increased more in the zilucoplan arm than the placebo arm at week 12 but does not provide a baseline adjustment of the VAS results. The trial publication and RAISE CSR do not report any further EQ-5D results.

The percentages of patients reporting no problems is an unconventional way of presenting EQ-5D results that might make the results look more favourable than would be seen in a standard comparison of EQ-5D scores. As such, this outcome appears to be at high risk of outcome selection bias (section 3.2.2). However, these concerns do not affect the company's economic analyses which use orthodox EQ-5D scores (section 4.2.7).

3.2.5.7.2 RAISE-XT

CS section B.2.6.2.3 summarises briefly the proportions of patients reporting no problems for selected EQ-5D-5L subscales in the RAISE-XT study but does not consistently report these results for both groups (placebo/zilucoplan and zilucoplan/zilucoplan) across all timepoints. CS Figure 23 shows the proportions of patients reporting no problems in the EQ-5D-5L scores from RAISE-XT baseline to week E84 for the mobility, self-care, and usual activities subscales (omitting pain/discomfort and anxiety/depression). Notably, a [redacted] proportion

of the placebo/zilucoplan group (i.e. those who had received zilucoplan for a shorter time period) reported no problems in the mobility subscale, throughout the monitoring period, than those in the zilucoplan/zilucoplan group. Also notable is that the proportions reporting no problems for each of these subscales diverged markedly from week E72 onwards, with the proportions in the zilucoplan/zilucoplan group apparently faring [redacted] than those in the placebo/zilucoplan group. The company do not discuss these patterns nor offer any explanations for them. It is unclear whether this outcome is subject to attrition bias because the sample sizes are not reported for any of the assessment timepoints in CS Figure 23. As with the EQ-5D outcomes in the RAISE trial we believe these results are at high risk of selection bias and may not give a true reflection of the changes in EQ-5D scores.

3.2.5.8 Other outcomes from the RAISE trial

Below we summarise the following three secondary/other outcomes:

- Time to clinically meaningful improvement in MG – an outcome specified in the NICE scope and company Decision Problem.
- Time to receipt of rescue therapy over 12 weeks.
- Proportion of patients experiencing minimal symptom expression (MSE) over 12 weeks.

3.2.5.8.1 Time to clinically meaningful improvement in MG

This outcome is not reported in the CS; we have reproduced the results from the RAISE CSR[29] and company Clarification Response A5(a). An MG-ADL threshold of ≥2 or a QMG threshold of ≥3 would indicate achievement of the MCID for the instrument (see Table 6 above) and therefore a clinically meaningful improvement in MG. The time to clinically meaningful improvement [redacted] the zilucoplan arm, for the analyses of the MG-ADL response and QMG response (Table 17). The differences between zilucoplan and placebo were [redacted] for the QMG response and the MG-ADL response using the MG-ADL ≥3 threshold, but not the MG-ADL ≥2 threshold (which is equivalent to the MCID); a [redacted] to response occurred in the placebo arm compared to the zilucoplan arm for the QMG response.

Table 17 Time to a clinically meaningful improvement in MG in the RAISE trial

Response threshold	Analysis	Median (95% CI) time to response, days		Difference [d]
		Zilucoplan	Placebo	
MG-ADL ≥2	mITT [a]	[redacted]	[redacted]	[redacted]

	Refractory subgroup [b]	[redacted]	[redacted]	[redacted]
MG-ADL ≥3	mITT [a]	[redacted]	[redacted]	[redacted]
QMG ≥5	mITT [c]	[redacted]	[redacted]	[redacted]

[a] From CSR section 8.3.5.1.
[b] From Clarification Response A5(a). The MG-ADL ≥3 threshold and QMG thresholds are not reported for the refractory subgroup.
[c] From CSR section 8.3.5.2.
[d] Nominal p-values.
For the refractory subgroup there were [redacted] censored data in the zilucoplan arm and [redacted] censored in the placebo arm; numbers censored are not reported for the mITT analyses.
NC: not calculated.

3.2.5.8.2 Time to receipt of rescue therapy over 12 weeks

Zilucoplan was favoured over placebo numerically but not statistically (log-rank test p=0.100) (CS Figure 11). At week 12 the cumulative proportions of patients receiving rescue therapy in the zilucoplan and placebo groups were 5% (4/86) and 12% (10/88) respectively (CS section B.2.6.1.2).

3.2.5.8.3 Proportion of patients experiencing minimal symptom expression (MSE) at week 12

This was defined as an MG-ADL score of 0 or 1 without rescue therapy. This is a strict outcome indicating that patients have become free or nearly free of symptoms. Zilucoplan was favoured over placebo: odds ratio 2.608 (95% CI 0.866 to 7.860) (CS section B.2.6.1.2).

3.2.5.9 Subgroup analyses

The company's intended use of zilucoplan is for patients with refractory generalised MG. Results for the pre-specified refractory subgroup of patients are reported for each outcome in sections 3.2.5.1 to 3.2.5.6 above.

Other pre-planned subgroup analyses are listed in CS section B.2.7 for a range of patient demographic characteristics, disease history characteristics and baseline outcome values. Altogether the CS lists a further 21 subgroups, but the CS and trial publication [24] do not present results of these analyses. Results for all these subgroup comparisons are reported in Tables 8-14 to 8-17 of the RAISE CSR[29] for each of the MG-ADL, QMG, MGC and MG-QoL15r change from baseline outcomes (except for chronic kidney disease subgroups which were reported for safety outcomes only). The CSR concludes that the treatment effect [redacted] for all subgroup comparisons, [redacted] for the change from baseline in MG-QoL15r where the treatment effect [redacted] for the subgroups

[redacted] ([redacted] sample size per arm, n=[redacted] to [redacted]), age ≥65 years, disease duration below the median, and MGFA Class II (CSR Table 8-17). The CSR does not discuss [redacted] the magnitude of the treatment effect between subgroups (e.g. [redacted] patients' history of crises, prior thymectomy, prior steroid therapy, among others). The clinical significance [redacted] is difficult to ascertain [redacted].

3.2.6 Safety results

The CS reports safety results from the RAISE trial and the RAISE-XT study in CS section B.2.10. We have summarised the key adverse events information here. A summary of patients' exposure to zilucoplan is provided in section 3.2.3.3 above.

3.2.6.1.1 Adverse events

RAISE. At week 12, slightly more participants in the zilucoplan group (76.7%) experienced any adverse event compared to the placebo group (70.5%), with the proportion experiencing treatment emergent serious adverse events being similar for the zilucoplan group (12.8%) and the placebo group (14.8%), and the proportion experiencing severe adverse events also being similar for the zilucoplan group (11.6%) and the placebo group (12.5%) (CS Table 42). Treatment-related adverse events were slightly more frequent in the zilucoplan group (32.6%) compared to the placebo group (25.0%); and four participants in the zilucoplan group experienced adverse events resulting in permanent withdrawal compared to two participants in the placebo group. Most adverse events in the RAISE trial were mild or moderate (CS Table 42).

RAISE-XT. At the [redacted] data cut, [redacted] of all participants experienced any adverse event, and the summary safety results for the placebo/zilucoplan group are [redacted] those for the zilucoplan/zilucoplan 0.3/0.3 mg/kg group (CS Table 45). [redacted] participants withdrew permanently from zilucoplan due to adverse events. The proportion of participants experiencing treatment-related adverse events was [redacted] (CS Table 45) and the most common of these was injection site bruising ([redacted]) (CS Table 46). Treatment-related adverse events reported in ≥2% of participants are mostly associated with the injection site but also include increased lipase ([redacted]), abdominal pain ([redacted]) and nasopharyngitis ([redacted]) (CS Table 46). The proportion of participants experiencing serious adverse events was [redacted] (CS Table 45) but only [redacted] of these were considered treatment-related: oesophagitis, injection site infection (at a non-recommended injection site), colonic abscess, and headache. Out of all the serious adverse

events reported, worsening of myasthenia gravis was the most common ([redacted]) followed by COVID-19 pneumonia ([redacted]), pneumonia ([redacted]) and myocardial infarction ([redacted]). All other serious adverse events reported in CS Table 47 affected less than 2% of the participants.

3.2.6.1.2 Adverse events of special interest

RAISE. CS Table 43 summarises the adverse events of special interest. Slightly more participants experienced infections in the zilucoplan group (26.7%) compared to the placebo group (18.2%), but the proportion experiencing serious infections was the same and was small, around [redacted]. The most common infection was urinary tract infection: 8.1% in the zilucoplan group and 4.5% in the placebo group, and no events of Neisseria infection were reported (RAISE CSR section 9.6.1) for which study participants were vaccinated. Few of the adverse events of special interest were serious and they did not differ much between the treatment groups: four participants experienced serious infections in each of the zilucoplan and placebo groups; there were no serious injection site reactions or serious hepatic events; one participant experienced a serious hypersensitivity event in the zilucoplan group; and one participant in each group experienced malignancy (CS Table 43).

RAISE-XT. Adverse events of special interest were experienced by [redacted] of all study participants (CS Table 48). The most common adverse event of special interest was infections experienced by [redacted] of participants, of which [redacted] were serious. Few of the other adverse events of special interest were serious: there were [redacted] serious injection site reactions or hypersensitivity events; there was [redacted] serious hepatic event; and there were [redacted] serious malignancies (CS Table 48).

3.2.6.1.3 Pancreatic adverse events

The FDA review of zilucoplan (section 7.7.1) [30] reported a pancreatic safety signal due to a delayed emergence of pancreatic adverse events seen in the extension studies. Pancreatic adverse events from the RAISE-XT and phase II studies are provided in clarification response A8 but it is not clear to what extent any new pancreatic events may have occurred since the publication of the FDA review, because Table 15 in the Clarification Response does not appear to list all the events included in Table 32 of the FDA review and it may include new ones. It is not clear whether the FDA and company followed the same reporting approaches for pancreatic adverse events. According to Table 15 of the clarification response, only [redacted] of the pancreatic adverse events was considered related to the study intervention (suspected investigator causality) but the event was [redacted].

3.2.6.1.4 *Hospitalisations*

RAISE. Table 5 in Clarification Response A5(b) reports the number of hospitalisations due to treatment-emergent adverse events. The proportion hospitalised was [redacted] in the zilucoplan group than the placebo group, both for the whole trial population ([redacted] versus [redacted]) and the refractory subgroup ([redacted] versus [redacted]).

RAISE-XT. Hospitalisations were not reported in the CS or Clarification Response.

3.2.6.1.5 Mortality

RAISE. Two deaths occurred during the RAISE trial, one in each treatment group, and neither were considered treatment-related (as determined by the investigator) (CS section B.2.10.1.1).

RAISE-XT. [redacted] deaths occurred during the RAISE-XT study: [redacted] in the placebo/zilucoplan 0.3 mg/kg group and [redacted] in the zilucoplan/zilucoplan 0.3/0.3 mg/kg group (CS Table 45) and there [redacted] fatal post-treatment [redacted]. None of the deaths were considered treatment-related (as determined by the investigator) (CS Table 45; RAISE-XT CSR section 8.3).

3.2.6.1.6 Phase II study (MG0009)

Safety results from the phase II study (MG0009) were not included in the CS because, as the company explain in Clarification Response A7, those results do not inform the economic model, and participants who completed the phase II study were able to continue into the RAISE-XT extension study which is reported in CS section B.2.10.1.2. However, the phase II study contains 12 study weeks of comparative safety data for two doses of zilucoplan compared to placebo in the 'Main portion' of the study and a further 84 weeks of data in the 'Extension portion' without a placebo comparison. The results reported in Clarification Response A7 do not report data from the placebo group. But they show that for the zilucoplan treatment groups treatment-related adverse events were experienced by [redacted] to [redacted] of participants, there were no serious treatment-related adverse events, and most adverse events were CTCAE Grade 3 or less in severity (Clarification Response Table 13).

EAG conclusion on the safety results

Zilucoplan appears to be well-tolerated as most adverse events were mild to moderate, and hospitalisations due to adverse events were fewer in the zilucoplan group; additionally, very few adverse events were considered to be treatment-related. Data for pancreatic adverse events are no more conclusive than when reported in the FDA review.

3.2.7 Pairwise meta-analysis of intervention studies

Two RCTs compared zilucoplan against placebo: the phase III RAISE trial[24] and the phase II trial reported by Howard et al.[25] The RAISE trial is the pivotal source of clinical efficacy evidence for zilucoplan in the CS. The company have not conducted a pairwise meta-analysis combining the RAISE trial and phase II trial, which is appropriate since the phase II trial did not include a pre-specified subgroup of refractory patients (the population of interest in the Decision Problem); and the phase II trial was small, with only 15 patients per arm. No RCTs comparing zilucoplan against efgartigimod, IVIg or PLEX are available and so the company utilised network meta-analyses to perform those comparisons, as described in the following sections.

EAG conclusion on pairwise meta-analysis

Pairwise meta-analysis was, appropriately, not conducted by the company. However, both trials that compared zilucoplan against placebo were included in network meta-analysis scenarios, reported in the following sections.

3.3 Critique of studies included in the network meta-analyses (NMAs)

Information on the studies included in NMAs are reported in the following sources:

- A sparse account of the methods and results of the NMAs (dated March 2023) is reported in CS section B.2.9.
- An NMA report, dated November 2023,[32] was received by the EAG on 12 December 2023 which provides the main information on the NMA methods and results. The November 2023 NM Report is divided into two parts: 1st Part (fixed-effect model results) and 2nd Part (random-effects model results).
- However, in Clarification Responses A9 and B8 the company explain that due to a data input error the March and November reports were superseded by an external report (not cited in the CS) dated January 2024[31]
- The January 2024 NMA report[31] was provided by the company in their Clarification Response. This report is limited to the MG-ADL response and change from baseline in MG-ADL score outcomes. The company state in Clarification Response B8 that the January 2024 NMA Report[31] was provided to correct an error in the input data for MG-ADL response. The company also say in Clarification Response A11(b) that the January 2024 NMA Report[31] describes NMAs that included refractory patients.

However, as explained in section 3.4.1 below, the EAG are uncertain whether the refractory subgroup was included in these analyses or not.

3.3.1 Rationale for the NMAs

As stated in CS section B.2.8, according to the company's Decision Problem the key comparators for zilucoplan are efgartigimod, IVIg and PLEX. No direct head-to-head trials exist for these comparisons and so the company conducted NMAs to enable them. The EAG agree that these indirect comparisons are appropriate, but we believe the company could have explored other statistical approaches for conducting them (discussed in section 3.4.3 below).

3.3.2 Identification, selection and feasibility assessment of studies for the NMAs

CS section B.2.9.1.1 lists 47 studies identified from the company's systematic literature search that "qualified for inclusion" in the NMAs but the selection process for identifying these 47 studies from the search results is not fully explained. According to CS Appendix D.1.2.1, the 47 studies were those "aligning with the zilucoplan trial". We assume this means that the 47 selected trials were RCTs that had similar PICO criteria to the RAISE trial, albeit allowing for a wider range of comparators (as listed in CS Table 7). The company then applied a second selection step to these 47 studies which resulted in 14 studies being eligible for inclusion in NMAs (CS Table 37), having excluded 33 studies for reasons that are summarised in CS Table 38. As explained by the company in Clarification Response A9, not all treatments included in the NMAs are relevant to the present technology appraisal (rozanolixizumab, eculizumab, ravulizumab are included in the analyses but their results are not discussed).

Despite the lack of clarity in the selection process, and the searches being eight months out of date when the CS was received by the EAG, we believe it likely that all key trials relevant for the present technology appraisal are identified in CS Table 38. Our clinical experts were not aware of any relevant studies being omitted, and we note that two recently published NMAs of therapies for MG [33, 34] did not identify any further trials that the company should have included.

The 14 trials included in the company's NMAs are shown in Table 18. An additional trial by Barth et al. 2011 [2] which compared IVIg against PLEX was considered potentially relevant for one outcome, the change in QMG score from baseline, and listed in the NMA Report.[32] However, Barth et al.[2] had a duration of only 2 weeks, was appropriately excluded (see section 3.1) and was not included in any NMA analyses. The NMAs therefore could not

provide any comparisons of zilucoplan against PLEX. The remaining comparators shown in **bold** in Table 18 are those relevant to the company's Decision Problem and we present the NMA results for these comparisons in this report.

Of the trials included in the NMAs, only four included refractory populations. These are the refractory subgroup of the RAISE trial, refractory patients in the ADAPT trial of efgartigimod (Clarification Response A11(b)), and the REGAIN and phase II trials of eculizumab, whose randomised populations were defined as refractory, but the efgartigimod and eculizumab trials had slightly less strict definitions of refractory compared to the company's Decision Problem (Table 18). However, eculizumab is not a comparator of interest and no comparisons are made between zilucoplan and eculizumab in the present technology appraisal. Therefore, the RAISE trial refractory subgroup represents the only data that are for refractory patients alone, although the majority of patients in the NMAs comparing zilucoplan against efgartigimod (51% in RAISE and 63% in ADAPT) were refractory (the generalisability of the NMAs to a purely refractory population in clinical practice is discussed in Key Issue 2 in section 1 above).

Table 18 Trials included in the company's NMAs

Therapy	Trials included	Risk of bias	MG severity [e]	N per arm [e]	Outcome assessment [e]
Eculizumab	REGAIN[35]	Low [a, b, c]	Refractory [f]	62-63	26 weeks
	Howard 2013[36]	Unclear [a] Low [c]	Refractory [f]	7	16 weeks
Efgartigimod	ADAPT[37]	Low [a, c]	Mild-moderate	83-84	10 weeks
	Howard 2019[38]	Low [a, c]	Mild-moderate	12	6 weeks
IVIg	NCT02473952	Unclear [a]	Severe	30-32	24 weeks
	Wolfe 2002[39]	Low [a]	Mild-moderate	6-9	6 weeks
	Zinman 2007[40]	Low [a]	Mild-severe	24-27	7 weeks
Ravulizumab	CHAMPION-MG[41]	Unclear [c] Low [a]	Mild-severe	86-89	26 weeks
Rituximab	BeatMG[42]	Low [a, c]	Mild-severe	20-23	52 weeks
	RINOMAX[43]	High [c] Unclear [a]	Mild-moderate	15-22	16 weeks
Rozano-lixizumab	MycarinG[44] (7mg & 10mg)	Low [a]	Moderate-severe	62-64	6 weeks
	Bril 2021[45] (7mg)	Low [a, c]	Moderate-severe	21-22	4 weeks

Zilucoplan	RAISE[24]	Unclear [d] Low [a]	Moderate-severe	86-88	12 weeks
	Howard 2020[25]	High [c] Low [a]	Moderate-severe	14-15	12 weeks

[a] As assessed by the company (SLR Report[46]) using the NICE checklist for randomised controlled trials.
[b] As assessed by Saccà et al. 2023[33] using the Cochrane ROB2.0 tool.
[c] As assessed by Ma et al. 2024[34] using the original (2011) Cochrane risk of bias tool.
[d] As assessed by the EAG (see section 3.2.2 and Appendix 9.1). NB the RAISE trial was assessed by the EAG as having high risk of bias only for one specific outcome which does not influence the economic analysis, so we have noted the overall judgement as unclear here.
[e] As reported by the company in CS Appendix Table 82 and the November 2023 NMA Report[32]
[f] The definition of refractory in this trial[35] differs from that of the company's Decision Problem definition; however, eculizumab is not within the scope of this technology appraisal and is not compared against zilucoplan.

According to CS Table 39, one outcome was considered of relevance to the NMAs: MG-ADL response rate, defined as the proportion of patients who had a ≥3 point improvement in MG-ADL score. However, the November 2023 NMA Report[32] provides results for six outcomes: MG-ADL response rate, QMG response rate (defined as a ≥5 point reduction in QMG score without rescue therapy), MG-ADL change from baseline, QMG change from baseline, MGC change from baseline, and MG-QoL15r change from baseline. Of these outcomes, only the MG-ADL response rate informs the company's economic model (section 4.2.6.1). But these physician- and patient-reported outcome measures assess different aspects of patients' disease severity, symptoms, and HRQoL (section 3.2.3) and collectively provide an overall picture of patients' response to therapy. We therefore present the NMA results for these outcomes in this report.

3.3.3 Clinical and statistical heterogeneity assessment

A fundamental assumption of NMA methods is that the distribution of treatment effect modifiers is similar across the different comparisons in the network.[47] However, the balance of effect modifiers is not discussed in the CS or NMA Report.[32] CS section B.2.9.4.3 states that "Heterogeneity could not be estimated" without explaining why. In response to Clarification Questions 10(a) and 10(b) the company provided tables of the included trials' baseline population characteristics and a narrative discussion of these. The company acknowledge heterogeneity in population characteristics and MG severity across the trials and that some trials had very small sample sizes (as summarised in Table 18). The company referred to their NMA sensitivity analyses (described in section 3.4.2) that included/excluded phase II trials[31, 32] as evidence that the NMA results would be robust to the inclusion/exclusion of certain trials. However, this approach assumes that the primary NMA analysis, which did not adjust for any baseline characteristics, had correctly estimated

the true treatment effect. As discussed in section 3.4.3 below, the EAG believe that a MAIC analysis comparing zilucoplan against efgartigimod (based on the RAISE and ADAPT trials) should be feasible to account for the heterogeneity of trial populations included in the NMAs.

3.3.4 Risk of bias assessments for studies included in the NMAs

Apart from the RAISE trial (see section 3.2.2), the CS does not report any risk of bias assessments for the trials included in the company's network meta-analyses. However, in Clarification Response A9 the company provided a Systematic Literature Review (SLR) report[46] that contains risk of bias assessments for all 14 trials included in the NMAs, assessed using the NICE checklist for RCTs. The SLR Report gives overall risk of bias judgements but does not explain the judgements. We have summarised the company's assessments alongside those from two recently published NMAs[33, 34] where available (Table 18). Although there are some inconsistencies, most of the trials included in the NMAs were rated as having low or unclear, but in only two cases high, risks of bias. These high risks of bias were identified by Ma et al.[34] and related to judgements of unbalanced baseline data in the zilucoplan phase II trial and RINOMAX rituximab trial. However, NMA sensitivity analyses conducted by the company including/excluding phase II trials and trials with different assessment timepoints (see section 3.4.2) suggest that the NMA results would not be sensitive to the inclusion/exclusion of these trials. Moreover, the key trials of interest in the NMAs, i.e. the phase III trials involved in the comparison of zilucoplan against efgartigimod (RAISE and ADAPT) were not judged in any assessments to be at high risk of bias.

EAG conclusion on the studies included in the NMAs

The process for selecting trials for NMA analyses is not fully clear but the EAG and our clinical experts are not aware of any relevant trials that are missing from the NMA analyses. The risk of bias assessments have limitations, but most trials were judged to have low or unclear risks of bias and the EAG believe the NMA results are unlikely to be sensitive to within-trial risks of bias. However, as we have noted in Key Issue 2 (see section 1 of this report), the relevance of the trial populations included in the NMAs to patients with refractory generalised MG is uncertain.

3.4 EAG critique of the NMA methods

3.4.1 Data inputs to the NMAs

Data inputs for MG-ADL outcomes are taken from the company's January 2024 updated NMA Report[31] which, as explained in Clarification Response B8, corrects an error in the November 2023 NMA Report[32] for the ADAPT trial MG-ADL response data. The data inputs

for the other outcomes are taken from the company's November 2023 NMA Report.[32] The NMA input data are clearly tabulated within each NMA report and appear to be consistent with the WinBUGS code provided by the company.

As well as correcting the error in the MG-ADL input data (Clarification Response B8), the company claim in Clarification Response 11(b) that the January 2024 NMA Report[31] provides a scenario analysis for MG-ADL outcomes for refractory patients. However, the tabulated input data within the January 2024 NMA Report[31] suggest that the mITT population rather than the refractory subgroup from RAISE was included. The EAG are therefore uncertain whether the results of the MG-ADL response provided by the company from this NMA are for the refractory subgroup or not.

As explained in section 4.2.6.1 below, the company report MG-ADL response rates of [redacted] for zilucoplan and [redacted] for efgartigimod from the January 2024 NMA Report[31] (Clarification Response Table 34), which are used in the economic analysis. However, these data are not included within the January 2024 NMA Report[31] and we have therefore been unable to corroborate them.

3.4.2 NMA sensitivity analyses

For each outcome the company conducted a 'primary' analysis and (depending on data availability) up to five analyses which they refer to either as sensitivity analyses or scenarios. These analyses varied mainly according to whether phase II and phase III trials were included, and according to the trials' assessment timepoints (Table 19).

Table 19 Summary of NMA sensitivity analyses

Analysis	For the MG-ADL and QMG response outcomes	For the change from baseline outcomes (MG-ADL, QMG, MGC, MG-QoL15r)
Primary	Phase III trials only, primary study endpoint	Phase III trials only, week 12±2
Scenario 1	Phase II & III trials, primary study endpoint	Phase II & III trials, week 12±2
Scenario 2	Conducted for QMG response only. As scenario 1, but included QMG ≥3 point threshold for IVIg trials (other trials ≥5 point)	Phase II & III trials, week 12±2 or primary study endpoint if different

Scenario 3	Not conducted	Phase III only, primary study endpoint
Scenario 4	Not conducted	Phase II & III, primary study endpoint
Scenario 5	Not conducted	Phase II & III, 4 weeks
Source: Abridged from Table 2 in November 2023 NMA Report 1st Part.[32] The rationale for each of these scenarios is explained in Table 2 of the NMA report.		

Of these analyses, the primary analysis and scenario 1 align most closely with the RAISE trial, whilst for the change from baseline outcomes scenario 2 includes a larger network of trials, albeit at the expense of heterogeneity in the outcome assessment times. Scenarios 3 to 5 are less informative and are not considered further in this report. The company do not explain in Clarification Response Table 34 whether the MG-ADL response rates referred to in section 3.4.1 above were from the primary analysis or scenario 1.

3.4.3 Statistical methods of the NMAs

The NMA models have been correctly specified. The November 2023 NMA Report [32] (1st Part) states that both fixed-effect and random-effects models were considered for the NMAs, but the fixed-effect model was chosen because the networks generally consisted of only one trial per direct comparison. The random effects 95% credible intervals provided in the November 2023 NMA Report [32] (2nd Part) are very wide since there are insufficient data to reliably estimate the random effects standard deviation. The EAG agree that the company's choice of fixed-effect model is pragmatic, but the company did not provide any justification for the plausibility of the fixed-effect assumption, and the relatively narrow credible intervals for the fixed-effect model results likely underestimate the heterogeneity present. However, in their economic modelling the company use only the point estimates for the response outcomes (section 4.2.6.1) which did not differ between the fixed and random-effects models for the primary NMA analyses.

There is evidence of population heterogeneity between the RAISE and ADAPT trials in terms of the proportion who are female (57% vs 71%), age (53 years vs 47 years), proportion in MGFA class II at baseline (28% vs 39%), proportion who had prior thymectomy (47% vs 57%), the mean MG-ADL score at baseline (10.6 vs 9.0), and mean QMG score at baseline (19.1 vs 15.9) [Clarification Response A10(a)]. If these are important differences in treatment effect modifiers, the similarity assumption underpinning the NMAs would be violated and the results biased.

Furthermore, we do not agree with the company's rejection of the MAIC approach in clarification response A10(c). In our view the sample sizes of RAISE (N=174) and ADAPT (N= 167) would not preclude MAIC analysis. We believe a MAIC comparing zilucoplan to efgartigimod controlling for known prognostic factors should be feasible and would help to clarify whether the NMA results are reliable.

The November 2023 NMA Report[32] notes that the observed responses in the placebo arms for QMG and MG-ADL were higher in RAISE trial and zilucoplan phase II trial compared to the other trials and this could act as a treatment effect modifier and contribute to heterogeneity in the NMAs. The company did not explore whether an adjustment could be used to account for the imbalance in placebo responses. Instead, the NMA Report suggests that caution should be exercised when interpreting the results of responder outcomes.[32]

3.4.4 Summary of the EAG's critique of the NMAs

- The statistical methods of NMAs were appropriately implemented. The fixed-effect model was preferred by the company as there were insufficient studies to reliably estimate the random-effects standard deviation. The two modelling approaches gave similar point estimates for outcomes but different credible intervals (wider in the random-effects analysis). The economic analysis is based only on point estimates of the outcomes (i.e. not including their credible intervals) so does not capture any between-trial heterogeneity.
- No feasibility assessment was conducted to determine whether an NMA is the most appropriate method of indirect treatment comparison. There is heterogeneity between the zilucoplan and efgartigimod trials suggesting population matching may have been a better option. If there are differences in treatment effect modifiers, then the results of the NMAs could be biased. The EAG requested the company conduct a MAIC but this was not done.
- Results of the NMAs are subject to several sources of uncertainty: (i) heterogeneity among the populations of the included trials that was not adjusted for; (ii) different placebo responses between the included trials that were not adjusted for; (iii) uncertainty whether the MG-ADL response and change from baseline outcomes taken from the January 2024 NMA Report included refractory patients from RAISE; and (iv) the EAG could not corroborate all data from the January 2024 NMA Report. The uncertainties in the NMA results due to heterogeneity in the trial characteristics is noted as a Key Issue for further consideration (see Key Issue 3 in section 1 of this report).

- The only refractory-specific data available for inclusion in NMAs are in the RAISE trial refractory subgroup. The generalisability of the NMA results to patients with refractory generalised MG in clinical practice is noted as a Key Issue for further consideration (see Key Issue 2 in section 1 of this report).

3.5 Results from the NMAs

The CS presents NMA results only for the MG-ADL response rate (see section 3.5.1 below), which informs the economic model for the comparison of zilucoplan against efgartigimod (no comparisons against IVIg, PLEX or rituximab were available for this outcome). Results for five other clinical outcomes, which do not inform the economic model, are provided in the separate company NMA Reports and we have also summarised these below: QMG response rate (section 3.5.2); MG-ADL score change from baseline (section 3.5.3); QMG score change from baseline (section 3.5.4); MGC score change from baseline (section 3.5.5); and MG-QoL15r score change from baseline (section 3.5.6).

3.5.1 MG-ADL response rate

Results for this outcome are only available for the comparison of zilucoplan against efgartigimod (Table 20).

Table 20 NMA results for the MG-ADL response rate (achieving ≥3 point improvement)

Comparator	Analysis approach	Odds ratio (95% CrI)
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	Not reported

Source: January 2024 NMA Report[31] Fixed-effect model. In Clarification Response 11(b) the company say that this analysis included refractory patients from RAISE, but the NMA Report suggests the full trial population was used (see section 3.4.1).
CrI: credible interval

MG-ADL response rate [redacted] zilucoplan and efgartigimod at 12±2 weeks irrespective of whether only phase III trials were included (5 trials, primary analysis) or both phase II and phase III trials were included (7 trials, scenario 1).

3.5.2 QMG response rate

Results for this outcome are available for the comparisons of zilucoplan against efgartigimod, and IVIg (Table 21).

Table 21 NMA results for the QMG response rate (achieving ≥5 point improvement)

Comparator	Analysis approach	Odds ratio (95% CrI)
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	[redacted]
IVIg	Primary	No data
	Scenario 1	No data
	Scenario 2	[redacted]
Source: November 2023 NMA Report[32] 1st Part, Figures 7, 9, 11. Fixed-effect model. CrI: credible interval		

Zilucoplan had a QMG response rate that was [redacted] than for efgartigimod, irrespective of whether the analysis was limited to phase III trials (5 trials, primary analysis), both phase II and phase III trials (8 trials, scenario 1), or included published outcome assessment times for additional phase II and phase III trials that did not report outcomes at 12±2 weeks (9 trials, scenario 2).

The only QMG response rate data available comparing zilucoplan to IVIg were for scenario 2 which included nine trials that had a range of outcome assessment times, from 4 to 52 weeks. This analysis showed [redacted] zilucoplan and IVIg.

3.5.3 MG-ADL score change from baseline

Results for this outcome are available for the comparisons of zilucoplan against efgartigimod and IVIg (Table 22).

Table 22 NMA results for the MG-ADL score change from baseline

Comparator	Analysis approach	Mean (95% CrI) change from baseline
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	[redacted]
IVIg	Primary	No data
	Scenario 1	No data
	Scenario 2	[redacted]
Source: January 2024 NMA Report[31] Fixed-effect model. In Clarification Response 11(b) the company say that this analysis included refractory patients from RAISE, but the NMA Report suggests the full trial population was used (see section 3.4.1). CrI: credible interval		

Zilucoplan exhibited a [redacted] reduction in the MG-ADL score than efgartigimod, irrespective of whether the analysis approach was limited to phase

III trials (5 trials, primary analysis), included both phase II and phase III trials (7 trials, scenario 1), or included trials with assessment timepoints other than 12±2 weeks (ranging 4 to 52 weeks) (12 trials, scenario 2).

MG-ADL score change from baseline for the comparison of zilucoplan against IVIg was only available for scenario 2 which included 12 trials that had a range of outcome assessment times, from 4 to 52 weeks. This analysis showed zilucoplan to be [redacted] to IVIg.

3.5.4 QMG score change from baseline

Results for this outcome are available for the comparisons of zilucoplan against efgartigimod and IVIg (Table 23).

Table 23 NMA results for the QMG score change from baseline

Comparator	Analysis approach	Mean (95% CrI) change from baseline
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	[redacted]
IVIg	Primary	No data
	Scenario 1	No data
	Scenario 2	[redacted]
Source: November 2023 NMA Report[32] 1st Part, Figures 25, 27, 29. Fixed-effect model. CrI: credible interval		

Zilucoplan exhibited a [redacted] reduction in the QMG score than efgartigimod, irrespective of whether the analysis approach was limited to phase III trials (5 trials, primary analysis), included both phase II and phase III trials (8 trials, scenario 1), or included trials with assessment timepoints other than 12±2 weeks (ranging 4 to 52 weeks) (14 trials, scenario 2).

QMG score change from baseline for the comparison of zilucoplan against IVIg was only available for scenario 2 which included 14 trials that had a range of outcome assessment times, from 4 to 52 weeks. This analysis showed zilucoplan exhibited a [redacted] reduction in the QMG score compared to IVIg.

3.5.5 MGC score change from baseline

Results for this outcome are available only for the comparison of zilucoplan against efgartigimod (Table 24).

Table 24 NMA results for the MGC score change from baseline

Comparator	Analysis approach	Mean (95% CrI) change from baseline
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	[redacted]
Source: November 2023 NMA Report[32] 1st Part, Figures 37, 39, 41. Fixed-effect model. CrI: credible interval		

Zilucoplan exhibited a [redacted] reduction in the MGC score than efgartigimod, irrespective of whether the analysis approach was limited to phase III trials (4 trials, primary analysis), included both phase II and phase III trials (6 trials, scenario 1), or included trials with assessment timepoints other than 12±2 weeks (ranging 4 to 52 weeks) (8 trials, scenario 2).

3.5.6 MG-QoL15r score change from baseline

Results for this outcome are available only for the comparison of zilucoplan against efgartigimod (Table 25).

Table 25 NMA results for the MG-QoL15r score change from baseline

Comparator	Analysis approach	Mean (95% CrI) change from baseline
Efgartigimod	Primary	[redacted]
	Scenario 1	[redacted]
	Scenario 2	[redacted]
Source: November 2023 NMA Report[32] 1st Part, Figures 49, 51, 53. Fixed-effect model. CrI: credible interval		

Zilucoplan exhibited a [redacted] reduction in the MG-QoL15r score than efgartigimod, irrespective of whether the analysis approach was limited to phase III trials (4 trials, primary analysis), included both phase II and phase III trials (6 trials, scenario 1), or included trials with assessment timepoints other than 12±2 weeks (ranging 4 to 52 weeks) (9 trials, scenario 2).

3.5.7 Summary of the NMA results

Comparisons of zilucoplan against efgartigimod were available for all six outcomes (MG-ADL response, QMG response, and the changes from baseline in MG-ADL, QMG, MGC, and MG-QoL15r). For the QMG response zilucoplan had a [redacted] odds of response than efgartigimod. For the remaining five outcomes the treatment effect for the comparison of zilucoplan against

efgartigimod was [redacted], although for the outcomes assessing changes from baseline zilucoplan therapy did exhibit a [redacted] in scores compared to efgartigimod.

Comparisons of zilucoplan against IVIg were only available for three outcomes: the QMG response, MG-ADL score change from baseline, and the QMG score change from baseline. In all cases these results were only available for scenario 2 which included more heterogeneous trials than in the primary analysis (Table 19). For the QMG, the odds of response [redacted] zilucoplan and IVIg. For the MG-ADL score change from baseline, zilucoplan was [redacted] to IVIg (i.e. [redacted] the score by a greater amount). For the QMG score change from baseline, there was [redacted] zilucoplan and IVIg.

As noted in section 3.4.4 above, these results are subject to several uncertainties.

3.6 Conclusions on the clinical effectiveness evidence

- The company's Decision Problem focuses on patients with refractory generalised MG which is narrower than the population specified in the NICE scope and marketing authorisation (section 2.3). The company's pivotal RAISE trial had a pre-planned refractory subgroup that was defined in a broadly similar way to the Decision Problem population (section 3.2.1.1.1).
- The NICE scope defines standard of care (SoC) to include corticosteroids and immunosuppressants with or without IVIg or PLEX. The company's Decision Problem does not include SoC as defined in this way (that is, as an overall 'basket' of care) but instead specifies IVIg and PLEX as separate individual comparators (section 2.3).
- Results of the RAISE trial show a placebo effect for all outcomes, which is particularly strong for the MG-ADL response (46%) and QMG response (33%). Nevertheless, zilucoplan was favoured statistically over placebo for all outcomes presented in this report (section 3.2.5).
- The refractory subgroup in RAISE showed [redacted] treatment effect compared to the mITT population, for most outcomes [redacted] (section 3.2.5.6.1). However, there is statistical imprecision in the subgroup outcome estimates.
- In the RAISE-XT study, outcomes for the refractory subgroup were reported for the first 12 weeks only. For both the placebo/zilucoplan and zilucoplan/zilucoplan cohorts, changes from baseline to week E12 in MG-ADL and QMG scores were

[redacted] in the mITT population than the refractory subgroup, whereas [redacted] was true for the changes in MGC and MG-QoL15r scores (3.2.5). However, there is statistical imprecision in the subgroup outcome estimates.

- In RAISE-XT, after week E24 there was a [redacted] rate of dropout in the placebo/zilucoplan group than the zilucoplan/zilucoplan group for the MG-ADL, QMG, MGC and MG-QoL15r scores. There was also a tendency for a separation between these groups in the outcome measure, [redacted] the placebo/zilucoplan group towards the end of the assessment period, after week E48, which was most pronounced for the change in MGC score (section 3.2.5.5.2). The explanation for this pattern is unclear.
- Overall, no safety concerns have been identified.
- Network meta-analyses were feasible for comparing zilucoplan against efgartigimod and IVIg. The NMA models were correctly specified (section 3.4.4) and the EAG believe that all trials relevant to the company's Decision Problem have been included in the evidence networks (section 3.3.2).
- Results of the NMAs (section 3.5.7) show that patients receiving zilucoplan had a [redacted] odds of achieving a ≥5-point improvement in QMG score (i.e., QMG response) than those receiving efgartigimod. And patients receiving zilucoplan had a [redacted] in the MG-ADL score change from baseline than those receiving IVIg. However, there were [redacted] for five other outcomes that were tested (including the odds of achieving a MG-ADL response (≥3-point improvement) which informs the economic analysis), [redacted] for two other outcomes that were tested (neither of which inform the economic analysis).
- These NMA results are subject to uncertainty because heterogeneity in the trial populations and differences between trials in the placebo responses were not adjusted for (section 3.4.4). We have raised this uncertainty as a key issue for further consideration (see Key Issue 3 in section 1 of this report). The uncertainty might be reduced by using alternative methods of indirect treatment comparison such as MAIC to account for the heterogeneity in treatment effect modifiers.
- The only refractory-specific data available for inclusion in NMAs are in the RAISE trial refractory subgroup. The generalisability of the NMA results to patients with refractory generalised MG in clinical practice is noted as a Key Issue for further consideration (see Key Issue 2 in section 1 of this report).

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review (SLR) on economic evidence of treatments for patients with refractory generalised MG (CS Appendix G). Databases were searched on 01 May 2023, with searches finalized in October 2023. Although the review identified twelve studies containing economic evaluations, the company did not consider any of them relevant for their economic evaluation of zilucoplan. None of the studies were UK-based.

No grey literature searches were reported in CS Appendix G. Conference proceedings were manually searched for publications from 2017 to 2023. The company provide comprehensive tables of all search strings in Section G.1.2 of CS Appendix G. The company found eight studies reporting cost data from published literature, hospitals, Medicare average sales pricing, and administration. The company also discuss studies that provided assumptions used in other economic models (Table 90 of CS Appendix G).

EAG conclusions on cost-effectiveness searches

Overall, we view the company's searches were appropriate. The cost-effectiveness studies identified in the company's search are not pertinent to the current appraisal.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The company's economic model fulfils the requirements of NICE's reference case (Table 26).

Table 26 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, direct patient effects are included (section 4.2.5)
Perspective on costs	NHS and PSS	Yes (section 4.2.5)
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes (section 4.2.2)
Time horizon	Long enough to reflect all important differences in costs or outcomes between	Yes (lifetime) (section 4.2.5)

	the technologies being compared	
Synthesis of evidence on health effects	Based on systematic review	Yes (section 4.2.7)
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes (section 4.2.7)
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes (section 4.2.7)
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes (section 4.2.7)
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes (severity modifier does not apply, CS B.3.6 and section 7)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes (section 4.2.8)
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes (section 4.2.5)
Source: EAG assessment based on the company submission		

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company describe the structure and key features of their model in CS Section B.3.2.2. They summarise the model assumptions in CS Table 65, the parameters in CS Sections B.3.3 to B.3.5 and CS Tables 52 to 62. The model is a seven-state cohort state-transition model, developed in Microsoft Excel®: see Figure 6. The Markov model has a cycle length of 2-weeks and a 52.50-year time horizon (effectively lifetime from a starting baseline age of 51.80 years). Costs and QALYs are discounted at an annual rate of 3.5% and the analyses are conducted from the perspective of the NHS and Personal Social Services (PSS). The clinical effectiveness data were informed by the RAISE trial and RAISE-XT study, described earlier in section 3.2.1. Briefly, the company model consists of six active health states, and a death state. Patients enter the model in the 'uncontrolled on high dose steroids and ISTs' health state. Those meeting the definition for treatment response (a ≥3 point change in MG-ADL score) transition to the 'response' state at the response assessment timepoints (which

differ by treatments as shown in CS Table 53). These patients can transition to the 'continued response' state (with ongoing improvement in MG-ADL score), the 'stable response' state (no change in MG-ADL score), or the 'loss of response' (an increase, i.e. worsening, of MG-ADL scores). Within each of the active health states, patients can experience exacerbations, crises, or death. Detailed discussion of the clinical parameters is given in section 4.2.6 below. To estimate utilities, the company used EQ-5D-5L data obtained from the RAISE trial and mapped to EQ-5D-3L using the Hernandez-Alava et al. (2017)[48] algorithm, in line with the NICE reference case. Costs were sourced from standard UK databases. For further discussion on utilities and costs, see sections 4.2.7 and 4.2.8 below, respectively.

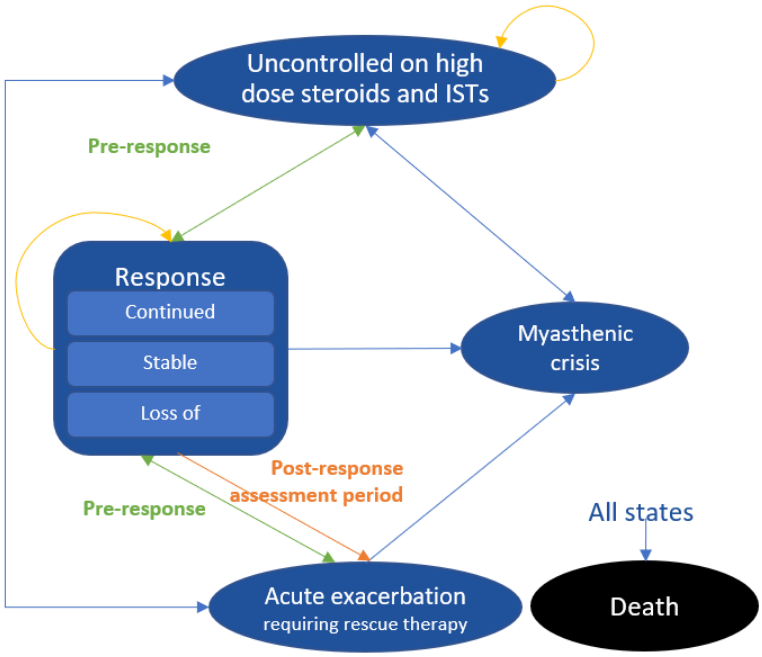

Figure 5 Company's model structure

Source: CS Figure 29

EAG conclusion on the model structure

The overall model structure is appropriate and reflective of the patient pathway, based on our clinical experts' opinion.

4.2.3 Population

The company noted that the anticipated marketing authorisation of zilucoplan is for use as an add-on to standard therapy for treating adult patients with generalised MG who are acetylcholine receptor (AChR) antibody positive. However, they cited clinical opinion that there is an optimised population within the anticipated authorization, who have experienced sub-optimal response to all preceding treatments in the pathway. In the current appraisal,

the company target this subgroup. To reflect this, the population included in the company model is adult patients with AChR-antibody positive refractory generalised MG. The company use the baseline characteristics of the refractory patients in the RAISE trial in their base case model, reproduced below in Table 27. Comparing these with the baseline characteristics of the whole RAISE trial population and the RAISE-XT open-label extension study (which provides an additional 60 weeks' evidence for patients receiving zilucoplan, including patients who switched from the placebo arm of the RAISE trial), we note some slight differences. However, these are unlikely to have any significant impact on the overall cost-effectiveness results.

Table 27: Modelled population characteristics

Characteristic	Refractory patients in the RAISE trial (used in the company model)	RAISE trial-whole population	RAISE-XT Open label study
Mean age, years	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]
Mean weight, kg	[redacted]	[redacted]	[redacted]
Mean MG-ADL	[redacted]	[redacted]	[redacted]
Baseline BMI (kg/m^2)	[redacted]	[redacted]	[redacted]
Source: CS Table 52, RAISE CSR,[49] and RAISE-XT CSR Feb 2022[50]			

EAG conclusion on the modelled population

Clinical advice to the EAG was that the patient characteristics in the company's model, based on the RAISE trial population, are broadly reflective of the patients who would be treated with zilucoplan in England. Although it is clinically observed that the incidence of generalised MG is bimodal, there is insufficient data to estimate results for subgroups based on age of onset. The EAG conducted scenario analyses using the population characteristics from the whole RAISE population as well as the RAISE-XT open label study. For further details, see section 6 below.

4.2.4 Interventions and comparators

The economic model evaluates the intervention, zilucoplan, against three comparators:

- Efgartigimod
- Chronic intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg), and
- Chronic plasma exchange (PLEX).

The company describe the intervention in CS Section B.1.2 and we discuss the intervention and its intended use in practice earlier in Section 2.2 of this report. The dosing regimen for

zilucoplan is consistent with that used in the RAISE trial, the RAISE-XT open label extension study (in which all patients received zilucoplan), and the anticipated approved posology in the EU product label. In practice, zilucoplan is used as an add-on to a basket of standard care therapies, shown in Table 28. Consultation with our clinical experts indicates that while the composition of drugs within the standard of care basket used in the company's model is broadly reflective of current clinical practice in England, fewer people would receive tacrolimus and cyclosporine and more would receive mycophenolate instead.

With respect to the comparators, the company deviated from the NICE scope, which specifies efgartigimod (subject to approval) and standard of care (including corticosteroids and immunosuppressive therapies, with or without IVIg or PLEX) as comparators for the current appraisal. As explained earlier (section 2.3), standard of care was excluded as a comparator from the company's Decision Problem. In response to EAG Clarification Question B1, the company argued that chronic IVIg/SCIg or chronic PLEX is standard of care in refractory patients.

Table 28 Standard of care treatments included in the company model

Treatment	Patients receiving treatment
Corticosteroids	63.2%
Azathioprine	17.8%
Mycophenolate mofetil	19.0%
Cyclosporine	7.5%
Tacrolimus	5.7%
Methotrexate	2.3%
Pyridostigmine	80.5%
Source: Company's economic model	

EAG conclusion on the modelled intervention and comparators

The comparators in the economic model are inconsistent with the NICE scope: the company have excluded standard of care and they compare zilucoplan directly with IVIg and PLEX separately. We do not view this as an appropriate reflection of clinical practice in England. Our clinical experts said that both IVIg and PLEX are used in patients with refractory generalised MG as part of standard of care. While some centres use IVIg for regular chronic therapy, there are other centres (with a strict protocol for IVIg use) that instead use PLEX for treating these patients. Furthermore, a proportion of refractory patients could potentially receive neither of these therapies. To reflect this, we conducted a scenario analysis wherein patients in the comparator arm receive standard of care, with patients split between three groups: a proportion receiving IVIg along with the basket of standard treatments (shown in Table 28), a proportion receiving PLEX plus the basket of standard treatments, and a proportion

receiving only the basket of standard treatments. Further details of the percentage split of the patients across these three groups within the SoC arm are discussed in section 6.1 below.

The basket of drugs included within the modelled standard of care treatments is broadly reflective of current clinical practice in England. However, based on our clinical experts' opinions, we conducted a scenario analysis (reported in section 6 below) incorporating the revised percentages of patients receiving tacrolimus, cyclosporine, and mycophenolate. This has a limited impact on the ICER because of the low drug prices, and the costs are cancelled out when used in the comparator arms alongside IVIg and PLEX.

Finally, as discussed in section 2.3 above, rituximab is not included as a comparator, which is consistent with the NICE scope.

4.2.5 Perspective, time horizon and discounting

The company appropriately use a lifetime horizon to reflect the condition of generalised MG. Their analyses take the perspective of the NHS and PSS, which aligns with the NICE manual for health technology evaluations. Costs and outcomes (life years and QALYs) are discounted at 3.5%.

4.2.6 Clinical parameters

The key clinical parameters and sources used in the company's economic analysis are presented in Table 29 below.

Table 29 Key clinical parameter sources for the company's economic model

Parameter	Sources
Response rates	NMA and published literature
MG-ADL reduction	NMA and expert opinion
Time on treatment	RAISE and RAISE-XT
Clinical event: Exacerbation	Published literature
Clinical event: Crisis	
Mortality	ONS Life tables and published literature
Transitional probabilities	All the above
Source: produced by the EAG	

4.2.6.1 Response rate

The company conducted network meta-analyses to estimate the response rates for zilucoplan and efgartigimod (discussed earlier in section 3.3). Response in the NMAs was defined as a ≥3-point improvement in the MG-ADL score. The EAG asked the company to repeat the NMA for the MG-ADL response outcome using the MG-ADL responder definition of a ≥2-point improvement in MG-ADL score, to align with the efgartigimod (ADAPT) trial outcome definition. The company conducted this analysis, which gave response rates of [redacted] for zilucoplan and [redacted] for efgartigimod, respectively (see the company's response to Clarification Question A13).

Treatment specific response rates for zilucoplan and efgartigimod were obtained by applying the following steps:

- First, odds ratios obtained from the NMA for zilucoplan versus efgartigimod were converted to relative risks, using the formula stated in CS Section B.3.3.1.2
- The relative risks were then applied to the referent response rate (calculated as the average response rate across the studies used in the NMA, which was [redacted]) to estimate each treatment's response rate.

In the company's revised economic model (discussed further in section 5.1), the response rates applied for zilucoplan and efgartigimod are [redacted] and [redacted], respectively. The company stated these data are from their January 2024 NMA that included the refractory patients in the RAISE trial. However, as noted above (section 3.4.1) we were unable to locate these results within the January 2024 NMA report; and the information in the tables of input data within the NMA report suggest that the refractory subgroup from RAISE was not included. We are therefore unable to verify these estimates and are uncertain whether the refractory subgroup was included in the January 2024 NMA or not. Another limitation of the NMAs is that, unlike RAISE, no other trials included in the analyses had refractory subgroups and so the analyses were based on the overall populations of the comparator trials, although the ADAPT trial of efgartigimod had a majority of refractory patients (see Key Issue 2 in section 1 of this report).

The response rates for IVIg and PLEX were not available from NMAs and were instead obtained from a study by Barth et al.[2] We noted an inconsistency in the rate reported in CS Table 53 for PLEX, which the company corrected in their response to Clarification Question B2. These rates were converted to odds ratios using the referent response rate stated above. Table 30 summarises the treatment specific response rates.

There are several key limitations to the Barth et al. study data. The study was conducted in Canada, with uncertain relevance to UK patients; the study population was not explicitly defined as having refractory MG (patients were described as having moderate to severe MG with a QMG score >10.5); the response was reported as a ≥3-point improvement in QMG score because the MG-ADL response outcome was not available from the study; and no confidence intervals or standard errors were provided with the response rates.

The company applied the response probabilities until the 'response assessment time point' which represented the waiting period to see if a patient responds to the treatment. The timepoints for the base case were obtained from the trial endpoint associated with each of the comparators (see Table 30). The EAG note that the company back-calculated the odds ratios for IVIg and PLEX from response rates for these two treatments obtained from the study by Barth et al. After the response assessment time- point, those who have not responded discontinue treatment. The model assumes zero probability of patients transitioning from the 'uncontrolled on high dose steroids' health state to the 'response' health state after the response assessment timepoint. The company acknowledged response was assumed to be constant across treatments, although this may not reflect efgartigimod which is dosed cyclically and therefore its response can wax and wane during its treatment cycle.

Table 30 Response rates and timepoints applied in the company base case

Treatment	Response rate	Response assessment time point (weeks)
Zilucoplan	[redacted]	12
Efgartigimod	[redacted]	10
IVIg/SCIg	51.00%	6
PLEX	57.00%	6
Source: Company's revised economic model and their response to clarification questions A11 and B2.		

EAG conclusions on the modelled response rate

The company's model uses relative treatment effects for the MG-ADL response rates from the comparison of zilucoplan against efgartigimod obtained from their NMAs. In principle, we agree with this approach but their NMAs have several limitations, discussed in detail in sections 3.3 and 3.4 above. We have summarised our concerns with the company's response rates below:

- We are unable to verify the response rates for zilucoplan and efgartigimod used in the company's revised base case and are uncertain whether the refractory subgroup was included in the January 2024 NMA or not, as claimed by the company in their responses to Clarification Questions A11 and B2. Because of these uncertainties, we use the response rates for zilucoplan and efgartigimod based on the RAISE and ADAPT trials respectively, shown in Table 31 and applied in EAG analyses reported in section 6 below. We validated these response rates with our clinical experts.
- The Barth et al. 2011 study used as a source of IVIg and PLEX response rates has several key limitations, and we identified an inconsistency in the response rate for PLEX, which the company corrected in their revised model. We validated the company's reported treatment response rates with our clinical experts. Two experts commented that, in general, most patients (about 70%) would respond to IVIg and PLEX. We explored the impact of this assumption in our scenario analysis, see section 6.
- With respect to the response assessment timepoint, the clinical experts noted that in clinical practice, treatment effects are seen (and maintained) much earlier, after 1-2 weeks, and patients are often assessed 3-4 weeks after starting IVIg or PLEX. Furthermore, one of our experts considered assessing PLEX after 6 weeks, as proposed by the company, to be inappropriate as patients may have responded and lost response by that time. We conducted a scenario analysis to explore the impact of assessing response after three weeks for all treatments; further details are in section 6.1 below.
- Finally, we are uncertain about the response rates obtained for zilucoplan and efgartigimod using the MG-ADL responder definition of a ≥2 point improvement in MG-ADL score. The company cited Figure 3 of the study by Howard 2023 et al.[24] as the source for this analysis but acknowledged the result was subject to biases (further details are in Clarification Response A13). Applying these response rates within the company's revised base case significantly increases the ICER for zilucoplan versus efgartigimod to [redacted]. However, the robustness of this analysis is uncertain.

Table 31 Alternative inputs for the response rates and timepoints used by EAG

Treatment	Response rate	Response assessment time point (weeks)
Zilucoplan	73.1%	3
Efgartigimod	73%	3

IVIg/SCIg	70%	3
PLEX	70%	3
Source: Response rates for zilucoplan and efgartigimod are obtained from the clinical trial publication (CS Table 75); response rates for IVIG and PLEX and the response assessment timepoints for all the treatments based on EAG expert clinical opinions.		

4.2.6.2 Efficacy (MG-ADL reduction)

The company use the change in MG-ADL score (decrease indicates improvement) to assess treatment response. The baseline MG-ADL score used in the model is the mean baseline score for the refractory patients in the RAISE trial, MG-ADL [redacted], indicating that patients have severe disease. The speed and magnitude of symptom improvement, as well as the sustained response level, were obtained by tracking MG-ADL scores over time where patients could experience the following:

- Initial response (as shown above in Table 29).
- Continued response, meaning MG-ADL scores continue to fall over time.
- Loss of initial initial treatment response, meaning MG-ADL scores decrease initially and then start increasing over time.
- Stable response, meaning a stable MG-ADL score over time.

The above trajectories of the MG-ADL scores are captured by the three health states in the model: continued response, stable response, and loss of response (shown in Figure 6 above). The company made the following assumptions for applying the MG-ADL scores across the health states:

- All responders across the treatment arms are assumed to have the same treatment-specific MG-ADL score, thereby assuming equivalence to stable response, until the response assessment timepoints (as shown in Table 30).
- After the response assessment timepoint, of those patients in the response health state, [redacted] are assumed to be on stable response, [redacted] are assumed to lose response, and the remaining [redacted] are assumed to have a continued response. These assumptions are based on the opinion of two clinical experts consulted by the company.
- The model assumes patients who lose response slowly return to the baseline MG-ADL score over a period of 14 weeks of response assessment. This time-period is based on the time taken for patients to return to a QMG score similar to their baseline after switching treatments in the phase 2 eculizumab clinical trial, which the company applied to the immature discontinuation data from RAISE. The company assume that the MG-ADL score worsens linearly back to the baseline MG-ADL score.

Table 32 summarises the average MG-ADL score change from baseline used in the company's revised model. The company stated the estimates for the stable response (shown in Table 33 below) were obtained from the January 2024 NMA (i.e. the zilucoplan versus efgartigimod comparison) using refractory patient data for zilucoplan, and data from the randomised (ITT) populations for the comparator trials. However, as noted above (section 3.4.1) we are uncertain whether the company's NMA using the January 2024 data cut-off includes the refractory subgroup or whole trial population from the RAISE trial. The CS presents data specifically for the refractory subgroup in the RAISE trial (i.e. the zilucoplan versus placebo comparison) in CS Table 28 which we have reproduced in Table 34 below.

The estimates for the stable response were used to calculate the continued response (column 4 in Table 32) by applying a [redacted] increase in change from baseline MG-ADL score. The CS states that the estimate ([redacted] was obtained from the difference between the change from baseline of MG-ADL score at week 12 in the RAISE trial (-4.79) and the lowest score reported in RAISE-XT ([redacted]). The EAG replicated this calculation and obtained a value of [redacted]. This discrepancy between the EAG and company's estimates has a negligible impact on the cost-effectiveness results.

The placebo results, reported in Table 33, were used as a proxy for IVIg and PLEX.

Table 32 Change in MG-ADL score from baseline used in the company's revised model

Treatments	Continued response	Loss of response	Stable response
Zilucoplan	[redacted]	0.00	[redacted]
Efgartigimod	[redacted]	0.00	[redacted]
IVIg/SCIg	[redacted]	0.00	[redacted]
Plasma exchange	[redacted]	0.00	[redacted]
Source: reproduced from the company's revised model			

Table 33 Reported mean change in MG-ADL score from baseline for stable responders used in the company's revised model

Intervention	Mean (SE)
Zilucoplan	[redacted]
Efgartigimod	[redacted]
Placebo	[redacted]
Source: reproduced from Table 33 and Table 38 of the company's response to clarification question A11 and B8 respectively	

Table 34 Change in MG-ADL score from baseline for the refractory subgroup in RAISE trial

Intervention	Mean (SD)
Zilucoplan	[redacted]
Placebo	[redacted]
Source: reproduced from CS Table 28	

EAG conclusions on MG-ADL score reduction

The EAG have concerns with the company's estimates applied for the change in MG-ADL score from baseline, due to the uncertainties inherent in the NMAs from which these estimates are obtained (as discussed earlier in sections 3.3 and 3.4 above). We were unable to corroborate the company's assertion (company response to Clarification Questions A11 and B8) that the NMA scenario analysis using the January 2024 NMA included only refractory patients. Secondly, we view that these estimates based on the January 2024 NMA (used in the company's revised base case) underestimates the placebo change in MG-ADL score from the RAISE refractory subgroup (shown above in Table 33). We conducted a scenario analysis to assess the impact of these alternative inputs on the overall results. Applying the estimates from the RAISE trial refractory subgroup increases the ICER for zilucoplan versus IVIg/SCIg whereas the ICER decreases slightly when compared versus standard of care. There is no impact on the overall results versus efgartigimod and PLEX. Further details are in section 6 of this report.

Finally, all three of our clinical experts agreed with the company's assumption regarding the percentage split of patients in the response having loss of response ([redacted]), continued response ([redacted]) and stable response ([redacted]).

4.2.6.3 Clinical events

Two clinical events were modelled: exacerbation and myasthenic crisis. In the model, a lower MG-ADL score is associated with lower probabilities of experiencing the clinical events, indicating that changes in MG-ADL score impact the probability of transitioning to the crisis- and exacerbation- health states. The company obtained the annual event rates from a study by Abuzinadah et al.[51] reproduced below in Table 35.

Table 35 Clinical event rates

Health states	Exacerbation	Myasthenic crisis	Source
Response	0.244	0.023	Abuzinadah et al. 2021
Uncontrolled	0.651	0.062	A relative risk of 2.67 (obtained from the same source as above) was applied to the rates in the response state.
Source: reproduction of CS Table 55 with minor adjustment			

The company also accounted for patients who might experience an exacerbation, but further worsen to a crisis, by applying a 2-week event rate of 0.184 to those patients in the exacerbation health state.

EAG conclusions on the clinical event rates

Overall, we agree with the company's approach to modelling the two clinical events. The EAG identified an inconsistency in the 2-week event rate for patients experiencing an exacerbation who might further worsen to a crisis as reported in the CS and the original company model. The company clarified this in their response to Clarification Question B9. We could replicate the company's calculations in their revised model.

4.2.6.4 Time on treatment

In the economic model, patients receiving zilucoplan and responding to the treatment will receive treatment for the rest of their lifetime. Those who do not respond or who lose their initial response at the response assessment time point (and do not experience a crisis, or an exacerbation, or die) discontinue treatment due to lack of efficacy and move to the uncontrolled health state, with a return to the baseline MG-ADL score.

4.2.6.5 Adverse events

Adverse events were excluded from the company's base case model. In their response to clarification question B10, the company justified their approach by stating that the only adverse event that is Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 with an incidence of ≥ 2% in the zilucoplan arm is 'myasthenia gravis', which was already incorporated into the overall modelling within the exacerbation and crisis health states. With respect to the comparators, they stated that the trial publications did not list Grade ≥3 adverse events. Further details on adverse events are given in the company's response to Clarification Question B10.

4.2.6.6 Mortality

General population mortality adjusted for age and gender was appropriately implemented in the economic model. In addition, the model assumed 4.47% patients in the crisis health state would experience death within 2 weeks.

4.2.6.7 Transition probabilities

All the clinical parameters discussed in the above sub-sections informed the transition probabilities for the Markov trace. The model did not apply time-dependent transitional probabilities, but the number of patients at the start and end of a period was used to estimate these probabilities, which were then applied over the model time horizon. The company updated their transition probabilities in their revised economic model, submitted as part of their Clarification Response.

EAG conclusions on time on treatment, adverse events, mortality, and transition probabilities

Overall, we agree with the company's approach to modelling time on treatment, adverse events, and transition probabilities. The company addressed the EAG's concerns about the clinical parameters that informed the transition probabilities in their revised model, which was submitted as part of the Clarification Response. We did not identify any further errors in the estimated transition probabilities in the company's revised model.

We acknowledge that the literature on the mortality associated with generalised MG is limited. Therefore, it may be reasonable to use UK general population mortality as background mortality due to lack of other data. However, advice from the clinical experts indicates that there is likely to be excess mortality associated with the condition, related to the chronic therapies. As an example, use of corticosteroids may be associated with higher hip fractures which may, in turn, increase the risk of mortality. Considering this, we conducted a scenario analysis with an increased mortality rate associated with generalised MG, based on a proxy condition: rheumatoid arthritis (all-cause mortality rate ratio compared with general population 1.4).[52] Further details are provided in section 6 below.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature review of existing HRQoL studies in generalised MG and report their search and findings in CS Appendix H. Ninety-five studies

were found in the search that met the population, intervention, comparator, and study design inclusion criteria. Of these, four reported utilities among patients with MG using EQ-5D and SF-6D. The utilities for the overall MG population obtained from using the EQ-5D index ranged from 0.68 to 0.8. For further details, see CS Table 56. We noted that a recent study by Dewilde et al.[53] estimated HRQoL of people with MG using the MyRealWorld-MG and POPUP observational datasets, from adults with MG in nine countries, and reported an EQ-5D-5L value of 0.468 for patients with severe disease (i.e., MG-ADL ≥ 10) in the UK. We use this value for the EQ-5D baseline value in our scenario analyses shown in section 6.1.

4.2.7.2 Study-based health related quality of life

HRQoL data from the RAISE trial were used to estimate utilities in the model. EQ-5D-5L data were collected at baseline and at Day 1, 8, 15, 29, 57 and 84. The EQ-5D-5L data from the trial were mapped onto EQ-5D-3L using the method designed by Hernandez-Alava et al. (2017).[48]

4.2.7.3 Health related quality of life data used in cost-effectiveness analysis

Utility values based on EQ-5D-5L scores from the RAISE trial were used in the regression model and fitted for all patients in the trial. The company's base case utility regression model included baseline EQ-5D, MG-ADL scores, and baseline BMI as independent variables, as shown in Table 36 below.

The Excel model did not explore any alternative regression specifications, including additional covariates of baseline disease duration and exacerbation or crisis. The company reported to have used a stepwise method for covariate selection, which identified BMI as the only significant parameter. The EAG are unable to verify this assertion.

The economic model applies an appropriate age- and gender- adjustment to the overall utility, based on the regression algorithm designed by Ara and Brazier (2010).[54]

Table 36 Regression parameters for utility equation

Parameter	Estimate	SE	P-value
Baseline EQ-5D	0.5521		
Baseline BMI, kg/m2	[redacted]	Company's data	
Intercept [β0]	0.5868	0.05453	<0.0001
Coefficient of baseline EQ-5D (β1)	-0.4350	0.04150	<0.0001
Coefficient of MG-ADL score (β2)	-0.02183	0.001957	<0.0001
Coefficient of BMI (β3)	-0.00326	0.001293	0.0126
Source: reproduction of CS Table 57			

4.2.7.4 Disutilities for adverse events and clinical events

The economic model does not include any adverse events, as discussed earlier in section 4.2.6.4. The company obtained the disutility for an exacerbation from the REGAIN trial for eculizumab. They applied a weighted average disutility for the expected duration of the event (see Table 37). The patients are then assumed to incur the average utility across the response and uncontrolled health states, weighted by the proportion of patients in each health state for the remaining length of a cycle (2.2 days). After an exacerbation, patients are assumed to return to one of the three response sub-groups to continue treatment until the response assessment timepoint. At that point, if patients lose response, then they are assumed to discontinue treatment and transition to the uncontrolled health state.

The company applied a disutility for patients experiencing myasthenic crisis that was also obtained from the REGAIN trial. This disutility is applied for the full model cycle in which a patient transitions into a crisis health state; the company assumes a crisis lasts for 14 days (see Table 37). Patients transition to the uncontrolled health state following successful treatment for a crisis.

Table 37 Disutilities for clinical events

Clinical event	Disutility	Duration (days)
Exacerbation	-0.20	11.80
Myasthenic crisis	-0.39	14.00
Source: Disutilities for the clinical events were obtained from the REGAIN trial		

4.2.7.5 Disutilities for caregiver burden

The company's economic model does not capture the effect of generalised MG on caregiver disutilities. The company discuss the potential impact in CS section B.3.1 within the benefits not captured in the QALY calculation.

EAG conclusions on HRQoL

Overall, the company's approach for modelling utilities is appropriate. However, the EAG have some concerns. The company did not provide any regression statistics in either the company submission or in the company base case model to show whether adding or removing alternative covariates improves the fit of the regression model. Two of our three experts considered that the duration of a crisis is underestimated in the company model. On average, our experts considered patients are likely to spend three weeks in crisis, and the CS states 20% of patients would be ventilated beyond

one month in the ICU.[55] We conducted a scenario analysis to explore the impact of this assumption, reported in section 6.1 below. Furthermore, we explored the impact of using a baseline EQ-5D estimate of 0.468 based on the study by Dewilde et al.[53], also shown in section 6.1. Lastly, the EAG consider it appropriate to not include caregiver disutilities in the model.

4.2.8 Resources and costs

The company conducted a systematic literature review to identify the sources of costs and resource use used in the model. Further details are in CS Section B.3.5.1, CS Appendices I, G1.1 and G1.2. Briefly, they identified 63 studies out of which only two were based in England [56, 57] and one was based in the UK.[58] In addition, the company surveyed four UK clinical experts with experience of treating patients with generalised MG to obtain costs and resource use estimates relevant to the UK setting (see the company's response to Clarification Question B3).

The economic model included the following healthcare resource use and costs, which we discuss in the following sub-sections of this report:

- Drug acquisition and administration
- Routine care
- Vaccination costs
- Management of clinical events
-

EAG conclusions on the company's searches

The EAG consider the company to have searched appropriate databases and conference proceedings, we have no concerns about their search strategy, and we believe it is unlikely that any key studies have been missed. We view that appropriate sources have been used to inform the unit costs in the model,[59] [60, 61] and the spread of clinical expertise to be reasonable, but note that none of the experts were based in London.

4.2.8.1 Drug acquisition

The mean drug acquisition costs for zilucoplan and comparators are presented in CS Table 60. Zilucoplan dosage is based on patient weight at approximately 0.3 mg/kg/day; total daily dose by body weight range (kg):

- <56 kg: 16.6 mg dose
- ≥56 to <77 kg: 23 mg dose
- ≥77 kg: 32.4 mg dose

The model uses a weighted list price of [redacted] per mg for zilucoplan, after applying the PAS discount of [redacted]. The weighted price is based on the distribution of patients in the different weight bands who receive different doses of zilucoplan. This results in a cost per model cycle of [redacted].

For the comparators, 10mg/kg efgartigimod is given weekly, 1000mg/kg IVIg/SCIg is given every three weeks, and PLEX is administered every four weeks (CS Table 59). The costs of these treatments in the first, second and subsequent model cycles are shown in CS Table 60. Efgartigimod is also subject to a patient access scheme (PAS) discount and results including these data will (subject to confirmation of the PAS) be presented in a separate confidential addendum to this report. Two of our clinical experts explained that IVIg is given every 4-8 weeks, and the third mentioned the interval can be extended to 12 weeks, and very rarely to 16 weeks, depending on patient response. Our experts also explained that PLEX is usually administered every 4-8 weeks. We apply the costs for IVIg and PLEX every 6 weeks in our base case and explore applying the costs for PLEX every 8 weeks in a scenario analysis. Further details are given in section 6.

All three of our clinical experts advised us that all refractory patients are eligible for IVIg and PLEX, unless they are contraindicated. PLEX is only available at specialist centres, whereas IVIg is available more widely. Two of our experts commented that most patients (about 70%) would respond to IVIg and about 70% would respond to PLEX. They also highlighted that patients with venous access problems cannot receive PLEX treatment. In addition, one expert explained that a small percentage of patients who do not respond to, or cannot tolerate, or cannot physically receive IVIg or PLEX treatment, would be extremely symptomatic and have a diminished quality of life. However, our experts highlighted that it would be very unusual for a patient not to respond to both IVIg and PLEX.

The company weight the cost of immunoglobulin as 50% IVIg and 50% subcutaneous immunoglobulin (SCIg) as they anticipate use of SCIg to increase in the future. Our clinical experts' use of SCIg varied, but all expect its use to increase, unless other treatment options for generalised MG become available. We investigated the effect of using 100% SCIg in a scenario analysis, as reported in section 6.1 below.

4.2.8.2 Drug administration

CS Table 61 and Table 62 present details of the administration costs used in the model. Zilucoplan is a self-administered subcutaneous injection given once a day using a pre-filled syringe. The company apply a one-off administration cost for a subcutaneous injection (£41;

60mins, Band 5 hospital nurse) to cover the cost of training the patient or their carer to inject the treatment in future model cycles. The EAG note the cost to train either the patient or their carer to inject zilucoplan would be the same. Efgartigimod and IVIg are given as infusions for which the company use appropriate NHS reference costs. The EAG agree with the company and consider these costs to be appropriate.

The company conservatively assume that the administration cost for PLEX is the same as a subcutaneous injection. We disagree with this approach and prefer to use the NHS reference cost SA44A for 'Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over' (£910 for elective treatment),[59] as shown in section 6.1 below.

4.2.8.3 Resource use

Costs and resource use for patients with a) uncontrolled disease, b) responding to treatment, c) transitioning through an exacerbation or d) a crisis, are presented in CS Table 63. Consultation with our experts indicated several differences in the company's assumptions for resource use when compared to the current clinical practice in England:

- The EAG's clinical experts considered that patients with controlled disease would have 8-10 visits to a GP and other healthcare professionals instead of 15 visits (9 to GP and 6 to other healthcare professionals) as reported by the company. We explored the effect of reducing the number of visits (6 to a GP and 4 to other healthcare professionals) in a scenario analysis, reported in section 6.
- Our experts explained that patients rarely go to their GP for their generalised MG, usually contacting the specialist nurse or going to the clinic. However, patients do go to their GP for managing the sequelae caused by treatment of their generalised MG; management of diabetes arising from chronic high dose corticosteroid use, for example. GPs also perform regular blood monitoring for patients on standard of care treatments such as azathioprine. Refractory patients are usually reviewed by their clinician every three months.
- It was unclear why a patient responding to treatment would be using the ICU
- All three of our experts agreed that patients experiencing a crisis would use the ICU for 2-4 weeks, not necessarily 15 days as assumed by the company.
- One of our experts commented that the model does not capture the full burden of refractory generalised MG, as discussed previously in section 2.2.1.4.

We note that monitoring costs are not discussed in the CS. These are possibly captured in the costs given in CS Table 63, but this is not stated explicitly. We explored the effect of extending ICU use during a crisis to three weeks in a scenario analysis, reported in section 6.1. Finally, the company applied the cost of the meningococcal vaccine to 4% of patients (CS Table 64). We note that section 4.4 of the zilucoplan SmPC states all patients receiving zilucoplan must have this vaccine. However, we understand that the meningococcal C (MenC) vaccine is part of the routine childhood vaccination schedule for children (initially at 12-13 months of age with a booster at age 14 years) and that the MenACWY vaccine for teenagers is also available, so most patients in England are likely to have received at least one vaccination in their lifetime. We explored applying the vaccine cost to all patients in a scenario analysis (see section 6.1).

4.2.8.4 Adverse reaction resource use

The company's base case does not include adverse event costs, as discussed earlier in section 4.2.6.5. Overall, we consider excluding adverse event costs in either arm as a conservative assumption favouring the comparator.

EAG conclusion on resource use and costs

We disagree with comparing zilucoplan directly to IVIg or PLEX. Our base case attempts to capture how the population with refractory generalised MG is currently managed via standard of care. We note that there is possibly a percentage of patients with refractory disease not receiving either IVIg or PLEX therapy due to being contraindicated, unable to tolerate the treatment or not physically able to receive the treatment.

Clinical advice to the EAG was that IVIg is given every 4-8 weeks, and we apply the costs for IVIg every 6 weeks in our base case. We consider the administration costs for efgartigimod and IVIg to be suitable but disagree with the company's choice of administration cost for PLEX. Our base case uses the NHS reference cost for 'Single Plasma Exchange' (SA44A).[59] We note that the company have applied costs for corticosteroid use, but not the costs for managing the complications associated with the chronic use of them. These may be captured in CS Table 63, but this is not stated explicitly. We conducted a range of scenarios to explore these assumptions, as reported in section 6.1 below.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company report their base case incremental cost-effectiveness analysis results for zilucoplan versus efgartigimod, IVIg/SCIg and PLEX in CS Table 66, using the PAS discount price for zilucoplan and list prices for all other treatments. Efgartigimod is also subject to a PAS discount and the results including this will be presented in a separate confidential addendum to this report, subject to confirmation of the PAS.

In their response to Clarification Questions, the company updated their model, which changed their original base case results. The revised model includes:

- Response rates for zilucoplan and efgartigimod of [redacted] and [redacted], respectively (Company response to Clarification Questions A11 Table 34). The company state these data are from the January 2024 NMA, but the EAG are unable to verify these data.
- A revised odds ratio for PLEX of 2.38, based on the response rate reported in Barth et al. (2011)[2] of 57% (Clarification Response B2(d)). The company identified this error in the original version of their base case and addressed it as part of their Clarification Response.
- The change from baseline in MG-ADL score, using results from the January 2024 NMA report (Clarification Response Table 38, partially reproduced in Table 38 below).
- A 2-week event rate of 0.184 applied to all patients in the exacerbation health state who may worsen to myasthenic crisis (Clarification Response B9(b)).

Table 38 Change in MG-ADL score reported in the January 2024 NMA, data used in the company's revised model

Treatment	Zilucoplan data for the refractory population
Zilucoplan	[redacted]
Efgartigimod	[redacted]
Placebo	[redacted]
Source: adapted from Table 38 in Clarification Response B.8. ITT: intention to treat; MG-ADL: myasthenia gravis activities of daily living; NMA: network meta analysis.	

All results in this section use the PAS discount of [redacted] applied to the list price for zilucoplan. Table 39 presents the company's base case results using the revised model

received as part of the company's Clarification Response. The pairwise ICERs for zilucoplan in comparison with efgartigimod, IVIg/SCIg, and PLEX are [redacted], respectively. Zilucoplan [redacted]

Table 39 Revised company base case results, pairwise results

Technologies	Total		Incremental vs. zilucoplan		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Zilucoplan	[redacted]	9.82	-	-	-
Efgartigimod	£1,224,683	9.80	[redacted]	0.016	[redacted]
IVIg/SCIg	£628,862	9.65	[redacted]	0.165	[redacted]
PLEX	£783,124	9.66	[redacted]	0.158	[redacted]

Source: adapted from CS Table 66.
excl.: excluding; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; PLEX: plasma exchange; SCIg: subcutaneous immunoglobulin; SoC: standard of care

5.1.1 Deterministic sensitivity analyses

The company report deterministic sensitivity analysis results in the form of tornado diagrams, showing the top 10 most influential parameters. The comparison versus efgartigimod, IVIg, and PLEX using the revised base case are shown in Figure 6, Figure 7, and Figure 8, respectively. CS Appendix N.2 reports the input parameters used in the company's deterministic sensitivity analysis. The range of variation for the input parameters was based on published standard errors where available, or a range of +/- 20%. The company consider the net monetary benefit to be the most appropriate primary outcome for the DSA rather than the ICER, stating that the latter may produce extreme values that could cause issues with interpretation. The company use a threshold of £30,000 in their net monetary benefit calculations, which the EAG consider to be appropriate.

Figure 6 Tornado diagram for zilucoplan versus efgartigimod, updated base case

Figure 7 Tornado diagram for zilucoplan versus IVIg/SCIg, updated base case

Figure 8 Tornado diagram for zilucoplan versus PLEX, updated base case

5.1.2 Scenario analysis

The company's scenario analyses using their revised base case are shown in Table 40. Only two scenarios were investigated: whole population weight, using the average weight of the overall population with generalised MG from the RAISE clinical trial (89.1kg) in place of the base case value of [redacted]; and the source of the response rate data. For the latter, CS Table 75 presents the responder data used in the scenario, taken from clinical trial publications.

Table 40 Company scenario analyses results, pairwise comparison, revised base case

Scenario	Treatment	ICER(£/QALY)
Whole population weight: 89.1kg from RAISE clinical trial	Zilucoplan	-
	Efgartigimod	[redacted]
	IVIg/SCIg	[redacted]
	PLEX	[redacted]
Response rate data source: clinical trial publication	Zilucoplan	-
	Efgartigimod	[redacted]
	IVIg/SCIg	[redacted]
	PLEX	[redacted]

Source: Adapted from CS Table 76
excl.: excluding; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; PLEX: plasma exchange; SCIg: subcutaneous immunoglobulin; SoC: standard of care.

5.1.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis results from 1000 iterations of a Monte-Carlo simulation, using the revised base case, are given in Table and the cost-effectiveness scatterplot is depicted in Figure 9.

The pairwise ICER per QALY gained is reported as [redacted] for efgartigimod, IVIg/SCIg, and PLEX, respectively.

The company present the variation between the original base case and probabilistic sensitivity analysis (PSA) results in CS Table 71, stating that the different cost for each treatment arm is the main driver for the differences in base case and PSA results, and that further variations in results are due to healthcare resource use and effectiveness parameters. The company note, however, that the PSA does not include cost parameters. CS Appendix N.1 reports the input parameters used in the probabilistic sensitivity analysis.

Table 41 Company probabilistic sensitivity analyses, pairwise results, updated base case

Technologies	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	(£/QALY)
Zilucoplan	[redacted]	9.801	-	-	-

Efgartigimod	£1,114,401	9.703	[redacted]	0.105	[redacted]
IVIg/SCIg	£648,756	9.600	[redacted]	0.209	[redacted]
PLEX	£806,631	9.607	[redacted]	0.201	[redacted]

Adapted from CS Table 70
Abbreviations: excl., excluding; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; SCIg, subcutaneous immunoglobulin; SoC, standard of care

Uncertainty in the ICER calculation is demonstrated by the cost-effectiveness scatter plots for zilucoplan versus comparators (Figure 9). Zilucoplan [redacted]. Consequently, the company present their willingness-to-pay (WTP) analysis using incremental net monetary benefit results. At a WTP threshold of £30,000 per QALY gained, the company's revised model indicates that zilucoplan would be [redacted].

Figure 9 Incremental cost and QALY cloud in the cost-effectiveness plane, with PAS discount, revised base case

EAG conclusions on the company's probabilistic sensitivity analyses

The EAG consider the company's choice of parameter distributions to be appropriate. Relevant parameters are included in the probabilistic sensitivity analyses. The company could have varied cost parameters, but the EAG note appropriate resource use parameters were varied in the model instead. We also note that the company's revised base case and PSA ICERs for zilucoplan compared with IVIg/SCIg are similar, and zilucoplan [redacted] in both the base case and PSA results.

5.2 Model validation and face validity check

5.2.1 Company model validation

The company's approach to validating their model is described in CS section B.3.13. Furthermore, they consulted four clinical experts in generalised MG based in England to validate the choice of comparator, generalisability of the baseline characteristics of the refractory subgroup in the RAISE trial, model framework, patient care pathway (listed in CS section B.3.3.6), healthcare resources and duration of a model cycle. The CS also states that the company held a clinical advisory board in the UK in September 2023 to discuss these themes further, focussing on the refractory patient population.

EAG conclusion on the company's model validation

The clinical expert opinion sought by the company covers all the important model inputs. The EAG consider the number and location of the clinical experts to be reasonable, but we note that none of the company's experts were based in London. We also note that the company do not state whether a formal validation checklist was used to assess the model. Consequently, uncertainty remains around the model validation completed by the company.

5.2.2 EAG model validation

The EAG conducted a range of tests to verify model inputs, calculations, and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses
- Checking individual equations within the model ('white box' checks)
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks)

5.2.3 Company corrections to the model

The company's corrections to their original model are described in section 5.1 above, and Table 42 shows the cumulative effect of each of these changes on the ICER. The EAG were able to replicate the results of the company's revised base case after applying the changes

described in the company's response to Clarification Questions A11, B2, B8 and B9 to the original version of the model (Table 42).

Table 42 Cumulative changes to the company's original base case, zilucoplan versus comparators, pairwise results

No.	Scenario description	Cumulative change to ICER (£/QALY)		
		Efgartigimod	IVIg/SCIg	PLEX
Original company base case		[redacted]	[redacted]	[redacted]
1	Using the updated response rates for zilucoplan, efgartigimod and PLEX (response to CQs A.11 and B.2)	[redacted]	[redacted]	[redacted]
2	Using the change from baseline in MG-ADL score, using results from the January 2024 NMA report (response to CQ B.8 Table 38)	[redacted]	[redacted]	[redacted]
3	0.184 2-week event rate applied to all patients in the exacerbation health state who may worsen to myasthenic crisis (response to CQ B.9.b)	[redacted]	[redacted]	[redacted]
Revised company base case		[redacted]	[redacted]	[redacted]

Source: Company results reproduced by the EAG as part of the model check
CQ: Clarification Question

5.2.4 EAG corrections to the company model

Other than the issues raised by the EAG in the Clarification Question stage of this appraisal, we did not identify any technical calculation errors in the company's economic model.

As part of the EAG's Clarification Question B1, the company were asked to provide a version of the model that included standard of care as a comparator, with an option to include IVIg and PLEX within standard of care. The company did not conduct this analysis and maintained that IVIg and PLEX were the appropriate comparators for zilucoplan. The EAG have endeavoured to code a standard of care arm including IVIg and PLEX within the company's revised model. We discuss this in section 6 of this report and have raise it as a Key Issue for further consideration (see Key Issue 1 in section 1.3 above).

5.3 EAG summary of key issues and additional analyses

The EAG's observations on key aspects of the company base case are presented below (Table 43). We investigated these uncertainties through additional scenario analyses, described in section 6.1.

Table 43 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG analyses
Population characteristics			
General	CS Table 52	We agree.	We tested population characteristics from the whole RAISE population and the RAISE-XT population in scenario analyses (population characteristics shown in Table 44).
Initial MG-ADL score		We agree. Our clinical expert advised that the non-White population was underrepresented in the RAISE trial and that Black people can have more severe disease.	We increased the initial MG-ADL score to 13.7 in a scenario analysis, because a 3-point change is considered significant in the CS.
Patient age		We agree. Clinical advice to the EAG was that gMG is a disease of the elderly and clinicians regularly treat 80–90-year-old patients.	We increased the initial age to 65 in a scenario analysis.
Patient weight		We agree. The EAG note that the company conducted a scenario analysis using the weight of the whole RAISE trial population.	No change.
Comparator			
Comparator	CS section B.3.9 and Table 66	The EAG do not consider it appropriate to compare zilucoplan with IVIg and PLEX separately, because this does not reflect standard of care in England for patients with refractory generalised MG. Instead, across the patient population, a proportion receive IVIg and a proportion receive PLEX. The EAG note a recent publication describing therapies received by patients in the efgartigimod EAMS cohort, which we consider to be a reasonable approximation of the patient group zilucoplan is intended for.[1]	The EAG prefer to use SoC as the comparator (including IVIg and PLEX): 43.8% of patients receive IVIg; 14.6% of patients receive PLEX; 41.6% of patients receive neither based on a recent publication;[1] all patients receive the basket of standard treatments (Table 28).
Clinical parameters			
Time on treatment	CS section B.3.3.2	We agree.	No change.

Parameter	Company base case	EAG comment	EAG analyses
Treatment response rates – zilucoplan and efgartigimod	CQ response A13 Table 36	As part of the Clarification Questions, the company were asked to repeat the NMAs for the MG-ADL responder outcome using the MG-ADL responder definition of a ≥2 point improvement in MG-ADL score, to align with the ADAPT trial outcome definition.	This analysis gave a [redacted] response rate for zilucoplan and a [redacted] response rate for efgartigimod, which we discuss in section 4.2.6.1. The company quote their January 2024 NMA as the source of these results, but the EAG could not verify this.
Treatment response rates – all treatments	CS Table 53	The company used data from the NMA for the zilucoplan and efgartigimod response rates and derived the IVIg and PLEX response rates from Barth et al.[2] Clinical advice to the EAG was that about 70% of patients respond to both IVIg and PLEX treatment and we view it is appropriate to use the response rates for zilucoplan and efgartigimod based on the clinical trials (Table 31)	We conducted a scenario analysis using the alternative response rates for IVIg and PLEX suggested by our clinical experts and response rates for zilucoplan and efgartigimod based on the RAISE and ADAPT trials, respectively.
Time to treatment response		The response timepoints in the model used the time of the primary endpoint from the clinical trials. Our clinical experts noted that treatment effect was seen (and maintained) after only 1-2 weeks in the trials, and we were advised that patients are often assessed after 3-4 weeks after starting IVIg or PLEX. Furthermore, one expert felt that assessing PLEX after 6 weeks was inappropriate, because a patient may have responded and lost response by then.	We conducted a scenario analysis using a response timepoint of 3 weeks, based on our clinical experts' advice.
Transition probabilities	CS section B.3.3.4	The company assume that of those patients in the response health states, [redacted] had loss of response, [redacted] had continued response, and [redacted] had stable response. We agree.	No change.
Adverse events	CS section B.3.4.5	We agree. The company threshold for including AEs was an incidence rate of 5%. The usual incidence threshold used in trial reporting is 2% ≥ CTCAE grade 3, but the only AE reaching this threshold was 'myasthenia gravis'.	No change.

Parameter	Company base case	EAG comment	EAG analyses
Change from baseline in MG-ADL score	Response to CQ B8	The company used data from their January 2024 NMA, which the EAG could not verify.	We conducted a scenario analysis using the change in MG-ADL score from the RAISE trial refractory subgroup.
Utilities			
Health state utilities	CS section B.3.4.6, Table 57	We agree. The EAG note a recent paper providing utilities for people in the UK with severe gMG that are calculated from two observational data sets (MyRealWorldMG and POPUP) [53]	No change. We tested the utilities from MyRealWorldMG and POPUP in a scenario analysis.
Clinical event disutilities and duration	CS section B.3.4.6.1	We agree with the disutility values used for exacerbations and myasthenic crises. However, clinical advice to the EAG was that a myasthenic crisis would likely last about three weeks, not 14 days.	We conducted a scenario analysis by increasing the duration of a myasthenic crisis to 21 days.
Resource use and costs			
Administration costs - PLEX	CS Table 61	We disagree with assuming PLEX admin costs are equal to subcutaneous administration costs.	We prefer to use the NHS reference cost SA44A – Single Plasma Exchange (£910).[59]
IVIg treatment costs	CS Table 59	Costs for chronic IVIg therapy were applied every 3 weeks in the model. Clinical advice to the EAG was that chronic IVIg is given 4-8 weeks.	We prefer to apply chronic IVIg costs every 6 weeks.
PLEX treatment costs		Treatment costs for PLEX were applied every 4 weeks in the model. Clinical advice to the EAG was that PLEX is given every 4-8 weeks.	We prefer to apply chronic PLEX costs every 6 weeks, and test applying this cost every 8 weeks in a scenario analyses, including applying the SA44A administration cost every 6 or 8 weeks, as appropriate.
SoC treatment costs	ModelSheet! DrugCostsDetail_Popup!	Clinical advice to the EAG was that there is very little use of cyclosporine and tacrolimus in the UK; mycophenolate is used more often instead.	We use different proportions of SoC therapies in a scenario analysis: 4% tacrolimus, 4% cyclosporin, 4% methotrexate; 25% mycophenolate
Meningococcal vaccine costs	CS Table 64	Section 4.4 of the SmPC states all patients receiving zilucoplan must have this vaccine.	We explore 100% of patients receiving the vaccine in a scenario analysis.

Parameter	Company base case	EAG comment	EAG analyses
Use of SCIg	CS B.3.5.4.1	The model weights the immunoglobulin cost based on 50% use of IVIg and 50% of SCIg to anticipate the increase in use of SCIg. We agree. Clinical advice to the EAG from one expert was that their specialist centre has offered SCIg to all patients receiving IVIg.	We explore using 100% SCIg in a scenario analysis.
Resource use – length of stay in ICU for a myasthenic crisis	CS Table 63	Clinical advice to the EAG was 15 days in the ICU for a myasthenic crisis was too short. Our experts thought a crisis would last at least 3 weeks.	We increase the resource use for time in ICU due to a myasthenic crisis to 21 days.
Resource use – number of visits to GP and other healthcare professionals		The company considered patients with controlled disease experience 15 healthcare visits in a year: 9 to a GP and 6 to other healthcare professionals. Our clinical experts considered that patients with controlled disease would have 8-10 visits to their GP and other healthcare professionals a year.	We explore reducing the number of visits to a GP (6 visits) and other healthcare professionals (4 visits) in a scenario analysis.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; CQ: Clarification Questions; ICU: intensive care unit; IVIg: intravenous immunoglobulin; MG-ADL: Myasthenia Gravis Activities of Daily Living score; PLEX: plasma exchange; SCIg: subcutaneous immunoglobulin; SmPC: Summary of Product Characteristics; SoC: standard of care.

Table 44 Sources of alternative patient characteristics

Characteristic	RAISE – whole population	RAISE-XT
Mean age (years)	[redacted]	[redacted]
Proportion of males (%)	[redacted]	[redacted]
Mean MG-ADL score	[redacted]	[redacted]
Mean weight (kg)	[redacted]	[redacted]
Mean baseline BMI	[redacted]	[redacted]

Source: RAISE CSR,[49] RAISE-XT CSR Feb 2022[50]
BMI: Body mass index; MG-ADL: Myasthenia Gravis Activities of Daily Living score.

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted additional scenario analyses on the company's revised base case to explore the issues described in section 5.3 and to investigate other areas of uncertainty not included in the company's scenario analyses (Table 45).

A recent study by Moniz Dionisio et al. reported the real-world experience of using efgartigimod in patients with generalised MG in the UK (n=48).[1] In the EAG's opinion, this patient cohort in the efgartigimod Early Access to Medicine Scheme (EAMS) is comparable to the patient group of interest for zilucoplan in the current appraisal, because:

- Patients in EAMS had AChR antibody-positive generalised MG
- The average age was 49.2 years (21.0 – 75.0 years, SD = 14.2)
- Most patients (75%) were female
- Most patients (66.7%) had a disease duration of over 10 years
- The average MG-ADL score at baseline was 11.2 (5-19, SD = 3.2)
- All patients had utilized at least one non-steroidal immunosuppressant treatment in the past, and the average number tried prior to efgartigimod was 2.6 (range 1 - 6)

Before the introduction of the EAMS scheme, clinical consensus was achieved with UK MG clinicians that efgartigimod use in EAMS would be reserved for patients with refractory disease who had not responded to ≥ 2 non-steroidal immunosuppressant agents, those who were intolerant or ineligible for such therapies, and those patients who were dependent on IVIg and PLEX.[1]

We note that at the time of initiating efgartigimod treatment, 43.8% of patients in the EAMS cohort were receiving chronic IVIg treatment,14.6% of patients were receiving chronic PLEX treatment, and 41.6% of patients were receiving neither.[1] The EAG are unsure why so many patients in the EAMS cohort did not receive regular IVIg or PLEX therapy, the reasons may include: contraindications, inability to tolerate the treatment, being physically unable to receive the therapy (venous access problems in the case of PLEX, for example), or the patient had received the treatment in the past and not responded to it. Alternatively, patients may have been receiving IVIg and PLEX therapy, but as rescue treatment rather than chronic therapy.

We conducted a scenario analysis (scenario 5, Table 45) that involved 43.8% of patients

receiving IVIg, 14.6% of patients receiving PLEX and 41.6% of patients receiving neither; all patients receive the basket of standard treatments (Table 28). This resulted in a response rate of 40.88% in the comparator arm of the EAG base case: 41.6% of patients are not on active therapy (these patients receive the cheaper standard therapies only) and so are considered non-responders. Furthermore, only 70% of the 43.8% of patients on IVIg would be considered responders (i.e., 30.66%), and 70% of the 14.6% of patients on PLEX would be considered responders (i.e., 10.22%). The ICER is reduced to [redacted] per QALY for zilucoplan compared with standard of care in this scenario.

All three of our clinical experts stated that nearly all patients eligible for chronic IVIg or PLEX treatment would receive it, reflecting each expert's experience in their own centre. However, none of our experts suggested what proportions of patients with refractory generalised MG would receive chronic IVIg and PLEX at the patient population level. The EAMS dataset is a marked contrast to our experts' opinions, and the EAG notes that the EAMS cohort includes patients treated at multiple centres. We explored different proportions of patients receiving IVIg and PLEX therapy (i.e., all patients receive one of the treatments) in scenario analyses (scenarios 6-8, Table 45) to address the advice we received from our clinical experts and note that the model is extremely sensitive to these changes.

Zilucoplan [redacted] PLEX drug and administration costs are applied every six or eight weeks instead of every four, resulting in an ICER of [redacted] (scenario 13) and [redacted] per QALY (scenario 14), respectively. Zilucoplan [redacted] compared with IVIg/SCIg in all scenarios, [redacted] compared with standard of care (i.e., the 'basket' of cheaper standard therapies: corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine). However, further clinical advice is needed regarding the proportion and frequency of IVIg and PLEX use for patients with refractory generalised MG in England (Key Issue 1 in section 1.3 of this report).

Table 45 EAG scenario results, company's revised base case

No.	Scenario description	Pairwise ICER (£/QALY), zilucoplan vs comparator			
		Efgartigimod	IVIg/SCIg	PLEX	SoC [a]
Company revised base case		[redacted]	[redacted]	[redacted]	[redacted]
1	Population characteristics from the whole RAISE population	[redacted]	[redacted]	[redacted]	[redacted]
2	Population characteristics from RAISE-XT	[redacted]	[redacted]	[redacted]	[redacted]

No.	Scenario description	Pairwise ICER (£/QALY), zilucoplan vs comparator			
		Efgartigimod	IVIg/SCIg	PLEX	SoC [a]
3	Increase initial MG-ADL score to 13.7	[redacted]	[redacted]	[redacted]	[redacted]
4	Increasing the initial age to 65 years	[redacted]	[redacted]	[redacted]	[redacted]
5	Include IVIg and PLEX in SoC: 43.8% of patients receive IVIg; 14.6% of patients receive PLEX; 41.6% of patients receive neither; all patients receive the cheaper standard therapies (EAG report Table)	[redacted]	[redacted]	[redacted]	[redacted]
6	Include IVIg and PLEX in SoC: 80% of patients receive IVIg; 20% of patients receive PLEX; 0% of patients receive neither; all patients receive the cheaper standard therapies (EAG report Table)	[redacted]	[redacted]	[redacted]	[redacted]
7	Include IVIg and PLEX in SoC: 20% of patients receive IVIg; 80% of patients receive PLEX; 0% of patients receive neither; all patients receive the cheaper standard therapies (EAG report Table)	[redacted]	[redacted]	[redacted]	[redacted]
8	Include IVIg and PLEX in SoC: 50% of patients receive IVIg; 50% of patients receive PLEX; 0% of patients receive neither; all patients receive the cheaper standard therapies (EAG report Table)	[redacted]	[redacted]	[redacted]	[redacted]
9	Using 70% response rates for IVIg and PLEX and trial response rates for zilucoplan (73.1%) and efgartigimod (73.0%)	[redacted]	[redacted]	[redacted]	[redacted]
10	Using a response time point of 3 weeks for all treatments (including zilucoplan)	[redacted]	[redacted]	[redacted]	[redacted]
11	Increasing the duration of a myasthenic crisis to 21 days	[redacted]	[redacted]	[redacted]	[redacted]
12	Using the NHS reference cost SA44A – Single Plasma Exchange (£910) - applied every 4 weeks, for the PLEX administration costs	[redacted]	[redacted]	[redacted]	[redacted]
13	Applying chronic PLEX costs every 6 weeks; apply admin costs every 6 weeks; use the SA44A administration cost	[redacted]	[redacted]	[redacted]	[redacted]
14	Applying chronic PLEX costs every 8 weeks; apply admin costs every 8	[redacted]	[redacted]	[redacted]	[redacted]

No.	Scenario description	Pairwise ICER (£/QALY), zilucoplan vs comparator			
		Efgartigimod	IVIg/SCIg	PLEX	SoC [a]
	weeks; use the SA44A administration cost				
15	Applying chronic IVIg costs every 6 weeks	[redacted]	[redacted]	[redacted]	[redacted]
16	Adapting the proportions of SoC therapies (4% tacrolimus, 4% cyclosporin, 4% methotrexate; 25% mycophenolate)	[redacted]	[redacted]	[redacted]	[redacted]
17	100% of patients receive the meningococcal vaccine	[redacted]	[redacted]	[redacted]	[redacted]
18	100% SCIg use	[redacted]	[redacted]	[redacted]	[redacted]
19	Increasing the resource use for time in ICU due to a myasthenic crisis to 21 days	[redacted]	[redacted]	[redacted]	[redacted]
20	Using the change in MG-ADL score from the RAISE trial refractory subgroup (CS Table 28)	[redacted]	[redacted]	[redacted]	[redacted]
21	Increased mortality rate associated with gMG, (all-cause mortality rate ratio compared with general population of 1.4)[52]	[redacted]	[redacted]	[redacted]	[redacted]
22	Use utilities from MyRealWorldMG and POPUP for people in the UK with severe gMG[53]	[redacted]	[redacted]	[redacted]	[redacted]
23	Reducing the number of visits to the GP and other HCPs for patients who are responding to treatment: 6 GP visits and 4 HCP visits	[redacted]	[redacted]	[redacted]	[redacted]

[a] SoC excludes IVIg and PLEX, unless stated in the scenario description.
[b] Due to the model design, using SoC as the comparator must also be selected to run these scenarios. Consequently, to see the changes they cause, these ICERs should be compared with the SoC result in scenario 5.
Grey cells = these analyses have no effect on the ICER
CQ: Clarification Question; gMG: generalised myasthenia gravis; HCP: healthcare professional; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IVIg: intravenous immunoglobulin; MG-ADL: Myasthenia Gravis Activities of Daily Living score; PLEX: plasma exchange; QALY: quality-adjusted life-year; SCIg: subcutaneous immunoglobulin; SoC: standard of care

6.2 EAG's preferred assumptions

The EAG note that the company's revised base case did not include the cost for standard of care treatments (specifically the proportions of corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate and pyridostigmine) in the company's Decision Problem comparator therapies (zilucoplan, IVIg/SCIg, efgartigimod, and PLEX), presumably because this cost is common to all the comparators. We do apply this cost to

these. The standard of care arm already includes costs for these treatments, but we also include the costs for IVIg and PLEX within standard of care in our base case.

Based on the EAG's critique of the company's model (discussed in section 5.3) and the scenarios described in section 6.1, we have identified several aspects of the company's revised base case with which we disagree. Our preferred model assumptions are:

1. Using standard of care (including IVIg and PLEX) as the comparator with 43.8% of patients receiving IVIg; 14.6% of patients receiving PLEX; 41.6% of patients receiving neither;[1] all patients receive the cheaper standard therapies (EAG report Table 25) (EAG report section 6.1). However, we acknowledge there is uncertainty regarding the proportions of IVIg and PLEX used in standard of care. We have conducted scenarios comparing zilucoplan directly to efgartigimod, IVIg and PLEX using our base case (scenarios 1-3 in Table 47 of this report).
2. Adapting the proportions of SoC therapies (4% tacrolimus, 4% cyclosporin, 4% methotrexate; 25% mycophenolate) (EAG report section 4.2.4)
3. Include standard of care costs (corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine; proportions shown in Table 27) in targeted therapies (zilucoplan, efgartigimod, IVIg/SCIg, PLEX)
4. Using a 70% response rate for IVIg and PLEX and trial response rates for zilucoplan (73.1%) and efgartigimod (73.0%) (EAG report section 4.2.6.1)
5. Using the change in MG-ADL score from the RAISE trial refractory subgroup (CS Table 28) (EAG report section 4.2.6.2)
6. Using a response timepoint of three weeks for all treatments (EAG report section 4.2.6.1)
7. Chronic IVIg costs applied every 6 weeks (EAG report section 4.2.8.1)
8. Chronic PLEX administration costs (NHS reference cost SA44A, Single Plasma Exchange) applied every 6 weeks (EAG report section 4.2.8.2)
9. Chronic PLEX treatment costs applied every 6 weeks (EAG report section 4.2.8.1)
10. Increasing the duration of a myasthenic crisis to 21 days (EAG report section 4.2.8.3)
11. Increasing the resource use for time in ICU due to a myasthenic crisis to 21 days (EAG report section 4.2.8.3)

Table 46 shows the cumulative effect of each of these changes to the company's base case ICER and Table 47 gives detailed results (breakdown of total costs and QALYs) of the EAG's base case. The EAG's preferred assumptions decrease the ICER for zilucoplan compared with standard of care (including IVIg and PLEX) to [redacted] per QALY.

Table 46 Cumulative effect of the EAG's preferred model assumptions, zilucoplan versus standard of care

Scenario	Cumulative ICER £/QALY
Company revised base case (excluding IVIg and PLEX in SoC arm)	[redacted]
+ Include IVIg and PLEX in SoC: 43.8% of patients receive IVIg; 14.6% of patients receive PLEX; 41.6% of patients receive neither, but do receive the cheaper standard therapies (EAG report Table 28)	[redacted]
+ Adapting the proportions of SoC therapies (4% tacrolimus, 4% cyclosporin, 4% methotrexate; 25% mycophenolate)	[redacted]
+ Include SoC costs (corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine; proportions shown in Table 27) in targeted therapies (zilucoplan, efgartigimod, IVIg/SCIg, PLEX)	[redacted]
+ Using a response rate of 70% for both IVIg and PLEX, giving a response rate of 40.88% in our comparator arm (SoC including IVIg and PLEX), and trial response rates for zilucoplan (73.1%) and efgartigimod (73.0%)	[redacted]
+ Using the change in MG-ADL score from the RAISE trial refractory subgroup (CS Table 28)	[redacted]
+ Using a response time point of 3 weeks for all treatments (including zilucoplan)	[redacted]
+ Applying chronic IVIg costs every 6 weeks	[redacted]
+ Using the NHS reference cost SA44A – Single Plasma Exchange - applied every 6 weeks, for PLEX administration costs	[redacted]
+ Applying chronic PLEX costs every 6 weeks	[redacted]
+ Increasing the duration of a myasthenic crisis to 21 days	[redacted]
+ Increasing the resource use for time in ICU due to a myasthenic crisis to 21 days	[redacted]
EAG base case	[redacted]

[a] SoC includes IVIg and PLEX in these cumulative ICERs

ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; IVIg: intravenous immunoglobulin; MG-ADL: Myasthenia Gravis Activities of Daily Living score; PLEX: plasma exchange; QALY: quality-adjusted life-year; SoC: standard of care.

6.2.1 Probabilistic sensitivity analysis

The results for the PSA using the EAG's preferred assumptions are shown in Table 47. The mean probabilistic ICER is similar to the deterministic result; however, there is considerable variability in the PSA results, as shown by the incremental cost and QALYs scatterplot (Figure 10). The EAG note that the deterministic total costs and QALYs for zilucoplan have

changed from the company's revised base case, because we have changed the response timepoint to three weeks for all drugs.

Table 47 Deterministic and probabilistic results for zilucoplan compared with standard of care (including IVIg and PLEX), EAG base case

Analysis	Treatments	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£ per QALY)
Deterministic	Zilucoplan + SoC (excl. IVIg and PLEX)	[redacted]	[redacted]	-	-	-
	SoC (incl. IVIg and PLEX)	£520,298	9.62	[redacted]	[redacted]	[redacted]
PSA	Zilucoplan + SoC (excl. IVIg and PLEX)	[redacted]	[redacted]	-	-	-
	SoC (incl. IVIg and PLEX)	£538,029	9.61	[redacted]	[redacted]	[redacted]

Excl: excluding; ICER: incremental cost-effectiveness ratio; Incl: including; Incr: incremental; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; SoC: standard of care.

Figure 10 Incremental cost and QALY cloud in the cost-effectiveness plane, EAG base case

6.3 Scenario analyses conducted on the EAG's preferred assumptions

The EAG ran scenario analyses on our base case assumptions (Table 48). IVIg and PLEX are expensive treatments; consequently, the model is extremely sensitive to the proportions of patients receiving IVIg and PLEX and how frequently patients receive them. Increasing the proportions of patients who receive chronic IVIg and PLEX therapy (and all patients receive one or other treatment) in the standard of care arm substantially decreases the ICER, to [redacted], [redacted] or [redacted] per QALY, depending on the proportions of patients receiving each treatment (scenarios 1, 2 and 3).

Table 48 Scenario results for zilucoplan plus SoC (including IVIg and PLEX) versus comparators, EAG base case

No.	Scenario description	ICER (£/QALY)			
		Efgartigimod	IVIg/SCIg	PLEX	SoC[a]
EAG base case		[redacted]	[redacted]	[redacted]	[redacted]
1	Include IVIg and PLEX in SoC: 80% of patients receive IVIg; 20% of patients receive PLEX; 0% of patients receive neither; all patients receive the cheaper standard therapies[b]				[redacted]
2	Include IVIg and PLEX in SoC: 20% of patients receive IVIg; 80% of patients receive PLEX; 0% of patients receive neither; all patients receive the cheaper standard therapies[b]				[redacted]
3	Include IVIg and PLEX in SoC: 50% of patients receive IVIg; 50% of patients receive PLEX; 0% of patients receive neither; all patients receive the cheaper standard therapies[b]				[redacted]
4	Company response rates for zilucoplan, efgartigimod, IVIg and PLEX (CS Table 53) Please note: Scenario requires user to manually enter '35.78%' in Response!E17 in the model.				[redacted]
5	Company drug response timepoints (CS Table 53)				[redacted]
6	Chronic PLEX costs (including company admin cost) applied every 4 weeks				[redacted]
7	Chronic PLEX costs (including company admin cost) applied every 8 weeks				[redacted]
8	Chronic IVIg costs applied every 3 weeks				[redacted]
9	Use the change in MG-ADL score from the January 2024 NMA (CQ B8 Table 38)				[redacted]

[a] SoC includes IVIg and PLEX

[b] Response rate for the comparator arm (SoC including IVIg and PLEX) is 70%, because all patients are receiving either IVIg or PLEX

CQ, clarification question; ICER: incremental cost-effectiveness ratio; IVIg: intravenous immunoglobulin; MG-ADL: Myasthenia Gravis Activities of Daily Living score; NMA: network meta-analysis; PLEX: plasma exchange; QALYs: quality-adjusted life years; SCIg: subcutaneous immunoglobulin; SoC: standard of care.

6.4 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost effectiveness of zilucoplan plus standard of care compared with efgartigimod, IVIg/SCIg and PLEX, which includes a simple PAS discount for zilucoplan. The EAG consider it to be a well-structured model, which uses treatment effectiveness data from the RAISE and RAISE-XT studies. The EAG did not identify any significant technical calculation errors in the company's original model. However, we identified some inconsistencies in the company model assumptions, which we raised in our clarification questions.

The company made some changes to the model inputs in response to Clarification Questions. These decreased their base case ICER from [redacted] per QALY to [redacted] per QALY for zilucoplan compared with IVIg/SCIg; zilucoplan [redacted] after the changes (Table 42).

The EAG disagree with treating IVIg/SCIg and PLEX as separate comparators. This approach is inconsistent with the NICE scope, and the EAG do not consider this to be an appropriate reflection of standard of care in England. The EAG prefer to include IVIg and PLEX treatment within standard of care and use this as the comparator. The proportions of patients receiving IVIg and PLEX in our definition of standard of care are based on publicly available data taken from the UK efgartigimod EAMS patient cohort.[1] We acknowledge this may be an inaccurate estimate of chronic IVIg and PLEX use for patients with refractory generalised MG in England, especially as our three clinical experts stated that practically all patients eligible for chronic IVIg or PLEX would receive it. We highlight this discrepancy as part of Key Issue 1 discussed in section 1.3, and explore alternative proportions of patients receiving IVIg and PLEX in scenario analyses (Table 48).

The EAG's preferred assumptions and their effects are presented in Table 46 in section 6.2. Our preferred assumptions decrease the ICER for zilucoplan, compared with standard of care (including IVIg and PLEX), from [redacted] per QALY in the company's revised base case to [redacted] per QALY. We also conducted a range of scenario analyses on the EAG base case including comparing zilucoplan directly with efgartigimod, IVIg and PLEX; further details are in Table 48 in section 6.3 of this report. The model results are

sensitive to the proportions of patients receiving IVIg and PLEX treatment, and how frequently patients receive them.

Finally, based on our clinical experts' advice, we consider that the model may not capture the full cost of refractory generalised MG as it does not account for carers' burden and any additional costs associated with managing patients' symptoms or complications of treatment, as described in section 2.2.1.4.

7 SEVERITY

The company do not expect that zilucoplan treatment will be eligible for any form of severity weighting. The EAG agree with this assessment, because the absolute and proportional QALY shortfalls for the company and EAG base cases do not meet the thresholds for severity),[62] i.e. all of the scores are below 12 for the absolute QALY shortfall and all scores are lower than 0.85 for the proportional QALY shortfall (Table 49).

Table 49: Summary of QALY shortfall analysis

Analysis	Expected total discounted QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
Company base case vs efgartigimod	15.35	[redacted]	[redacted]	[redacted]
Company base case vs IVIg/SCIg	15.35	[redacted]	[redacted]	[redacted]
Company base case vs PLEX	15.35	[redacted]	[redacted]	[redacted]
Company base case vs standard of care (excluding IVIg and PLEX)	15.35	[redacted]	[redacted]	[redacted]
EAG base case vs standard of care (including IVIg and PLEX)	15.35	[redacted]	[redacted]	[redacted]

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9 APPENDICES

9.1 EAG appraisal of systematic literature review methods

Summary of the EAG's appraisal of the clinical effectiveness review

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The PICOD in CS Table 7 were initially unclear but resolved with Clarification Response A1 and the provision of the separate SLR report in Clarification Response A9. The PICOD criteria excluded observational studies, however the observational RAISE-XT study was appropriately included as an extension study of the company's pivotal RCT.
Were appropriate sources of literature searched?	Yes	The main healthcare databases were searched (MEDLINE and Embase); trials registers: Cochrane CENTRAL, ClinicalTrials.gov, EudraCT; hand searching of specific MG and neuromuscular conferences; the references of systematic reviews and meta-analyses were also checked, although it is unclear where these were identified from.
What time period did the searches span and was this appropriate?	Yes	From database inception to May 2023. The searches were 7 months old at time of submission, but the EAG and our clinical experts have not identified any more recent relevant studies.
Were appropriate search terms used and combined correctly?	Probably	MEDLINE and Embase were searched simultaneously in Embase.com, but it is not reported whether mapping was applied to the subject headings to ensure both MeSH terms and Emtree terms were used.

		Otherwise, the searches were carried out transparently and appropriately.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the Decision Problem?	Yes	Plasma exchange (PLEX) is an exclusion criterion and also an inclusion criterion depending on which company document is referred to. However, clarification response A1 and a separate SLR report provided in clarification response A9 confirmed that although PLEX was originally excluded it was an included in the SLR for this appraisal.
Were study selection criteria applied by two or more reviewers independently?	Yes	Two independent researchers performed the screening with a third reviewer resolving any discrepancies (CS appendix D.1.2.1).
Was data extraction performed by two or more reviewers independently?	Yes	Two reviewers conducted the data extraction with disputes referred to a third reviewer (CS appendix D.1.2.1).
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Partly	The NICE RCT checklist was used for both RAISE and RAISE-XT (CS section B.2.5; CS Appendix D.1.2.2 and D.1.4). However, RAISE-XT is not an RCT and a tool appropriate to observational studies should have been used. Discussed further in section 3.2.2 and Appendix 9.2 of this report.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Yes	Two independent reviewers assessed the RAISE and RAISE-XT studies with reconciliation of any differences by a third independent reviewer (CS appendix D.1.2.2).
Is sufficient detail on the individual studies presented?	Partly	The study documents (CSRs, SAPs, protocols) and references were not provided with the CS and had to be requested by the EAG. The CSRs, SAPs, protocols and confidential company

		references were subsequently provided by the company on 12/12/2023, but non-confidential references and the RAISE trial SAP were not provided. The EAG had to use the public redacted version of the SAP via ClinicalTrials.gov watermarked as not suitable to support marketing authorisations. Similarly, the description of the NMA methods and results was lacking, but a confidential NMA report in two parts, not referenced in the CS, was also supplied on 12/12/2023. A further 'corrected' NMA report was provided with the company's responses to Clarification Questions A11(b) and B8 but does not appear to include the refractory subgroup of patients stated in the Clarification Responses. An additional SLR report describing the clinical efficacy SLR in more detail but not referenced in the CS was provided in response to Clarification Question A9.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Partly	NMAs were conducted to estimate the comparative efficacy of zilucoplan, efgartigimod, IVIg, and PLEX (CS section B.2.9). The company did not explore whether alternative statistical methods of indirect treatment comparisons (such as matching-adjusted indirect comparison) might have better captured heterogeneity in the comparison of zilucoplan against efgartigimod. See section 3.4.4 of this report for discussion.
CSR: clinical study report; EudraCT: European Union Drug Regulating Authorities Clinical Trials; IVIg: intravenous immunoglobulin; MeSH: Medical Subject Headings; NMA: network meta-analysis; PLEX: plasma exchange; RCT: randomised controlled trial; SAP: statistical analysis plan; SLR: systematic literature review.		

9.2 Risk of bias assessments for RAISE and RAISE-XT

The company's 'quality assessment' used the NICE checklist for randomised controlled trials (CS Table 19). The company applied this tool to assess the RAISE trial (which is appropriate) and to the RAISE-XT study which is inappropriate since RAISE-XT was a non-randomised cohort study. The company did not frame their overall conclusions as risk of bias statements. Below we have reproduced the company's judgements for RAISE and RAISE-XT from CS Table 19 and added our comments and risk of bias interpretation. Risks of bias for other studies included in the company's network meta-analyses are considered in section 3.3.4 of this report.

	RAISE	RAISE-XT
Was randomisation carried out appropriately?	**Company:** Yes. Study participants who met inclusion criteria were randomized in a 1:1 ratio to receive daily zilucoplan 0.3mg/kg/day or placebo. Randomisation was stratified based on the Baseline MG-ADL score (≤9 versus ≥10), QMG score (≤17 versus ≥18), and geographical region (North America, Europe, and East Asia) **EAG:** The method of random sequence generation is	**Company:** N/A. As RAISE-XT was an open-label extension study, all study participants received zilucoplan 0.3mg/kg and therefore no randomisation was required. Study participants retained their unique study participant number from their parent study **EAG:** Patients had been randomised within each of the RAISE and MG0009 source trials using a computer algorithm and enrolment into RAISE-XT followed a pre-specified plan. **Low risk of bias**

	not reported in the CS, CSR, or trial publication, but the trial protocol says a computerised randomisation algorithm would be used. **Low risk of bias**	
Was the concealment of treatment allocation adequate?	**Company:** Yes. RAISE was a double-blind, placebo-controlled study. Study participants and staff remained blinded to treatment assignments until after the data had been cleaned, locked, and unblinded. **EAG:** Note that blinding occurs after allocation concealment and has a separate question below. We assume that the interactive response technology would have concealed the allocation	**Company:** N/A. Investigators and study participants were kept blinded to their original treatment in the parent studies (MG0009/RAISE) at the time of the clinical cut-off date. However, RAISE-XT is an open-label study and all study participants received zilucoplan 0.3mg/kg **EAG:** This question is not relevant because treatment allocation to RAISE-XT from RAISE and MG0009 did not require a random allocation sequence.

	sequence, although this is not explicit in the CS, publication, CSR, or trial protocol. **Low risk of bias**	
Were the groups similar at the outset of the study in terms of prognostic factors?	**Company:** Yes. Demographics were balanced across treatment arms, apart from sex, where there was a slightly higher proportion of females in the zilucoplan 0.3mg/kg treatment group (60.5%) compared with the placebo treatment group (53.4%) **EAG:** Agree with the company for the overall randomised (mITT) trial population. However, the participant baseline characteristics are not reported in the CS, CSR, trial publication, or	**Company:** Yes. The demographics of the study population was generally well-balanced between groups with respect to the key demographic variables **EAG:** For the two groups within RAISE-XT with most relevance to the current appraisal, i.e. the placebo/zilucoplan 0.3mg and zilucoplan 0.3mg/zilucoplan 0.3mg groups, the baseline characteristics, including the proportion of patients who were refractory, were generally well balanced (CS Tables 14 and 15). Exceptions were the median baseline MG-ADL and QMG scores which were [redacted] and [redacted] respectively in the placebo/zilucoplan group, which would be consistent with the effect of the therapy from the preceding RAISE and phase II trials. **Low risk of bias**

	in Clarification Response A10(a) separately for the refractory subgroup zilucoplan and placebo arms (Clarification Response Tables 24 and 25). **mITT population: Low risk of bias** **Refractory subgroup: Unclear risk of bias**	
Were the care providers, participants and outcome assessors blind to treatment allocation?	**Company:** Yes. Study participants and study staff remained blinded to treatment assignments until after the data had been cleaned, locked, and unblinded **EAG:** All relevant trial personnel and participants appear to have been blinded. **Low risk of bias**	**Company:** N/A. As RAISE-XT is an open-label study and all study participants received zilucoplan 0.3mg/kg **EAG:** Open-label study without blinding of participants or study investigators. **High risk of bias**
Were there any	**Company:** No. In total, four	**Company:** No. Discontinuation from the study was defined as discontinuing at any point during MG0011,

unexpected imbalances in drop-outs between groups?	study participants discontinued RAISE in both the zilucoplan (4.7%) and placebo (4.5%) groups. **EAG:** Agree with the company. **Low risk of bias**	not limited to the first 12 weeks. In total, [redacted] discontinued the study, [redacted] in the placebo/ zilucoplan 0.3mg/kg treatment group **EAG:** For the changes from baseline in the MG-ADL score (Figure 1 above), QMG score (Figure 2), MGC score (Figure 3) and MG-QoL15r score (Figure 4) the placebo/zilucoplan group experienced a greater improvement in the outcome (decrease) than the zilucoplan/ zilucoplan group near the end of the assessment period, this being particularly notable for the change in MGC score (Figure 3 above). We note that for these outcomes the rate of attrition towards the end of the study was higher in the placebo/zilucoplan group after week E24. It is unclear why patients who had previously received placebo had a higher dropout rate and whether this explains the observed differences between the groups. We also note that a similar difference between groups near the end of RAISE-XT occurred for the proportion of patients reporting no problems with EQ-5D subscales, although attrition rates were not reported (section 3.2.5.6.2 above). The EAG's clinical experts could not offer any explanations for these outcome differences between the zilucoplan/zilucoplan and placebo/zilucoplan groups towards the end of RAISE-XT. **Unclear risk of bias**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**Company:** No. All outcomes were related to the clinical goals of gMG therapy, and safety **EAG:** Results are reported in the CS for all outcomes stated in the	**Company:** No. All outcomes were related to the clinical goals of gMG therapy, and safety **EAG:** Results are reported in the CS for all key outcomes stated in the CSRs (the trial protocol was not provided). **Low risk of outcome reporting bias** for primary and secondary outcomes. However, for the EQ-5D (exploratory outcome) the reporting of EQ-5D subscales as discussed in section 3.2.5.7.2 above has **high risk of outcome reporting bias**, although this has no bearing on the company's economic analysis.

	trial protocol. **Low risk of outcome reporting bias** for primary and secondary outcomes. However, for the EQ-5D (exploratory outcome) the reporting of EQ-5D subscales as discussed in section 3.2.5.7.1 above has **high risk of outcome reporting bias**, although this has no bearing on the EQ-5D scores used in the company's economic model.	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Company:** Yes. The mITT population included all randomised study participants who received at least one dose of zilucoplan and had at least 1one post-	**Company:** Yes. The ITT population included all enrolled study participants in MG0011. The mITT population included all enrolled study participants in MG0011 who received at least one dose of zilucoplan and had at least one post-dosing MG-ADL score. Missing data for safety, PK, and PD endpoints were not imputed; observed cases were used. This included observations occurring after a study participant received rescue therapy. Missing total scores of QMG, MG-ADL, MGC, and MG-QoL15r were not imputed. In addition, data after rescue medication were not imputed **EAG:** Missing data were not imputed. CS Table 11 says the placebo/zilucoplan 0.3mg and zilucoplan 0.3mg/zilucoplan 0.3mg groups had N=90 and N=93

	dosing MG-ADL score Study participants with missing data at the timepoint of interest were treated as non-responders. If a study participant received rescue therapy, efficacy endpoints that occurred after rescue therapy were censored **EAG:** The mITT population included all randomised participants and therefore equates to an ITT analysis. The methods to account for missing data appear appropriate but with uncertainty over the timepoints at which the data were missing in each trial arm making it uncertain whether the	with [redacted] and [redacted] discontinuations respectively. But data for the secondary efficacy outcomes in CS Figures 17 to 20 for the secondary outcomes show fewer dropouts than this up to week 12. As noted above, for the changes from baseline in the MG-ADL score, QMG score, MGC score, and MG-QoL15r score the numbers of dropouts were higher in the placebo/zilucoplan group after week E24, although the CS does not discuss or explain this. **Unclear risk of bias**

	imputed data might have differed systematically between the arms. **Unclear risk of bias**	

Single Technology Appraisal

Zilucoplan for treating antibody positive generalised myasthenia gravis [ID4008]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 27 February 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Please note that page numbers referred to in the EAG responses below refer to the report view with track changes displayed.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table in section 1.3 (page 15) reads: 'Further clinical opinion to clarify the proportions of patients with refractory generalised MG in England receiving chronic IVIg and PLEX treatment, and the proportion of this patient group who would be eligible to receive chronic IVIg or PLEX but receive neither', but the second row of the same table (page 14) states that: 'practically all patients who are eligible for treatment with chronic IVIg or PLEX would receive it'	Please could the point be removed from the 'what additional evidence or analysis might help to resolve this key issue' row?	The statements contradict each other.	Not a factual inaccuracy. The table for Key Issue 1 on EAG Report page 15 states that "further" clinical opinion may be helpful, i.e. additional to the opinion of the EAG's 3 clinical experts, to clarify uncertainty around clinical practice more widely in the NHS. So, we do not believe this to be contradictory. No change made.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table in section 1.4 (page 16) reads: 'Other trials of comparators relevant to the company's Decision Problem (efgartigimod, IVIg, PLEX) which the company included in network meta-analyses (NMAs) **did not enroll any patients defined as being refractory**.'	Please change the sentence to: 'Other trials of comparators relevant to the company's Decision Problem (efgartigimod, IVIg, PLEX) which the company included in network meta-analyses (NMAs) did not include prespecified refractory subgroups. The ADAPT trial included 63% refractory patients, but this was not defined and specific results for refractory patients were not available to be included in the NMA'	This is inaccurate as the efgartigimod trials did include refractory patients (although the definition was not stated in the publications).	Thank you for highlighting this. Given the information provided in the CADTH review (Clarification Response reference 16) we have reworded the Key Issue 2 table on pages 15-17 to clarify that the ADAPT trial contained 63% refractory patients, albeit not as a defined subgroup.
Similar to the row above, the table in section 1.4 (page 16) reads: 'However, it is unclear whether such an assumption could be applied to the NMAs which (depending on the analysis) **included either no refractory patients at all or only the RAISE trial refractory subgroup'**. and 'The EAG are uncertain whether it is appropriate to use the results of NMAs that	Please can the sentence be reworded to state that although there are no refractory-specific results apart from in RAISE, the other trials (when full population of RAISE and ADAPT) included a majority of refractory patients.	Both statements are inaccurate as either all patients (including the refractory cohort) or only zilucoplan or placebo-treated (including the refractory cohort) patients from RAISE were included in the NMA; there wasn't one using no refractory patients. It is also inaccurate as per technical report as eculizumab was included and the REGAIN trial only included refractory patients- so the	The issue in this row of the table has been addressed in the amendment described above, thank you. Note that we have not referred to the eculizumab trials as these are not relevant to the company's Decision Problem and are not influential in the NMA networks.

included few or no refractory patients…'.		placebo-calculated response has this included. There are no refractory-specific results apart from in RAISE, but the other trials (when full population of RAISE and ADAPT) included a majority of refractory patients.	
Table in section 1.4 (page 16) reads: 'The company confirmed that only the RAISE trial enrolled any refractory patients.'	Please can the sentence be reworded to say 'The company confirmed that RAISE and ADAPT both enrolled refractory patients but there are no refractory-specific results or definition in ADAPT.'	This is inaccurate as the company stated that ADAPT included 63% refractory patients but that this was not defined and there were no endpoint analyses conducted on the subgroup.	The issue in this row of the table has been addressed in the amendment described above, thank you.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table in section 1.4 (page 17) reads: 'Note that such an analysis would not address the uncertainty arising from a lack of refractory patients in the ADAPT trial'	Please could the sentence be removed?	This is inaccurate as there were refractory patients in the trial (also see issue 2 above).	We agree that this sentence in the table for Key Issue 3 on page 18 is not strictly necessary; we have removed it so the Key Issue is now more concise.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
IVIg and PLEX are not included in the in the EAG standard of care basket	Please could the EAG clarify which analyses include IVIg and PLEX in the SoC basket in the EAG analyses and justify why they've not been included if/where they aren't.	It is unclear which analyses include IVIg and PLEX in the SoC basket in the EAG analyses.	Thank you for highlighting this ambiguity. A footnote has been added to EAG Report Table 45 (EAG scenarios on the company's base case) and Table 46 (cumulative effect of the EAG's preferred assumptions on the company's base case) to explain which ICER results include IVIg and PLEX within SoC. Table 48 (scenario results, EAG base case) has been updated to show that IVIg and PLEX are included within SoC for all ICERs comparing zilucoplan with SoC. Table 49 (summary of QALY shortfall analysis) has been updated to show that SoC excludes IVIg and PLEX in the company's base case and includes IVIg and PLEX in the EAG's base case.

Other inaccuracies:

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2 (page 25) states that: 'classes **III** to IV refers to generalised disease involving other muscles impacting mobility, breathing, and swallowing', which is inaccurate.	Please re-word the sentence to: 'classes II to IV refers to generalised disease involving other muscles impacting mobility, breathing, and swallowing' (as described in CS section 1.3.1).	It is factually inaccurate as a description of how MG is classified according to the Myasthenia Gravis Foundation of America (MGFA) classification system (may have been a typographical error)	Thank you for highlighting this typographical error. We have corrected this on page 26.
Section 2.2.3.2 (page 30) states: 'The company description of the treatment pathway omits rituximab, without discussing whether rituximab is a part of SoC or a relevant comparator in relation to zilucoplan'.	Please remove the sentence.	The clinical experts consulted all agreed that rituximab would not be considered a relevant comparator for zilucoplan. Whether it is part of SoC and whether it is a relevant comparator was discussed by the company in sections 1.3.2.2., 3.2.8.2 in the CS.	Thank you for highlighting this inconsistency. As rituximab is used off-label in only a few refractory patients, with varied success, and as our clinical experts agreed it is not an appropriate comparator, we have removed the sentence from page 31.
Section 2.2.3.2 (page 30) states: 'There is lack of clarity in the company description of	Please remove the sentence.	The company believe that the proposed positioning of zilucoplan has been clearly described in Figure 4 in	Thank you for highlighting this point. There is uncertainty in the CS regarding whether zilucoplan would be used in addition to or instead of IVIg and PLEX.

zilucoplan's position in the treatment pathway leading to uncertainty about relevant comparators and standard of care'		the CS. All three clinical experts confirmed that all refractory patient would receive either IVIg and/or PLEX as chronic therapy if they are eligible.	However, as this has been addressed by the EAG text in section 2.2.3.2 we agree that the statement in the EAG conclusion section is unnecessary, and we have removed this on page 31.
Section 3.2.1.2.1 (first bullet point on page 43) states that 'the RAISE trial eligibility criteria had an upper age limit of age 75 years'	Please change the sentence to: 'there were patients aged up to 75 years in the RAISE trial, which our clinical experts did not view as being fully representative of clinical practice since they treat many patients in their 80s and 90s, explaining that most of their patients are elderly'	The eligibility criteria were up to age 74 years; however, there were patients aged up to 75 years in the trial	Thank you for clarifying the eligibility criteria and age of patients in the trial. We have amended the sentence on page 44 as suggested.
Section 3.2.3.1, table 6 states that the MG-ADL change from baseline at week 12 does not inform the economic model.	Please replace 'no' with 'yes' in the 'informs economic analysis' column.	This is inaccurate as MG-ADL change from baseline at week 12 was used to input the NMA, which informed the model	Thank you for highlighting this error. We have corrected the information in Table 6 on page 49.
Section 3.4.2, table 19. The wrong timepoints have been reported (S3 instead of primary analysis)	Please amend the results.	The company will provide the correct report with this document.	Not a factual inaccuracy. The data reported in Table 19 correspond to the source cited in the table footnote. The EAG are unclear which aspect of Table 19 the company are claiming to be incorrect, and we have not been provided with any "correct report"

			as a basis for making any amendment. No change made.
Section 4.2.6.1 states: 'We are therefore unable to verify these estimates and are uncertain whether the refractory subgroup was included in the January 2024 NMA or not.'	Please remove the sentence.	The company will provide the correct report with the relevant table to make it clear that only refractory patients were included in the clarification questions response.	Not a factual inaccuracy. The EAG have not been provided with a "correct report" with which to verify the company's assertion. No change made.
Section 5.3 Table 43 (page 113) states: 'The EAG consider that these data underestimated the placebo change in MG-ADL score from the RAISE trial refractory subgroup'.	Please remove the sentence.	The data came from the NMA, therefore are not underestimated. The company will provide the NMA report with this document	Thank you for highlighting this inconsistency. We have removed the sentence from the table on page 112.
Section 2.3, table 4 states: 'The EAG's three clinical experts agreed that this population is appropriate in terms of unmet need, although the comparative clinical evidence for refractory patients is limited to a relatively small pre-specified subgroup in the pivotal trial'.	Please remove 'although the comparative clinical evidence for refractory patients is limited to a relatively small pre-specified subgroup in the pivotal trial' be removed.	The refractory subgroup is not a small population (n=88 [n=44 in each arm]) given that MG is a rare disease, and relative to patient numbers in trials for other rare disease.	Thank you for highlighting this. We have removed the subjective interpretation of whether the subgroup size is "relatively small" from Table 4 on page 33.

Section 3.3.2 (page 69) states: 'We are uncertain whether trials that did not enroll refractory patients can adequately reflect outcomes for refractory patients and have noted this as a key issue for consideration'	Please add: 'Other trials (e.g. ADAPT) have included refractory patients as part of the whole trial population, but data are lacking specifically just for refractory patients (i.e. the majority of the patients in the NMA will be refractory).	Other trials included in the NMA did enroll refractory patients, but RAISE is the only trial there are data for in refractory patients only.	Thank you for highlighting this point. We have reworded the final paragraph on page 70 to address this.
Section 3.4.4 (page 75) states: 'The only refractory patients available for inclusion in NMAs are in the RAISE trial refractory subgroup'	Please remove the bullet point. Please change this sentence to 'The only refractory-specific' data available for inclusion in NMAs are in the RAISE trial refractory subgroup'	Other trials included in the NMA did enroll refractory patients, but RAISE is the only trial there are data for in refractory patients only.	Thank you for highlighting this. We have retained the bullet point on page 76 but reworded it as suggested to make this clarification.
Section 3.5 (page 75) states: 'Results for five other clinical outcomes, which do not inform the economic model, are provided in the separate company NMA Reports and we have also summarised these below: QMG response rate (section 3.5.2); MG-ADL score change from baseline (section 3.5.3)..'	Please remove all results from the NMA that aren't MG-ADL, since it doesn't inform the model and was submitted in error.	Results from the NMA that aren't MG-ADL don't inform the model and were submitted in error	Not a factual inaccuracy. NICE technology appraisals should consider all the clinical evidence submitted that is relevant to the NICE scope, not limited to those outcomes that inform the economic analysis. No change made.
Section 3.6 (page 81) states:	Please reword the sentence as explained in other instances	Other trials included in the NMA did enroll	Thank you for highlighting this point. To address this and ensure

'The EAG are uncertain whether the treatment effects estimated from NMAs (or other types of indirect treatment comparison) that do not include refractory patients would reflect the treatment effects experienced by a refractory population'		refractory patients, but RAISE is the only trial there are data for in refractory patients only.	that the report is internally consistent we have made the same change to the final bullet point on page 82 as we made to the final bullet on page 76 in section 3.4.4 noted above.
Section 3.6 (page 81) states: 'The relative risks were then applied to the referent response rate (calculated as the average response rate across the studies used in the NMA, which was [redacted]) to estimate each treatment's response rate.'	Please change [redacted] to [redacted] or [redacted]	[redacted] is the exact figure in the NMA and clarification responses document	Thank you for highlighting this discrepancy. We have corrected the value to [redacted] on page 89.
Section 4.2.6.1 (page 88) states: 'Another limitation of the NMAs is that, unlike RAISE, no other trials included in the analyses had refractory subgroups and so the analyses were based on the overall populations of the comparator trials.'	Please reword the sentence to: 'Another limitation of the NMAs is that, unlike RAISE, no other trials included in the analyses had refractory subgroups and so the analyses were based on the overall populations of the comparator trials that included a majority of patients who were refractory'	Other trials included in the NMA did enroll a majority of refractory patients	Thank you for highlighting this. We have amended the text on page 89 to clarify that the ADAPT trial had a majority of refractory patients.

Section 4.2.6.2 (page 91) states: 'The model assumes patients slowly return to the baseline MG-ADL score over a period of 14 weeks of response assessment'	Please change the sentence to: 'The model assumes patients who lose response slowly return to the baseline MG-ADL score over a period of 14 weeks of response assessment'	Adding 'who lose response' improves clarity	Thank you for highlighting this ambiguity. We have amended the text as suggested on page 92.
Section 4.2.6.2 (page 91) states: 'However, as noted above (section 3.4.1) we are uncertain whether the company's NMA using the January 2024 data cut-off does include refractory patients'	Please remove the sentence.	This would include refractory patients even if it was the whole cohort, which is made clear in the correct NMA report (shared with this document).	We have amended the text to clarify that it is unclear whether the refractory subgroup or whole trial population was included. We have not been provided with the "correct" NMA report so could not make any further amendment here.
Section 4.2.6.2 (page 92) Table 32: Values (apart from zero) in Table 32 should all be negative.	Please change all values to negative values (apart from zero).	All values (apart from zero) should be negative values (an improvement from baseline in MG-ADL score).	Thank you for highlighting these typographic errors. Non-zero values in Table 32 have been corrected to negative values.
Section 4.2.6.2 (page 93) states: 'We were unable to corroborate the company's assertion (company response to Clarification Questions A11	Please change the sentence to: 'We were unable to corroborate the company's assertion (company response to Clarification Questions A11 and B8) that the NMA scenario analysis using the	The scenario analysis included refractory patients	Thank you for highlighting this. We have made the suggested amendment on page 94.

and B8) that the NMA scenario analysis using the January 2024 NMA included refractory patients'	January 2024 NMA included only refractory patients'		
Section 4.2.6.1 (page 89) states: 'The EAG note that the company back-calculated the response timepoints for IVIg and PLEX to obtain the same response rates for these two treatments as obtained from the study by Barth et al.'	Please change to '…the company back-calculated the odds ratios for IVIg and PLEX from response rates for these two treatments…'.	The calculated ORs were back-calculated from the response rates from Barth, not the response assessment time point.	Thank you for highlighting this discrepancy. We have corrected the sentence on page 90.
Section 1.4, Page 17 Zilucoplan is incorrectly spelt	Please update zilucoplan with zilucoplan	Incorrect name	Thank you for highlighting this typographic error which has been corrected on page 17.

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
Give full details of inaccurate marking -	Give details of incorrect confidential marking		

document title and page number			
ID4008 zilucoplan EAG report: • Section 1.2, main body and table 2, page 13 • Section 1.3, page 15 • Section 1.5, page 19-21 • Section 1.7, page 22-23 • Section 4.2.8.1, page 98 • Section 5.1 main body and table 39, page 103 • Section 5.1.2 (table 40 and 41) • Section 5.1 (page 103) • Section 4.2.6.1 (page 90)	Confidential marking is missing on ICERs, costs and 'dominant'.	Please redact ICERS, costs and 'dominant' throughout the report (see list and additional rows below) like they were in the CS. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	All CON marking, as highlighted by the company, have been corrected to match that in the CS i.e. zilucoplan total costs, all incremental costs and all ICERs and 'dominant' are marked as confidential; total costs for the comparators, total QALYs and incremental QALYs are not confidential. The EAG noted the following inconsistencies in the company's list of sections requiring confidential marking: • Section 4.2.8.1, page 98: The drug prices and discount were already

• Section 5.1.2, table 40 (page 105) • Section 5.2.3, main body and table 45 (page 116-118) • Section 5.1.3 (page 107) • Section 5.1.3 (page 106) • Section 5.1.3, table 41 (page 106) • Section 5.1.3 (page 106) • Section 5.2.3, table 42 (page 108-109) • Section 6.2, main body and table 46 (page 119-120) • Section 6.2, table 47 (page 120-121)			marked as confidential in the original EAG report. Hence, no changes were made. (NB page 98 is now page 99 in the track changes report view) • Section 5.2.3, table 45 (page 116-118): The company's referencing is incorrect as Table 45 is in section 6.1, whilst section 5.2.3 consists of Table 42 (pages 109-110 in track changes view). We have corrected the CIC markings in both these sections (5.2.3 and 6.1) and tables (42 and 45).

• Section 6.3, main body and table 48 (page 121-122) • Section 6.4 (page 123) • Section 5.2.3, table 45 (page 116-118)			
ID4008 zilucoplan EAG report, table 4, page 32	The table is missing confidential marking	The evidence base for zilucoplan is based on a proportion of patients (50.6%) who had refractory gMG at baseline in the pivotal phase lll trial (RAISE) and as such provides sufficient subgroup data to perform meaningful indirect comparisons or allow cost cost-effectiveness analyses in refractory MG	This information (50.6%) can be deduced from Table 1 of the trial publication and is therefore not confidential. No change made.
ID4008 zilucoplan EAG report, section 1.2, table 2, page 13	The section is missing confidential marking	As above, please redact ICERS and costs be redacted throughout the report (see list and additional rows below) like they were in the CS. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the price to be back-calculated.	We have corrected the confidential marking to match that in the CS i.e. zilucoplan total costs, all incremental costs and all ICERs and 'dominant' are marked as confidential; total costs for the comparators, total QALYs and incremental

			QALYs are not confidential.
ID4008 zilucoplan EAG report, section 1.5, page 19	The section is missing confidential marking	Using the trial response rates for zilucoplan and efgartigimod, and a response rate of 70% for IVIg and PLEX increases the ICER from [redacted] to [redacted] per QALY for zilucoplan compared with standard of care (including corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, methotrexate, pyridostigmine). Comparing zilucoplan directly with IVIg, efgartigimod and PLEX: the ICER decreases from [redacted] per QALY for zilucoplan versus IVIg; whereas the ICERs remain dominant for zilucoplan versus efgartigimod and versus PLEX (i.e., zilucoplan is cheaper and more effective). Please redact ICERS, costs and 'dominant' throughout the report (see list and additional rows below) like they were in the CS. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	We have added this confidential marking (page 20).
ID4008 zilucoplan EAG report, section 5.1, page 103	The section is missing confidential marking	The pairwise ICERs for zilucoplan in comparison with efgartigimod, IVIg/SCIg, and PLEX are dominant, [redacted] per QALY, and dominant, respectively. Zilucoplan dominates efgartigimod and PLEX, and the ICER compared with IVIg/SCIg is reduced from [redacted] per QALY in the company's original base case. Please redact ICERS, costs and 'dominant' throughout the report (see list and additional rows below) like they were in the CS. As QALYs are unredacted in the submission and ICERs	We have added this confidential marking (page 104).

		are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	
ID4008 zilucoplan EAG report, section 5.1.2 (table 40 and 41)	The section is missing confidential marking	As above, please redact ICERS and costs be redacted throughout the report (see list and additional rows below) like they were in the CS. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the price to be back-calculated.	We have corrected the confidential marking to match that in the CS i.e. zilucoplan total costs, all incremental costs and all ICERs and 'dominant' are marked as confidential; total costs for the comparators, total QALYs and incremental QALYs are not confidential.
ID4008 zilucoplan EAG report, section 3.2.3.1 (page 49)	The section is missing confidential marking	The RAISE-XT extension study reported the same outcomes as the RAISE trial (CS Table 9) for up to week E84 i.e., 96 weeks total from the RAISE baseline (CS sections B.2.6.2.1 to B.2.6.2.3).	It is unclear why the assessment timepoint of RAISE-XT should be confidential, especially as the treatment effects are also marked confidential and no efficacy or economic information could be revealed by knowing the assessment time. We note that there are numerous instances in the EAG report where

			the company have not requested E84 or any other timepoints from RAISE-XT to be marked confidential, so applying markup here would be inconsistent. No change made.
ID4008 zilucoplan EAG report, section 3.2.5.4.2 (page 56)	Could more of the sentence be redacted to make interpretation less obvious?	The long-term change in QMG score up to week E84 of RAISE-XT (reported only for the mITT analysis) (Figure 2) [redacted] for the MG-ADL score	We have extended the confidential marking as requested (page 57).
ID4008 zilucoplan EAG report, section 3.2.5.5.2 (page 58)	Could more of the sentence be redacted to make interpretation less obvious?	The change in MGC score up to week E84 of RAISE-XT (Figure 3) [redacted] for the MG-ADL and QMG scores discussed above	We have extended the confidential marking as requested (page 59).
ID4008 zilucoplan EAG report, section 3.2.5.6.2 (page 60)	Could more of the sentence be redacted to make interpretation less obvious?	The change in MG-QoL15r score up to week E84 of RAISE-XT (Figure 4) [redacted] for the MG-ADL, QMG and MGC scores discussed above	We have extended the confidential marking as requested (page 61).
ID4008 zilucoplan EAG report, section 3.2.5.8.1 (page 63)	Could ‘statistically’ be redacted as well as ‘significant’ to make interpretation less obvious?	The differences between zilucoplan and placebo were [redacted] for the QMG response and the MG-ADL response using the MG-ADL ≥3 threshold	We have extended the confidential marking as requested (page 64).

ID4008 zilucoplan EAG report, section 3.2.6.1.1 (page 65)	Could ‘to’ be redacted after ‘broadly similar’ to make interpretation less obvious (it would be ‘than’ instead of ‘to’ if it was greater or less)?	The summary safety results for the placebo/zilucoplan group are [redacted] those for the zilucoplan/zilucoplan 0.3/0.3 mg/kg group	We have extended the confidential marking as requested (page 66).
ID4008 zilucoplan EAG report, section 3.5.1 (page 76)	Please redact more of the sentence to make interpretation less obvious.	MG-ADL response rate [redacted] zilucoplan and efgartigimod at 12±2 weeks irrespective of whether only phase III trials were included	We have extended the confidential marking as requested (page 77).
ID4008 zilucoplan EAG report, section 3.5.2 (page 76)	Please redact more of the sentence to make interpretation less obvious.	Zilucoplan had a QMG response rate that was [redacted] than for efgartigimod	We have extended the confidential marking as requested (page 77).
ID4008 zilucoplan EAG report, section 3.5.2 (page 76)	Please redact more of the sentence to make interpretation less obvious.	This analysis showed [redacted] zilucoplan and IVIg.	We have extended the confidential marking as requested (page 77).
ID4008 zilucoplan EAG report, section 3.5.7 (page 79)	Please redact more of the sentence to make interpretation less obvious.	For the QMG, the odds of response [redacted] zilucoplan and IVIg	We have extended the confidential marking as requested (page 80).
ID4008 zilucoplan EAG report, section 3.5.7 (page 79)	Please redact more of the sentence to make interpretation less obvious.	For the QMG score change from baseline, there was [redacted].	We have extended the confidential marking as requested (page 80).

ID4008 zilucoplan EAG report, section 3.6 (page 80)	Please redact more of the sentence to make interpretation less obvious.	The refractory subgroup in RAISE showed [redacted] treatment effect compared to the mITT population, for all outcomes [redacted]	We have extended the confidential marking as requested, with some minor rewording to avoid the redaction changing the meaning (page 81).
ID4008 zilucoplan EAG report, section 3.6 (page 80-81)	Please redact more of the sentence to make interpretation less obvious.	Results of the NMAs (section 3.5.7) show that patients receiving zilucoplan had a [redacted] odds of achieving a ≥5-point improvement in QMG score (i.e., QMG response) than those receiving efgartigimod. And patients receiving zilucoplan had a [redacted] in the MG-ADL score change from baseline than those receiving IVIg. However, there were [redacted] for five other outcomes that were tested (including the odds of achieving a MG-ADL response (≥3-point improvement) which informs the economic analysis), [redacted] for two other outcomes that were tested (neither of which inform the economic analysis).	We have extended the confidential marking as requested (pages 81-82).
ID4008 zilucoplan EAG report, section 4.2.6.1 (page 90)	The section is missing confidential marking	As above, please redact ICERS and costs be redacted throughout the report (see list and additional rows below) like they were in the CS. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and	We have added this confidential marking (page 91).

		with the model structure and changes outlined in detail, it would be possible for the price to be back-calculated. 'Applying these response rates within the company's revised base case significantly increases the ICER for zilucoplan versus efgartigimod to [redacted]. However, the robustness of this analysis is uncertain'	
ID4008 zilucoplan EAG report, (page 51)	The section is missing confidential marking	The RAISE-XT extension study reported the same outcomes as the RAISE trial (CS Table 9) for up to week [redacted]	It is unclear why the assessment timepoint of RAISE-XT should be confidential, especially as the treatment effects are also marked confidential and no efficacy or economic information could be revealed by knowing the assessment time. We note that there are numerous instances in the EAG report where the company have not requested E84 or any other timepoints from RAISE-XT to be marked confidential, so applying markup here would be inconsistent. No change made.

ID4008 zilucoplan EAG report, section 5.1 (page 103)	The section is missing confidential marking	The pairwise ICERs for zilucoplan in comparison with efgartigimod, IVIg/SCIg, and PLEX are [redacted], respectively. Zilucoplan [redacted] As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	We have added this confidential marking (page 104).
ID4008 zilucoplan EAG report, section 5.1.2, table 40 (page 105)	The table is missing confidential marking	Please redact the ICER values and 'dominant' in the far-right column. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	We have added this confidential marking (page 106).
ID4008 zilucoplan EAG report, section 5.1.3 (page 106)	The section is missing confidential marking	The pairwise ICER per QALY gained is reported as [redacted] for efgartigimod, IVIg/SCIg, and PLEX, respectively. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	We have added this confidential marking (page 107).
ID4008 zilucoplan EAG report, section	The table is missing confidential marking	Please redact the ICER value and 'dominant' in the far-right column.	We have corrected the confidential marking to match that in the CS i.e. zilucoplan total costs,

5.1.3, table 41 (page 106)		As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	all incremental costs and all ICERs and 'dominant' are marked as confidential; total costs for the comparators, total QALYs and incremental QALYs are not confidential.
ID4008 zilucoplan EAG report, section 5.1.3 (page 106)	The section is missing confidential marking	Zilucoplan [redacted]. At a WTP threshold of £30,000 per QALY gained, the company's revised model indicates that zilucoplan would be [redacted]. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	We have added this confidential marking (page 107).
ID4008 zilucoplan EAG report, section 5.1.3 (page 107)	The section is missing confidential marking	We also note that the company's revised base case and PSA ICERs for zilucoplan compared with IVIg/SCIg are similar, and [redacted] in both the base case and PSA results. Please redact ICERS, costs and 'dominant' throughout the report (see list and additional rows below) like they were in the CS. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure	We have added this confidential marking (page 108).

		and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	
ID4008 zilucoplan EAG report, section 5.2.3, table 42 (page 108-109)	The table is missing confidential marking	Please redact all of the results in the table. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	We have added this confidential marking (page 109).
ID4008 zilucoplan EAG report, section 5.2.3, table 45 (page 116-118)	The table is missing confidential marking	Please redact all of the results in the table. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	Section 5.2.3 consists of Table 42 while Table 45 is in Section 6.1. We have added the confidential marking in both these sections (5.2.3 and 6.1) and tables (42 and 45).
ID4008 zilucoplan EAG report, section 6.2, table 46 (page 119-120)	The table is missing confidential marking	Please redact all of the results in the table. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	We have added this confidential marking (pages 120-121).
ID4008 zilucoplan EAG report, section 6.2, table 47 (page 120-121)	The table is missing confidential marking	Please redact the ICER values in the far-right column. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	We have corrected the confidential marking to match that in the CS i.e. zilucoplan total costs, all incremental costs and all ICERs and

			‘dominant’ are marked as confidential; total costs for the comparators, total QALYs and incremental QALYs are not confidential.
ID4008 zilucoplan EAG report, section 6.3, table 48 (page 121-122)	The table is missing confidential marking	Please redact all of the results in the table. As QALYs are unredacted in the submission and ICERs are unredacted in the EAG report, and with the model structure and changes outlined in detail, it would be possible for the confidential price to be back-calculated.	We have added this confidential marking (page 123).