Medicinrådet

Bilag til Medicinrådets anbefaling vedr. zilucoplan til behandling af generaliseret myastenia gravis

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. zilucoplan
2. Amgros' forhandlingsnotat vedr. zilucoplan
3. Ansøgning vedr. zilucoplan

Inspired by patients.
Driven by science.

Den 24. januar 2025

Notat vedrørende udkast til Medicinrådets vurderingsrapport vedr. zilucoplan til behandling af generaliseret myastenia gravis

Vi takker for, at Medicinrådet har gennemført en omfattende og saglig vurdering af zilucoplan til behandling af generaliseret myastenia gravis, samt for den konstruktive dialog igennem vurderingsprocessen.

Vi anerkender og værdsætter den professionelle tilgang, som Medicinrådet har udvist gennem hele processen, og UCB er enige i Medicinrådets vurdering og anerkendelse af behovet for nye behandlingsmuligheder for patienter der ikke opnår tilstrækkelig symptomkontrol med nuværende behandling,

Vi ser frem til det fortsatte samarbejde omkring at forbedre patientbehandlingen i Danmark.

Med venlig hilsen
UCB Nordic A/S

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29.01.2025

CAF/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.02.2025
Leverandør	UCB Nordic
Lægemiddel	Zilbrysq (zilucoplan)
Ansøgt indikation	Behandling af generaliseret myastenia gravis
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Zilbrysq (zilucoplan):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Zilbrysq	16,6 mg (7 stk. præfyldt sprøjte)	[redacted]	[redacted]	[redacted]
Zilbrysq	23 mg (7 stk. præfyldt sprøjte)	[redacted]	[redacted]	[redacted]
Zilbrysq	32,4 mg (7* stk. præfyldt sprøjte)	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Aftaleforhold

[redacted]Levera
ndøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

[redacted]

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Zilbrysq	16,6 mg (7*1 vial) 23 mg (7*1 vial) 32,4 mg (7*1 vial)	En gang dagligt (daglig dosis efter kropsvægtinterval), SC	[redacted]	[redacted]

[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til anbefaling
England	Under vurdering		Link til anbefaling
Sverige	Under vurdering		Link til anbefaling

Opsummering

[redacted].

Application for the assessment of Zilbrysq® (zilucoplan) for the treatment of generalised myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive

Colour scheme for text highlighting	
Colour of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-coded]

Contact information

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Abbreviations

Abbreviation	Definition
AChR	Acetylcholine receptor
AChR-Ab	Acetylcholine receptor antibody
AChR-Ab+ MG	Patients with MG who are seropositive for anti-AChR antibodies
AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body mass index
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DB	Double blind
DEXA	Dual-Energy X-ray Absorptiometry
DMC	Danish Medicines Council
DNA	Deoxyribonucleic acid
EBMR	Evidence-Based Medicine Reviews
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimensions
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
FcRn	Neonatal Fc receptor
gMG	Generalised myasthenia gravis
HRQoL	Health-related quality of life
ICE1	Rescue therapy
ICE2	Death or myasthenic crisis
IgG	Immunoglobulin G
IMP	Investigational medicinal product
IST	Immunosuppressive therapy
ITT	Intention-to-treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
LS	Least squares

MAC	Membrane attack complex
MG	Myasthenia gravis
MGC	Myasthenia gravis composite
MGFA	Myasthenia Gravis Foundation of America
MG-ADL	Myasthenia Gravis Activities of Daily Living
MG-QoL	Myasthenia gravis quality of life
MG-QOL15r	Myasthenia Gravis Quality of Life 15r
mITT	Modified intention-to-treat
MMRM	Mixed model repeated measure
MRR	Mortality rate ratio
MSE	Minimal symptom expression
MuSK	Muscle-specific tyrosine kinase
NEC	Not elsewhere classified
NICE	The National Institute for Health and Care Excellence
NMJ	Neuromuscular junction
NR	Not reported
nRCT	Non-randomised controlled trial
N/A	Not applicable
oMG	Ocular myasthenia gravis
OLE	Open-label extension
OR	Odds ratio
PBO	Placebo
PICOS	Population, Intervention, Comparator, Outcome, Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QMG	Quantitative myasthenia gravis
QoL	Quality of life
Q1	First quartile
Q3	Third quartile
RCT	Randomised controlled trial
RNA	Ribonucleic acid
SC	Subcutaneous
SE	Standard error
SD	Standard deviation
SMR	Standardised mortality ratio
SoC	Standard of care
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Zilbrysq
Generic name	Zilucoplan
Therapeutic indication as defined by European Medicines Agency (EMA)	Zilbrysq is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.
Marketing authorization holder in Denmark	UCB Pharma S.A.
ATC code	L04AJ06
Combination therapy and/or co-medication	Zilucoplan is expected to be administered in addition to current standard treatments (such as immunosuppressants).
(Expected) Date of EC approval	Approved 01-12-2023
Has the medicine received a conditional marketing authorization?	No.
Accelerated assessment in the EMA	No.
Orphan drug designation (include date)	This product is no longer an orphan medicine. It was originally designated an orphan medicine on 18 July 2022.
Other therapeutic indications approved by EMA	No other therapeutic indications approved.
Other indications that have been evaluated by the Danish Medicines Council (DMC) (yes/no)	No.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Zilbrysq (zilucoplan) 16.6 mg solution for injection in pre-filled syringe, 7 units per pack Zilbrysq (zilucoplan) 23 mg solution for injection in pre-filled syringe, 7 units per pack Zilbrysq (zilucoplan) 32.4 mg solution for injection in pre-filled syringe, 7 units per pack

Abbreviations: AChR = acetylcholine receptor; DMC = Danish Medicines Council; EMA = European Medicines Agency; gMG = generalised myasthenia gravis.
Sources: European Medicines Agency, 2023 (1); European Medicines Agency, 2023 (2).

2. Summary table

<table>
<tr><th colspan="2">Summary</th></tr>
<tr><td>Therapeutic indication relevant for the assessment</td><td>Zilbrysq is indicated as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-AChR antibody positive.</td></tr>
<tr><td>Dosage regiment and administration</td><td>The recommended dose should be given as a subcutaneous (SC) injection once daily and administered about the same time every day.
Total daily dose by body weight range:
<table>
<tr><th>Body weight</th><th>Dose*</th><th>Number of pre-filled syringes by colour</th></tr>
<tr><td><56 kg</td><td>16.6 mg</td><td>1 (rubine red)</td></tr>
<tr><td>≥56 to <77 kg</td><td>23 mg</td><td>1 (orange)</td></tr>
<tr><td>≥77 kg</td><td>32.4 mg</td><td>1 (dark blue)</td></tr>
</table>
Note: The recommended dose corresponds to approximately 0.3 mg/kg.</td></tr>
<tr><td>Choice of comparator</td><td>Standard of care (SoC)</td></tr>
<tr><td>Prognosis with current treatment (comparator)</td><td>Generalised myasthenia gravis is characterised by fluctuating weakness, with increased fatiguability upon repeated stimulation (3).
Patients with gMG are at increased risk of excess mortality, especially in younger patients and women, and experience lower quality of life (QoL) compared to patients without myasthenia gravis (MG), especially in subgroup of patients with more severe disease (4-8).
Patients with gMG can experience rapid and unpredictable worsening of their symptoms that requires intervention or treatment change (a myasthenic exacerbation). These episodes may deteriorate into a myasthenic crisis, which may involve a life-threatening respiratory failure requiring intubation or non-invasive ventilation (9).
The standardised mortality ratio (SMR) is higher for patients with MG (1.32; 95% confidence interval (CI): 1.23, 1.42)) compared with the general population in Denmark. Further, in Denmark the SMR is higher among women with MG (1.56; 95% CI: 1.41, 1.71) compared to men with MG (1.14; 95% CI: 1.03, 1.26) (7).
Patients' QoL is detrimentally impacted because of the debilitating and fluctuating symptoms of gMG, with patients having lower QoL scores than the general population (4, 8). In addition, more severe MG is associated with lower QoL scores (5, 6).</td></tr>
<tr><td>Type of evidence for the clinical evaluation</td><td>Head-to-head study.</td></tr>
<tr><td>Most important efficacy endpoints (Difference/gain compared to comparator)</td><td>Mean difference in change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score week 12, zilucoplan minus placebo: -2.09 (standard error (SE): 0.58; 95% CI: -3.24, -0.95; p <0.001).
Mean difference in change from baseline in quantitative myasthenia gravis (QMG) score week 12, zilucoplan minus placebo: -2.94 (SE: 0.73; 95% CI: -4.39, -1.49; p <0.001).
Mean difference in change from baseline in Myasthenia Gravis Composite (MGC) score week 12, zilucoplan minus placebo: -3.20 (SE: 1.03; 95% CI: -5.24, -1.16; p=0.0023).</td></tr>
</table>

Summary	
	Mean difference in change from baseline in Myasthenia Gravis-Quality of Life 15r (MG-QOL15r) score week 12, zilucoplan minus placebo: -2.49 (SE: 0.99; 95% CI: -4.45, -0.54; p=0.0128).
Most important serious adverse events for the intervention and comparator	The only serious adverse event experienced by at least 5% in either of the treatment groups in the RAISE study was myasthenia gravis worsening (2.3% in the zilucoplan group and 5.7% in the placebo group). As myasthenia gravis as a serious adverse event was more common in the placebo group, the cases of myasthenia gravis (as adverse event) in the zilucoplan group are unlikely to be related to treatment and is expected to be caused by the underlying disease.
Impact on health-related quality of life	Clinical documentation: At baseline, no significant difference in EQ-5D-5L score was identified between the zilucoplan and the placebo group, 0.0100 (-0.0829 - 0.1029) p=0.83. At Week 12, a notable difference was seen, however, the difference was not significant, 0.0559 (-0.0396 - 0.1514) p=0.25. For EQ-VAS, no significant difference was seen at baseline either, 4.5 (-1.38 - 10.38) p=0.13, however, at week 12 a significant difference was seen in favour of zilucoplan, 7.5 (0.7 - 14.3) p=0.03. Health economic model: Based on the health economic model using trial EQ-5D-5L data with Danish preference weights, zilucoplan is associated with an increase in health-related quality-of-life.
Type of economic analysis that is submitted	A cost-utility analysis was applied using a Markov model.
Data sources used to model the clinical effects	The clinical effects of the model were based on RAISE (10) and RAISE-XT (11) with the addition of inputs from published literature.
Data sources used to model the health-related quality of life	Health-related quality of life was based on a regression analysis on RAISE data (10). Danish preference weights were applied. Clinical events were associated with disutilities from published literature.
Life years gained	0.0025 years
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	[redacted]
Number of eligible patients in Denmark	Incidence: 68; Prevalence: 936 Estimated eligible patients: 94 (10% of prevalence) at year 1, followed by addition of 7 incident patients for each subsequent year.
Budget impact (in year 5)	[redacted]

Abbreviations: AChR = acetylcholine receptor; CI = confidence interval; gMG = generalised myasthenia gravis; MG = myasthenia gravis; MGC = Myasthenia Gravis Composite; MGFA = Myasthenia Gravis Foundation of America; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis-Quality of Life 15r; QMG = quantitative myasthenia gravis; QoL = quality of life; SC = subcutaneous; SE = standard error; SMR = standardised mortality ratio; SoC = standard of care.
Sources: European Medicines Agency, 2023 (1); UCB, 2022 (12).

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology

MG is a chronic autoimmune neuromuscular disorder. In patients with MG seropositive for anti-AChR antibodies (AChR-Ab+ MG) complement activation is a key contributor to the pathogenesis, as the complement-mediated destruction of the neuromuscular junction (NMJ) leads to muscle weakness.

Myasthenia gravis is characterised by dysfunctional synaptic transmission at the NMJ, leading to impaired muscle contraction, which results from immunological dysfunction and loss of tolerance to self-antigens (13, 14).

Synaptic transmission is impaired in MG. As a result of a loss of self-tolerance, autoreactive T cells may escape the thymus and activate B cells. These B cells differentiate into plasma cells that subsequently produce autoantibodies that bind to components of the postsynaptic membrane of the NMJ, such as AChRs and/or muscle-specific tyrosine kinase (MuSK) (3, 15). The autoantibodies disrupt normal signalling between nerve fibres and muscles (15), and ultimately lead to chronic and debilitating motor weakness and fatigue for patients (3, 14, 16-20). Serum levels of immunoglobulin G (IgG) antibodies, including the autoantibodies seen in patients with MG, are maintained through the neonatal Fc receptor (FcRn), a natural recycling pathway that rescues IgG from lysosomal degradation (21).

Patients with MG may be seropositive for anti-AChR antibodies, antibodies against MuSK, other antibodies such as LRP4, or may be seronegative. In addition, it is possible to be seropositive to more than one autoantibody (14, 15, 22, 23).

In patients with AChR-Ab+ MG, circulating autoantibodies against AChRs disrupt NMJ signalling through three different mechanisms, which are not mutually exclusive. One is by blocking acetylcholine from binding to and activating AChRs, impairing neuromuscular transmission at the NMJ. Another mechanism is by cross-linking adjacent AChR molecules, accelerating their degradation and internalisation. Lastly, a potent inflammatory response can be stimulated through activation of the complement cascade (3, 17, 24, 25).

The complement cascade is an important part of the immune system which enhances the capacity of antibodies and phagocytic cells to clear microbes (17). However, in AChR-

Ab+ MG, autoantibodies bind to the AChR and form immune complexes, resulting in persistent, localised activation of the complement cascade (17). This cascade culminates in the assembly of multiple membrane attack complexes (MACs), via complement proteins C5b–C9 at the postsynaptic membrane (17, 26). MACs are proteins that insert themselves into cell membranes and cause cell lysis through an uncontrolled influx of water and ions into the muscle cell (17).

In the healthy NMJ, the postsynaptic muscle cell membrane is characterised by deep junctional folds, the tops of which are rich in densely packed AChRs (17, 27). However, as a result of MACs, fragments of the muscle cell membranes are shed, which leads to the destruction of the folded structure of the NMJ and a significant reduction in the number of functional AChRs (28, 29). Constant activation of the complement cascade by the immune system, culminating in assembly of the MAC, causes chronic damage to the NMJ and impairs neuromuscular signal transmission (17). Complement activation is therefore a key contributor to pathogenesis in patients with AChR-Ab+ MG.

The complement-mediated destruction of the NMJ leads to muscle weakness via two mechanisms: The reduced AChR density lowers the sensitivity of the post-synaptic membrane to ACh, causing a progressive loss in AChR signalling (14, 30). In addition, the density of post-synaptic voltage-gated sodium channels, which generate post-synaptic signalling when activated, is reduced by complement-mediated damage at the NMJ. This elevates the level to which the membrane needs to be depolarised to initiate an impulse and elicit and sustain muscle contraction (14).

The effects of complement-mediated damage to the NMJ, as well as direct binding of autoantibodies to AChRs, leads to fluctuating, chronic, and debilitating muscle weakness and fatigue in AChR-Ab+ MG (3, 14, 16, 18-20, 31, 32).

3.1.2 Clinical presentation and symptoms of the condition

Generalised myasthenia gravis is characterised by fluctuating weakness, with increased fatiguability upon repeated stimulation (3). The weakness can affect several muscles including muscles responsible for vital functions. Further, physical fatigue has been identified as an important aspect of patients' experiences of MG symptoms.

Initially, many patients experience episodes of transient muscle weakness, separated by asymptomatic intervals, before the weakness develops and becomes persistent (33). Worsening symptoms are often triggered by infection and stress (34-36). Following diagnosis, the severity of disease increases, with the weakness gradually extending beyond the area of initial involvement; typically, symptoms reach their maximum severity within three years (33).

In gMG, weakness can affect the muscles in the head, neck, arms, hands, chest, limbs, and torso, and can occur at rest. Weakness can also affect muscles responsible for vital functions, leading to severe, debilitating, and potentially life-threatening consequences. For example, when weakness affects respiratory muscles, this can lead to dyspnoea upon exertion, or orthopnoea, and patients may require ventilatory assistance (37). The

different manifestations of muscle weakness – such as ocular, bulbar, and generalised muscle weakness – appear to respond differently to different therapies (15).

Patients with gMG can experience rapid and unpredictable worsening of their symptoms that requires intervention or treatment change (a myasthenic exacerbation; defined as an episode of severe acute and/or serious weakness requiring urgent treatment). These episodes may deteriorate into a myasthenic crisis, which may involve a life-threatening respiratory failure requiring intubation or non-invasive ventilation (9).

During an exacerbation, gMG symptoms interfere with patients' daily activities significantly more than usual. This can include impaired mobility (difficulty walking or climbing stairs or driving), difficulty with chewing swallowing, speech disorders, altered facial expressions, urinary problems, or sexual disorders (38-41). Exacerbations are common, particularly in those with inadequate disease control (38, 39). In addition, exacerbation rate increases in patients with a higher MG-ADL score (42) and further one exacerbation is commonly followed by another (43).

Myasthenic crises are the most severe, life-threatening complication of gMG, and can be precipitated by a range of factors including some antibiotics and physical stressors such as infection, temperature extremes, surgery, pregnancy, or the tapering of immunosuppressive treatments including corticosteroids (44). It is estimated that 15–20% of patients with gMG experience at least one myasthenic crisis during their lifetime, typically within the first two years after diagnosis (45-48).

The contribution of signs and symptoms to clinical disability may vary, but collectively, symptoms impact health-related quality of life (HRQoL) (49, 50). One model of the patient experience of MG conceptualises the effects of MG as resulting from direct bodily symptoms (e.g., limbs, bulbar, or ocular) and more functional symptoms such as fatigue, cognitive functioning, impact on daily activities, and psychological impacts, such as anger, anxiety, and a loss of self-confidence. (49).

As mentioned above, one of the main symptoms experienced by patients with gMG is persistent and debilitating fatigue (51). Patients lack energy or experience a feeling of tiredness not related to muscle weakness or pain (central fatigue), interfering with their daily activities (52). Physical fatigue has been identified as an important aspect of patients' experiences of MG symptoms (49, 50), and in a recent study, the most common goal for symptom management identified by MG patients was to reduce fatigue followed by achieving 'stability' (53).

3.1.3 Prognosis with current treatments

Patients with gMG are at increased risk of excess mortality, especially in younger patients and women, and experience lower QoL compared patients without MG, especially in subgroup of patients with more severe disease (4-8).

In a nationwide study in Denmark, of 702 AChR autoantibody-seropositive patients with gMG, the overall age and sex-adjusted mortality rate ratio (MRR) was 1.4 compared with the general population. Mortality was highest during the first 5 years after diagnosis with an adjusted MRR of 1.7 (54). In a recent study in the Nordics, the SMR was higher for

patients with MG (1.32; 95% CI: 1.23, 1.42)) compared with the general population in Denmark. In addition, the SMR was higher in women (1.56; 95% CI: 1.41, 1.71) than in men (1.14; 95% CI: 1.03, 1.26). Further, in patients over 60 years of age, the SMR was relatively stable in men, while the SMR decreased with increasing age in women over 60 years (7).

In a population-based register study investigating health care resource utilisation in the Nordics, the mean annual number of all-cause secondary healthcare contacts per MG patient was 3.4 (standard deviation (SD): 8.3) in Denmark during the follow-up period (2000-2018). Further, 87% of patients with MG in Denmark had inpatient periods during the follow-up, and the mean duration of inpatient periods was 13.9 days per patient per year (55).

3.1.4 Patients' functioning and health-related quality of life

Overall, worsening severity of MG negatively impacts the patients QoL. The MG-ADL scale is used to assess the impact of MG on patients' daily activities. Some patients will experience a low symptom burden, including those with ocular myasthenia gravis (oMG) or very mild physical gMG symptoms (33). These patients may have an MG-ADL score between 0–1, which is termed minimal symptom expression (MSE). In contrast, an MG-ADL score of ≥6 is considered to correspond to moderate-to-severe disease, with symptoms that impact on daily activities of living (20). Patients with moderate-to-severe gMG are more likely to live with chronic, uncontrolled symptoms, leading to extreme fatigue and higher levels of disability than those with more controlled disease (56).

A 2018–2019 Swedish cross-sectional prevalence cohort study (N=1,077 patients with MG) found that 18% of patients had a self-reported MG-ADL score ≥6 (57). In addition, the study found that female sex (odds ratio (OR) 1.62; 1.09-2.41; p_{adj}=0.017), obesity (OR 1.72; 1.12-2.64; p_{adj}=0.013), and a diagnostic delay of two years or more (OR 1.69; 1.14-2.48; p_{adj}=0.018) were significantly correlated with high disease activity. Similarly, in a large patient-reported database (N=1,140) of people with MG, the median MG-ADL score was 6, regardless of how long patients had lived with the disease (58). Worsening disease severity negatively impacts QoL for patients: an observational longitudinal study (N=841 patients with MG) found that each 1-point MG-ADL worsening corresponded with a utility decline of 0.02. However, the utility decline associated with 1-point MG-ADL worsening depends on the MG-ADL domain affected, i.e., patients with the same MG-ADL score can experience a different burden depending on the domain affected (5).

A recent qualitative, cross-sectional study in 28 patients with MG demonstrated that gMG symptoms and their fluctuations in severity adversely affect many aspects of a patient's life (53). Nearly all patients (96%) reported fluctuations in symptoms and severity. Impacts on physical functioning included an inability to participate in hobbies/sports, need for increased planning, and difficulties performing activities of daily living. Furthermore, all patients reported emotional impacts and impacts on their work and finances.

A Swedish study investigating the correlation of disease activity and EQ-5D-3L-derived utility in MG patients utilising patient-level data from the Swedish nationwide MG registry found impaired health status in patients with active disease (59). Average utility was

0.7, compared with 0.83 in an age- and sex-adjusted reference population. For patients with an MG-ADL score of ≤2, the average utility was 0.85 (reference 0.83) compared with 0.66 and 0.59 in patients with an MG-ADL score of ≥3 and ≥6, respectively (the reference was 0.82 for both groups). In addition, negative correlations were found between MG-ADL or Myasthenia Gravis Quality of Life (MG-QoL) score and utility were observed (ρ=-0.57 and -0.71, respectively, both p<0.001). When adjusting for sex, age, and disease duration in a multivariate regression, change in utility was associated primarily with change in disease activity (59).

3.2 Patient population

The Danish patient population relevant for this application is adult patients with gMG who are anti-AChR antibody positive, and who do not achieve satisfactory symptom control with acetylcholinesterase inhibitors and immunosuppressive treatment.

One patient characteristic that affects the prognosis is comorbidity, as comorbidities have been shown to be associated with a poorer prognosis of MG (40, 60, 61). The combined effects of multiple health issues represent a major challenge in treating patients (24). In addition, there is a general lack of understanding regarding the prognostic factors for disease remission. An SLR on the disease course and prognosis of MG found that a time from symptom onset to diagnosis of less than one year was a robust prognostic factor for remission, with strong evidence of predicting better disease remission. Similarly, there was strong evidence that age of onset of <40 years was a prognostic factor for complete, stable remission (62). Information on these variables in the Danish population is shown in Table 1.

Table 1: Distribution of patient characteristics affecting prognosis (Danish population)

Patient characteristic	Danish population
Comorbidity	42%
Mean time to diagnosis	331 days (range 5-4,492 days)
Age at diagnosis, mean (standard deviation)	60.5 (14.9)

Source: Vissing et al., 2024 (7); Vissing et al., 2023 (63); UCB, 2024 (64).

The mean time to diagnosis (in Table 1) is based on retrospective data from 350 patients treated for MG at the Neuromuscular Unit, Rigshospitalet, Copenhagen, between 1980 and 2022. The data analysis, currently unpublished, was funded by an unrestricted grant from UCB Biopharma. The team at Rigshospitalet, led by Professor John Vissing, is currently working towards publication of the data (64).

In a recent Nordic study, the incidence of MG in Denmark was higher in men (1.38 per 100,000; 95% CI: 1.28, 1.48) than in women (1.30 per 100,000: 95%CI 1.21 to 1.39). The age-specific incidence of MG differed in men and women. In women, a higher incidence was seen in the younger age groups (patients < 50 years) with a moderate increase with age, whereas a steeper increase in the incidence of MG was observed in men from 50 years onward. Overall, the incidence of MG was 1.34 (95% CI: 1.27, 1.41) per 100,000, while the prevalence was 18.56 (95% CI: 18.31, 18.81) in Denmark (7). For 80–90% of patients with oMG, their disease progresses to gMG within two years (3, 27, 33). The

information on overall incidence, prevalence, and patients progressing to gMG (85% of patients progressing to gMG) as well as information on the population size in Denmark in 2019-2023 (65) is used to populate Table 2.

Table 2: Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	66	66	67	67	68
Prevalence in Denmark	916	919	921	927	936
Global prevalence *	N/A	N/A	N/A	N/A	N/A

* For small patient groups, also describe the worldwide prevalence.
Abbreviations: N/A = not applicable.
Sources: Vissing et al., 2024 (7); Conti-Fine et al., 2006 (27); Luchanok & Kaminski, 2012 (33); Melzer et al., 2016 (3); Statistics Denmark, 2024 (65).

Table 3 includes the expected number of patients, the estimated number of eligible patients were estimated based on the prevalence found at year 2023 as shown in Table 2, for Year 1 and adding the incidence for subsequent years. [redacted]

Table 3: Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3 Current treatment options

The medicinal treatment of MG is divided into three categories: symptomatic, immunomodulatory, and immunosuppressive treatment (66).

3.3.1 Symptomatic treatment

Overall, symptomatic treatment includes the use of acetylcholinesterase inhibitors that results in an increase of the concentration of acetylcholine in the synapse. The effect is rapidly onsetting (0.5-1 hour), and the treatment is initially used as long-term therapy and during exacerbations of myasthenia (66).

Specifically, pyridostigmine (Mestinon®) is administered orally and should be given every 3-4 hours. Pyridostigmine in an extended-release formulation has a duration of action of 8 hours. The initial dose is 60 mg four times daily. The dose varies depending on the severity of symptoms (up to 120 mg four to six times daily, possibly supplemented with 180 mg extended release preparation at night) (66).

3.3.2 Immunosuppressive treatment

Overall, immunosuppressive agents are the preferred long-term treatment for moderate to severe myasthenia. Immunosuppressive agents cause lymphopenia, and the effect occurs within 3-9 months. Glucocorticoids have a faster onset of effect (weeks) and often takes an intermediate position between symptomatic and immunosuppressive treatment. Due to dose-dependent side effects, treatment for extended periods is discouraged (66).

Azathioprine is a purine analogue that blocks the synthesis of nucleic acids, thereby inhibiting deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis. Azathioprine primarily affects proliferating lymphocytes and induces B- and T-cell lymphopenia. It is used at a dose of 1-2(3) mg/kg body weight. The effect occurs after 3-6 months. Azathioprine is the first-choice drug for immunosuppression in Denmark (66). In both a Danish and Swedish register-based study, azathioprine specifically and corticosteroid-sparing immunosuppressants generally have been associated with increased risk of cancer (67, 68).

In addition, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, cyclophosphamide, and rituximab can be used by specialists with highly specialised functions (66).

3.3.3 Immunomodulatory treatment

Overall, the immunomodulatory treatment includes plasma exchange, immunoglobulin therapy, and immunoadsorption. The effect occurs over days and typically lasts for some weeks. The immune response is modulated without reducing the number of lymphocytes and plasma cells. This treatment is used for significant exacerbations of myasthenia and impending myasthenic crisis. It is important to avoid using these treatments as maintenance therapy (66).

Specifically, plasmapheresis is used for severe myasthenia or impending myasthenic crisis. The effect is rapidly onset, typically within 5 to 10 days. Plasmapheresis lowers the concentration of antibodies against acetylcholine and MuSK receptors as well as complement proteins. Typically, 3 litres of plasma are exchanged at a time, 3 to 5 times over 1-2 weeks, not more frequently than every other day. Albumin is used as a plasma expander (66).

Intravenous treatment with immunoglobulin (IVIG) can be used in severe exacerbations of myasthenia and impending myasthenic crisis. Administered at 1-2 g/kg body weight over 5 days. It is not recommended to use IVIG as long-term maintenance therapy for myasthenia (66).

3.3.4 Treatment pathway

In Denmark and generally in the Nordics, patients with myasthenia are initially treated with pyridostigmine, which is sufficient for approximately half of the patients. For the remaining, additional immunosuppression is required. Immunosuppression is performed with one or more of the drugs described above, among which azathioprine is recommended as the first-choice non-steroidal immunosuppressant. It is important to initiate

immunosuppressive treatment early in the course of the disease to avoid permanent complement-mediated endplate destruction with atrophy and paresis. Only a few patients with myasthenia (approximately 5%) cannot achieve a satisfactory anti-myasthenic response with conventional immunosuppressants (66, 69).

Immunomodulatory treatment (i.e., plasmapheresis and IVIG, and in rare cases immunoadsorption) is almost exclusively used in the treatment of myasthenic crisis and should generally not be used for maintenance treatment (66).

3.3.5 Prognosis with current treatments

Please see section 3.1.3.

3.4 The intervention

Table 4: Overview of the intervention

Overview of intervention			
Therapeutic indication relevant for the assessment	Zilbrysq is indicated as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-AChR antibody positive.		
Method of administration	Subcutaneous injection once daily.		
Dosing	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 to <77 kg	23 mg	1 (orange)
	≥77 kg	32.4 mg	1 (dark blue)
	Note: The recommended dose corresponds to approximately 0.3 mg/kg/day.		
Dosing in the health economic model (including relative dose intensity)	The 32.4 mg dose is used in the health economic model, as the base case average patient weight was ≥ 77 kg.		
Should the medicine be administered with other medicines?	While zilucoplan may be administered as an add-on to other therapies, this is not a requirement.		
Treatment duration / criteria for end of treatment	Until potential loss of response.		
Necessary monitoring, both during administration and during the treatment period	Zilucoplan is intended for use under the guidance and supervision of healthcare professionals experienced in the management of patients with neuromuscular disorders.		
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No.		
Package size(s)	Zilbrysq (zilucoplan) 16.6 mg solution for injection in pre-filled syringe, 7 units per pack		

Overview of intervention	
	Zilbrysq (zilucoplan) 23 mg solution for injection in pre-filled syringe, 7 units per pack
	Zilbrysq (zilucoplan) 32.4 mg solution for injection in pre-filled syringe, 7 units per pack

Abbreviations: AChR = acetylcholine receptor; gMG = generalised myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America.
Sources: European Medicines Agency, 2023 (1).

3.4.1 Treatment with Zilucoplan

Zilucoplan is a fast-acting, targeted therapy for adult AChR+ gMG patients (10) who experience debilitating and fluctuating symptoms despite treatment with the current SoC, or intolerable treatment-related adverse events.

In addition to the packages mentioned in Table 4, an autoinjector is expected to be approved in the end of 2026, which will make administration of zilucoplan easier for patients.

3.4.1.1 Mechanism of action

Zilucoplan is a small molecule (macrocyclic peptide) complement inhibitor, which directly binds to C5 and its cleavage product C5b within the complement cascade to prevent MAC formation and therefore damage and functional impairment of the NMJ in patients with AChR-Ab positive gMG (1).

3.4.2 The intervention in relation to Danish clinical practice

Zilucoplan is expected to be used for the treatment of patients who do not achieve satisfactory symptom control with acetylcholinesterase inhibitors and immunosuppressive or immunomodulatory treatment. Zilucoplan will not necessarily replace treatments currently used in clinical practice but will be an additional treatment option in the treatment algorithm.

No specific test is needed but patients must be vaccinated against *Neisseria meningitidis* before starting treatment (1).

3.5 Choice of comparator(s)

As zilucoplan is indicated as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-AChR antibody positive, the relevant comparator for a treatment regimen consisting of SoC plus zilucoplan is SoC alone.

According to Danish treatment guidelines and clinicians, the immunosuppressive treatments azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, cyclophosphamide, and rituximab are used in Danish clinical practice and represent current standard immunosuppressive treatments (66, 70). All of these treatments, except for azathioprine, are used off-label.

3.6 Cost-effectiveness of the comparator(s)

Not applicable.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Efficacy outcomes relevant for this application are described in Table 5. The MG-ADL scale, which is correlated with changes in disease severity, is a widely used patient-reported outcome measure in Europe and in clinical trials and observational studies (33, 71), assessing the impact of MG on patients' daily activities.

The QMG scale is widely used in clinical trials in MG, and has been shown to be well correlated with the MG-ADL (72, 73).

The MGC scale is a reliable and valid instrument used to measure the clinical status of patients with MG in both clinical practice and clinical trials (74).

The MG-QOL15r score and earlier iterations have been shown to have high internal consistency and correlate with other MG-specific and general outcome measures (75, 76).

Achieving MSE is a relevant outcome in this application, as MSE is a measure of how many MG patients become free or virtually free of MG symptoms (77).

Reduction in corticosteroid use is a relevant outcome in this application, as corticosteroids are associated with systemic side-effects that can persist with long-term use (10).

Table 5: Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Change from baseline in MG-ADL score	Week 12 and 120	Least squares (LS) mean change from baseline in MG-ADL score through week 12 or 120Ω.	Interviewer-administered patient-reported outcome. Data was analysed using the mixed model repeated measure (MMRM) analysis of covariance (ANCOVA).
Change from baseline in QMG score	Week 12 and 120	LS mean change from baseline in QMG score through week 12 or 120Ω.	Physician-evaluated assessment. Data was analysed using the MMRM ANCOVA.
Change from baseline in MGC score	Week 12 and 120	LS mean change from baseline in MGC score through week 12 or 120Ω.	Physician- and patient-reported assessment. Data was analysed using the MMRM ANCOVA.
Change from baseline in MG-QOL15r score	Week 12 and 120	LS mean change from baseline in MG-QOL15r score through week 12 or 120Ω.	Patient-reported. The MG-QOL15r was administered on an e-device that was handed to study participants to fill out on site.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			Data was analysed using the MMRM ANCOVA.
Achieving MSE	Week 12 and 120	Achieving MSE is defined as an MG-ADL of 0 or 1 at week 12 or 120 Ω without rescue therapy.	Data from RAISE was analysed using logistic regression. Data from RAISE-XT was analysed by number and percentage.
Corticosteroid use	Week 60 and 120	Reduction in corticosteroid use	Data from RAISE on this endpoint is not available. The investigator determined whether a dose reduction should be initiated. I.e., data was collected via the investigator. Data from RAISE-XT was analysed by number and percentage.
Use of immunosuppressants	Week 120	Reduction in use of immunosuppressants	Data from RAISE on this endpoint is not available. The investigator determined whether a dose reduction should be initiated. I.e., data was collected via the investigator. Data from RAISE-XT was analysed by number and percentage.

Abbreviations: ANCOVA = analysis of covariance; ICE1 = rescue therapy; ICE2 = death or myasthenic crisis; LS = least squares; MGC = myasthenia gravis composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis Quality of Life 15r; MMRM = mixed model repeated measure; MSE = minimal symptom expression; QMG = quantitative myasthenia gravis.
Notes:
- In the RAISE/MG0010 study, missing data for each outcome was handled as described in the following. If a study participant was missing a response for one of the individual MG-ADL, QMG, MGC, or MG-QOL15r items, respectively, the study participant's corresponding item score from the previous assessment was imputed for the missing item score (and the total score calculated using this imputed value and the nonmissing item scores). If the item response was also missing from the previously scheduled MG-ADL, QMG, MGC, or MG-QOL15r, respectively, the total score was set to missing for that visit. If the study participant was missing responses to more than one of the items, the total score was set to missing for that visit. Missing data for the MSE outcome were handled as described in the following. Missing MG-ADL scores were imputed under the missing at random assumption. Following to the imputation, study participants were considered as responders or non-responders; study participants who received rescue therapy (ICE1) or experienced an AE of death or myasthenic crisis (ICE2) were considered also as non-responders after the date of the intercurrent event (non-responder imputation approach).
- In the RAISE-XT/MG0011 study, no data were censored for the outcomes MG-ADL, QMG, MGC, or MG-QOL15r, and any missing data were assumed to be missing at random.
* Time point for data collection used in analysis (follow up time for time-to-event measures).
Ω Week 12 in the RAISE/MG0010 study and week 120 in the RAISE-XT/MG0011 study.
Source: UCB, 2022 (12); Howard Jr. et al., 2017 (78); UCB Inc., 2019, (72); Burns et al., 2010 (74); UCB 2024 (11); UCB, 2024 (79).

Validity of outcomes

The MG-ADL is an 8-item outcome designed to evaluate MG symptom severity. Each item is scored on a 0 to 3-point scale (i.e., 0=none, 1=mild, 2=moderate, and 3=severe). The total score is the sum of the 8 individual scores; range 0 to 24. Higher scores are associated with more severe symptoms of MG. A 2-point change in MG-ADL score is considered clinically meaningful (56, 80). Although, as stated in section 3.1.4, patients with the same MG-ADL score can experience a different burden depending on which MG-ADL domain is affected (5).

The QMG is a standardised and validated quantitative strength scoring system that was developed specifically for MG. It consists of 13 individual assessments, each scored on a 0 to 3-point scale (i.e., 0=none, 1=mild, 2=moderate, and 3=severe). The total score is the sum of the individual scores; range 0 to 39. Higher scores are representative of more severe impairment. A change in the QMG score of 3 points or more may be considered clinically meaningful, in a typical clinical study population of MG patients (81, 82).

The MGC is a 10-item scale. The total score is the sum of the 10 individual scores; range 0 to 50. Higher scores on the MGC indicate more severe impairment due to the disease. A 3-point change in this assessment is considered clinically meaningful (83, 84).

The MG-QOL15r is a 15-item self-administered patient-reported outcome designed to assess QoL in patients with MG. Each it is scored on a 0 to 2-point scale (0=Not much at all, 1=Somewhat, 2=Very Much). The total score is the sum of the 15 individual item scores; range 0 to 30. Higher scores indicate more severe impact of the disease on aspects of the patient's life (85, 86). To the best of our knowledge, no minimum clinically relevant difference has been identified for the for the MG-QOL15r.

Achieving MSE has previously been assessed as a useful tool in in measuring patient progress following therapeutic intervention (77).

4. Health economic analysis

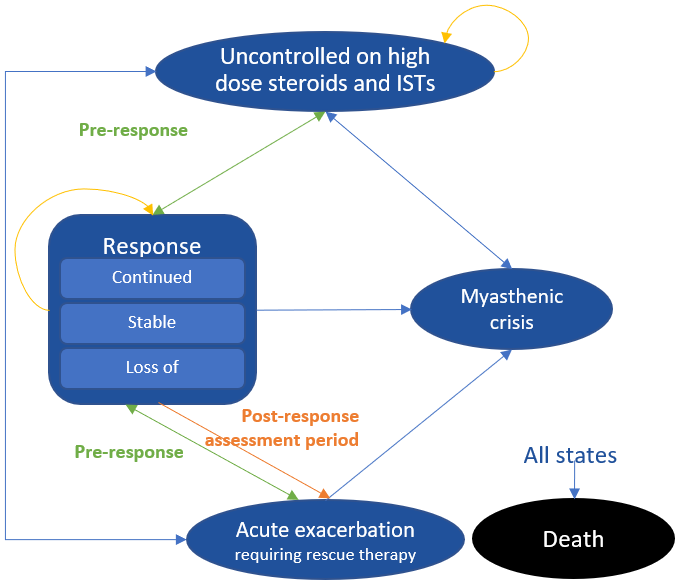
4.1 Model structure

A *de novo* cost-effectiveness model was developed to evaluate the cost-effectiveness of zilucoplan as a treatment for adult patients with gMG. The structure captures the chronic nature of gMG and the variability in symptom severity experienced by gMG patients and is presented in Figure 1. A Markov model was selected to illustrate the progression through seven different health states, encompassing patients on high-dose steroids and immunosuppressive therapies (ISTs), which models their response to treatment and associated rates of exacerbation and myasthenic crisis. It captures the chronic nature of gMG and incorporates the variability in symptom severity experienced by gMG patients throughout their lives.

The primary comparison was zilucoplan versus SoC, utilising the RAISE trial as the source of clinical characteristics. The cycle length was 2 weeks, which was considered by clinicians to be 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). A lifetime time horizon was applied, since MG is a chronic, lifelong, life-limiting condition requiring extensive care and treatment throughout the patient's lifetime.

Clinical experts identified 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 includes only those patients who are uncontrolled on high dose CSs and ISTs from the RAISE study.

Figure 1: Structure of the health economic model



Abbreviations: ISTs = immunosuppressive therapies.

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. Patients who meet the treatment response criteria (a decrease of ≥3 in MG-ADL score) at the response assessment will have transitioned to the 'response' health state at the response assessment timepoint. Patients that did not respond, will stay in the uncontrolled health state. 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. The response assessment for SoC is at week 12, equal to the length of the RAISE trial, after which patients were allowed to cross over to zilucoplan. For zilucoplan, the response assessment is at week 24, to capture the treatment effect observed in the RAISE-XT trial.

Patients in the response health state will separate into one of the three response subgroups (continued, loss or stable response). As such, the model is structured around four response-based health states, uncontrolled, stable response, continued response, and loss of response, as described in Table 5. Please note, that the base case efficacy data are using the endpoints defined in the RAISE trial: ≥ 5 CFB MGADL = Continued response, 3-4 CFB MGADL = Stable response; 'loss of response' is not populated, assuming patients losing response directly enter the uncontrolled health state.

Beside these four response-based health states, the model allows the patients to transition into the two clinical event health states 'exacerbation' and 'myasthenic crisis', and the absorbing health state 'death'. Within each health state (except death), patients are at risk of 'exacerbation' and 'myasthenic crisis'. 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. At any time, patients are at risk of moving to the 'death' health state.

Table 5: Health states included in the model

Health state	Definition
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 In the base case using endpoint definitions from RAISE: 3-4 CFB MG-ADL
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. In the base case using endpoint definitions from RAISE: ≥ 5 CFB MG-ADL
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 This health state is not used in the base case, since the endpoint was not defined in the RAISE trial. Patients losing response are instead moved to Uncontrolled on high dose steroids and ISTs
Uncontrolled on high dose steroids and ISTs	Patients with MG who do not achieve an adequate response or are intolerant to conventional treatment. In the base case, this health state includes patients ≤ 3 CFB MG-ADL as defined in the RAISE trial.
Myasthenic crisis	Exacerbation requiring intubation
Exacerbation	New worsening of symptoms reported by the patient accompanied by at least one of the following: • New weakness quantified by the 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
Death	Death health state

Abbreviations: MG-ADL = Myasthenia Gravis Activities of Daily Living score; ISTs = Intravenous immunoglobulin; MG = Myasthenia Gravis; MRC = medical research council; PLEX = plasma exchange; IVIg = intravenous immunoglobulin.

4.2 Model features

The main model features are presented in Table 6.

Table 6: Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with gMG	Aligning with the description in section 3.2
Perspective	Limited societal perspective	According to DMC guidelines

Model features	Description	Justification
Time horizon	Lifetime (52.5 years)	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	14 days	Considered sufficient time to account for the time patients may spend recovering from a worsening of symptoms by clinical experts.
Half-cycle correction	No	Due to the short cycle-length employed by the model, half-cycle correction was not implemented
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Zilucoplan in addition to standard treatment	Intervention of interest
Comparator(s)	SoC treatments	Follows the standard treatment received in the trial.
Clinical outcome	MG-ADL score	Primary outcome of the RAISE clinical trial which is used to assess the impact of MG on patients' daily activities.
Response criteria	A minimum of 3-point reduction from baseline in MG-ADL total score	Change in MG-ADL score was the primary endpoint in the RAISE trial and predictor of HRQoL.
Model outcomes	QALYs, Costs, ICER, NMB	Standard model outcomes

Abbreviations: DMC = Danish medicines Council; MG = Myasthenia Gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living score.

5. Overview of literature

5.1 Literature used for the clinical assessment

Although this application is based on a head-to-head study with a comparator (SoC plus zilucoplan versus SoC plus placebo) relevant to Danish clinical practice, a literature search was conducted (see Appendix H). Literature used in the clinical assessment is presented in Table 7. The full publication of RAISE-XT, described in Howard et al. (2024) (87) was published after the systematic literature search. It was included in the submission, as it describes RAISE-XT (however it is based on an earlier data-cut (8 September 2022) than used in this submission).

Table 7: Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
UCB. Zilucoplan. Clinical Study Report (MG0010). [Data on file]. 30 Jun 2022. (12). Howard JF Jr, Bresch S, Genge A, et al. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Neurol. 2023 May;22(5):395-406 (10).	RAISE/MG0010	NCT04115293	Start: 17/09/2019 Completion: 30/12/2021	Zilucoplan vs. placebo for adult patients with gMG who are anti-AcHR antibody positive.
UCB. RAISE-XT: A Phase 3, Multicenter, Open-Label Extension Study of Zilucoplan in Subjects with Generalised Myasthenia Gravis. Data cut-off: 11 November 2023. [Data on file]. 2024 (11). Howard JF Jr, Bresch S, Farmakidis C, et al. Long-term safety and efficacy of zilucoplan in patients with generalized myasthenia gravis: interim analysis of the RAISE-XT open-label extension study. Ther Adv Neurol Disord. 2024 Apr 17;17 (87).	RAISE-XT/MG0011	NCT04225871	Start: 23/12/2019 Data cut-off: 11/11/2023Ω Estimated completion: 20/05/2026	Zilucoplan vs. placebo for adult patients with gMG who are anti-AcHR antibody positive.

Abbreviations: AcHR = acetylcholine receptor; gMG = genralised myasthenia gravis.
Notes: * If there are several publications connected to a trial, include all publications used. Ω The median duration of exposure was 2.2 years (range: 0.11-5.6).
Sources: ClinicalTrials.gov, 2019 (88); ClinicalTrials.gov, 2020 (89); Howard et al., 2024 (87); UCB, 2024 (11).

5.2 Literature used for the assessment of health-related quality of life

The main health-related quality of life data was obtained from the RAISE trial (87). Disutilities for clinical events and use of corticosteroids were based on literature. The health-related quality of life literature search is described in Appendix I, while the results of the literature search was not found relevant to include in this submission due to the data obtained from the RAISE trial (87). The literature used for health-related quality of life is presented in Table 8.

Table 8: Relevant literature included for health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
UCB. Zilucoplan. Clinical Study Report (MG0010). [Data on file]. 30 Jun 2022. (12). Howard JF Jr, Bresch S, Genge A, et al. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Neurol. 2023 May;22(5):395-406 (10).	Full utility regression based on Danish preference weights.	Described in section 10.1
Canadian Agency for Drugs and Technologies in Health. Common Drug Review. Pharmacoeconomic report: Eculizumab (Soliris); Company: Alexion Pharma Canada Corporation. 2020. (90)	Exacerbation disutility	Described in section 10.3
Saunders R, Geogopoulos D. Evaluating the Cost-Effectiveness of Proportional-Assist Ventilation Plus vs. Pressure Support Ventilation in the Intensive Care Unit in Two Countries. Frontiers in Public Health. 2018;6:168. (91)	Myasthenic crisis disutility	Described in section 10.3
Medicinrådets anbefaling vedr. efgartigimod alfa til behandling af myastenia gravis. (92)	Corticosteroid-use disutility	Described in section 10.3

5.3 Literature used for inputs for the health economic model

The main efficacy input was based on trial data. Rates for exacerbation and myasthenic crisis was derived from literature. Gajdos et al., 2005 (93) was identified in the SLR, which is presented in Appendix H. Both Abuzinadah et al 2021 (94) and Alshekhlee et al., 2009 (95) were identified via desktop searches, thus these are not described in Appendix J. The studies are presented in Table 9.

Table 9: Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Abuzinadah AR, Alanazy MH, Butt NS, Barohn RJ, Dimachkie MM. Exacerbation Rate in Generalized Myasthenia Gravis and Its Predictors. European neurology. 2021;84(1):43-8. (94)	Clinical event rates for exacerbations and myasthenic crisis.	Desktop research	Described in section 8.2.2.1

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. Neurology. 2009 May 5;72(18):1548-54. doi: 10.1212/WNL.0b013e3181a41211. PMID: 19414721. (95).	Increased risk of death during myasthenic crisis.	Desktop research	Described in section 8.2.2.1
Gajdos P, Tranchant C, Clair B, et al. Treatment of Myasthenia Gravis Exacerbation With Intravenous Immunoglobulin: A Randomized Double-blind Clinical Trial. Arch Neurol. 2005;62(11):1689–1693. doi:10.1001/archneur.62.11.1689 (93)	Clinical event rates myasthenic crisis for patients already in exacerbation.	Systematic literature search	Described in section 8.2.2.1

6. Efficacy

6.1 Efficacy of zilucoplan compared to placebo for adult patients with gMG who are anti-AChR antibody positive

6.1.1 Relevant studies

The comparative efficacy of zilucoplan vs. placebo is informed by the head-to-head study RAISE/MG0010 (double-blind (DB) phase). In addition, long-term safety and efficacy data is informed by the RAISE-XT/MG0011 study, which is an open label extension (OLE) study. The studies are presented in Table 10.

In both studies, the study participants were expected to remain on stable doses of all medications unless medically indicated changes became necessary. Thus, unless otherwise indicated, all SoC therapy medications for gMG were kept at the same dose throughout the study, including corticosteroids and immunosuppressant therapy drugs. If escalation of gMG therapy (i.e., 'rescue therapy') became necessary due to major deterioration of a study participant's clinical status, or risk of MG crisis as per the investigator's judgment, the study participant may have received IVIG or plasma exchange treatment as 'rescue therapy'.

Table 10: Overview of study design for studies included in the comparison of zilucoplan vs. placebo for adult patients with gMG who are AChR-Ab positive

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
RAISE (MG0010), NCT04115293 (10)	Randomised, double-blind, placebo-controlled, phase 3 study	The total duration of study participation for all study participants was up to approximately 16 weeks, including a screening period of up to 4 weeks and a 12-week treatment period.	Adult patients with gMG and positive serology for AChR autoantibodies.	Zilucoplan 0.3 mg/kg/day SC injection	Placebo administered SC daily	Change from baseline to week 12 in MG-ADL score, change from baseline to week 12 in QMG score, change from baseline to week 12 in MGC score, change from baseline to week 12 in MG-QOL15r score, time to first administration of rescue therapy over the 12-week treatment period, achieving MSE (defined as an MG-ADL of 0 or 1 at week 12 without rescue therapy), achieving a ≥3-point reduction in MG-ADL score at week 12 without rescue therapy, achieving a ≥5-point reduction in QMG score at week 12 without rescue therapy, and percentage of participants with treatment-emergent adverse events (TEAEs) at week 19.
RAISE-XT (MG0011), NCT04225871 (87)	Ongoing open label single-group assignment phase 3 study.	From week 12 of the phase 3 study (RAISE/MG0010 (88)) and the phase 2 study (MG0090 (96)) (baseline of the extension study) until week 84 of the extension study.	Adult patients with gMG and positive serology for AChR autoantibodies.	Zilucoplan 0.3 mg/kg/day SC injection	N/A	Incidence of TEAEs (from baseline (day 1) to safety follow-up visit (up to 36 months)), change from baseline to week 12 in MG-ADL score, change from baseline to week 12 in QMG score, change from baseline to week 12 in MGC score, change from baseline to week 12 in MG-QOL15r score, achieving MSE (defined as an MG-ADL of 0 or 1 at week 12 without rescue therapy), decrease in corticosteroid use (week 60 and 120)Ω, decrease in use of immunosuppressants (week 120).

Abbreviations: AChR = acetylcholine receptor; AChR-Ab = acetylcholine receptor antibody; gMG = generalised myasthenia gravis; MGC = myasthenia gravis composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis Quality of Life 15r; MSE = minimal symptom expression; N/A = not applicable; QMG = quantitative myasthenia gravis; SC = subcutaneous; TEAE = treatment-emergent adverse event.
Notes: Ω Decrease in corticosteroids is based on 8 September 2022 data cut-off date and the 11 November 2023 data cut-off. The other outcomes of RAISE-XT are based on the 11 November 2023 data cut-off date.
Sources: UCB, 2022 (12); ClinicalTrials.gov, 2019 (88); UCB, 2024 (11); ClinicalTrials.gov, 2020 (89); UCB, 2024 (79).

6.1.2 Comparability of studies

Not applicable.

6.1.2.1 Comparability of patients across studies

In Table 11, the baseline characteristics of patients included the RAISE study is presented for the modified intention-to-treat (mITT) population (all randomised study participants who received at least one dose of the investigational medicinal product (IMP) and had at least 1 post-dosing MG-ADL score). In addition, in Table 11 the baseline characteristics of patients included the RAISE-XT study is presented for the intention to treat (ITT) population.

Table 11. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety in RAISE (mITT population) and RAISE-XT (ITT population)

	RAISE (DB phase)		RAISE-XT (OLE phase)				
	Placebo (N=88)	Zilucoplan 0.3 mg/kg (N=86)	PBO/ZLP 0.1mg/kg/0.3mg /kg (N=5)	PBO/ZLP 0.3mg/kg (N=90)	ZLP 0.1mg/ kg/0.1mg/ kg/0.3mg/kg (N=12)	ZLP 0.3mg/kg/0.3mg / kg (N=93)	All ZLP (N=200)
Sex, n (%)							
Female	47 (53.4)	52 (60.5)	4 (80)	48 (53)	6 (50)	52 (56)	110 (55)
Male	41 (46.6)	34 (39.5)	1 (20)	42 (47)	6 (50)	41 (44)	90 (45)
Race, n (%)							
American Indian or Alaska Native	1 (1.1)	0	N/A	N/A	N/A	N/A	N/A
Asian	14 (15.9)	7 (8.1)	0	15 (16.7)	0	8 (8.6)	23 (11.5)
Black	7 (8.0)	6 (7.0)	0	7 (7.8)	2 (16.7)	8 (8.6)	17 (8.5)
Native Hawaiian or other Pacific Islander	0	0	N/A	N/A	N/A	N/A	N/A
White	62 (70.5)	66 (76.7)	5 (100)	65 (72.2)	10 (83.3)	72 (77.4)	152 (76.0)
Other/Mixed	0	0	N/A	N/A	N/A	N/A	N/A
Missing	4 (4.5)	7 (8.1)	0	3 (3.3)	0	5 (5.4)	8 (4.0)
Ethnicity, n (%)							
Hispanic or Latino	5 (5.7)	7 (8.1)	0	6 (6.7)	1 (8.3)	7 (7.5)	14 (7.0)

Not Hispanic or Latino	79 (89.8)	72 (83.7)	5 (100)	81 (90.0)	11 (91.7)	82 (88.2)	179 (89.5)
Missing	4 (4.5)	7 (8.1)	0	3 (3.3)	0	4 (4.3)	7 (3.5)
Region, n (%)							
East Asia	9 (10.2)	7 (8.1)	0	9 (10)	0	7 (8)	16 (8)
Europe	33 (37.5)	34 (39.5)	0	32 (36)	0	33 (35)	65 (33)
North America	46 (52.3)	45 (52.3)	5 (100)	49 (54)	12 (100)	53 (57)	119 (60)
Age (years) [a], mean (SD)	53.3 (15.7)	52.6 (14.6)	60.6 (14.8)	53.7 (15.5)	50.4 (15.3)	52.9 (14.5)	53.3 (15.0)
Age group, n (%) [b]							
≤18 years	0	0	N/A	N/A	N/A	N/A	N/A
19 years to <65 years	62 (70.5)	64 (74.4)	N/A	N/A	N/A	N/A	N/A
≥65 years	26 (29.5)	22 (25.6)	N/A	N/A	N/A	N/A	N/A
Weight (kg), mean (SD)	88.2 (26.58)	90.1 (22.87)	89.0 (29.57)	88.5 (26.25)	96.0 (23.54)	93.1 (23.96)	91.1 (25.06)
Weight (kg) group, n (%)							
<56	6 (6.8)	5 (5.8)	N/A	N/A	N/A	N/A	N/A
56 to <77	25 (28.4)	21 (24.4)	N/A	N/A	N/A	N/A	N/A
77 to <150	54 (61.4)	60 (69.8)	N/A	N/A	N/A	N/A	N/A
≥150	3 (3.4)	0	N/A	N/A	N/A	N/A	N/A
Height (cm), mean (SD)	169.52 (9.98)	169.25 (10.51)	N/A	N/A	N/A	N/A	N/A
Body mass index (BMI) (kg/m²), mean (SD)	30.5 (8.02)	31.4 (7.22)	N/A	N/A	N/A	N/A	N/A
MGFA class, n (%)							
Class II	27 (30.7)	22 (25.6)	2 (40)	29 (32)	3 (25)	25 (27)	59 (30)
Class III	57 (64.8)	60 (69.8)	3 (60)	57 (63)	9 (75)	60 (65)	129 (65)
Class IV	4 (4.5)	4 (4.7)	0	4 (4)	0	8 (9)	12 (6)

Age at disease onset (years), mean (SD)	44.02 (18.67)	43.47 (17.35)	52.60 (12.66)	44.03 (18.70)	38.58 (16.46)	43.43 (17.61)	43.64 (17.94)
Time to diagnosis	Not collected	Not collected	Not collected	Not collected	Not collected	Not collected	Not collected
Duration of disease (years), mean (SD)	8.96 (10.43)	9.34 (9.47)	7.30 (8.09)	9.25 (10.45)	11.53 (8.19)	9.35 (9.36)	9.38 (9.73)
Symptoms at onset, n (%)							
Ocular	34 (38.6)	28 (32.6)	N/A	N/A	N/A	N/A	N/A
Generalised	54 (61.4)	58 (67.4)	N/A	N/A	N/A	N/A	N/A
Prior thymectomy, n (%)	37 (42.0)	45 (52.3)	1 (20.0)	39 (43.3)	7 (58.3)	49 (52.7)	96 (48.0)
Prior MG crisis, n (%)	29 (33.0)	28 (32.6)	0	29 (32.2)	3 (25.0)	30 (32.3)	62 (31.0)
Time since most recent crisis (months) [c], mean (SD)	72.26 (109.76)	75.61 (91.81)	N/A	N/A	N/A	N/A	N/A
gMG refractory, n (%) [d]	44 (50.0)	44 (51.2)	N/A[e]	42 (50, N=84)[e]	N/A[e]	43 (52, N=82)[e]	85 (51, N=166)[e]
MG-ADL score, mean (SD)	10.9 (3.4)	10.3 (2.5)	6.4 (1.5)	7.7 (4.5)	4.3 (3.1)	5.2 (3.9)	6.3 (4.3)
MG-ADL score, n (%)							
≤9	33 (37.5)	33 (38.4)	N/A	N/A	N/A	N/A	N/A
≥10	55 (62.5)	53 (61.6)	N/A	N/A	N/A	N/A	N/A
QMG score, mean (SD)	19.4 (4.5)	18.7 (3.6)	12.6 (2.7)	15.6 (6.0)	13.4 (6.0)	12.5 (5.6)	14.0 (5.9)
QMG score, n (%)							
≤17	38 (43.2)	38 (44.2)	N/A	N/A	N/A	N/A	N/A
≥18	50 (56.8)	48 (55.8)	N/A	N/A	N/A	N/A	N/A
Baseline gMG specific medication [f, g], n (%)							
IVIG, SC immunoglobulin, or PLEX	0	0	N/A	N/A	N/A	N/A	N/A
Cholinesterase inhibitors	73 (83.0)	74 (86.0)	5 (100)	73 (81)	10 (83)	79 (85)	167 (84)
Ambenonium	3 (3.4)	4 (4.7)	N/A	N/A	N/A	N/A	N/A
Pyridostigmine	70 (79.5)	70 (81.4)	N/A	N/A	N/A	N/A	N/A

Corticosteroids	51 (58.0)	59 (68.6)	4 (80)	53 (59)	7 (58)	60 (65)	124 (62)
Prednisone	33 (37.5)	38 (44.2)	N/A	N/A	N/A	N/A	N/A
Prednisolone	16 (18.2)	20 (23.3)	N/A	N/A	N/A	N/A	N/A
Methylprednisolone	2 (2.3)	1 (1.2)	N/A	N/A	N/A	N/A	N/A
Immunosuppressive therapy	N/A	N/A	3 (60)	48 (53)	6 (50)	44 (47)	101 (51)
Azathioprine	18 (20.5)	13 (15.1)	N/A	N/A	N/A	N/A	N/A
Mycophenolate	17 (19.3)	17 (19.8)	N/A	N/A	N/A	N/A	N/A
Cyclosporine	7 (8.0)	6 (7.0)	N/A	N/A	N/A	N/A	N/A
Cyclophosphamide	0	0	N/A	N/A	N/A	N/A	N/A
Methotrexate	1 (1.1)	3 (3.5)	N/A	N/A	N/A	N/A	N/A
Tacrolimus	7 (8.0)	3 (3.5)	N/A	N/A	N/A	N/A	N/A
Rituximab	0	0	N/A	N/A	N/A	N/A	N/A

Abbreviations: BMI = body mass index; DB = double blind; gMG = generalised myasthenia gravis; ITT = intention to treat; IVIG = intraveneous immunogolobulin; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MG-ADL = Myasthenia Gravis Activities of Daily Living; mITT = modified intention to treat; N/A = not applicable; PBO = placebo; PLEX = plasma exchange< OLE = open-label extension; QMG = quantitative myasthenia gravis; SC = subcutaneous; SD = standard deviation; ZLP = zilucoplan.

Notes: [a] Age was calculated as: Year informed consent signed–year of birth. [b] Clinicaltrials.gov age categories. [c] Time since most recent crisis (months) was calculated as: (Date of Study Day 1–Date of crisis)/(365.25/12). [d] 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 SC immunoglobulin at least every 3 months for the 12 months prior to enrollment. [e] Refractory status was not recorded for patients in the phase 2 study. The N for 'PBO/ZLP 0.3mg/kg', 'ZLP 0.3mg/kg/0.3mg/kg', and 'all ZLP groups were 84, 82, and 166 patients, respectively. [f] Baseline medications include any medications that started prior to dosing (in RAISE-XT, it is prior to dosing in the OLE) and continued after (classified as prior and concomitant medications). [g] In RAISE, baseline gMG specific medication is based on the safety population (placebo N=88, zilucoplan N=86).

Sources: UCB, 2022, table 7-4, table 7-5, and table 7-7 (12); Howard et al., 2023, table 1 (10); ClinicalTrials.gov, 2019 (88); UCB, 2024, table 7-4, table 7-5, table 7-6, and table 7-7 (11); Howard et al., 2024 (87).

As seen in Table 11, the demographics of the study population in RAISE were generally well-balanced between the two treatment groups with respect to the key demographic variables, except for sex, where there was a slightly higher proportion of females in the zilucoplan group (60.5%) compared with the placebo group (53.4%).

The observed baseline disease characteristics of the study population in RAISE demonstrated that a broadly selected gMG population with a range of disease severity and across a wide range of disease duration was successfully enrolled. Key measurements used for the primary (MG-ADL) and first secondary (QMG) efficacy endpoints were well-balanced between treatment groups at baseline.

Baseline disease characteristics of the study population in RAISE, including age at disease onset, duration of disease, prior MG crisis, and gMG refractory status were similar between the treatment groups. There was a similar distribution of gMG disease severity between the treatment groups, as measured by MGFA classification, with the majority of study participants in both treatment groups in MGFA Class II (mild disease severity) or class III (moderate disease severity). Approximately 5% of study participants in both treatment groups were in MGFA Class IV (severe disease). A slightly higher proportion of study participants in the zilucoplan group had prior thymectomy compared with the placebo group (52.3% vs, 42.0%, respectively).

gMG-specific baseline characteristics of the study population in RAISE were well-balanced across the primary (MG-ADL) and first secondary (QMG) endpoint measurements, with mean MG-ADL scores of 10.3 and 10.9, and mean baseline QMG scores of 18.7 and 19.4, in the zilucoplan and placebo groups, respectively.

The usage of baseline gMG-specific medications in the study population in RAISE was generally balanced between treatment groups. In RAISE-XT, thirty-four (17%) and 166 (83%) patients were enrolled from the phase 2 and phase 3 studies, respectively, including all patients who completed RAISE (87). Overall, the mean age was 53.3 (SD: 15.0) years. The majority of study participants were female (55.0%) and white (76.0%), and 89.5% of study participants were not of Hispanic or Latino ethnicity in RAISE-XT. A broadly selected gMG population with mild to severe gMG as per MGFA classification was enrolled.

Overall, the patients included in RAISE-XT and RAISE are similar, except from that mean MG-ADL score was 6.3 (SD: 4.3) in the RAISE-XT study compared to 10.3 (SD: 2.5) in the RAISE study, which is expected as the phase 2 study (MG0009) did not require a MG-ADL score, unlike the phase 3 RAISE study, in which patients were required to have an MG-ADL score of $\geq$6 at screening and baseline (12, 87).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

In Table 12, characteristics are shown of the population of Danish patients and of the trial population representing the modelled population.

Table 12: Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (Vissing et al., 2024 and Andersen et al., 2021) Ω	Value used in health economic model (RAISE clinical trial (10))
Sex, %		
Female	49% [a]	56.9%
Male	51% [a]	43.1%
Age at index date (years), mean	60.5 [a]	53.0
Age at index date (years), median (Q1, Q3)	64.9 (49.0, 75.0) [a]	55.0*
BMI (kg/m²), mean (SD)	27.6 (6.1) [b, c]	31.0
Time to diagnosis	331 days (range 5-4,492 days)	N/a
Duration of disease (years), mean (SD)	11.6 (11.0) [b, c]	9.38*
Prior thymectomy, %	27% [b, c]	48.0%*
MG Treatment, %		
Pyridostigmine	74% [b, d]	80.5%
Azathioprine	46% [b, d]	17.8%
Glucocorticoids	18% [b, d]	63.2%
Atropine	15% [b, d]	0.0%
Mycophenolic acid	8% [b, d]	19.0%
Methotrexate	6% [b, d]	2.3%
Immunosuppressive drugs, other	13% [b, d]	Cyclosporine 7.5% Tacrolimus 5.7%
Immunoglobulin	4% [b, d]	0.0%
Plasmapheresis	1% [b, d]	0.0%
No treatment	0% [b, d]	0.0%
MG-ADL, median (interquartile range)	3 (1–5) [b, c]	10.7

Abbreviations: BMI = body mass index; MG-ADL = Myasthenia Gravis Activities of Daily Living; Q1 = first quartile; Q3 third quartile; SD = standard deviation.
Notes: Ω Time to diagnosis is not based on these two publications, as it is based on unpublished data (described in section 3.2) (64). *Parameter not used in the model, but the numbers represent those of the modelled population. [a] Based on a Danish population of 1,559 patiens when restricting to ≥2 new diagnoses of MG during the study period (2000-2020) (7). [b] Based on a Danish population of 486 patients with MG, who were regularly followed by a neurologist and were on active MG treatment (97). [c] As some responders completed the questionnaires partially there was missing data in the sub-sample: thymectomy (n=1), BMI (n=4), MG-duration (n=2), and MG-ADL (n=39). [d] Multiple answers so percentages do not add to 100%.
Sources: Vissing et al., 2024 (7); Andersen et al., 2021 (97); UCB, 2024 (64).

The Danish population and the trial population are similar with regards to sex, BMI, and duration of disease. The Danish population is older (60.5 years at index date) than the trial population (54.0 years at index date). In addition, less patients in the Danish population have had prior thymectomy (27%) than in the trial population (48%). Further, the

trial population has a higher MG-ADL score than the Danish population, and the distribution of patients using each treatment differs between the trial and the Danish population (Table 12).

6.1.4 Efficacy – results per RAISE

The number and proportion of patients that discontinued the study in the zilucoplan and placebo arm, respectively, and the reason for discontinuation are presented in Table 13.

Table 13: Discontinuation in RAISE (mITT population)

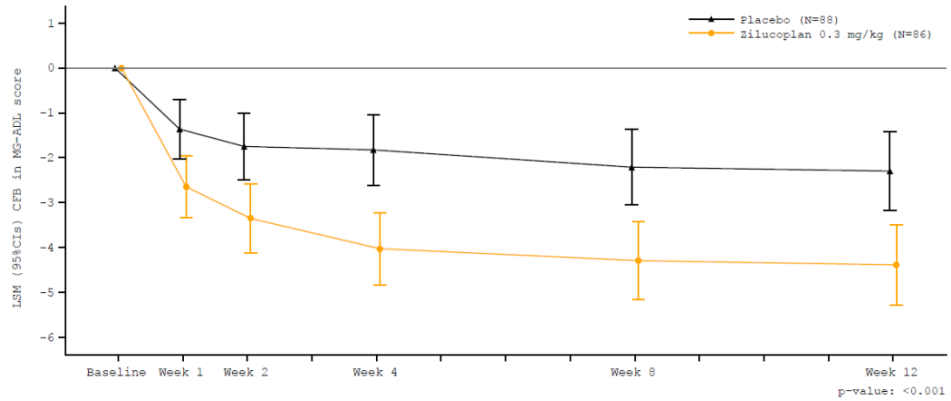
	Placebo (N=88)	Zilucoplan 0.3 mg/kg (N=86)
Discontinued, n (%)	4 (4.5)	4 (4.7)
Primary reason for discontinuation, n (%)		
Adverse event, n (%)	0	2 (2.3)
Lost to follow-up, n (%)	0	0
Withdrawal by study participant, n (%)	2 (2.3)	1 (1.2)
Physician decision, n (%)	1 (1.1)	0
Protocol violation, n (%)	0	0
Death, n (%)	1 (1.1)	1 (1.2)
Safety reasons as determined by the investigator or sponsor, n (%)	0	0
Intolerability of IMP, n (%)	0	0
Other, n (%)	0	0

Abbreviations: IMP = investigational medicinal product; mITT = modified intention-to-treat.
Source: UCB, 2022, table 7-1 (12); Howard et al., 2023 (10).

6.1.4.1 MG-ADL score

The mean change from baseline through week 12 in MG-ADL score using MMRM ANCOVA is presented for the mITT population in Figure 2; a summary of the change is presented in Table 14.

Figure 2: LS mean change from baseline to week 12 in MG-ADL score (mITT population [MMRM ANCOVA])



Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; LS = least squares; LSM = least squares mean; MG-ADL = Myasthenia Gravis Activities of Daily Living; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; QMG = quantitative myasthenia gravis.
Notes: 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.
Source: UCB, 2022, figure 8-1 (12); Howard et al., 2023, figure 2 (10).

Table 14: LS mean change from baseline to week 12 in MG-ADL score (mITT population, MMRM ANCOVA)

Statistic	Placebo (N=88)	Zilucoplan 0.3 mg/kg (N=86)
LS mean (SE; 95% CI)	-2.30 (SE: 0.44; 95% CI: -3.17, -1.43)	-4.39 (SE: 0.45; 95% CI: -5.28, -3.50)
LS mean difference [a] (SE; 95% CI; p-value [b])	N/A	-2.09 (SE: 0.58; 95% CI: -3.24, -0.95; p <0.001)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ICE1 = rescue therapy; ICE2 = death or myasthenic crisis; IMP = investigational medicinal product; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; N/A = not applicable; QMG = quantitative myasthenia gravis; SE = standard error.
Notes: [a] The LS mean difference presented was zilucoplan 0.3mg/kg minus placebo. [b] p-value corresponded to the primary analysis of the primary endpoint of change from baseline to week 12 in MG-ADL score.
- Baseline was defined as the last available predose value prior to the first injection of IMP in the treatment period, or if missing, the screening value.
- MG-ADL scores after rescue therapy (ICE1) or any death or myasthenic crisis (ICE2) were censored and considered as treatment failure. Any missing data due to ICE1 or ICE2 were imputed based on baseline MG-ADL score or on the last available MG-ADL score, whichever was worst. Other missing scores were handled based on the maximum likelihood estimation method under the missing at random assumption.
- Analysis was based on a MMRM ANCOVA model 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. The MMRM ANCOVA includes weeks 1, 2, 4, 8, and 12.
Source: UCB, 2022, table 8-1 (12); Howard et al., 2023, table 2 (10).

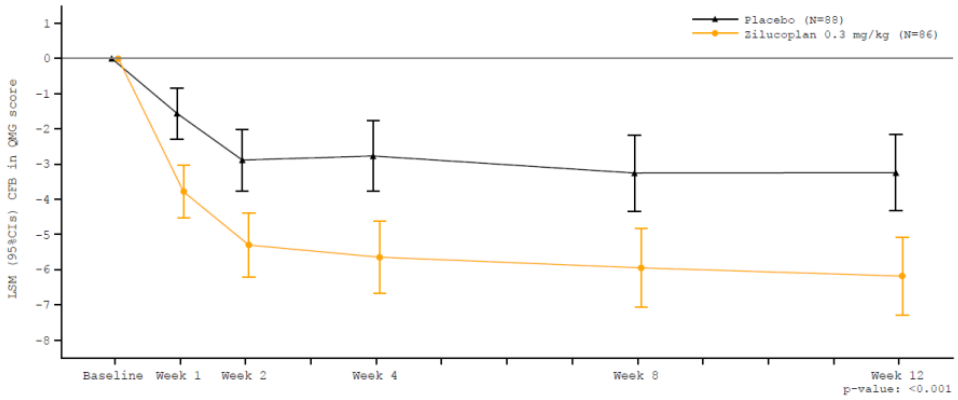
There was a rapid onset of action in the zilucoplan group, based on separation from placebo, in the change from baseline in MG-ADL score. This separation started at week 1, increased through week 4 with stabilisation thereafter, and was maintained through week 12. At each visit after baseline, the 95% CI for the mean difference in MG-ADL score between the zilucoplan and the placebo groups did not include 0. Additionally, no fluctuation of the placebo effect was observed for the change from baseline in MG-ADL score (Figure 2).

The mean change from baseline in MG-ADL score at week 12 was -4.39 in the zilucoplan group and -2.30 in the placebo group. A clinically meaningful and highly statistically significant improvement from baseline to week 12 in MG-ADL score was observed in the zilucoplan group compared with the placebo group, with a mean difference of -2.09 (p<0.001) (Table 14).

6.1.4.2 QMG score

The mean change from baseline through week 12 in QMG score using MMRM ANCOVA is presented for the mITT population in Figure 3; a summary of the LS mean change from baseline to week 12 is presented in Table 15.

Figure 3: LS mean change from baseline to week 12 in QMG score (mITT population [MMRM ANCOVA])



Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; LS = least quares; LSM = least squares mean; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; QMG = quantitative myasthenia gravis.
Source: UCB, 2022, figure 8-3 (12); Howard et al., 2023, figure 2 (10).

Table 15: LS mean change from baseline to week 12 in QMG score (mITT population, MMRM ANCOVA)

Statistic	Placebo (N=88)	Zilucoplan 0.3 mg/kg (N=86)
LS mean (SE; 95% CI)	-3.25 (SE: 0.55; 95% CI: -4.32, -2.1)	-6.19 (SE: 0.56; 95% CI: -7.29, -5.08)
LS mean difference [a] (SE; 95% CI; p-value [b])	N/A	-2.94 (SE: 0.73; 95% CI: -4.39, -1.49; p <0.001)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; IMP = investigational medicinal product; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; N/A = not applicable; QMG = quantitative myasthenia gravis; SE = standard error.
Notes: [a] The LS mean difference presented was zilucoplan 0.3mg/kg minus placebo. [b] p-value corresponded to the primary analysis of the secondary endpoint of change from baseline to Week 12 in QMG score. Following the multiplicity adjustment, a result was considered statistically significant if the primary analysis of change from baseline to week 12 in MG-ADL score was also statistically significant at α=0.05 using 2-sided statistical testing.
- Baseline was defined as the last available predose value prior to the first injection of IMP in the treatment period, or if missing, the screening value.
- QMG scores after ICE1 or any ICE2 were censored and considered as treatment failure. Any missing data due to ICE1 or ICE2 were imputed based on baseline QMG score or on the last available QMG score, whichever was worst. Other missing scores were handled based on the maximum likelihood estimation method under the missing at random assumption.
- Analysis was based on a MMRM ANCOVA model 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. The MMRM ANCOVA included weeks 1, 2, 4, 8, and 12.
Source: UCB, 2022, table 8-8 (12); Howard et al., 2023, table 2 (10).

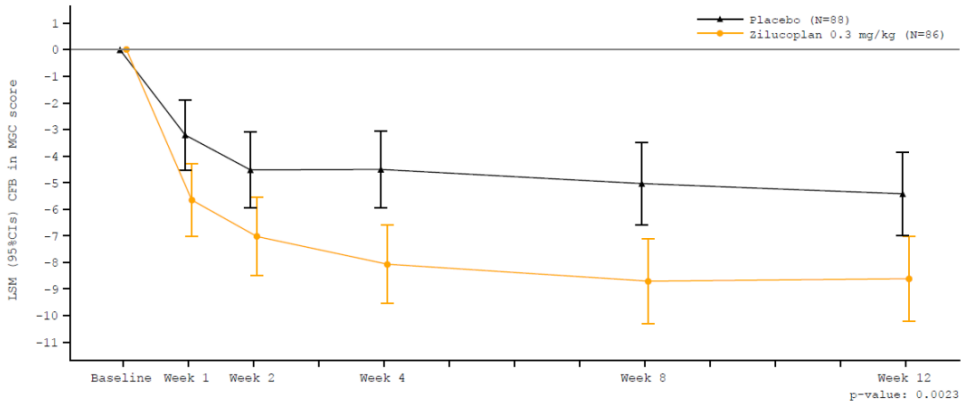
There was a rapid onset of action in the zilucoplan group, based on separation from placebo, in the change from baseline in QMG score. This separation started at week 1, increased through week 4 with stabilisation thereafter, and was maintained through week 12. At each visit after baseline, the 95% CI for the LS mean difference in QMG score between the zilucoplan and the placebo 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 3).

The mean change from baseline to week 12 in QMG score was -6.19 in the zilucoplan group and -3.25 in the placebo group. A highly statistically significant improvement from baseline to Week 12 in QMG score was observed in the zilucoplan group compared with the placebo group, with a mean difference of -2.94 (p<0.001) (Table 15). The mean difference in QMG score of -2.94 favouring the zilucoplan group was consistent with the -3.0 threshold for clinical meaningfulness.

6.1.4.3 MGC score

The mean change from baseline through week 12 in MGC score using MMRM ANCOVA is presented for the mITT population in Figure 4; a summary of the mean change from baseline to week 12 is presented in Table 16.

Figure 4: LS mean change from baseline to week 12 in MGC score (mITT population [MMRM ANCOVA])



Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; LS = least quares; LSM = least squares mean; MG-ADL = Myasthenia Gravis Activities of Daily Living, MGC = myasthenia gravis composite; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; QMG = quantitative myasthenia gravis.
Note: 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.
Source: UCB, 2022, figure 8-4 (12); Howard et al., 2023, figure 2 (10).

Table 16: LS mean change from baseline to week 12 in MGC score (mITT population, MMRM ANCOVA)

Statistic	Placebo (N=88)	Zilucoplan 0.3 mg/kg (N=86)
LS mean (SE; 95% CI)	-5.42 (SE: 0.79; 95% CI: -6.98, -3.86)	-8.62 (SE: 0.81; 95% CI: -10.22, -7.01)
LS mean difference [a] (SE; 95% CI; p-value [b])	N/A	-3.20 (SE: 1.03; 95% CI: -5.24, -1.16; p=0.0023)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ICE1 = rescue therapy; ICE2 = any death or myasthenic crisis; IMP = investigational medicinal product; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; N/A = not applicable; QMG = quantitative myasthenia gravis; SE=standard error.
Notes: [a] The LS mean difference presented was zilucoplan 0.3mg/kg minus placebo. [b] The p-value corresponds to the primary analysis of the secondary endpoint of change from baseline to week 12 in MGC score. Following

the multiplicity adjustment, result was considered statistically significant if the primary analysis of the primary efficacy endpoint of change from baseline to Week 12 in MG-ADL score and the primary analysis of the secondary efficacy endpoint of change from baseline to week 12 in QMG scores were also statistically significant at α=0.05 using 2-sided statistical testing.
- Baseline was defined as the last available predose value prior to the first injection of IMP in the treatment period, or if missing, the screening value.
- The MGC scores after ICE1 or ICE2 were censored and considered as treatment failure. Any missing data due to ICE1 or ICE2 were imputed based on baseline MGC score or on the last available MGC score, whichever was worst. Other missing scores were handled based on the maximum likelihood estimation method under the missing at random assumption.
- Analysis was based on a MMRM ANCOVA model using an unstructured correlation matrix with treatment, baseline MG-ADL score, baseline QMG score, baseline MGC 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. The MMRM ANCOVA included weeks 1, 2, 4, 8, and 12.
Source: UCB, 2022, table 8-9 (12); Howard et al., 2023, table 2 (10).

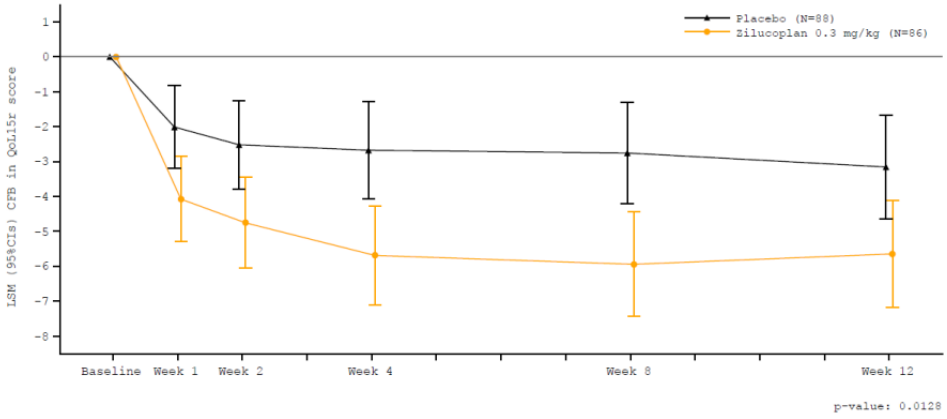
There was a rapid onset of action in the zilucoplan group, based on separation from placebo, in the change from baseline in MGC score. This separation started at week 1 and increased through week 4 with stabilisation thereafter; this effect was maintained through week 12. At each visit after baseline, the 95% CI for the LS mean difference in MGC score between the zilucoplan and the placebo groups did not include 0. Additionally, no fluctuation of the placebo effect was observed for the change from baseline in MGC score (Figure 4).

The mean change from baseline to week 12 in MGC score was -8.62 in the zilucoplan group and -5.42 in the placebo group. A clinically meaningful and statistically significant improvement from baseline to week 12 in MGC score was observed in the zilucoplan group compared with the placebo group, with a mean difference of -3.20 (p=0.0023) (Table 16).

6.1.4.4 MG-QOL15r score

The mean change from baseline through week 12 in MG-QOL15r score is presented using MMRM ANCOVA for the mITT population in Figure 5; a summary of the mean change from baseline to week 12 is presented in Table 17.

Figure 5: LS mean change from baseline to week 12 in MG-QOL15r score (mITT population [MMRM ANCOVA])



Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; LS = least squares: LSM = least squares mean; MG-ADL=Myasthenia Gravis Activities of Daily Living; MG-QOL15r =

Myasthenia Gravis-Quality of Life 15r; mITT=modified intention-to-treat; MMRM = mixed model repeated measure, QMG = quantitative myasthenia gravis.
Note: 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.
Source: UCB, 2022, figure 8-4 (12); Howard et al., 2023, fiugre 2 (10).

Table 17: LS mean change from baseline to week 12 in MG-QOL15r score (mITT population, MMRM ANCOVA)

Statistic	Placebo (N=88)	Zilucoplan 0.3 mg/kg (N=86)
LS mean (SE; 95% CI)	-3.16 (SE: 0.76; 95% CI: -4.65, -1.67)	-5.65 (SE: 0.77; 95% CI: -7.17, -4.12)
LS mean difference [a] (SE; 95% CI; p-value [b])	N/A	-2.49 (SE: 0.99; 95% CI: -4.45, -0.54; p=0.0128)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ICE1 = rescue therapy; ICE2 = any death or myasthenic crisis; IMP = investigational medicinal product; LS = least squares; MGC = Myasthenia Gravis Composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis Quality of Life 15r; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; N/A = not applicable; QMG = quantitative myasthenia gravis; SE = standard error.
Notes: [a] The LS mean difference presented was zilucoplan 0.3mg/kg minus placebo. [b] The p-value corresponded to the primary analysis of the secondary endpoint of change from baseline to week 12 in MG-QOL15r score. Following the multiplicity adjustment, a result was considered statistically significant if the primary analysis of change from baseline to week 12 in MG-ADL score and the primary analyses of change from baseline to Week 12 in QMG and MGC scores were also statistically significant at α=0.05 using 2-sided statistical testing.
- Baseline was defined as the last available predose value prior to the first injection of IMP in the treatment teriod, or if missing, the screening value.
- The MG-QOL15r scores after ICE1 or ICE2 were censored and considered as treatment failure. Any missing data due to ICE1 or ICE2 were imputed based on baseline MG-QOL score or on the last available MG-QOL score, whichever was worst. Other missing scores were handled based on the maximum likelihood estimation method under the missing at random assumption.
- Analysis was based on a MMRM ANCOVA model using an unstructured correlation matrix with treatment, baseline MG-ADL score, baseline QMG score, baseline MG-QOL15r, region (North America, Europe, and East Asia) and interactions terms treatment-by-visit and baseline MG-QOL15r score by-visit as fixed effects; study participants were added as random effects in the model. The MMRM ANCOVA included Weeks 1, 2, 4, 8, and 12.
Source: UCB, 2022, table 8-10 (12); Howard et al., 2023, table 2 (10).

There was a rapid onset of action in the zilucoplan group, based on separation from placebo, in the mean change from baseline in MG-QOL15r score. 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 mean difference in MG-QOL15r score between the zilucoplan and the placebo groups did not include 0. Additionally, no fluctuation of the placebo effect was observed for the change from baseline in MG-QOL15r score (Figure 5).

The mean change from baseline to week 12 in MG-QOL15r score was -5.65 in the zilucoplan group and -3.16 in the placebo group. A statistically significant improvement from baseline to week 12 in MG-QOL15r score was observed in the zilucoplan group compared with the placebo group, with a mean difference of -2.49 (p=0.0128) (Table 17).

6.1.4.5 MSE achievement

A summary of MSE without rescue therapy at week 12 is presented for the mITT population in Table 18.

Table 18: MSE without rescue therapy at week 12 (mITT population, logistic regression)

Statistic	Placebo (N=88)	Zilucoplan 0.3 mg/kg (N=86)
Responder (imputed), %	5.8	14.0
Odds ratio [a] (95% CI; p-value)	N/A	2.608 (95% CI: 0.866, 7.860; p=0.0885)

Abbreviations: AE = adverse event; CI = confidence interval; ICE1 = rescue therapy; ICE2 = death or myasthenic crisis; MGC = Myasthenia Gravis Composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis Quality of Life 15r; mITT = modified intention-to-treat; MSE = minimal symptom expression; N/A = not applicable; QMG = quantitative myasthenia gravis.
Notes: [a] The odds ratio was estimated and tested between treatment groups using a logistic regression model with treatment as factor, baseline MG-ADL score at each imputed dataset. Treatment effects and standard errors were combined across 100 imputed datasets to produce an overall treatment effect p-value. An odds ratio >1 indicated a greater likelihood of response on zilucoplan 0.3mg/kg compared with placebo.
- Missing MG-ADL scores were imputed under the missing at random assumption. Following to the imputation, study participants were considered as responders or non-responders; study participants who received rescue therapy (ICE1) or experienced an AE of death or myasthenic crisis (ICE2) were considered also as non-responders after the date of the intercurrent event (non-responder imputation approach).
- Following the multiplicity adjustment, result was considered statistically significant if the primary analysis of change from baseline to week 12 in MG-ADL score and the primary analysis of change from baseline to week 12 in QMG, MGC, and MG-QOL15r scores were also statistically significant at α=0.05 using 2-sided statistical testing and if p-value passed the criteria based on Holms procedure for multiplicity, within primary analysis of the endpoints of time to rescue therapy, achieving ≥3-point improvement in MG-ADL score and ≥5-point improvement in QMG score without rescue therapy.
Source: UCB, 2022, table 8-13 (12).

The imputed percentage of study participants achieving MSE at week 12 was higher in the zilucoplan group (14.0%) compared with the placebo group (5.8%). This difference favoured zilucoplan numerically (p=0.0885) Table 18.

6.1.5 Efficacy – results per RAISE-XT

The number and proportion of patients that discontinued the study in the different treatment arms and the reason for discontinuation are presented in Table 19.

Table 19: Discontinuation in RAISE-XT (ITT population, 11 November 2023)

	PBO/ZLP 0.1mg/kg/0.3mg/kg (N=5)	PBO/ZLP 0.3mg/kg (N=90)	ZLP 0.1mg/kg/0.1mg/kg/0.3mg/kg (N=12)	ZLP 0.3mg/kg/0.3mg/ kg (N=93)	All ZLP (N=200)
Discontinued, n (%)	1 (20.0)	32 (35.6)	1 (8.3)	7 (7.5)	54 (27.0)
Primary reason for discontinuation, n (%)					
Adverse event, n (%)	0	7 (7.8)	0	2 (2.2)	9 (4.5)
Lost to follow-up, n (%)	0	0	0	3 (3.2)	3 (1.5)
Withdrawal by study participant, n (%)	0	12 (3.3)	1 (8.3)	7 (7.5)	20 (10.0)
Physician decision, n (%)	0	6 (6.7)	0	2 (2.2)	8 (4.0)

Death, n (%)	0	2 (2.2)	0	4 (4.3=	6 (3.0)
Other, n (%)	1 (20.0)	4 (4.4)	0	2 (2.2)	7 (3.5)
Missing, n (%)	0	1 (1.1)	0	0	1 (0.5)

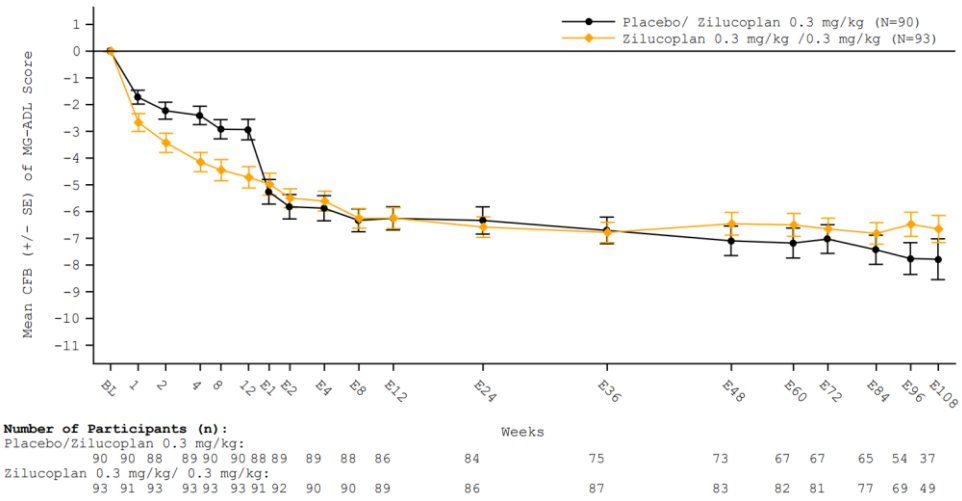
Abbreviations: ITT = intention-to-treat; PBO = placebo; ZLP = zilucoplan.
Source: UCB, 2024, table 14.1.1.4 (11).

In the following, efficacy analyses were performed on the mITT population (all participants who received at least one dose of study drug and had at least one post-dosing MG-ADL score), which included all enrolled patients in RAISE-XT who received at least one dose of zilucoplan and had at least one post-dosing MG-ADL score. Efficacy data are reported for the PBO/ZLP 0.3 (n=90) and ZLP 0.3/ZLP 0.3 (n=93) groups only due to low patient numbers in the PBO/ZLP 0.1/ZLP 0.3 (n=5) and ZLP 0.1/ZLP 0.1/ZLP 0.3 (n=12) groups, and in anticipation of a possible influence on efficacy after receiving 0.1mg/kg zilucoplan in the OLE period of the phase II study before the protocol amendment (87).

6.1.5.1 MG-ADL score (11 November 2023)

The mean change from baseline through week 120 (extension study week E108) in MG-ADL score using MMRM ANCOVA is presented for the mITT population in Figure 6; a summary of the change is presented in Table 20.

Figure 6: LS mean change from baseline of MG-ADL score (mITT population [MMRM ANCOVA])



Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; SE = standard error.
Note: Baseline was defined as the last available assessment before first administration in the double-blind study or parent study. E denotes extension. I.e., E12 is week 12 of RAISE-XT (OLE phase) but week 24 or the DB phase. No data were censored, and any missing data were assumed to be missing at random.
Source: UCB, 2024, figure 1.1.4 (11).

Table 20: LS mean change from baseline in MG-ADL score (mITT population, MMRM ANCOVA)

Statistic	PBO/ZLP 0.3 mg/kg (N=90)	ZLP 0.3 mg/kg / 0.3 mg/kg (N=93)	ZLP 0.3 mg/kg pooled (N=183)*
LS mean CFB at week 12 (SE; 95% CI)	-2.20 (SE: 0.68; 95% CI: -3.53, -0.87)	-4.59 (SE: 0.53; 95% CI: -5.62, -3.56)	-3.69 (SE: 0.34; 95% CI: -4.36, -3.02)

LS mean CFB at week 24 (week E12) (SE; 95% CI)	-6.17 (SE: 0.59; 95% CI: -7.32, -5.02)	-5.90 (SE: 0.47; 95% CI: -6.82, -4.98)	-4.19 (SE 0.35; 95% CI: -4.88, -3.49)
LS mean difference week 12 vs. week 24 (95% CI; p-value)	3.97 (95% CI: 2.20, 5.74; p<0.0001)	-1.31 (95% CI: -0.05, 2.68; p=0.0597)	N/A
LS mean CFB at week 120 (week E108) (SE; 95% CI)	-7.09 (SE: 0.70; 95% CI: -8.46, -5.73)	-6.37 (SE: 0.54; 95% CI: -7.42, -5.31)	N/A

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; N/A = not applicable; PBO = placebo; QMG = quantitative myasthenia gravis; SE = standard error; ZLP = zilucoplan.
Notes: Baseline is defined as the baseline in the parent study (MG0009/MG0010). CFB in MG-ADL were estimated using a MMRM ANCOVA with baseline MG-ADL score, baseline QMG score, geographical region, parent study factor and baseline score X visit (interaction term) as fixed effects and participant as a random effect. The model included weeks 1 to 12 (double-blind treatment period) and week E1 to week E108 (open-label extension). An AR(1) correlation structure was used. Separate model was fitted for each group: PBO/ ZLP 0.3 mg/kg and ZLP 0.3 mg/kg /0.3 mg/kg. * In the pooled ZLP group, the week number indicates the number of weeks on ZLP treatment (i.e., the baseline is the start of ZLP treatment). For instance, week 24 represents 24 weeks of ZLP treatment, which is measured at week 24 in the ZLP/ZLP group and at week 36 in the PBO/ZLP group, where patients crossed over to ZLP at week 12.
Source: UCB, 2024, table 14.2.1.10.1 and table 14.2.1.10.2 (11).

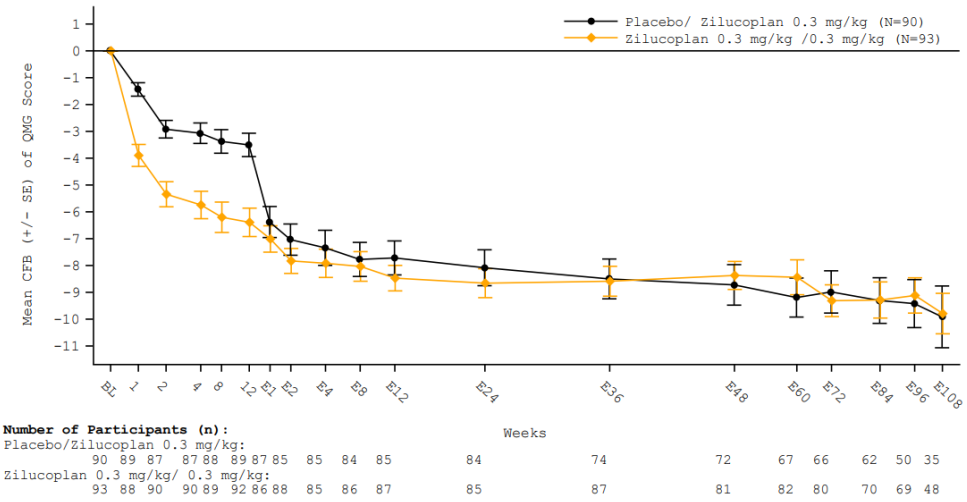
In the zilucoplan/zilucoplan group, MG-ADL score continued to improve further through week 24 and was sustained through week 120. In the placebo/zilucoplan group, a rapid improvement was observed at week 13 after switching to zilucoplan, with further improvement observed through week 24 and sustained through week 120 (Figure 6 and Table 20).

In the pooled zilucoplan/zilucoplan 0.3 mg/kg and placebo/zilucoplan 0.3 mg/kg groups from week 24, there was a sustained improvement in MG-ADL score up to week 120 (Table 20).

6.1.5.2 QMG score (11 November 2023)

The mean change from baseline through week 120 (week E108) in QMG score using MMRM ANCOVA is presented for the mITT population in Figure 7; a summary of the change is presented in Table 21.

Figure 7: LS mean change from baseline of QMG score (mITT population [MMRM ANCOVA])



Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; LS = least squares; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; QMG = Quantitative myasthenia gravis; SE = standard error.
Note: Baseline was defined as the last available assessment before first administration in the double-blind study or parent study. E denotes extension. I.e., E12 is week 12 of RAISE-XT (OLE phase) but week 24 or the DB phase. No data were censored, and any missing data were assumed to be missing at random.
Source: UCB, 2024, figure 1.2.4 (11).

Table 21: LS mean change from baseline in QMG score (mITT population, MMRM ANCOVA)

Statistic	PBO/ZLP 0.3 mg/kg (N=90)	ZLP 0.3 mg/kg / 0.3 mg/kg (N=93)	ZLP 0.3 mg/kg pooled (N=183)*
LS mean CFB at week 12 (SE; 95% CI)	-2.94 (SE: 0.90; 95% CI: -4.71, -1.17)	-6.56 (SE: 0.73; 95% CI: -8.00, -5.12)	-5.94 (SE: 0.45; 95% CI: -6.84, -5.05)
LS mean CFB at week 24 (week E12) (SE; 95% CI)	-8.53 (SE: 0.79; 95% CI: -10.08, -6.98)	-8.78 (SE: 0.66; 95% CI: -10.08, -7.48)	-6.75 (SE: 0.47; 95% CI: -7.68, -5.82)
LS mean difference week 12 vs. week 24 (95% CI; p-value)	5.59 (95% CI: 3.33, 7.84; p<0.0001)	2.22 (95% CI: 0.38, 4.06; p=0.0181)	N/A
LS mean CFB at week 120 (week E108) (SE; 95% CI)	-9.56 (SE: 0.95; 95% CI: -11.43, -7.70)	-10.38 (SE: 0.75; 95% CI: -11.86, -8.90)	N/A

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; N/A = not applicable; PBO = placebo; QMG = quantitative myasthenia gravis; SE = standard error; ZLP = zilucoplan.
Notes: Baseline is defined as the baseline in the parent study (MG0009/MG0010). CFB in QMG were estimated using a MMRM ANCOVA with baseline MG-ADL score, baseline QMG score, geographical region, parent study factor and baseline QMG score X visit (interaction term) as fixed effects and participant as a random effect. The model included weeks 1 to 12 (double-blind treatment period) and week E1 to week E108 (open-label extension). An AR(1) correlation structure was used. Separate model was fitted for each group: PBO/ZLP 0.3 mg/kg and ZLP 0.3 mg/kg /0.3 mg/kg. * In the pooled ZLP group, the week number indicates the number of weeks on ZLP treatment (i.e., the baseline is the start of ZLP treatment). For instance, week 24 represents 24 weeks of ZLP treatment, which is measured at week 24 in the ZLP/ZLP group and at week 36 in the PBO/ZLP group, where patients crossed over to ZLP at week 12.
Source: UCB, 2024, table 14.2.2.10.1 and table 14.2.2.10.2 (11).

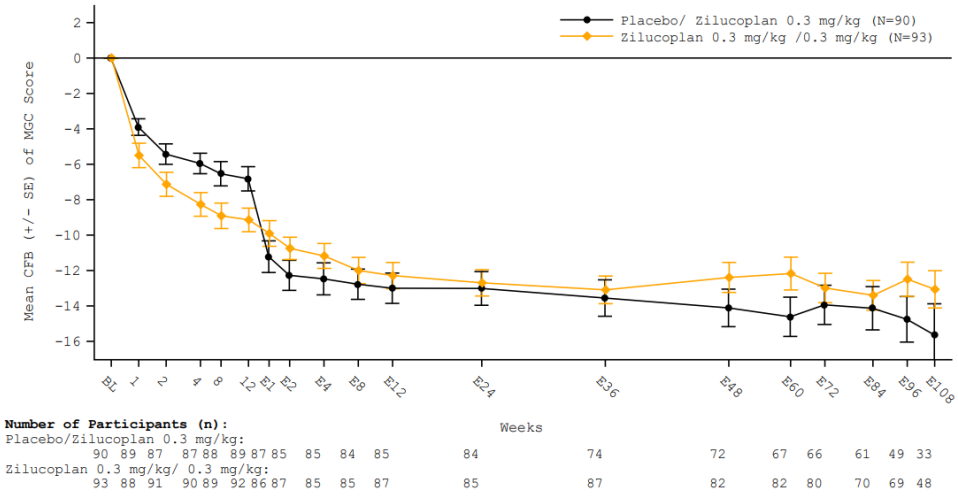
In the zilucoplan/zilucoplan group, QMG score continued to improve further through week 24 and was sustained through week 120. In the placebo/zilucoplan group, a rapid

improvement was observed at week 13 after switching to zilucoplan, with further improvement observed through week 24 and sustained through week 120 (Figure 7 and Table 21). In the pooled zilucoplan/zilucoplan 0.3 mg/kg and placebo/zilucoplan 0.3 mg/kg groups from week 24, there was a sustained improvement in QMG score up to week 120 (Table 21).

6.1.5.3 MGC score (11 November 2023)

The mean change from baseline through week 120 (week E108) in MGC score using MMRM ANCOVA is presented for the mITT population in Figure 8; a summary of the change is presented in Table 22.

Figure 8: LS mean change from baseline of MGC score (mITT population [MMRM ANCOVA])



Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; LS = least squares; mITT = modified intention-to-treat; MGC = Myasthenia Gravis Composite; MMRM = mixed model repeated measure; SE = standard error.
Note: Baseline was defined as the last available assessment before first administration in the double-blind study or parent study. E denotes extension. I.e., E12 is week 12 of RAISE-XT (OLE phase) but week 24 or the DB phase. No data were censored, and any missing data were assumed to be missing at random.
Source: UCB, 2024, figure 1.3.4 (11).

Table 22: LS mean change from baseline in MGC score (mITT population, MMRM ANCOVA)

Statistic	PBO/ZLP 0.3 mg/kg (N=90)	ZLP 0.3 mg/kg / 0.3 mg/kg (N=93)	ZLP 0.3 mg/kg pooled (N=183)*
LS mean CFB at week 12 (SE; 95% CI)	-6.97 (SE: 1.27); 95% CI: -9.47, -4.47)	-9.33 (SE: 0.95; 95% CI: -11.20, -7.46)	-7.67 (SE: 0.63; 95% CI: -8.90, -6.43)
LS mean CFB at week 24 (week E12) (SE; 95% CI)	-12.30 (SE: 1.12; 95% CI: -14.50, -10.09)	-11.77 (SE: 0.86; 95% CI: -13.46, -10.09)	-8.41 (SE: 0.67; 95% CI: -9.74, -7.09)
LS mean difference week 12 vs. week 24 (95% CI; p-value)	5.33 (95% CI: 1.89, 8.77; p=0.0024)	2.24 (95% CI: -0.09, 4.97; p=0.0587)	N/A
LS mean CFB at week 120 (week E108) (SE; 95% CI)	-13.75 (SE: 1.37; 95% CI: -16.45, -11.06)	-13.58 (SE: 0.99; 95% CI: -15.53, -11.64)	N/A

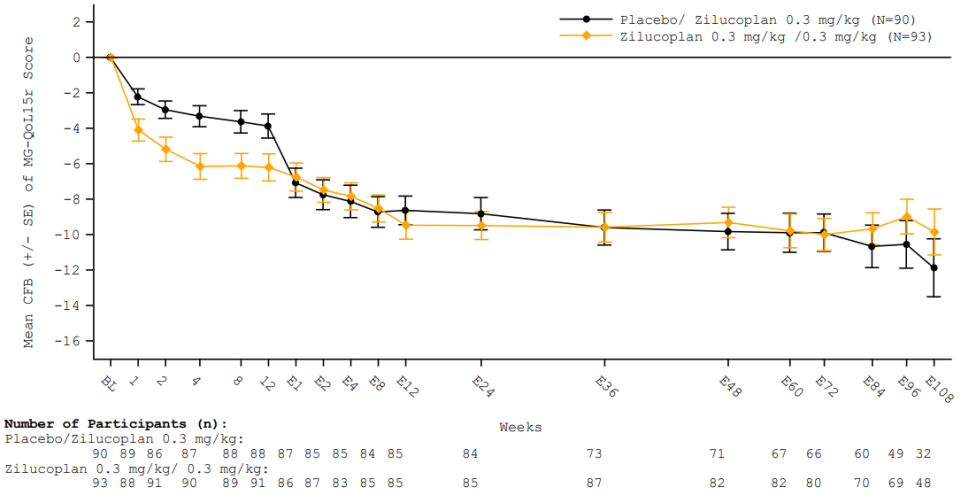
Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; LS = least squares; MGC = Myasthenia Gravis Composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; N/A = not applicable; PBO = placebo; QMG = quantitative myasthenia gravis; SE = standard error; ZLP = zilucoplan.
Notes: Baseline is defined as the baseline in the parent study (MG0009/MG0010). CFB in MGC were estimated using a MMRM ANCOVA with baseline MG-ADL score, baseline QMG score, baseline MGC score, geographical region, parent study factor and baseline score X visit (interaction term) as fixed effects and participant as a random effect. The model included weeks 1 to 12 (double-blind treatment period) and week E1 to week E108 (open-label extension). An unstructured correlation structure was used. Separate model was fitted for each group: PBO/ZLP 0.3 mg/kg and ZLP 0.3 mg/kg /0.3 mg/kg. * In the pooled ZLP group, the week number indicates the number of weeks on ZLP treatment (i.e., the baseline is the start of ZLP treatment). For instance, week 24 represents 24 weeks of ZLP treatment, which is measured at week 24 in the ZLP/ZLP group and at week 36 in the PBO/ZLP group, where patients crossed over to ZLP at week 12.
Source: UCB, 2024, table 14.2.3.10.1 and table 14.2.3.10.2 (11).

In the zilucoplan/zilucoplan group, MGC score continued to improve further through week 24 and was sustained through week 120. In the placebo/zilucoplan group, a rapid improvement was observed at week 13 after switching to zilucoplan, with further improvement observed through week 24 and sustained through week 120 (Figure 8 and Table 22). In the pooled zilucoplan/zilucoplan 0.3 mg/kg and placebo/zilucoplan 0.3 mg/kg groups from week 24, there was a sustained improvement in MGC score up to week 120 (and Table 22).

6.1.5.4 MG-QOL15r score (11 November 2023)

The mean change from baseline through week 120 (week E108) in MG-QOL15r score using MMRM ANCOVA is presented for the mITT population in Figure 9; a summary of the change is presented in Table 23.

Figure 9: LS mean change from baseline of MG-QOL15r score (mITT population [MMRM ANCOVA])



Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; LS = least squares; mITT = modified intention-to-treat; MG-QOL15r = Myasthenia Gravis-Quality of Life 15r; MMRM = mixed model repeated measure; SE = standard error.
Note: Baseline was defined as the last available assessment before first administration in the double-blind study or parent study. E denotes extension. I.e., E12 is week 12 of RAISE-XT (OLE phase) but week 24 or the DB phase. No data were censored, and any missing data were assumed to be missing at random.
Source: UCB, 2024, figure 1.4.4 (11).

Table 23: LS mean change from baseline in MG-QOL15r score (mITT population, MMRM ANCOVA)

Statistic	PBO/ZLP 0.3 mg/kg (N=90)	ZLP 0.3 mg/kg / 0.3 mg/kg (N=93)	ZLP 0.3 mg/kg pooled (N=183)*
LS mean CFB at week 12 (SE; 95% CI)	-2.71 (SE: 1.22); 95% CI: -5.11, -0.31)	-6.15 (SE: 1.05; 95% CI: -8.21, -4.08)	-5.80 (SE: 0.61; 95% CI: -7.00, -4.60)
LS mean CFB at week 24 (week E12) (SE; 95% CI)	-8.07 (SE: 1.08; 95% CI: -10.20, -5.94)	-9.92 (SE: 0.95; 95% CI: -11.79, -8.04)	-6.52 (SE: 0.64; 95% CI: -7.78, -5.26)
LS mean difference week 12 vs. week 24 (95% CI; p-value)	5.36 (95% CI: 2.44, 8.28; p=0.0003)	3.77 (95% CI: -1.19, 6.35; p=0.0042)	N/A
LS mean CFB at week 120 (week E108) (SE; 95% CI)	-8.87 (SE: 1.29; 95% CI: -11.40, -6.34)	-10.21 (SE: 1.08; 95% CI: -12.32, -8.10)	N/A

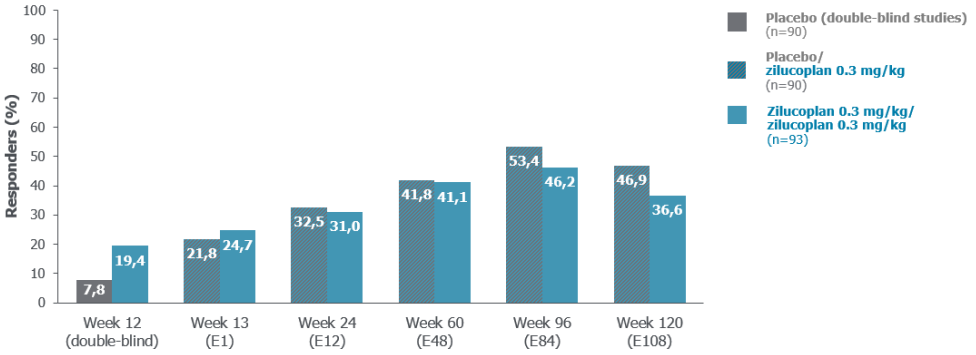
Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis-Quality of Life 15r; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; N/A = not applicable; PBO = placebo; QMG = quantitative myasthenia gravis; SE = standard error; ZLP = zilucoplan.
Notes: Baseline is defined as the baseline in the parent study (MG0009/MG0010). CFB in MG-QOL15r were estimated using a MMRM ANCOVA with baseline MG-ADL score, baseline QMG score, baseline MG-QOL15r score, geographical region, parent study factor and baseline score X visit (interaction term) as fixed effects and participant as a random effect. The model included weeks 1 to 12 (double-blind treatment period) and week E1 to week E108 (open-label extension). An AR(1) correlation structure was used. Separate model was fitted for each group: PBO/ZLP 0.3 mg/kg and ZLP 0.3 mg/kg /0.3 mg/kg. * In the pooled ZLP group, the week number indicates the number of weeks on ZLP treatment (i.e., the baseline is the start of ZLP treatment). For instance, week 24 represents 24 weeks of ZLP treatment, which is measured at week 24 in the ZLP/ZLP group and at week 36 in the PBO/ZLP group, where patients crossed over to ZLP at week 12.
Source: UCB, 2024, table 14.2.4.10.1 and table 14.2.4.10.2 (11).

In the zilucoplan/zilucoplan group, MG-QOL 15r score continued to improve further through week 24 and was sustained through week 120. In the placebo/zilucoplan group, a rapid improvement was observed at week 13 after switching to zilucoplan, with further improvement observed through week 24 and sustained through week 120 (Figure 9 and Table 23). In the pooled zilucoplan/zilucoplan 0.3 mg/kg and placebo/zilucoplan 0.3 mg/kg groups from week 24, there was a sustained improvement in MG-QoL 15r score up to week 120 (Table 23).

6.1.5.5 MSE achievement

A summary of MSE without rescue therapy at week 12 to 120 is presented for the mITT population in Figure 10 and in Table 24.

Figure 10: MSE without rescue therapy up to week 120 (mITT population)



Abbreviations: mITT = modified intention-to-treat; MSE = minimal symptom expression.
Notes: Percentages are based on N, i.e., the number of subjects who have completed each individual time point. Week number of RAISE-XT is denoted with an E.
Source: UCB, 2024 (11).

Table 24: MSE without rescue therapy up to week 120 (mITT population)

Statistic	PBO/ZLP 0.3 mg/kg (N=90)*	ZLP 0.3 mg/kg / 0.3 mg/kg (N=93)*	ZLP 0.3 mg/kg pooled (N=183)*
Responders at week 12, n (%)	7 of 90 (7.8)	18 of 93 (19.4)	25 of 183 (13.7)
Responders at week 13, n (%)	19 of 87 (21.8)	22 of 89 (24.7)	41 of 176 (23.3)
Responders at week 24, n (%)	27 of 79 (32.5)	26 of 81 (31.0)	53 of 160 (31.7)
Responders at week 60, n (%)	28 of 67 (41.8)	30 of 73 (41.1)	58 of 140 (41.4)
Responders at week 96, n (%)	31 of 58 (53.4)	30 of 65 (46.2)	61 of 123 (49.6)
Responders at week 120, n (%)	15 of 32 (46.9)	15 of 71 (36.6)	30 of 73 (41.1)

Abbreviations: mITT = modified intention-to-treat; MSE = minimal symptom expression; PBO = placebo; ZLP = zilucoplan.
Notes: Percentages are based on n, i.e., the number of subjects who have completed each individual time point, e.g., 73 subjects have completed week 120. * N at baseline.
Source: UCB, 2024, table 14.2.8. 1 (11).

MSE responder rates at Week 12 of the double-blind period increased rapidly through week 24 and were sustained through week 120 (Figure 10 and Table 24).

6.1.5.6 Reduction in use of corticosteroids

Table 25 presents the number and percentage of patients, who either experienced a discontinuation or reduction in use of corticosteroids.

Table 25: Reduction in use of corticosteroids at week 60 (8 September 2022)

Statistic	PBO/ZLP 0.3 mg/kg (N=90)	ZLP 0.3 mg/kg / 0.3 mg/kg (N=93)
Discontinuation/reduction of corticosteroid use, n (%)	12 (41)	18 (41)

Abbreviations: PBO = placebo; ZLP = zilucoplan.

Notes: Discontinuation/reduction of corticosteroids use was investigated among participants, who received corticosteroids at baseline and completed the week 60 data cut-off (44 patients in the ZLP 0.3 mg/kg/0.3 mg/kg group and 29 in the PBO/ZLP 0.3 mg/kg group).
Source: Howard et al., 2024 (87).

In both treatment groups 41% of the participants who received corticosteroids at baseline and completed the week 60 data cut-off discontinued or reduced their use of corticosteroids (Table 25). Further, the mean dose reduction in the PBO/ZLP 0.3 mg/kg group was 16 mg (the mean dose at baseline in the double-blind study was 27 mg). The mean dose reduction in the ZLP 0.3 mg/kg / 0.3 mg/kg group was 14 mg (the mean dose at baseline in the double-blind study was 21 mg) (87).

[redacted] (11, 98). [redacted] (98).

6.1.5.7 Reduction in use of immunosuppressants

[redacted] (79).

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

Not applicable.

7.1.2 Method of synthesis

Not applicable.

7.1.3 Results from the comparative analysis

Results from the head-to-head study (RAISE) of zilucoplan vs. placebo as well as results from the OLE study, RAISE-XT, are presented in Table 26. The results presented for RAISE are the same as results presented in Table 14, Table 15, Table 16, and Table 17 in section 6.1.4. The results presented for RAISE-XT are the same as results presented in Table 20, Table 21, Table 22, Table 23 in section 6.1.5.

Table 26: Results from the analysis of the use zilucoplan for adult patients with gMG who are anti-AcHR antibody positive (mITT population, MMRM ANCOVA)

RAISE (DB phase) and RAISE-XT (OLE phase), respectively			
RAISE (DB phase)			
Outcome measure	**Placebo (N=88)**	**Zilucoplan 0.3 mg/kg (N=86)**	**LS mean difference (zilucoplan minus placebo)**
LS mean change in MG-ADL score, week 12	-2.30 (SE: 0.44; 95% CI: -3.17, -1.43)	-4.39 (SE: 0.45; 95% CI: -5.28, -3.50)	-2.09 (SE: 0.58; 95% CI: -3.24, -0.95; p <0.001)
LS mean change in QMG score, week 12	-3.25 (SE: 0.55; 95% CI: -4.32, -2.1)	-6.19 (SE: 0.56; 95% CI: -7.29, -5.08)	-2.94 (SE: 0.73; 95% CI: -4.39, -1.49; p <0.001)
LS mean change in MGC score, week 12	-5.42 (SE: 0.79; 95% CI: -6.98, -3.86)	-8.62 (SE: 0.81; 95% CI: -10.22, -7.01)	-3.20 (SE: 1.03; 95% CI: -5.24, -1.16; p=0.0023)
LS mean change in MG-QOL15r score, week 12	-3.16 (SE: 0.76; 95% CI: -4.65, -1.67)	-5.65 (SE: 0.77; 95% CI: -7.17, -4.12)	-2.49 (SE: 0.99; 95% CI: -4.45, -0.54; p=0.0128)
Achievement of MSE, week 12	5.8%	14.0%	Odds ratio: 2.608 (95% CI: 0.866, 7.860; p-value=0.0885)
RAISE-XT (OLE phase) (11 November 2023)			
Outcome measure	**PBO/ZLP 0.3 mg/kg N=90**	**ZLP 0.3 mg/kg / 0.3 mg/kg N=93**	**ZLP 0.3 mg/kg pooled[Ω] N=183**
LS mean CFB in MG-ADL score at week 12	-2.20 (SE: 0.68; 95% CI: -3.53, -0.87)	-4.59 (SE: (0.53; 95% CI: -5.62, -3.56)	-3.69 (SE: 0.34; 95% CI: -4.36, -3.02)

RAISE (DB phase) and RAISE-XT (OLE phase), respectively			
LS mean CFB in MG-ADL score at week 24 (week E12)	-6.17 (SE: 0.59; 95% CI: -7.32, -5.02)	-5.90 (SE: 0.47; 95% CI: -6.82, -4.98)	-4.19 (SE: 0.35; 95% CI: -4.88, -3.49)
LS mean difference in MG-ADL score week 12 vs. week 24	3.97 (95% CI: 2.20, 5.74; p<0.0001)	-1.31 (95% CI: -0.05, 2.68; p=0.0597)	N/A
LS mean CFB in MG-ADL score at week 120 (week E108)	-7.09 (SE: 0.70; 95% CI: -8.46, -5.73)	-6.37 (SE: 0.54; 95% CI: -7.42, -5.31)	N/A
LS mean CFB in QMG score at week 12	-2.94 (SE: 0.90; 95% CI: -4.71, -1.17)	-6.56 (SE: 0.73; 95% CI: -8.00, -5.12)	-5.94 (SE: 0.45; 95% CI: -6.84, -5.05)
LS mean CFB in QMG score at week 24	-8.53 (SE: 0.79; 95% CI: -10.08, -6.98)	-8.78 (SE: 0.66; 95% CI: -10.08, -7.48)	-6.75 (SE: 0.47; 95% CI: -7.68, -5.82)
LS mean difference in QMG score week 12 vs. week 24	5.59 (95% CI: 3.33, 7.84; p<0.0001)	2.22 (95% CI: 0.38, 4.06; p=0.0181)	N/A
LS mean CFB in QMG score at week 120 (week E108)	-9.56 (SE: 0.95; 95% CI: -11.43, -7.70)	-10.38 (SE: 0.75; 95% CI: -11.86, -8.90)	N/A
LS mean CFB in MGC score at week 12	-6.97 (SE: 1.27); 95% CI: -9.47, -4.47)	-9.33 (SE: 0.95; 95% CI: -11.20, -7.46)	-7.67 (SE: 0.63; 95% CI: -8.90, -6.43)
LS mean CFB in MGC score at week 24 (week E12)	-12.30 (SE: 1.12; 95% CI: -14.50, -10.09)	-11.77 (SE: 0.86; 95% CI: -13.46, -10.09)	-8.41 (SE: 0.67; 95% CI: -9.74, -7.09)
LS mean difference in MGC score week 12 vs. week 24	5.33 (95% CI: 1.89, 8.77; p=0.0024)	2.24 (95% CI: -0.09, 4.97; p=0.0587)	N/A
LS mean CFB in MGC score at week 120 (week E108)	-13.75 (SE: 1.37; 95% CI: -16.45, -11.06)	-13.58 (SE: 0.99; 95% CI: -15.53, -11.64)	N/A
LS mean CFB in MG-QOL5r score at week 12	-2.71 (SE: 1.22); 95% CI: -5.11, -0.31)	-6.15 (SE: 1.05; 95% CI: -8.21, -4.08)	-5.80 (SE: 0.61; 95% CI: -7.00, -4.60)
LS mean CFB in MG-QOL5r score at week 24 (week E12)	-8.07 (SE: 1.08; 95% CI: -10.20, -5.94)	-9.92 (SE: 0.95; 95% CI: -11.79, -8.04)	-6.52 (SE: 0.64; 95% CI: -7.78, -5.26)
LS mean difference in MG-QOL5r score week 12 vs. week 24	5.36 (95% CI: 2.44, 8.28; p=0.0003)	3.77 (95% CI: -1.19, 6.35; p=0.0042)	N/A
LS mean CFB in MG-QOL5r score at week 120 (week E108)	-8.87 (SE: 1.29; 95% CI: -11.40, -6.34)	-10.21 (SE: 1.08; 95% CI: -12.32, -8.10)	N/A
MSE responders at week 12, n (%)	7 of 90 (7.8)	18 of 93 (19.4)	25 of 183 (13.7)
MSE responders at week 13 (week E1), n (%)	19 of 87 (21.8)	22 of 89 (24.7)	41 of 176 (23.3)

RAISE (DB phase) and RAISE-XT (OLE phase), respectively			
MSE responders at week 24 (week E12), n (%)	27 of 79 (32.5)	26 of 81 (31.0)	53 of 160 (31.7)
MSE responders at week 60 (week E48), n (%)	28 of 67 (41.8)	30 of 73 (41.1)	58 of 140 (41.4)
MSE responders at week 96 (week E84), n (%)	31 of 58 (53.4)	30 of 65 (46.2)	61 of 123 (49.6)
MSE responders at week 120 (week E108), n (%)	15 of 32 (46.9)	15 of 71 (36.6)	30 of 73 (41.1)
Discontinuation/reduction of corticosteroid use at week 60, n (%)	12 (41)*	18 (41)*	47 (45.6)
Dose reduction of corticosteroid use at week 60, mean	16 mg*	14 mg*	13 mg
Discontinued corticosteroids at week 60, n (%)	N/A	N/A	9 (8.7)
Discontinuation/reduction of corticosteroid use at week 120, n (%)	N/A	N/A	33 (61.1)
Dose reduction of corticosteroid use at week 120, mean	N/A	N/A	15.5 mg
Discontinued corticosteroids at week 120, n (%)	N/A	N/A	11 (20.4)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AcHR = acetylcholine receptor; ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; DB = double blind; gMG = genralised myasthenia gravis; LS = least squares; MGC = Myasthenia Gravis Composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis Quality of Life 15r; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; MSE = minimal symptom expression; N/A = not applicable; OLE = open-label extension; PBO = placebo; QMG = quantitative myasthenia gravis; SE = standard error; ZLP = zilucoplan.
Notes: Details on the method of analysis used in RAISE is debribed in Table 14, Table 15, Table 16, Table 17, and Table 18 in section 6.1.4, as well as in Appendix B. Details on the method of analysis used in RAISE-XT is debribed in Table 20, Table 21, Table 22, Table 23, Table 24, and Table 25 in section 6.1.5, as well as in Appendix B. Ω In the pooled ZLP group, the week number indicates the number of weeks on ZLP treatment (i.e., the baseline is the start of ZLP treatment). For instance, week 24 represents 24 weeks of ZLP treatment, which is measured at week 24 in the ZLP/ZLP group and at week 36 in the PBO/ZLP group, where patients crossed over to ZLP at week 12. * These values are based on the 8 September 2022 data cut-off
Sources: UCB, 2022 (12); Howard et al., 2023 (10); UCB, 2024 (11); Howard et al., 2024 (87); Hewamadduma et al. 2024 (98); UCB, 2024 (79).

7.1.4 Efficacy – results per [outcome measure]

Not applicable.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

The objective of the economic model is to estimate the cost-effectiveness of zilucoplan in patients with gMG. MG-ADL data collected in the RAISE trial (99) is used to model treatment response and associated exacerbations and myasthenic crises. The RAISE-XT open-label extension (87) provides an additional long-term evidence for patients receiving zilucoplan, including patients who switched from the placebo arm of the RAISE trial, which is described in section 6.1.5. 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.

While a ≥2 point improvement was considered clinical meaningful (56, 80), the ≥3 point improvement in MG-ADL response was the most commonly assessed definition of this outcome across the trials identified in the SLR (see Appendix H). This also applies for the definitions of outcomes in the RAISE trial, which includes the percentage of participants achieving a ≥3-point reduction in MG-ADL score at week 12 without rescue therapy as a secondary outcome. As a result, patients with a minimum of 3-point reduction from baseline in MG-ADL total score after time of response assessment was considered 'responders' in the health economic model.

Figure 11: Health state occupation for zilucoplan

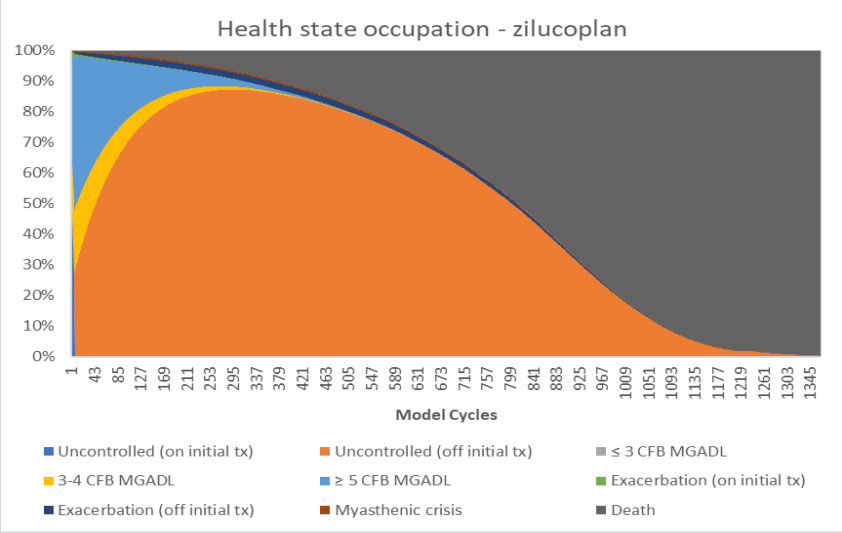
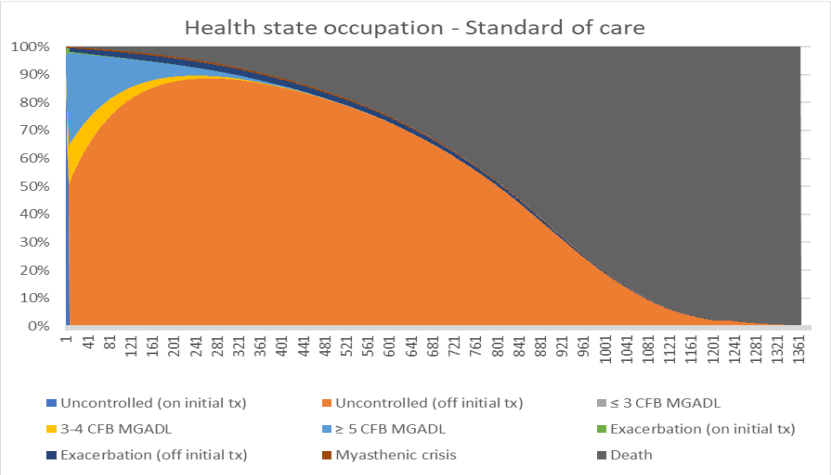


Figure 12: Health state occupation for standard of care



8.1.1 Extrapolation of efficacy data

While clinical efficacy was modelled using transition probabilities, time on treatment was modelled using the standard parametric models. Model selection was chosen based on visual fit and statistical fit, using Akaike information criteria (AIC) and Bayesian information criteria (BIC), as well as KOL input on expected long-term duration of treatment.

8.1.1.1 Extrapolation of time on treatment

Treatment discontinuation (not due to death) data from RAISE-XT was used to model time on treatment for both the zilucoplan and placebo arms. A parametric extrapolation of this treatment discontinuation data was implemented to estimate the percentage of patients on treatment per model cycle. The percentage of patients on treatment was recorded every three months, until month 39. Data for patients on the zilucoplan 0.3mg/kg/0.3mg/kg was used to generate Kaplan Meier data for the percentage of patients on treatment, censored for death.

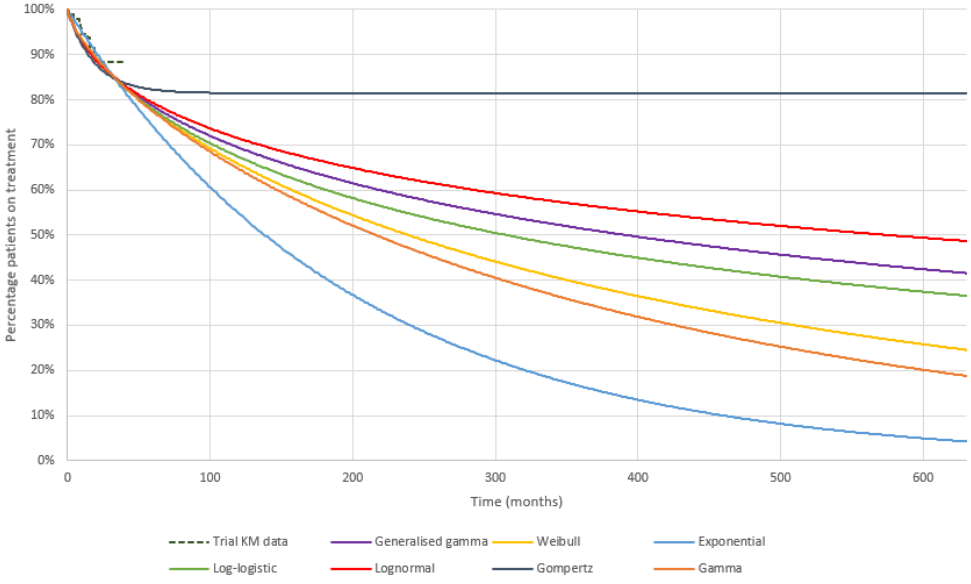
Treatment discontinuation data extrapolated for zilucoplan 0.3mg/kg/0.3mg/kg is assumed for both the zilucoplan and SoC-arm by multiplying the time on treatment parametric curves from RAISE-XT with the sum of on-treatment health states for each cycle in the model.

Table 27: Summary of assumptions associated with extrapolation of time on treatment

Method/approach	Description/assumption
Data input	RAISE-XT
Model	The seven standard parametric distributions were used to assess the most appropriate model
Assumption of proportional hazards between intervention and comparator	Proportional hazards were not tested, as only zilucoplan data was used due to the open-label extension study design of RAISE-XT.
Function with best AIC fit	Intervention: Gompertz
Function with best BIC fit	Intervention: Exponential

Method/approach	Description/assumption
Function with best visual fit	The Kaplan-Meier is immature and not providing support for any particular curve based on visual fit. The two statistically best-fitting curves (Gompertz and exponential) are both extreme in both directions when considering long-term extrapolations. Log-logistic was the 3rd statistical fit for both AIC and BIC and serves as a compromise between the tendency of plateau (few patients at risk) in the end of the RAISE-XT Kaplan-Meier curve, and input from clinicians suggesting that most patients will have discontinued zilucoplan after 2 years of treatment.
Function with best fit according to evaluation of smoothed hazard assumptions	Not assessed.
Validation of selected extrapolated curves (external evidence)	Not assessed.
Function with the best fit according to external evidence	Not assessed.
Selected parametric function in base case analysis	Log-logistic. Same time-on-treatment assumed for both the zilucoplan and SoC-arm
Adjustment of background mortality with data from Statistics Denmark	Not relevant for time-on-treatment. Background mortality was applied in the health economic model.
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 13: Parametric distributions against Kaplan Meier data for patients on treatment with zilucoplan



8.1.2 Calculation of 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. Response rate estimates were transformed into 2-week probabilities using the appropriate form of the equation:

$$P[t]=1-e^{(-rt)}$$

Where P[t] is the probability at time t, r is the corresponding constant rate and it is the time period over which the probability was assessed. At the outset, patients presented with a baseline MG-ADL score of 10.603, indicating a severe level of disease, posing significant treatment challenges. This was the mean MG-ADL score of patients in the RAISE trial. The transition probabilities used in the model are presented in Appendix K and the different health states used are presented in Table 28.

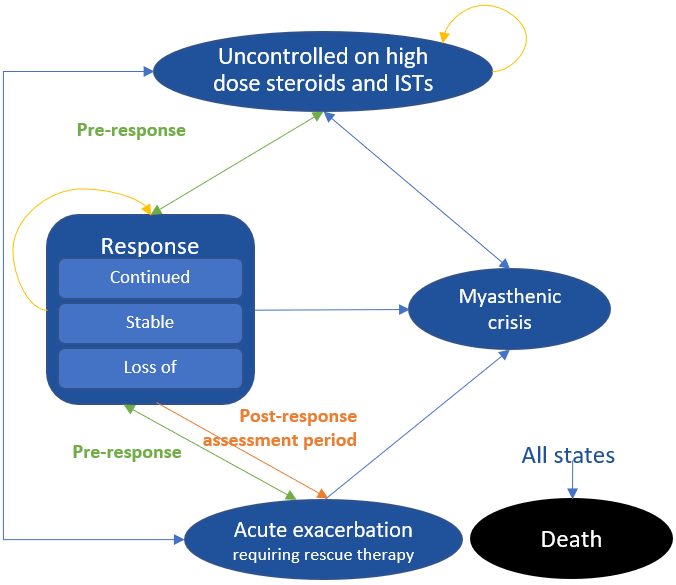


Table 28. Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Uncontrolled on high dose steroids and ISTs	Response	Based on observed data from RAISE and RAISE-XT	RAISE(10) and RAISE-XT(11)
	Myasthenic crisis		
Response	Uncontrolled on high dose steroids and ISTs		
	Myasthenic crisis		

	Acute exacerbation
Myasthenic crisis	Uncontrolled on high dose steroids and ISTs
Acute exacerbation	Response
	Uncontrolled on high dose steroids and ISTs
	Myasthenia crisis
All	Death (absorbing state)

8.1.2.1 Primary response

During the initial 12 weeks of the model, the efficacy was modelled using data from the RAISE trial (10). The response rates were determined based on the response criteria of a minimum of 3-point reduction from baseline in MG-ADL total score. The rates were converted to transition probabilities using the formula stated above. The response rates are presented in Table 29. Patient that did not respond to treatment stayed in the "uncontrolled" health state. Response probabilities were applied up until the "Response assessment time point" at 12 weeks for Soc and 24 weeks for zilucoplan. 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.

Table 29: Response rates and timepoints

Treatment	Response rate	Response timepoint used in the model	Reference
Zilucoplan	73.10%	24 weeks	Howard et al., 2023 (10).
SoC	46.10%	12 weeks	Howard et al., 2023 (10).

Abbreviations: Soc = Standard of Care.

8.1.2.2 Secondary response

Patients that did not achieve response during the response assessment time point was assumed to 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.

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 29)
- 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)

In the base case, the proportion of patients moving from initial response to continued response, loss of response, and stable response was based on RAISE-XT data (11). To avoid double counting of non-responders, patients with a MG-ADL CFB of <>3 was not considered in the data set from RAISE-XT. This was based on the argument that patients with a MG-ADL CFB of <3 point CFB was already discontinued treatment according to the primary response definition based on the RAISE data (10). Therefore, the proportions of responders who are 3-4 point and >5 point CFB were calculated and applied to the percentage of patients who respond to treatment. Patients with a MG-ADL CFB of 3-4 were assumed to have a stable response, while the patients with MG-ADL CFB of >5 points were assumed to have a continued response. As SoC patients switched to zilucoplan in the RAISE-XT trial, the secondary response proportions where not collected for SoC from week 12 and onwards. Therefore, these were assumed to be equal to the SoC secondary response proportions from week 0 to 12. Secondary response for zilucoplan and standard of care at week 0 to 12 and from 12 and onwards are presented in Table 31.

Table 30: Secondary response proportions used to derive transition probabilities

Treatments	Continued response (MG-ADL CFB >5)	Loss of response (MG-ADL CFB <3)	Stable response (MG-ADL CFB 3-4)	Reference
Week 0 to 12				
Zilucoplan	71.01%	0.00%	28.99%	RAISE-XT (11)
SoC	55.60%	0.00%	44.40%	RAISE-XT (11)
Week 12 and onwards				
Zilucoplan	80.28%	0.00%	19.72%	RAISE-XT (11)
SoC	55.60%	0.00%	44.40%	Assumption

The average change in MG-ADL score from baseline was assumed the same for zilucoplan and SoC, which is shown in Table 31. The average MG-ADL score in each health state is depicted in Figure 14.

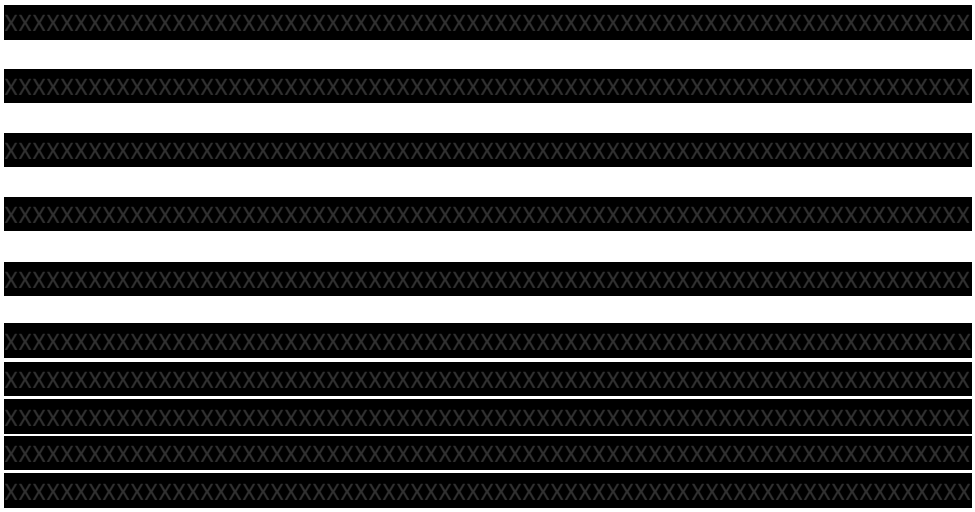
Table 31: Average change from baseline in MG-ADL score

Treatments	Continued response	Loss of response	Stable response	Reference
Zilucoplan	[redacted]	0.00	[redacted]	RAISE-XT (11)
SoC	[redacted]	0.00	[redacted]	RAISE-XT (11)

Abbreviations: SoC = Standard of Care.

In the uncontrolled response state, the average MG-ADL score did not change from baseline (Figure 14).

Figure 14: Average MG-ADL score for zilucoplan



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 clinical event health state. The calculations of transition probabilities into clinical event health are presented in section 8.2.2.1.

8.2 Presentation of efficacy data from published literature

8.2.1 Extrapolation of efficacy data

Not applicable.

8.2.2 Calculation of transition probabilities

8.2.2.1 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 the US study of Abuzinadah et al., 2021 (94). The annual rate of myasthenic crisis was based on the incidence of exacerbations requiring intubation and was estimated as 0.0231 (94). 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 (94). As the event rates were not derived from Danish patients, the rates were presented for two Danish clinical experts. A summary of the annual event rates used in the base case of the model is presented in

Table 32.

While the experts found it difficult to estimate whether the rates would match a Danish clinical context, they agreed that rates were within reasonable range of what is

expected. Therefore, the rates were applied in the base case, while the impact of lower rates were tested in scenario analysis.

Table 32: Annual clinical event rates

Health state	Exacerbation	Myasthenic crisis	Source
Uncontrolled	0.651	0.062	Abuzinadah et al 2021 (94)
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, from the French RCT of Gajdos et al., 2005 (93), which was assumed to be representative of the Danish clinical context. To test the sensitivity of this assumption, a scenario setting this rate to 0.00 was explored in scenario analysis. The incidence was converted to a two-weekly probability using the following formula:

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

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 based on an US cohort study of Alshekhlee et al., 2009, which was assumed to be relevant for the Danish patients (95). To test the sensitivity of this assumption, a scenario setting this rate to 0.00 was explored in scenario analysis.

Gajdos et al., 2005 (93) was identified in the SLR, which is presented in Appendix H. Both Abuzinadah et al 2021 (94) and Alshekhlee et al., 2009 (95) were identified via desktop searches, thus, no search string were provided for these references.

8.3 Modelling effects of subsequent treatments

Not applicable. Subsequent treatments were not modelled.

8.4 Other assumptions regarding efficacy in the model

Assumptions taken in the model are presented in Table 33.

Table 33: Base case model assumptions of the health economic model

Variable	Assumption	Rationale
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	This represents the time at which a healthcare professional assesses whether to continue/discontinue treatment depending on response

	respond and therefore discontinue treatment	
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.
	The model assumes patients return to baseline disease severity within 14 weeks of response assessment	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. This 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 (100), 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.
Mortality rate	Patients experience the same risk of mortality as the general public, unless patients experience a myasthenic crisis	Based on existing literature (101)
Time on treatment	Only patients in the 'Continued response' and 'Stable response' 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
Treatment discontinuation	A proportion of patients discontinue of other reasons than loss of treatment effect or death	Time to treatment discontinuation not due to death is available from RAISE XT and provides an estimate of other-cause discontinuations. Besides censoring for death, the observed events were not including loss of response.
Treatment costs	The model assumes 100% adherence and compliance	Simplification for the calculation of treatment costs
Administration costs	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

8.5 Overview of modelled average treatment length and time in model health state

The health economic outputs on treatment length and time in health states are presented in Table 34 and Table 35. The estimates are not modified with discounting and half-cycle correction. However, the estimates are adjusted for background mortality of the Danish population The estimate were derived using the Excel file 'Key figures including general mortality'.

Table 34: Estimates in the model

	Modelled average time on treatment (reference in Excel)	Modelled median time on treatment (reference in Excel)	Observed median from relevant study
Zilucoplan	2.52 years	N/a	Not obtained at latest data cut.
Standard of care	1.68 years	N/a	N/a

Table 35: Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

	Duration of treatment	Uncontrolled	Loss of response	Stable response	Continued response	Exacerbation	Myasthenic crisis
Zilucoplan	2.52	26.01	0.00	0.71	2.02	0.67	0.18
Standard of care	1.68	26.93	0.00	0.79	0.99	0.68	0.18

9. Safety

9.1 Safety data from the clinical documentation

The safety population in RAISE included all study participants who received at least one dose of IMP, with study participants to be analysed based on the actual IMP received. The safety population in RAISE-XT included all study participants who received at least one dose of zilucoplan in RAISE-XT. Safety data from RAISE-XT is presented for the full population (all zilucoplan, N=200). In Table 36, the adverse events (AEs) presented are TEAEs. Overall, zilucoplan showed a favourable safety and good tolerability profile; most AEs were mild or moderate in severity and no meningococcal infections were observed (11, 12).

Table 36: Overview of safety events (week 12 in RAISE, 11 November 2023 in RAISE-XT, safety population)

	Placebo N=88 (RAISE)	Zilucoplan 0.3mg/kg N=86 (RAISE)	All zilucoplan N=200 (RAISE-XT)
Number of adverse events, n	222	291	2.624
Number and proportion of patients with ≥ 1 adverse events, n (%)	62 (70.5)	66 (76.7)	194 (97.0)
Number of serious adverse events*, n	18	15	207
Number and proportion of patients with ≥1 serious adverse events*, n (%)	13 (14.8)	11 (12.8)	81 (40.5)
Number of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 events, n	14‡	24‡	180‡

	Placebo N=88 (RAISE)	Zilucoplan 0.3mg/kg N=86 (RAISE)	All zilucoplan N=200 (RAISE-XT)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	11 (12.5)‡	10 (11.6)‡	72 (36.0)‡
Number of adverse reactionsΩ, n	34	55	178
Number and proportion of patients with ≥1 adverse reactionsΩ, n (%)	22 (25.0)	28 (32.6)	73 (36.5)
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	4 (4.5)	4 (4.7)	54 (27.0)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	0	2 (2.3)	9 (4.5)

Abbreviations: CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; IMP = investigational medicinal product; N/A = not applicable; TEAE = treatment-related adverse event.
* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
§ CTCAE v. 5.0 must be used if available.
‡ Comprising those with CTCAE grade ≥3, or those without a CTCAE grading but classified as severe by the investigator.
Ω Adverse reactions comprise treatment-related TEAEs that were considered to be related to IMP by the investigator.
Source: UCB, 2022, table 9-2, table 9-4, and table 7-1 (12); Howard et al., 2023 (10); UCB 2024, table 14.3.2.1 and 14.1.1.4 (11).

The overall proportion of patients with ≥1 TEAE was higher in the zilucoplan group (76.7%) compared with the placebo group (70.5%). The proportion of ≥1 adverse reaction was higher in the zilucoplan group (32.6%) compared with the placebo group (25.0%). The proportion of patients who discontinued treatment due to AEs was higher in the zilucoplan group (2.3%) compared with the placebo group (0%). The number and proportion of remaining safety events were similar in the zilucoplan and placebo group (Table 36).

Overall, the number and proportion of patients experiencing safety events were higher in the RAISE-XT safety population than in the RAISE safety population, which is expected, as the RAISE-XT covers a longer duration (Table 36). In Table 37 the frequency of all serious adverse events with frequency of ≥ 5% recorded in RAISE and RAISE-XT is listed.

Table 37: Serious adverse events (week 12 in RAISE and 11 November 2023 in RAISE-XT, safety population)

Adverse events	Placebo N=88 (RAISE)		Zilucoplan 0.3mg/kg N=86 (RAISE)		All zilucoplan N=200 (RAISE-XT)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events

Any serious TEAE, n (%)	13 (14.8)	18	11 (12.8)	15	81 (40.5)	207
Myasthenia gravis worsening, n (%)	5 (5.7)	6	2 (2.3)	3	19 (9.5)	34

Abbreviations: TEAE = treatment-related adverse event.
* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Source: UCB, 2022, table 9-13 (12); Howard et al. 2023 (10); UCB 2024, table 14.3.4.1 (11).

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.

Table 38: Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)	N/A	N/Aa	(10).	No AEs were considered to meet the inclusion criteria of serious AEs with an incidence ≥5% in RAISE.

9.2 Safety data from external literature applied in the health economic model

Not applicable.

10. Documentation of health-related quality of life (HRQoL)

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.

Table 39: Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	RAISE	Utilities

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

In the RAISE trial, HRQoL was collected using EQ-5D-5L aligning with DMC's preferred instrument for measuring life quality. The data was from the modified ITT population. The group included 174 patients with between 161 and 167 completed questionnaires at each timepoint.

The EQ-5D-5L is comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, extreme problems. Participants answer questions based on symptoms and health status on the day the questionnaire is completed. There is also an overall health question on a 0-100-point EQ-visual analogue scale (EQ-VAS). A frequency table was produced to summarize answers provided to each of the 5 dimensions of the EQ-5D descriptive system at each scheduled visit. Observed values of EQ VAS scores and change from baseline were summarised by treatment group at each scheduled visit. The observed case method was used, and no further imputation was applied on missing items in EQ-5D descriptive system and EQ-VAS.

10.1.2 Data collection

EQ-5D-5L was collected at baseline, week 1, week 2, week 4, week 8, and week 12. The pattern of missing data is presented in Table 40. Patients without complete EQ-5D-5L or disease status were excluded from the analysis as multiple imputation was not undertaken. No further information can be provided.

Table 40: Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	174	13 (7.47%)	174	161 (92.53%)
Week 1	174	7 (4.02%)	174	167 (95.98%)
Week 2	174	7 (4.02%)	174	167 (95.98%)
Week 4	174	13 (7.47%)	174	161 (92.53%)
Week 8	174	12 (6.90%)	174	162 (93.10%)
Week 12	174	9 (5.17%)	174	165 (94.83%)

10.1.3 HRQoL results

The EQ-5D-5L results with index scores that are mapped using Danish preferences weights are presented in Table 41. The EQ-VAS results are presented in Table 42. No graphical presentation of EQ-5D-5L was available.

Table 41: HRQoL EQ-5D-5L summary statistics, including available data on change from baseline

	Zilucoplan 0.3mg/kg (n=86)		Placebo (n=88)		Intervention vs. comparator	Pooled change from baseline (n=174)	
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI) p-value	N	Mean (SD)
Baseline	78	0.6398 (0.3147)	83	0.6298 (0.2819)	0.0100 (-0.0829 - 0.1029) p=0.83	161	N/A
Week 1	81	0.7230 (0.2623)	86	0.6759 (0.2904)	0.0471 (-0.0376 - 0.1318) p=0.27	155	0.0771 (0.2103)
Week 2	83	0.7165 (0.2960)	84	0.7068 (0.2882)	0.0097 (-0.0796 - 0.099) p=0.83	154	0.0905 (0.2508)
Week 4	80	0.7618 (0.2461)	81	0.6899 (0.2900)	0.0719 (-0.0119 - 0.1557) p=0.09	150	0.0991 (0.2654)
Week 8	79	0.7163 (0.2917)	83	0.7088 (0.2815)	0.0075 (-0.0814 - 0.0964) p=0.87	151	0.0694 (0.2407)
Week 12	82	0.7326 (0.2854)	83	0.6767 (0.3334)	0.0559 (-0.0396 - 0.1514) p=0.25	155	0.0762 (0.2460)

Table 42: EQ-VAS scores – Change from baseline

	Zilucoplan 0.3mg/kg (n=86)		Placebo (n=88)		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI) p-value
Baseline	78	N/A	83	N/A	N/A
Week 1	73	7.49 (14.69)	82	5.70 (15.61)	1.79 (not available)
Week 2	75	7.09 (19.94)	79	6.10 (14.15)	0.99 (not available)

	Zilucoplan 0.3mg/kg (n=86)		Placebo (n=88)		Intervention vs. comparator
Week 4	72	8.99 (17.31)	78	7.26 (17.91)	1.73 (not available)
Week 8	72	5.51 (17.82)	79	5.22 (20.28)	0.29 (not available)
Week 12	74	8.97 (18.08)	81	5.81 (19.80)	3.16 (not available)

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

EQ-5D-5L with Danish preference weights were used to generate the utilities. A regression-based approach was used to calculate utility values. Further, the utilities were also age-adjusted using Wittrup-Jensen et al., 2009, data(102) . The regression outputs are presented in Table 43.

Table 43: Utility regression outputs

Effect	Estimate	Standard error	DF	T value
Intercept	0.6515	0.06328	184	10.30
Baseline EQ-5D coefficient	-0.4433	0.03984	163	-11.13
BMI coefficient	-0.00436	0.002296	485	-9.09
MG-ADL Coefficient	-0.02087	0.0001535	152	-2.84

Abbreviations: DF = degrees of freedom; BMI = Body Mass Index; MG-ADL = Myasthenia Gravis Activities of Daily Living.
Note: All reported coefficients are per one unit increase.

The health state utilities are calculated based on the MG-ADL score in the health state at the given time. The utility values are then calculated using a mixed effect model accounting for repeated measurements on the same individual:

$$Utility\ change = \beta_0 + \beta_1 \times EQ - 5D_{baseline} + \beta_2 \times BMI_{baseline} + \beta_3 \times MGADL$$

As an example, when using the ITT baseline values for EQ-5D (with Danish weights: 0.6346) and BMI (31) from the RAISE trial, the baseline MG-ADL of 10.603, would correspond to a utility value of 0.648.

10.2.1.1 Mapping

The EQ-5D-5L was mapped using Danish preference weights using the Jensen et al., 2021, (103) based on the DMC guidelines.

10.2.2 Disutility calculation

Disutilities were not included for adverse events, since no adverse events were considered to meet the inclusion criteria of serious AEs with an incidence ≥5% in the RAISE

trial(10). However, disutilities were included in the analysis for the clinical events myasthenic crisis and exacerbation, as well as the use of corticosteroids. The disutilities were based on published literature as described in section 10.3.

10.2.3 HSUV results

The utility values were derived using the regression analysis as seen above, which ultimately is derived were based on the MG-ADL score at a given time point in the model. Therefore, the utility values are based on the MG-ADL score in the given health states at a given time point the model. The utility regression was used to derive utility values for the four response-based health states, while the two clinical event health states 'exacerbation' and 'myasthenic crisis' were associated with a disutility value.

Table 44: Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Baseline / uncontrolled	0.648 [NR]	EQ-5D-5L	DK	MG-ADL of 10.603
Initial response	0.721 [NR]	EQ-5D-5L	DK	MG-ADL of 7.204
Stable response	0.721 [NR]	EQ-5D-5L	DK	MG-ADL of 7.204
Continued (improved) response	0.806 [NR]	EQ-5D-5L	DK	MG-ADL of 4.012
Loss of response	From 0.721 to 0.648 [NR]	EQ-5D-5L	DK	Utility decreases as MG-ADL increases during 14 weeks. MG-ADL from 7.204 to 10.603

Abbreviations: MG-ADL = Myasthenia Gravis Activities of Daily Living.

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

10.3.1 Study design

The exacerbation disutility was taken from the CADTH assessment of eculizumab (90), which was based on the Regain trial. The purpose of the Regain trial (104) is to determine if eculizumab is safe and effective for the treatment of refractory gMG. The trial was a randomised, double-blind, placebo-controlled, multi-centre study to evaluate the safety and efficacy of eculizumab in subjects with refractory gMG.

The myasthenic crisis was based on a Finnish cohort study by Vainiola et al., 2011, (105) which was identified in the Saunders et al., 2018 cost-effectiveness publication. The Finnish cohort study had examined the effect of different HRQoL instruments producing different scores for the same patient on the number of QALYs gained and the cost per QALY in the critical care setting.

The disutility of corticosteroid use was identified in the DMC's assessment of efgartigimod alfa in MG (92), which used a Swedish study by Bexelius et al., 2023, (106) to derive the utility decrement. The study explored the drivers of cost and health-related quality of life in patients with systemic lupus erythematosus, which was used as a proxy to derive the disutility for MG patients.

10.3.2 Data collection

In the Regain trial (104), 125 patients were enrolled to receive either eculizumab or placebo, with the main outcome being CFB in MG-ADL from baseline to week 26. EQ-5D was also collected.

In the Finnish cohort study by Vainiola et al., 2011, (105) 937 patients having been treated in the critical care setting in the Helsinki University Central Hospital the HRQoL scores were measured by the EQ-5D and 15-D 6 and 12 months after start of treatment, and QALYs were calculated using four different sets of assumptions regarding recovery from disease.

In the Swedish study by Bexelius et al., 2023 (106) a questionnaire was sent to members of a patient organisation with a self-reported diagnosis of SLE, requesting information on demographics and disease characteristics, medications, resource utilisation, informal care, loss of productivity, fatigue and HRQoL in relation to SLE. A total of 339 patients out of 737 returned the questionnaire.

10.3.3 HRQoL Results

It was found that Exacerbations were associated with disutilities in the model, derived from patient-level data in the REGAIN trial(104), and reported in eculizumab's CADTH model (90), 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.

Saunders et al., 2018, (91) used the Vainiola et al., 2011 (105) study to derive a disutility of 0.39, based on the disutility associated with emergency mechanical ventilation (107).

CS dosage was statistically significant predictor for lower HRQoL as the low-dose group had a score of 0.61 and the no-CS group had a score of 0.70. This was used to derive the disutility of 0.07. (92)

10.3.4 HSUV and disutility results

No health state utility values from literature were applied in the model. The disutilities derived from the literature, which are used in the base case are presented in Table 45. All health state utility values identified in the literature are presented in Table 46.

No health state utility values were identified that matched the heath states used in this health economic model, as these were based on either overall MG utility or different

MG-classes (not per response). Thus, these values were not presented here, but can be found in Appendix I. The overview of all literature-based health state utility values is therefore similar to the base case. In order to keep the structure of this template the overview is presented in Table 46.

Table 45: Overview of health state utility disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Disutilities				
Exacerbation	-0.20	EQ-5D	N/a	Duration 11.80 days which was equalling a -0.006 disutility. (90)
Myasthenic crisis	-0.39	EQ-5D	N/a	Duration 21.00 days which was equalling a -0.011 disutility. (91)
Corticosteroid use	-0.07	EQ-5D	N/a	Based on input used in the DMC's assessment of efgartigimod alfa in treatment of MG. (92)

Table 46: Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff	Comments
Exacerbation	-0.20 [NR]	EQ-5D	N/a	Duration 11.80 days which was equalling a -0.006 disutility. (90)
Myasthenic crisis	-0.39 [NR]	EQ-5D	N/a	Duration 21.00 days which was equalling a -0.011 disutility. (91)
Corticosteroid use	-0.07 [NR]	EQ-5D	N/a	Based on input used in the DMC's assessment of efgartigimod alfa in treatment of MG. (92)

11. Resource use and associated costs

The model included direct medical and healthcare costs as well as transport costs and time spent on treatment by patients, consistent with the restricted societal perspective as described in the DMC guidelines(108). Drug costs were sourced from Medicinpriser.dk (109) and applied as pharmacy purchasing prices (AIP). Disease management and AE costs were based on Danish diagnosis related groups (DRG) tariffs from 2024 (110) and the DMC catalogue for unit costs (111). Patient and transportation costs are based on the DMC catalogue for unit costs.

11.1 Medicine costs - intervention and comparator

This section includes information on the dosing and costs of medicines included in the model. The list price of zilucoplan were informed by the submitting company, while the remaining costs were derived from medicinpriser.dk.

11.1.1 Zilucoplan

Zilucoplan is available in three different pre-filled syringes of 16.6 mg, 23.0 mg, and 32.4 mg. The rubine red 16.6 mg syringes is used for patient of <56 kg bodyweight, the orange 23.0 mg syringes are used for patients of ≥56 to <77 kg bodyweight, while patients of ≥77 kg bodyweight will be using the dark blue 32.4 mg syringes. The RAISE trial average bodyweight was 89.10 kg with most patients receiving the daily dose 32.40 mg, although 32.7% patients were below 77 kg. The model assumed doses accordingly, as seen in Table 47. The list price for a pack of 7 syringes is [redacted] for 32.4 mg and [redacted] for 23.0 mg, equalling [redacted] per unit. A 100% relative dose intensity was assumed without vial sharing. The implication of applying only 16.6 mg or only 23.0 mg syringe 7-pack prices of [redacted] and [redacted] in the model was explored in scenario analyses.

In the base case, the cost of SoC was added to the zilucoplan arm, based on the zilucoplan EMA label. This assumption was explored in scenario analysis.

Table 47: Medicine dosing used for zilucoplan in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Zilucoplan	23.0 mg*	100%	Daily	No
Zilucoplan	32.4 mg*	100%	Daily	No

*In RAISE-XT, 32.7% of patients were below 77kg. The model conservatively assumes these patients received 23.0 mg. Please see doses for patients below 56 kg in Table 4.

11.1.2 Standard of care

Standard of care consisted of the medicines listed in Table 48. The percentage of patients using each agent was derived from the RAISE trial, while dose intensity was assumed to be 100% for all drugs. The doses for each drug were based on clinical expert statements and Danish treatment guideline (66).

Table 48: Medicine dosing used for standard of care in the model

Medicine	Dose	% of patients using	Frequency	Vial sharing
Corticosteroids	10.00 mg	63.2%	Daily	No
Azathioprine	200.00 mg	17.8%	Daily	No
Mycophenolate mofetil	2,000.00 mg	19.0%	Daily	No
Cyclosporine	300.00 mg	7.5%	Daily	No
Tacrolimus	10.00 mg	5.7%	Daily	No
Methotrexate	12.50 mg	2.3%	Once weekly	No
Pyridostigmine	60.00 mg	80.5%	Four time daily	No

The pack prices are presented in Table 49. If multiple packages where available for a given drug, the pack with the lowest cost per mg was chosen.

Table 49: Pack prices for standard of care

Medicine	Strength	Units per pack	AIP (DKK)	Nordic number
Corticosteroids – prednisolon	5 mg	300	99.00	491057
Azathioprine	50 mg	50	60.70	548497
Mycophenolate mofetil	250 mg	300	537.00	432712
Cyclosporine	100 mg	50	1,405.29	027734
Tacrolimus	2 mg	50	856.04	170231
Methotrexate	2.5 mg	100	46.00	084891
Pyridostigmine	60 mg	150	129.45	180071

Abbreviations: AIP = Apotekets indkøbs pris.

11.2 Medicine costs – co-administration

Not applicable.

11.3 Administration costs

The cost of administration was derived from the DRG tariff system (110). Oral administration was assumed to not incur any cost. For subcutaneous administration a cost were only applied for the first administration, as it was assumed that the patient could learn to self-administrate at the first visit. Cost per administration for each pharmaceutical is presented in Table 50.

Table 50: Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral corticosteroids	Daily	0	N/a	Assumption
Oral azathioprine	Daily	0	N/a	Assumption
Oral mycophenolate mofetil	Daily	0	N/a	Assumption
Oral cyclosporine	Daily	0	N/a	Assumption
Oral tacrolimus	Daily	0	N/a	Assumption
Oral methotrexate	Once weekly	0	N/a	Assumption
Oral pyridostigmine	Four time daily	0	N/a	Assumption

* The subcutaneous administration cost was only applied for the first administration.
Abbreviations: DRG = Diagnosis-related group.

11.4 Disease management costs

Disease management resource use was estimated with the support of two clinical experts. The resource use for "loss of response", "stable response", and "continued response" was estimated on an annual basis, while the resource use for exacerbation and myasthenic crises was estimated as events per clinical event. The resource use estimates are presented in Table 52 and Table 53. Cost per resource use was estimated using Danish DRG tariffs (110) and the DMC's unit cost (111). The cost of managing steroid use was based on the cost used in the DMC assessment of efgartigimod alfa in the treatment of MG.

Table 51: Disease management costs used in the model

Activity	Unit cost [DKK]	DRG code	Reference
IVig	143,535.00	01MP08	DRG 2024
PLEX	47,943.00	01MP10	DRG 2024
GP visit	154.98	N/a	DMC's unit cost: consultation (projected to 2024 cost)
Visit to other healthcare professionals	505.46	N/a	DMC's unit cost: nurse (projected to 2024 cost)
Outpatient visit	1,941.00	01MA98	DRG 2024
Emergency visit	1,941.00	01MA98	DRG 2024
Hospital stay	37,723.00	01MA06	DRG 2024
Cost of managing steroids	306.06	N/a	DMC assessment of efgartigimod alfa in the treatment of MG (projected to 2024 cost)

Abbreviations: DRG = Diagnosis-related group; DMC = Danish Medicines council; GP = general practitioner; IVig = Intravenous immunoglobulin; MG = Myasthenia Gravis; PLEX = Plasma exchange.

Table 52: Resource use for uncontrolled and response health states

	Uncontrolled	Response	Continued response
Resource	**Annual resource use**		
IVig	-	-	-
PLEX	-	-	-
GP visit	3 times per year	2 times per year	2 times per year
Visit to other healthcare professionals	7 times per year	4 times per year	4 times per year
Outpatient hospital visits	5 times per year	Once annual	Once annual
Presenting at emergency room	Every 2nd year	Every 4th year	Every 4th year
Hospital stay	Every 10th year	-	-

Abbreviations: IVig = Intravenous immunoglobulin; PLEX = Plasma exchange; GP = general practitioner.

Table 53: Resource use for exacerbations and myasthenic crisis

	Exacerbation	Myasthenic crisis
Resource	**Resource per clinical event**	
IVig	2 times per 5 events	1 time per 5 events

PLEX	1 time per 4 events	2 times per 5 events
GP visit	4 times per 5 events	-
Visit to other healthcare professionals	1 time per 2 events	1 time per 10 events
Outpatient hospital visits	4 times per 5 events	1 time per 4 events
Presenting at emergency room	1 time per 4 events	1 time per 2 events
Hospital stay	1 time per 10 events	Once every event

Abbreviations: IVig = Intravenous immunoglobulin; PLEX = Plasma exchange; GP = general practitioner.

11.5 Costs associated with management of adverse events

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 (10).

11.6 Subsequent treatment costs

Subsequent treatment costs were not included in the health economic model.

11.7 Patient costs

Based on DMC's unit cost catalogue (111), a cost of DKK 3.73 per kilometre and the average distance to the hospital of 20 km were applied in the model. This equals a unit cost of DKK 149.20 which was applied to all visits and healthcare activities in the model to account for travel expenses. A unit cost of DKK 203 was used for all patient hours spent on treatment-related activities.

Transportation and time use was aligned with patient resource use visits presented in section 0. Healthcare visits were assumed to afflict 2 hours of the patients' time, while hospital stays were assumed to be 48 hours, as presented in Table 54.

Table 54: Patient costs used in the model

Activity	Time spent
Healthcare visit	2 hours
Hospital stay	48 hours

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

An overview of the base case including the central aspects is provided in Table 55.

Table 55: Base case overview

Feature	Description
Comparator	Standard of care
Type of model	Markov model
Time horizon	52.5 years (lifetime)
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in study the RAISE trial. Danish population weights were used to estimate the utility regression
Costs included	Medicine costs Hospital costs Patient and transport costs
Dosage of medicine	Zilucoplan dosage is based on weight groups. As the RAISE trial average bodyweight was 89.10 kg, the daily dose used in the model was 32.4 mg of zilucoplan, with 32.7% receiving 23.0 mg. SoC dosage was based on the clinical expert statements and Danish treatment guideline (66).
Average time on treatment	Zilucoplan: 2.52 years Standard of care: 1.68 years
Inclusion of waste	No waste for zilucoplan. Oral drug rounded to nearest whole tablet.

Average time in model health state

	Duration of treatment	Uncontrolled	Loss of response	Stable response	Continued response	Exacerbation	Myasthenic crisis
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of care	1.68	26.93	0.00	0.79	0.99	0.68	0.18

Abbreviations: SoC = Standard of Care.

12.1.1 Base case results

The base case results for zilucoplan and SoC as well as the difference are presented in Table 56.

Table 56: Base case results, discounted estimates

	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: IST = Immunosuppressive therapy; QALY = quality-adjusted life year.

12.2 Sensitivity analyses

Parameter uncertainty was investigated both deterministically and probabilistically. Full details of parameter specifications can be found in Appendix G.

12.2.1 Deterministic sensitivity analyses

Univariate parameter uncertainty was tested using one-way sensitivity analysis, in which all model parameters were systematically and independently varied using standard errors or predefined upper and lower limits. If the neither were available, a plausible range determined by ±20% was applied to instead. The 10 most influential model parameters

with regards to impact on range of impact on the base case ICER are presented in Table 57 and also illustrated in the tornado diagram in Figure 15.

Table 57: One-way sensitivity analyses results

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[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: CFB = change from baseline, MG-ADL = Myasthenia Gravis Activities of Daily Living.

Figure 15: Tornado diagram illustrating the one-way sensitivity analysis of the 10 most influential parameters

[redacted]

12.2.1.1 Scenario analyses

A number of scenarios were considered in the deterministic sensitivity analyses exploring scenarios that divert from the base case model settings in order to test the sensitivity of main model assumptions. These are presented in Table 58.

Table 58: Scenario analyses

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[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: SoC = Standard of Care; QALY = quality-adjusted life year.

12.2.2 Probabilistic sensitivity analyses

Probabilistic analysis was to test the overall parameter uncertainty. Distributions were assigned to each parameter that was associated with uncertainty. The analysis used 1,000 iterations based on convergence testing iterations. Each iteration is reflected in the scatter plot presented in Figure 16. [redacted] Further a cost-effectiveness acceptability curve is presented in Figure 17, indicating that there is an [redacted] probability of zilucoplan being cost-effective at a willingness-to-pay of [redacted] The probabilistic ICER of [redacted].

The full set of parameters included in the model with details of distributional forms along with the convergence testing, are presented in Appendix G.

Figure 16: Cost-effectiveness scatter plot

Figure 17: Cost-effectiveness acceptability curve

13. Budget impact analysis

A budget impact analysis was embedded into the cost-effectiveness model to estimate the impact of recommending zilucoplan for treatment of gMG in Denmark. The budget impact result is representative of the populations in the cost per patient model. The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included. The analysis compares the budgetary consequences of a scenario where zilucoplan is recommended against the scenario where zilucoplan is NOT recommended.

Number of patients (including assumptions of market share)

Number of patients are based on Table 3. It is assumed that [redacted] of the eligible patients are receiving zilucoplan in the case of a recommendation. This is presented in Table 59.

Table 59: Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

3	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		

3	Year 1	Year 2	Year 3	Year 4	Year 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Budget impact was calculated based on the expected number of patients. Budget impact is presented in Table 60.

Table 60: Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

Professor, overlæge, John Vissing, neurologisk afdeling, Rigshospitalet.

Professor, overlæge, Henning Andersen neurologisk afdeling, Aarhus Universitetshospital.

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Appendix A. Main characteristics of studies included

Table 61: Main characteristic of RAISE (MG0010)

Trial name: RAISE (MG0010)	NCT number: NCT04115293
Objective	The primary objective was to confirm the efficacy of zilucoplan in study participants with gMG.
Publications – title, author, journal, year	Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. Howard JF Jr, Bresch S, Genge A, Hewamadduma C, Hinton J, Hussain Y, Juntas-Morales R, Kaminski HJ, Maniaol A, Mantegazza R, Masuda M, Sivakumar K, Śmiłowski M, Utsugisawa K, Vu T, Weiss MD, Zajda M, Boroojerdi B, Brock M, de la Borderie G, Duda PW, Lowcock R, Vanderkelen M, Leite MI; RAISE Study Team. Lancet Neurol. 2023 (10).
Study type and design	Double-blinded randomised placebo-controlled phase 3 study. Enrolled patients were randomly assigned 1:1. 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). The participants, care providers, investigators, and outcomes assessors were masked. Study participants and study staff remained blinded to treatment assignments until after the data had been cleaned, locked, and unblinded. No crossover was allowed. The study has been completed.
Sample size (n)	174
Main inclusion criteria	1. Male or female ≥18 years and < 75 years. 2. Able to provide informed consent, including signing and dating the informed consent form. 3. Diagnosis of gMG [MGFA class II-IV] at screening. 4. Positive serology for AChR autoantibodies. 5. MG-ADL score of ≥ 6 at screening and baseline. 6. QMG score ≥ 12 at screening and baseline. 7. Four or more of the QMG test items must have been scored at ≥2 at screening and baseline. 8. No change in corticosteroid dose for at least 30 days prior to baseline or anticipated to occur during the 12-week treatment period. 9. 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. 10. Vaccination with a quadrivalent meningococcal vaccine and, where available, meningococcal serotype B vaccine at least 14 days prior to the first dose of IMP at the day 1 visit. A booster vaccination should have also been administered as clinically indicated, according to the local SoC, for study participants who had been previously vaccinated against *Neisseria meningitidis*. 11. Female study participants of childbearing potential must have had a negative serum pregnancy test at screening and a

Trial name: RAISE (MG0010)		NCT number: NCT04115293
	negative urine pregnancy test within 24 hours prior to the first dose of IMP. 12. Sexually active female study participants of childbearing potential (i.e., women who were not postmenopausal or who had not had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and all male study participants (who had not been surgically sterilised by vasectomy) must have agreed to use effective contraception during the study and during the safety follow-up period of 40 days after the last dose of IMP. Postmenopausal women were, for the purposes of the protocol, defined as women who had not had menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may have been used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement was insufficient.	
Main exclusion criteria	1. Thymectomy within 12 months prior to baseline or scheduled to occur during the 12-week study. 2. Abnormal thyroid function as determined by local standard 3. Known positive serology for muscle-specific kinase. 4. Minimal manifestation status of gMG based on the clinical judgement of the investigator. 5. Fixed weakness ('burnt out' gMG) based on the clinical judgement of the investigator. 6. History of meningococcal disease. 7. Current or recent systemic infection within 2 weeks prior to baseline or infection requiring intravenous (IV) antibiotics within 4 weeks prior to baseline. 8. Pregnant, planning to become pregnant, or nursing female study participants. 9. Recent surgery requiring general anaesthesia within 2 weeks prior to screening or expected to have surgery requiring general anaesthesia during the 12-week treatment period. 10. Prior treatment with a complement inhibitor. 11. Treatment with an experimental drug within 30 days or 5 half-lives of the experimental drug (whichever was longer) prior to baseline. 12. Treatment with rituximab within 12 months prior to baseline or planned to occur during the 12-week study (this exclusion criterion was implemented out of an abundance of caution, in the absence of data showing that complement inhibition in the context of B-cell elimination by rituximab is safe). 13. Treatment with IVIG, SC immunoglobulin, or plasma exchange 4 weeks prior to baseline. 14. Active malignancy (except curatively resected squamous or basal cell carcinoma of the skin) requiring surgery, chemotherapy, or radiation within the prior 12 months (study participants with a history of malignancy who had undergone curative resection or otherwise not requiring treatment for at	

Trial name: RAISE (MG0010)	NCT number: NCT04115293
	least 12 months prior to screening with no detectable recurrence were allowed). 15. History of or current significant medical disorder, psychiatric disorder, or laboratory abnormality that in the opinion of the investigator would make the study participant unsuitable for participation in the study. 16. Participation in another concurrent clinical study involving an experimental therapeutic intervention (participation in observational studies and/or registry studies is permitted). 17. Unable or unwilling to comply with the requirements of the study. 18. Hypersensitivity to zilucoplan, any of its excipients, or to placebo.
Intervention	Zilucoplan 0.3 mg/kg/day SC injection (N=86)
Comparator(s)	Placebo administered SC daily (N=88)
Follow-up time	N/A
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary efficacy endpoint was change from baseline to week 12 in MG-ADL score. The key secondary efficacy endpoints were change from baseline to week 12 in QMG score, change from baseline to week 12 in MGC score, and change from baseline to week 12 in MG-QOL15r score. Another secondary efficacy endpoint included was achieving MSE (defined as an MG-ADL of 0 or 1 at week 12 without rescue therapy), The secondary safety endpoint was the incidence of TEAEs. **Other endpoints:** Other secondary efficacy endpoints (i.e., non-key secondary efficacy endpoints) were time to first administration of rescue therapy over the 12-week treatment period, achieving a ≥3-point reduction in MG-ADL score at week 12 without rescue therapy, and achieving a ≥5-point reduction in QMG score at week 12 without rescue therapy. The exploratory efficacy endpoints were: • Achievement of Minimal Manifestation Status per MGFA Post-Intervention Status at week 12 without rescue therapy • Change from baseline to week 12 in Work Productivity and Activity Impairment Questionnaire: Specific Health Problem • Change from baseline to week 12 in EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) (5-item questionnaire and visual analogue scale [VAS]) • Change from baseline to week 12 in QMG subscores (ocular, bulbar, respiratory, limb) • Change from baseline to week 12 in Quality of Life in Neurological Disorders Short Form fatigue scale • Responder analysis for changes in QMG, MG-ADL, MG-QOL15r, and MGC scores from baseline without rescue therapy

Trial name: RAISE (MG0010)	NCT number: NCT04115293
	• Change from baseline to week 12 in subscores (ocular, bulbar, respiratory, and limb/axial) of the QMG, MG-ADL, MG-QOL15r, and MGC scores. Other safety endpoints were TEAEs of interest, clinical laboratory tests, vital signs, electrocardiogram, physical examination, Columbia-Suicide Severity Rating Scale, and immunogenicity.
Method of analysis	Efficacy analyses were based on the mITT population (all randomised study participants who received at least one dose of IMP and had at least one post-dosing MG-ADL score). LS mean outcomes were estimated using an MMRM ANCOVA. Safety analyses were based on the safety population (all study participants who received at least 1 dose of IMP, with study participants to be analysed based on the actual IMP received).
Subgroup analyses	Safety analyses on TEAEs and the primary and secondary efficacy endpoints were analysed on the following pre-specified subgroups: • 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 ≥90mL/min/1.73m^2), mild (estimated glomerular filtration rate (eGFR) 60 to 89mL/min/1.73m^2 [CKD stage 2]), moderate (eGFR 30 to 59mL/min/1.73m^2 [CKD stage 3]), severe (eGFR 15 to 29mL/min/1.73m^2 [CKD stage 4]), and renal insufficiency end stage renal disease (eGFR <15mL/min/1.73m^2) • gMG refractory status (yes/no) Additionally, the primary and secondary efficacy endpoints were also analysed on the following pre-specified 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) at baseline (dichotomous yes/no class variable) • Prior history of IVIG or SC immunoglobulin or plasma exchange (dichotomous yes/no class variable) • Diagnosed with thymoma

Trial name: RAISE (MG0010)	NCT number: NCT04115293
	• By timing of study participants enrolment relative to COVID-19 pandemic periods (prior/during/post) • By timing of week 12 Visit relative to COVID-19 pandemic periods (prior/during/post). All subgroup analyses were descriptive; no statistical testing of treatment-by-subgroup interactions nor statistical testing of treatment effects within subgroups was carried out. For refractory and non-refractory study participants, the change from baseline to week 12 in MG-ADL was assessed in each stratum separately using a MMRM with treatment and visit (categorial) as fixed effects, baseline MG-ADL, baseline QMG, region (North America, Europe, and East Asia) as covariates, and baseline-by-time, treatment-by-time interactions. An "unstructured" covariance structure was used. In the event the "unstructured" covariance structure model failed to converge, an autoregressive covariance structure was used. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. The LS means and SEs of each treatment group, and the LS mean differences between zilucoplan and placebo were reported for the week 12 visit along with the corresponding 2-sided 95% CIs for each subgroup stratum. Subgroup analyses were only performed for subgroups where there are at least 5 study participants in each subgroup level, otherwise it was not performed.
Other relevant information	N/A

Abbreviations: AChR = acetylcholine receptor; ANCOVA = analysis of covariance; CI = confidence interval; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; gMG = generalised myasthenia gravis; IMP = investigational medicinal product; IV = intravenous; IVIG = intravenous immunoglobulin; LS = least squares; MGC = myasthenia gravis composite; MGFA = Myasthenia Gravis Foundation of America; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis Quality of Life 15r; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; MSE = minimal symptom expression; N/A = not applicable; QMG = quantitative myasthenia gravis; SC = subcutaneous; SE = standard error; SoC = standard of care; TEAE = treatment-related adverse event; VAS = visual analogue scale.
Sources: UCB, 2022 (12); ClinicalTrials.gov, 2019 (88).

Table 62: Main characteristic of RAISE-XT (MG0011)

Trial name: RAISE-XT (MG0011)	NCT number: NCT04225871
Objective	The RAISE-XT study is an open-label extension study to evaluate the long-term efficacy, safety, and tolerability of zilucoplan in subjects with gMG who have previously participated in MG0010 (88) and MG0090 (96).
Publications – title, author, journal, year	Long-term safety and efficacy of zilucoplan in patients with generalized myasthenia gravis: interim analysis of the RAISE-XT open-label extension study. Howard JF Jr, Bresch S, Farmakidis C, Freimer M, Genge A, Hewamadduma C, Hinton J, Hussain Y, Juntas-Morales R, Kaminski HJ, Maniaol A, Mantegazza R, Masuda M, Nowak RJ, Sivakumar K, Śmiłowski M, Utsugisawa K, Vu T, Weiss MD, Zajda M, Bloemers J, Boroojerdi B, Brock M, de la Borderie G, Duda PW, Vanderkelen M, Leite MI; RAISE-XT Study Team. Ther Adv Neurol Disord. 2024 (87).
Study type and design	Open label single-group assignment phase 3 study. The study is ongoing.

Trial name: RAISE-XT (MG0011)		NCT number: NCT04225871
Sample size (n)	200	
Main inclusion criteria	• Completion of a qualifying zilucoplan clinical study (MG0009 or MG0010). • Able to provide informed consent. • Vaccination with a quadrivalent meningococcal vaccine and, where available, meningococcal serotype B vaccine. A booster vaccination should also be administered as clinically indicated, according to the local SoC, for subjects who have been previously vaccinated against *Neisseria meningitidis*. • Sexually active female subjects of childbearing potential and all male subjects must agree to use effective contraception during the study and during the safety follow-up period of 40 days after the last dose of study drug	
Main exclusion criteria	• Pregnant, planning to become pregnant or nursing female subjects. • 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). • Unable or unwilling to comply with the requirements of the study. • Commenced any disallowed medication per the exclusion criteria from the qualifying zilucoplan study or alter the dose of any other concomitant medication, unless medically indicated. • Any new or worsening medical condition (since entry into the qualifying zilucoplan study) including active malignancy (except curatively resected squamous or basal cell carcinoma of the skin); significant medical disorder; psychiatric disorder; laboratory abnormality; or any other reason that, in the opinion of the investigator or sponsor, would disqualify the subject from participation in this study. • Hypersensitivity to zilucoplan, any of its excipients, or to placebo.	
Intervention	Zilucoplan 0.3 mg/kg (N=200). SC doses of zilucoplan were self-administered daily at home at approximately the same time each day.	
Comparator(s)	N/A	
Follow-up time	The median duration of exposure was 2.2 years (range: 0.11-5.6).	
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was incidence of TEAEs. Secondary endpoints include change from baseline to week 12 in the MG-ADL score, change from baseline to week 12 in the QMG score, change from baseline to week 12 in the MGC score, and change from baseline to week 12 in the MG-QOL15r score. Exploratory endpoints included were achieving MSE at up to week 120 (defined as an MG-ADL of 0 or 1 without rescue therapy), reduction in	

Trial name: RAISE-XT (MG0011)	NCT number: NCT04225871
	corticosteroid use (week 60 and 120), and reduction in use of immunosuppressants (week 120). **Other endpoints:** The secondary endpoint use of rescue therapy. The exploratory endpoints were: Achievement of Minimal Manifestation Status per MGFA-post-intervention status at week E12 without rescue therapy; CFB to week E12 in Work Productivity and Activity Impairment Specific Health Problem Questionnaire score; CFB to week E12 in EQ-5D-5L score; CFB to week E12 in Neuro-QoL Short Form Fatigue Scale score; MG-ADL responder rate (≥2.0 point improvement from baseline and ≥3.0 point improvement from baseline) without rescue therapy; QMG responder rate (≥3.0 point improvement from baseline and ≥5.0 point improvement from baseline) without rescue therapy; Responses to post-self-injection SIAQ (US only); and MGC responder rate (≥5.0 point improvement from baseline).
Method of analysis	All efficacy analyses were based on the mITT population (all participants who received at least one dose of study drug and had at least one post-dosing MG-ADL score). LS mean outcomes were estimated using an MMRM ANCOVA. Safety analyses were based on the safety population (all study participants who received at least one dose of zilucoplan in RAISE-XT).
Subgroup analyses	Pre-specified subgroup analysis of change from RAISE-XT baseline to week 60 in MG-ADL: • 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]) • Baseline MG-ADL (≤9/≥10) • Baseline QMG (≤17/≥18) • Region (North America, Europe, and East Asia) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino) • MG refractory (Yes, No) • 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) at baseline (dichotomous yes/no class variable) • Prior history of IVIG or SC immunoglobulin or plasma exchange (dichotomous yes/no class variable) • Diagnosed with thymoma By timing of study participants enrolment relative to COVID-19 pandemic periods (pre/during)

Trial name: RAISE-XT (MG0011)		NCT number: NCT04225871
Other relevant information	N/A	

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; gMG = generalised myasthenia gravis; LS = least squares; MG = myasthenia gravis; MGC = myasthenia gravis composite; MGFA = Myasthenia Gravis Foundation of America; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis Quality of Life 15r; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; MSE = minimal symptom expression: N/A = not applicable; QMG = quantitative myasthenia gravis; SC = subcutaneous; SoC = standard of care; TEAE = treatment-related adverse event.

Sources: ClinicalTrials.gov, 2020 (89); Howard et al., 2024 (87); UCB, 2024 (11); UCB, 2024 (79).

Appendix B. Efficacy results per study

Results per study

Table 63: Results per RAISE (mITT population)

Results of RAISE (MG0010), (NCT04115293)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
LS mean CFB in MG-ADL score (week 12)	Placebo	88	-2.30 (-3.17, -1.43)	-2.09	-3.24, -0.95	<0.001	N/A	N/A	N/A	MG-ADL scores after ICE1 or ICE2 were censored and considered as treatment failure. Any missing data due to ICE1 or ICE2 were imputed based on baseline MG-ADL score or on the last available MG-ADL score, whichever was worst. Other missing scores were handled based on the maximum likelihood estimation method under the missing at random assumption. Analysis was based on a MMRM ANCOVA model 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	UCB, 2022, table 8-1 (12); Howard et al., 2023, table 2 (10)
	Zilucoplan	86	-4.39 (-5.28, -3.50)								

										random effects in the model. The MMRM ANCOVA includes weeks 1, 2, 4, 8, and 12.	
LS mean CFB in QMG score (week 12)	Placebo	88	-3.25 (-4.32, -2.1)	-2.94	-4.39, -1.49	<0.001	N/A	N/A	N/A	Following the multiplicity adjustment, a result was considered statistically significant if the primary analysis of change from baseline to week 12 in MG-ADL score was also statistically significant at α=0.05 using 2-sided statistical testing. Quantitative myasthenia gravis scores after ICE1 or any ICE2 were censored and considered as treatment failure. Any missing data due to ICE1 or ICE2 were imputed based on baseline QMG score or on the last available QMG score, whichever was worst. Other missing scores were handled based on the maximum likelihood estimation method under the missing at random assumption. Analysis was based on a MMRM ANCOVA model 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	UCB, 2022, table 8-8 (12); Howard et al., 2023, table 2 (10)
	Zilucoplan	86	-6.19 (-7.29, -5.08)								

										model. The MMRM ANCOVA included weeks 1, 2, 4, 8, and 12.	
LS mean CFB in MGC score (week 12)	Placebo	88	-5.42 (-6.98, -3.86)	-3.20	-5.24, -1.16	0.0023	N/A	N/A	N/A	Following the multiplicity adjustment, result was considered statistically significant if the primary analysis of the primary efficacy endpoint of change from baseline to Week 12 in MG-ADL score and the primary analysis of the secondary efficacy endpoint of change from baseline to week 12 in QMG scores were also statistically significant at α=0.05 using 2-sided statistical testing. The MGC scores after ICE1 or ICE2 were censored and considered as treatment failure. Any missing data due to ICE1 or ICE2 were imputed based on baseline MGC score or on the last available MGC score, whichever was worst. Other missing scores were handled based on the maximum likelihood estimation method under the missing at random assumption. Analysis was based on a MMRM ANCOVA model using an unstructured correlation matrix with treatment, baseline MG-ADL score, baseline QMG score, baseline MGC score, region (North America, Europe, and East Asia) and interactions terms treatment-	UCB, 2022, table 8-9 (12); Howard et al., 2023, table 2 (10)
	Zilucoplan	86	-8.62 (-10.22, -7.01)								

										by-visit and baseline MGC score-by-visit as fixed effects; study participants were added as random effects in the model. The MMRM ANCOVA included weeks 1, 2, 4, 8, and 12.	
LS mean CFB in MG-QOL15r score (week 12)	Placebo	88	-3.16 (-4.65, -1.67)	-2.49	-4.45, -0.54	0.0128	N/A	N/A	N/A	Following the multiplicity adjustment, a result was considered statistically significant if the primary analysis of change from baseline to week 12 in MG-ADL score and the primary analyses of change from baseline to week 12 in QMG and MGC scores were also statistically significant at α=0.05 using 2-sided statistical testing. The MG-QOL15r scores after ICE1 or ICE2 were censored and considered as treatment failure. Any missing data due to ICE1 or ICE2 were imputed based on baseline MG-QOL score or on the last available MG-QOL score, whichever was worst. Other missing scores were handled based on the maximum likelihood estimation method under the missing at random assumption. Analysis was based on a MMRM ANCOVA model using an unstructured correlation matrix with treatment, baseline MG-ADL score, baseline QMG score, baseline MG-QOL15r, region (North	UCB, 2022, table 8-10 (12); Howard et al., 2023, table 2 (10)
	Zilucoplan	86	-5.65 (-7.17, -4.12)								

										America, Europe, and East Asia) and interactions terms treatment-by-visit and baseline MG-QOL15r score by-visit as fixed effects; study participants were added as random effects in the model. The MMRM ANCOVA included Weeks 1, 2, 4, 8, and 12.	
MSE achievement (week 12)	Placebo	88	5.8	N/A	N/A	N/A	Odds ratio: 2.608	0.866, 7.860	0.0885	Following the multiplicity adjustment, result was considered statistically significant if the primary analysis of change from baseline to week 12 in MG-ADL score and the primary analysis of change from baseline to week 12 in QMG, MGC, and MG-QOL15r scores were also statistically significant at α=0.05 using 2-sided statistical testing and if p-value passed the criteria based on Holms procedure for multiplicity, within primary analysis of the endpoints of time to rescue therapy, achieving ≥3-point improvement in MG-ADL score and ≥5-point improvement in QMG score without rescue therapy. Missing MG-ADL scores were imputed under the missing at random assumption. Following to the imputation, study participants were considered as responders or non-responders; study participants who received rescue therapy or experienced an AE of death	UCB, 2022, table 8-13 (12)
	Zilucoplan	86	14.0								

										or myasthenic crisis were considered also as non-responders after the date of the intercurrent event (non-responder imputation approach). The odds ratio was estimated and tested between treatment groups using a logistic regression model with treatment as factor, baseline MG-ADL score at each imputed dataset. Treatment effects and standard errors were combined across 100 imputed datasets to produce an overall treatment effect p-value. An odds ratio >1 indicated a greater likelihood of response on zilucoplan 0.3mg/kg compared with placebo.	

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; ICE1 = rescue therapy; ICE2 = any death or myasthenic crisis; LS = least squares; MGC = Myasthenia Gravis Composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis Quality of Life 15r; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; MMS = minimal symptom expression; N/A = not applicable; QMG = quantitative myasthenia gravis.
Notes: The LS mean difference presented was zilucoplan minus placebo.
Sources: UCB, 2022 (12); Howard et al., 2023, (10).

Table 64: Results per RAISE -XT (mITT population, 11 November 2023)

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
LS mean CFB in MG-ADL score (week 12)	PBO/ZLP 0.3 mg/kg	90	-2.20 (-3.53, -0.87)	N/A	N/A	N/A	N/A	N/A	N/A	Baseline is defined as the baseline in the parent study (MG0009/MG0010). CFB in MG-ADL were estimated using	UCB, 2024 (11)
	ZLP 0.3 mg/kg /	93	-4.59 (-5.62, -3.56)								

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	0.3 mg/kg									a MMRM ANCOVA with baseline MG-ADL score, baseline QMG score, geographical region, parent study factor and baseline score X visit (interaction term) as fixed effects and participant as a random effect. The model included weeks 1 to 12 (double-blind treatment period) and week E1 to week E108 (open-label extension). An AR(1) correlation structure was used. Separate model was fitted for each group: PBO/ ZLP 0.3 mg/kg and ZLP 0.3 mg/kg /0.3 mg/kg. In the pooled ZLP group, the week number indicates the number of weeks on ZLP treatmen (i.e., the baseline is the start of ZLP treatment). For instance, week 24 represents 24 weeks of ZLP treatment, which is measured at week 24 in the ZLP/ZLP group and at week 36 in the PBO/ZLP group.	
LS mean CFB in MG-ADL score (week 24, week E12)	PBO/ZLP 0.3 mg/kg	90	-6.17 (-7.32, -5.02)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	-5.90 (-6.82, -4.98)								
LS mean CFB in MG-ADL score (week 12)	ZLP 0.3 mg/kg pooled	183	-3.69 (-4.36, -3.02	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
LS mean CFB in MG-ADL score (week 24, week E12)	ZLP 0.3 mg/kg pooled	183	-4.19 (-4.88, -3.49)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
LS mean difference in MG-ADL score week 12 vs. week 24	PBO/ZLP 0.3 mg/kg	90	3.97 (2.20, 5.74; p<0.0001)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	-1.31 (-0.05, 2.68; p=0.0597)								
LS mean CFB in MG-ADL score (week 120	PBO/ZLP 0.3 mg/kg	90	-7.09 (-8.46, -5.73)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg /	93	-6.37 (-7.42, -5.31)								

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
(week E108))	0.3 mg/kg										
LS mean CFB in QMG score (week 12)	PBO/ZLP 0.3 mg/kg	90	-2.94 (-4.71, -1.17)	N/A	N/A	N/A	N/A	N/A	N/A	Baseline is defined as the baseline in the parent study (MG0009/MG0010). CFB in QMG were estimated using a MMRM ANCOVA with baseline MG-ADL score, baseline QMG score, geographical region, parent study factor and baseline QMG score X visit (interaction term) as fixed effects and participant as a random effect. The model included weeks 1 to 12 (double-blind treatment period) and week E1 to week E108 (open-label extension). An AR(1) correlation structure was used. Separate model was fitted for each group: PBO/ZLP 0.3 mg/kg and ZLP 0.3 mg/kg /0.3 mg/kg. In the pooled ZLP group, the week number indicates the number of weeks on ZLP treatment (i.e., the baseline is the start of ZLP treatment). For instance, week 24 represents 24	UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	-6.56 (-8.00, -5.12)								
LS mean CFB in QMG score (week 24 (week E12))	PBO/ZLP 0.3 mg/kg	90	-8.53 (-10.08, -6.98)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	-8.78 (-10.08, -7.48)								
LS mean CFB in QMG score (week 12)	ZLP 0.3 mg/kg pooled	183	-5.94 (-6.84, -5.05)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
LS mean CFB in QMG score (week 24 (week E12))	ZLP 0.3 mg/kg pooled	183	-6.75 (-7.68, -5.82)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
LS mean difference in QMG score week 12 vs. week 24	PBO/ZLP 0.3 mg/kg	90	5.59 (3.33, 7.84; p<0.0001)	N/A	N/A	N/A	N/A	N/A	N/A	weeks of ZLP treatment, which is measured at week 24 in the ZLP/ZLP group and at week 36 in the PBO/ZLP group.	UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	2.22 (0.38, 4.06; p=0.0181)	N/A	N/A	N/A	N/A	N/A	N/A		
LS mean CFB in QMG score (week 120 (week E108))	PBO/ZLP 0.3 mg/kg	90	-9.56 (-11.43, -7.70)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	-10.38 ((112)-11.86, -8.90)	N/A	N/A	N/A	N/A	N/A	N/A		
LS mean CFB in MGC score (week 12)	PBO/ZLP 0.3 mg/kg	90	-6.97 (-9.47, -4.47)	N/A	N/A	N/A	N/A	N/A	N/A	Baseline is defined as the baseline in the parent study (MG0009/MG0010). CFB in MGC were estimated using a MMRM ANCOVA with baseline MG-ADL score, baseline QMG score, baseline MGC score, geographical region, parent study factor and baseline score X visit (interaction term) as fixed effects and participant as a	UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	-9.33 (-11.20, -7.46)								
LS mean CFB in MGC score (week 24 (week E12))	PBO/ZLP 0.3 mg/kg	90	-12.30 (-14.50, -10.09)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	-11.77 (-13.46, -10.09)								

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
LS mean CFB in MGC score (week 12)	ZLP 0.3 mg/kg pooled	183	-7.67 (-8.90, -6.43)	N/A	N/A	N/A	N/A	N/A	N/A	random effect. The model included weeks 1 to 12 (double-blind treatment period) and week E1 to week E108 (open-label extension). An unstructured correlation structure was used. Separate model was fitted for each group: PBO/ZLP 0.3 mg/kg and ZLP 0.3 mg/kg /0.3 mg/kg. In the pooled ZLP group, the week number indicates the number of weeks on ZLP treatment (i.e., the baseline is the start of ZLP treatment). For instance, week 24 represents 24 weeks of ZLP treatment, which is measured at week 24 in the ZLP/ZLP group and at week 36 in the PBO/ZLP group.	UCB, 2024 (11)
LS mean CFB in MGC score (week 24 (week E12))	ZLP 0.3 mg/kg pooled	183	-8.41 (-9.74, -7.09)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
LS mean difference in MGC score week 12 vs. week 24	PBO/ZLP 0.3 mg/kg	90	5.33 (1.89, 8.77; p=0.0024)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	2.24 (-0.09, 4.97; p=0.0587)								
LS mean CFB in MGC score (week 120 (week E108))	PBO/ZLP 0.3 mg/kg	90	-13.75 (-16.45, -11.06)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	-13.58 (-15.53, -11.64)								
LS mean CFB in MG-QOL15r	PBO/ZLP 0.3 mg/kg	90	-2.71 (-5.11, -0.31)	N/A	N/A	N/A	N/A	N/A	N/A	Baseline is defined as the baseline in the parent study (MG0009/MG0010). CFB in MG-QOL15r were estimated	UCB, 2024 (11)
	ZLP 0.3 mg/kg /	93	-6.15 (-8.21, -4.08)								

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
score (week 12)	0.3 mg/kg									using a MMRM ANCOVA with baseline MG-ADL score, baseline QMG score, baseline MG-QOL15r score, geographical region, parent study factor and baseline score X visit (interaction term) as fixed effects and participant as a random effect. The model included weeks 1 to 12 (double-blind treatment period) and week E1 to week E108 (open-label extension). An AR(1) correlation structure was used. Separate model was fitted for each group: PBO/ZLP 0.3 mg/kg and ZLP 0.3 mg/kg /0.3 mg/kg. In the pooled ZLP group, the week number indicates the number of weeks on ZLP treatment (i.e., the baseline is the start of ZLP treatment). For instance, week 24 represents 24 weeks of ZLP treatment, which is measured at week 24 in the	
LS mean CFB in MG-QOL15r score (week 24 (week E12))	PBO/ZLP 0.3 mg/kg	90	-8.07 (-10.20, -5.94)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	-9.92 (-11.79, -8.04)								
LS mean CFB in MG-QOL15r score (week 12)	ZLP 0.3 mg/kg pooled	183	-5.80 (-7.00, -4.60)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
LS mean CFB in MG-QOL15r score (week 24 (week E12))	ZLP 0.3 mg/kg pooled	183	-6.52 (-7.78, -5.26)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
LS mean difference in MG-QOL15r score week 12	PBO/ZLP 0.3 mg/kg	90	5.36 (2.44, 8.28; p=0.0003)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	3.77 (-1.19, 6.35; p=0.0042)								

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
vs. week 24										ZLP/ZLP group and at week 36 in the PBO/ZLP group.	
LS mean CFB in MG-QOL15r score (week 120 (week E108))	PBO/ZLP 0.3 mg/kg	90	-8.87 (-11.40, -6.34)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	-10.21 (-12.32, -8.10)								
MSE responders at week 12, n (%) MSE responders at week 13 (week E1), n (%)	PBO/ZLP 0.3 mg/kg	90	7 of 90 (7.8)	N/A	N/A	N/A	N/A	N/A	N/A	N=90 and N=93 in the PBO/ZLP 0.3 mg/kg group and the ZLP 0.3 mg/kg / 0.3 mg/kg group, respectively, indicates N at baseline. Percentages are based on n, i.e., the number of subjects who have completed each individual time point.	UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	18 of 93 (19.4)								
MSE responders at week 24 (week E12), n (%) MSE responders at week 60	PBO/ZLP 0.3 mg/kg	90	19 of 87 (21.8)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	22 of 89 (24.7)								

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
(week E48), n (%)											
MSE responders at week 96 (week E84), n (%)	PBO/ZLP 0.3 mg/kg	90	27 of 79 (32.5)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	26 of 81 (31.0)								
MSE responders at week 12, n (%) MSE responders at week 13 (week E1), n (%)	PBO/ZLP 0.3 mg/kg	90	28 of 67 (41.8)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	30 of 73 (41.1)								
MSE responders at week 24 (week E12), n (%) MSE responders at week 60 (week E48), n (%)	PBO/ZLP 0.3 mg/kg	90	31 of 58 (53.4)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
	ZLP 0.3 mg/kg / 0.3 mg/kg	93	30 of 65 (46.2)								

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
MSE responders at week 96 (week E84), n (%)	PBO/ZLP 0.3 mg/kg	90	15 of 32 (46.9)	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (11)
MSE responders at week 120 (week E108), n (%)	ZLP 0.3 mg/kg / 0.3 mg/kg	93	15 of 71 (36.6)								
Discontinuation/reduction of corticosteroid use at week 60*, n (%)	PBO/ZLP 0.3 mg/kg	29	12 (41%)	N/A	N/A	N/A	N/A	N/A	N/A	Discontinuation/reduction of corticosteroids use was investigated among participants, who received corticosteroids at baseline and completed the week 60 data cut-off (44 patients in the ZLP 0.3 mg/kg/0.3 mg/kg group and 29 in the PBO/ZLP 0.3 mg/kg group).	Howard et al. 2024 (87)
	ZLP 0.3 mg/kg / 0.3 mg/kg	44	18 (41%)								
Discontinuation/reduction of corticosteroid use at week 60, n (%)	ZLP 0.3 mg/kg pooled	103	47 (45.6%)	N/A	N/A	N/A	N/A	N/A	N/A	Discontinuation/reduction of corticosteroids use was investigated among participants who received corticosteroids at double-blind baseline.	Hewamadduma et al. 2024 (98) and UCB, 2024 (11)

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Discontinuation of corticosteroid use at week 60, n (%)	ZLP 0.3 mg/kg pooled	103	9 (8.7%)	N/A	N/A	N/A	N/A	N/A	N/A	Discontinuation/reduction of corticosteroids use was investigated among participants who received corticosteroids at double-blind baseline.	Hewamadduma et al. 2024 (98) and UCB, 2024 (11)
Mean dose reduction of corticosteroid use at week 60*	PBO/ZLP 0.3 mg/kg	29	16 mg	N/A	N/A	N/A	N/A	N/A	N/A	Discontinuation/reduction of corticosteroids use was investigated among participants, who received corticosteroids at baseline and completed the week 60 data cut-off (44 patients in the ZLP 0.3 mg/kg/0.3 mg/kg group and 29 in the PBO/ZLP 0.3 mg/kg group).	Howard et al. 2024 (87)
	ZLP 0.3 mg/kg / 0.3 mg/kg	44	14 mg								
Mean dose reduction of corticosteroid use at week 60	ZLP 0.3 mg/kg pooled	103	13.0 mg	N/A	N/A	N/A	N/A	N/A	N/A	Reduction of corticosteroids use was investigated among participants, who received corticosteroids at double-blind baseline.	Hewamadduma et al. 2024 (98)
Mean baseline dose of corticosteroid use at week 60	ZLP 0.3 mg/kg pooled	103	14.4 mg	N/A	N/A	N/A	N/A	N/A	N/A	Investigated among participants who discontinued at week 60.	UCB, 2024 (11)

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Discontinuation/reduction of corticosteroid use at week 120, n (%)	ZLP 0.3 mg/kg pooled	54	33 (61.1%)	N/A	N/A	N/A	N/A	N/A	N/A	Discontinuation/reduction of corticosteroids use was investigated among participants, who received corticosteroids at double-blind baseline.	Hewamadduma et al. 2024 (98) and UCB, 2024 (11)
Discontinuation of corticosteroid use at week 120, n (%)	ZLP 0.3 mg/kg pooled	54	11 (20.4%)	N/A	N/A	N/A	N/A	N/A	N/A	Discontinuation/reduction of corticosteroids use was investigated among participants, who received corticosteroids at double-blind baseline.	Hewamadduma et al. 2024 (98) and UCB, 2024 (11)
Mean dose reduction of corticosteroid use at week 120	ZLP 0.3 mg/kg pooled	54	15.5 mg	N/A	N/A	N/A	N/A	N/A	N/A	Reduction of corticosteroids use was investigated among participants, who received corticosteroids at double-blind baseline.	Hewamadduma et al. 2024 (98)
Mean baseline dose of corticosteroid use at week 120	ZLP 0.3 mg/kg pooled	54	18.9 mg	N/A	N/A	N/A	N/A	N/A	N/A	Investigated among participants who discontinued at week 120.	UCB, 2024 (11)

Results of RAISE-XT (MG0011), (NCT04225871)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Reduction/discontinuation of immunosuppressants use was investigated among participants, who received immunosuppressants at double-blind baseline.	UCB, 2024 (79)
[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A		UCB, 2024 (79)

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; LS = least squares; MGC = Myasthenia Gravis Composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL15r = Myasthenia Gravis Quality of Life 15r; mITT = modified intention-to-treat; MMRM = mixed model repeated measure; MSE = minimal symptom expression; N/A = not applicable; PBO = placebo; QMG = quantitative myasthenia gravis; ZLP = zilucoplan.
Notes: * Data cut-off: 8 September 2022.
Sources: UCB, 2024 (11); Howard et al. 2024 (87); Hewamadduma et al. 2024 (98); UCB, 2024 (79).

Appendix C. Comparative analysis of efficacy

Not applicable.

Table 65: Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		

Appendix D. Extrapolation

D.1 Extrapolation of time on treatment

D.1.1 Data input

Kaplan Meier data from the RAISE-XT trial was applied to the seven standard parametric models. Treatment discontinuation data from RAISE-XT was provided until month 39 and was extrapolated using survival analysis modelling. The outputs of this analysis inform the percentage of patients on treatment until the maximum treatment duration timepoint. It should be noted that the treatment discontinuation data from RAISE-XT includes discontinuation due to all reasons except a lack of response.

D.1.2 Model

The seven standard parametric models were assessed to see which one provided the best fit.

D.1.3 Proportional hazards

Not applicable. All patients in RAISE-XT were on zilucoplan.

D.1.4 Evaluation of statistical fit (AIC and BIC)

The evaluation of statistical fit is presented in Table 66. Generalised Gamma had the lowest AIC, while the exponential had the lowest BIC.

Table 66: AIC and BIC goodness of fit

Model	AIC	BIC
Generalised gamma	139.77	147.36
Weibull	143.75	148.81
Exponential	142.67	145.20
Log-logistic	143.52	148.58
Log-normal	142.44	147.51
Gompertz	144.63	149.70
Gamma	143.58	148.64

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion.

D.1.5 Evaluation of visual fit

Generalised gamma is the only distribution that shows treatment discontinuation to level off over time, as with the RAISE-XT data.

D.1.6 Evaluation of hazard functions

The hazard plots were not produced for the extrapolation. Therefore, the evaluation of hazard functions is not available.

D.1.7 Validation and discussion of extrapolated curves

The generalised gamma distribution was deemed to be the best fit to the Kaplan Meier data, owing to its lower AIC (lowest) and BIC values (second lowest) compared to the other distributions. It is noted that, although the generalised gamma distribution has the lowest goodness-of-fit scores, it appears to have visual fit that is very different from the other distributions. However, it is the only distribution that shows treatment discontinuation to level off over time, as with the RAISE-XT data. Therefore, it was considered the best fit to the data in comparison to the other distributions.

This decision is conservative as fewer patients discontinue treatment over time using the generalised gamma distribution, compared to the other distributions. It is assumed that reasons for treatment discontinuation in RAISE-XT excluded patients who discontinue due to a lack of response to treatment as the model includes separate functionality to account for patients who stop their initial treatment due to a lack of response. As fewer patients discontinue treatment using the generalised gamma distribution, the potential for double-counting discontinuation due to lack of response is negated.

Treatment discontinuation data extrapolated for zilucoplan 0.3mg/kg/0.3mg/kg is assumed for both zilucoplan and standard of care.

D.1.8 Adjustment of background mortality

Not applicable for time on treatment. Background mortality was applied in the health economic model.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

Not applicable.

Appendix E. Serious adverse events

All serious adverse events recorded in the RAISE trial is provided in Table 67.

Table 67: Serious adverse events in RAISE (week 12)

System organ class Preferred term	Placebo N = 88 n (%) [#]	Zilucoplan N = 86 n (%) [#]
Any serious TEAE	13 (14.8) [18]	11 (12.8) [15]
Infections and infestations	4 (4.5) [6]	4 (4.7) [6]
COVID-19	2 (2.3) [2]	1 (1.2) [1]
COVID-19 pneumonia	2 (2.3) [2]	1 (1.2) [1]
Oesophageal candidiasis	0	1 (1.2) [1]
Oral candidiasis	0	1 (1.2) [1]
Pneumonia	0	1 (1.2) [1]
Sepsis	0	1 (1.2) [1]
Herpes simplex meningoencephalitis	1 (1.1) [2]	0
Nervous system disorders	7 (8.0) [8]	2 (2.3) [3]
Myasthenia gravis worsening	5 (5.7) [6]	2 (2.3) [3]
Cerebral haemorrhage	1 (1.1) [1]	0
Cerebrovascular accident	1 (1.1) [1]	0
Blood and lymphatic system disorders	0	1 (1.2) [1]
Anaemia	0	1 (1.2) [1]
Gastrointestinal disorders	1 (1.1) [1]	1 (1.2) [1]
Aphthous ulcer	0	1 (1.2) [1]
Vomiting	1 (1.1) [1]	0
Investigations	0	1 (1.2) [1]
Lipase increased	0	1 (1.2) [1]
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	1 (1.1) [1]	1 (1.2) [1]
Basal cell carcinoma	0	1 (1.2) [1]
Metastases to meninges	1 (1.1) [1]	0
Respiratory, thoracic, and mediastinal disorders	1 (1.1) [1]	1 (1.2) [1]
Pulmonary embolism	0	1 (1.2) [1]
Chronic obstructive pulmonary disease	1 (1.1) [1]	0
Skin and subcutaneous tissue disorders	0	1 (1.2) [1]
Angioedema	0	1 (1.2) [1]

Pregnancy, puerperium, and perinatal conditions	1 (1.1) [1]	0
Hyperemesis gravidarum	1 (1.1) [1]	0

Abbreviations: TEAE = treatment-related adverse event.
Notes: n=number of study participants reporting at least 1 serious TEAE. # is the number of individual occurrences of the serious TEAE.
Source: UCB, 2022, table 9-13 (12); ClinicalTrials.gov 2019 (88).

All serious adverse events recorded in the RAISE-XT trial is provided in Table 68.

Table 68: Serious adverse events in RAISE-XT (11 November 2023)

System organ class High level term Preferred term	All zilucoplan N = 200 n (%) [#]
Any serious TEAE	81 (40.5) [207]
Due To Worsening Mg Symptoms	
Hospitalisation For Watchman Procedure	1 (0.5) [1]
Increased Temperature And Vomiting	1 (0.5) [1]
Blood and lymphatic system disorders	2 (1.0) [2]
Anaemias NEC	2 (1.0) [2]
Anaemia	1 (0.5) [1]
Blood loss anaemia	1 (0.5) [1]
Cardiac disorders	13 (6.5) [20]
Coronary artery disorders not elsewhere classified (NEC)	2 (1.0) [2]
Coronary artery disease	1 (0.5) [1]
Coronary artery stenosis	1 (0.5) [1]
Heart failures NEC	2 (1.0) [5]
Cardiac failure	2 (1.0) [3]
Cardiac failure chronic	1 (0.5) [1]
Cardiac failure congestive	1 (0.5) [1]
Ischaemic coronary artery disorders	5 (2.5) [5]
Myocardial infarction	4 (2.0) [4]
Angina pectoris	1 (0.5) [1]
Rate and rhythm disorders NEC	1 (0.5) [1]
Bradycardia	1 (0.5) [1]
Supraventricular arrhythmias	2 (1.0) [4]
Atrial fibrillation	2 (1.0) [3]
Atrial flutter	1 (0.5) [1]
Ventricular arrhythmias and cardiac arrest	3 (1.5) [3]
Cardiac arrest	2 (1.0) [2]
Pulseless electrical activity	1 (0.5) [1]
Eye disorders (p. 1398, table 14.3.4.1)	2 (1.0) [2]

Ocular sensation disorders	1 (0.5) [1]
Photophobia	1 (0.5) [1]
Visual disorders NEC	1 (0.5) [1]
Diplopia	1 (0.5) [1]
Gastrointestinal disorders	14 (7.0) [17]
Abdominal hernias NEC	1 (0.5) [1]
Abdominal hernia	1 (0.5) [1]
Acute and chronic pancreatitis	3 (1.5) [4]
Obstructive pancreatitis	1 (0.5) [2]
Pancreatitis	1 (0.5) [1]
Pancreatitis acute	1 (0.5) [1]
Benign neoplasms gastrointestinal (excl. oral cavity)	2 (1.0) [2]
Large intestine polyp	2 (1.0) [2]
Cystic pancreatic disorders	1 (0.5) [1]
Pancreatic cyst	1 (0.5) [1]
Gastric ulcers and perforation	1 (0.5) [1]
Gastric ulcer	1 (0.5) [1]
Gastrointestinal and abdominal pains (excl. oral and throat)	2 (1.0) [2]
Abdominal pain	2 (1.0) [2]
Nausea and vomiting symptoms	1 (0.5) [1]
Vomiting	1 (0.5) [1]
Non-site specific gastrointestinal haemorrhages	1 (0.5) [1]
Gastrointestinal haemorrhage	1 (0.5) [1]
Oesophageal stenosis and obstruction	1 (0.5) [1]
Oesophageal stenosis	1 (0.5) [1]
Oesophagitis (excl. infective)	1 (0.5) [1]
Oesophagitis	1 (0.5) [1]
Pancreatic disorders NEC	1 (0.5) [1]
Pancreatic mass	1 (0.5) [1]
Peritoneal and retroperitoneal disorders	1 (0.5) [1]
Intra-abdominal fluid collection	1 (0.5) [1]
General disorders and administration site conditions	5 (2.5) [5]
Death and sudden death	1 (0.5) [1]
Death	1 (0.5) [1]
Inflammations	1 (0.5) [1]
Inflammation	1 (0.5) [1]
Oedema NEC	1 (0.5) [1]
Oedema peripheral	1 (0.5) [1]

Pain and discomfort NEC	1 (0.5) [1]
Non-cardiac chest pain	1 (0.5) [1]
Therapeutic and nontherapeutic responses	1 (0.5) [1]
Adverse event	1 (0.5) [1]
Hepatobiliary disorders	4 (2.0) [5]
Bile duct infections and inflammations	1 (0.5) [1]
Cholangitis	1 (0.5) [1]
Cholecystitis and cholelithiasis	3 (1.5) [3]
Cholecystitis	3 (1.5) [3]
Obstructive bile duct disorders (excl. neoplasms)	1 (0.5) [1]
Bile duct stenosis	1 (0.5) [1]
Infections and infestations	31 (15.5) [54]
Abdominal and gastrointestinal infections	5 (2.5) [6]
Diverticulitis	2 (1.0) [2]
Pancreas infection	2 (1.0) [2]
Abdominal infection	1 (0.5) [1]
Colonic abscess	1 (0.5) [1]
Bacterial infections NEC	4 (2.0) [4]
Cellulitis	4 (2.0) [4]
Bone and joint infections	1 (0.5) [1]
Osteomyelitis	1 (0.5) [1]
Candida infections	1 (0.5) [1]
Endocarditis candida	1 (0.5) [1]
Central nervous system and spinal infections	1 (0.5) [1]
Meningitis	1 (0.5) [1]
Meningitis aseptic	1 (0.5) [1]
Coronavirus infections	8 (4.0) [9]
COVID-19 pneumonia	6 (3.0) [6]
COVID-19	3 (1.5) [3]
Enterococcal infections	1 (0.5) [1]
Enterococcal bacteraemia	1 (0.5) [1]
Hepatitis virus infections	1 (0.5) [1]
Hepatitis C	1 (0.5) [1]
Hepatobiliary and spleen infections	2 (1.0) [2]
Cholecystitis infective	1 (0.5) [1]
Liver abscess	1 (0.5) [1]
Herpes viral infections	1 (0.5) [1]
Herpes simplex meningoencephalitis	1 (0.5) [1]

Infections NEC	2 (1.0) [2]
Infection	1 (0.5) [1]
Injection site infection	1 (0.5) [1]
Influenza viral infections	1 (0.5) [1]
Influenza	1 (0.5) [1]
Klebsiella infections	1 (0.5) [1]
Klebsiella infection	1 (0.5) [1]
Legionella infections	1 (0.5) [1]
Pneumonia legionella	1 (0.5) [1]
Lower respiratory tract and lung infections	7 (3.5) [7]
Pneumonia	5 (2.5) [5]
Bronchitis	2 (1.0) [2]
Male reproductive tract infections	1 (0.5) [1]
Epididymitis	1 (0.5) [1]
Respiratory syncytial viral infections	1 (0.5) [1]
Respiratory syncytial virus infection	1 (0.5) [1]
Sepsis, bacteraemia, viraemia and fungaemia NEC	3 (1.5) [5]
Sepsis	2 (1.0) [3]
Bacteraemia	1 (0.5) [1]
Post procedural sepsis	1 (0.5) [1]
Staphylococcal infections	2 (1.0) [4]
Staphylococcal bacteraemia	2 (1.0) [2]
Staphylococcal infection	1 (0.5) [2]
Viral infections NEC	3 (1.5) [3]
Gastroenteritis viral	1 (0.5) [1]
Gastrointestinal viral infection	1 (0.5) [1]
Viral infection	1 (0.5) [1]
Injury, poisoning and procedural complications	12 (6.0) [15]
Anaesthetic and allied procedural complications	1 (0.5) [1]
Delayed recovery from anaesthesia	1 (0.5) [1]
Cardiovascular injuries	1 (0.5) [1]
Heart injury	1 (0.5) [1]
Gastrointestinal and hepatobiliary procedural complications	1 (0.5) [1]
Gastrointestinal anastomotic leak	1 (0.5) [1]
Limb fractures and dislocations	1 (0.5) [1]
Hip fracture	1 (0.5) [1]
Non-site specific injuries NEC	1 (0.5) [1]
Fall	1 (0.5) [1]

Non-site specific procedural complications	3 (1.5) [3]
Post procedural complication	2 (1.0) [2]
Post procedural haemorrhage	1 (0.5) [1]
Pelvic fractures and dislocations	1 (0.5) [1]
Acetabulum fracture	1 (0.5) [1]
Site specific injuries NEC	2 (1.0) [2]
Head injury	2 (1.0) [2]
Skull fractures, facial bone fractures and dislocations	1 (0.5) [1]
Facial bones fracture	1 (0.5) [1]
Spinal fractures and dislocations	1 (0.5) [1]
Spinal compression fracture	1 (0.5) [1]
Spinal fracture	1 (0.5) [1]
Thoracic cage fractures and dislocations	1 (0.5) [1]
Rib fracture	1 (0.5) [1]
Investigations	4 (2.0) [4]
Carbohydrate tolerance analyses (incl. diabetes)	1 (0.5) [1]
Blood glucose fluctuation	1 (0.5) [1]
Heart rate and pulse investigations	1 (0.5) [1]
Heart rate irregular	1 (0.5) [1]
Liver function analyses	1 (0.5) [1]
Transaminases increased	1 (0.5) [1]
Therapeutic drug monitoring analyses	1 (0.5) [1]
Anticoagulation drug level above therapeutic	1 (0.5) [1]
Musculoskeletal and connective tissue disorders	7 (3.5) [8]
Bursal disorders	1 (0.5) [1]
Bursitis	1 (0.5) [1]
Intervertebral disc disorders NEC	1 (0.5) [1]
Intervertebral disc degeneration	1 (0.5) [1]
Muscle related signs and symptoms NEC	1 (0.5) [1]
Haematoma muscle	1 (0.5) [1]
Musculoskeletal and connective tissue pain and discomfort	2 (1.0) [2]
Back pain	2 (1.0) [2]
Osteoarthropathies	1 (0.5) [1]
Osteoarthritis	1 (0.5) [1]
Spine and neck deformities	1 (0.5) [1]
Lumbar spinal stenosis	1 (0.5) [1]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (2.5) [5]
Bone neoplasms unspecified malignancy	1 (0.5) [1]

Bone neoplasm	1 (0.5) [1]
Myeloproliferative disorders (excl. leukaemia)	1 (0.5) [1]
Myeloproliferative neoplasm	1 (0.5) [1]
Neoplasms malignant site unspecified NEC	1 (0.5) [1]
Metastatic neoplasm	1 (0.5) [1]
Skin melanomas (excl. ocular)	1 (0.5) [1]
Metastatic malignant melanoma	1 (0.5) [1]
Uterine neoplasms benign	1 (0.5) [1]
Uterine leiomyoma	1 (0.5) [1]
Nervous system disorders	26 (13.0) [45]
Central nervous system haemorrhages and cerebrovascular accidents	2 (1.0) [3]
Carotid artery thrombosis	1 (0.5) [1]
Embolic stroke	1 (0.5) [1]
Ischaemic stroke	1 (0.5) [1]
Disturbances in consciousness NEC	2 (1.0) [3]
Syncope	2 (1.0) [3]
Headaches NEC	1 (0.5) [1]
Headache	1 (0.5) [1]
Memory loss (excl. dementia)	1 (0.5) [1]
Amnesia	1 (0.5) [1]
Neuromuscular junction dysfunction	21 (10.5) [37]
Myasthenia gravis	19 (9.5) [34]
Myasthenia gravis crisis	2 (1.0) [3]
Pregnancy, puerperium and perinatal conditions	1 (0.5) [1]
Unintended pregnancies	1 (0.5) [1]
Unintended pregnancy	1 (0.5) [1]
Renal and urinary disorders	4 (2.0) [7]
Renal failure and impairment	3 (1.5) [3]
Acute kidney injury	1 (0.5) [1]
Renal failure	1 (0.5) [1]
Renal impairment	1 (0.5) [1]
Renal lithiasis	1 (0.5) [1]
Nephrolithiasis	1 (0.5) [1]
Urinary tract lithiasis (excl. renal)	2 (1.0) [2]
Ureterolithiasis	2 (1.0) [2]
Reproductive system and breast disorders	2 (1.0) [2]
Ovarian and fallopian tube cysts and neoplasms	1 (0.5) [1]

Ovarian cyst	1 (0.5) [1]
Prostate and seminal vesicles infections and inflammations	1 (0.5) [1]
Prostatitis	1 (0.5) [1]
Respiratory, thoracic and mediastinal disorders	6 (3.0) [6]
Breathing abnormalities	1 (0.5) [1]
Dyspnoea	1 (0.5) [1]
Bronchospasm and obstruction	1 (0.5) [1]
Chronic obstructive pulmonary disease	1 (0.5) [1]
Lower respiratory tract inflammatory and immunologic conditions	1 (0.5) [1]
Pneumonia aspiration	1 (0.5) [1]
Pulmonary thrombotic and embolic conditions	1 (0.5) [1]
Pulmonary embolism	1 (0.5) [1]
Respiratory failures (excl. neonatal)	2 (1.0) [2]
Acute respiratory failure	2 (1.0) [2]
Surgical and medical procedures	2 (1.0) [2]
Gastric therapeutic procedures	1 (0.5) [1]
Gastric bypass	1 (0.5) [1]
Induced abortions	1 (0.5) [1]
Abortion induced	1 (0.5) [1]
Vascular disorders	2 (1.0) [2]
Peripheral embolism and thrombosis	1 (0.5) [1]
Deep vein thrombosis	1 (0.5) [1]
Vascular hypotensive disorders	1 (0.5) [2]
Hypotension	1 (0.5) [1]
Orthostatic hypotension	1 (0.5) [1]

Abbreviations: NEC = not elsewhere classified; TEAE = treatment-related adverse event.
Notes: n=number of study participants reporting at least 1 serious TEAE. # is the number of individual occurrences of the serious TEAE.
Source: UCB, 2024, table 14.3.4.1 (11).

Appendix F. Health-related quality of life

Not applicable.

Appendix G. Probabilistic sensitivity analyses

The data and assumptions (point estimate, and lower and upper bound) which form the basis for the selected probability distributions used in the probabilistic analysis are presented in Table 69. The convergence tests are presented in

Figure 18 and Figure 19.

Table 69: Overview of parameters in the PSA

Parameter	Included in sensitivity analysis	Point estimate	Lower bound	Upper bound	Distribution
Cycle length	No	2.00	1.60	2.40	Normal
Time horizon (years)	No	52.50	42.00	63.00	Normal
Discount rate (costs)	No	0.04	0.03	0.04	Normal
Discount rate (health outcomes)	No	0.04	0.03	0.04	Normal
Avg. age of population	Yes	53.00	19.00	75.00	Normal
Average patient weight (kg)	Yes	89.10	41.00	169.00	Normal
% males	Yes	0.43	0.34	0.52	Beta
Average patient BSA (m^2)	Yes	2.05	1.64	2.46	Normal
Average MG-ADL score at start	No	10.60	6.00	19.00	Normal
Baseline BMI (kg/m2)	Yes	31.00	16.00	54.00	Normal
Fixed percentage of responders: Zilucoplan	No	104.00	83.20	124.80	Normal
Fixed percentage of responders: Standard of care	No	104.00	83.20	124.80	Normal
Response rate - Zilucoplan	Yes	0.73	0.58	0.88	Beta
Response rate - Standard of care	Yes	0.46	0.37	0.55	Beta
Response assessment timepoint - Zilucoplan	Yes	24.00	19.20	28.80	Normal
Response assessment timepoint - Standard of care	Yes	12.00	9.60	14.40	Normal
Proportion who discontinue - Zilucoplan	Yes	1.00	0.80	1.00	Beta
Proportion who discontinue - Standard of care	Yes	1.00	0.80	1.00	Beta
Weeks before return to uncontrolled	No	14.00	11.20	16.80	Normal
% showing continued response - Zilucoplan	No	0.05	0.04	0.06	Dirichlet
% showing loss of response - Zilucoplan	No	0.05	0.04	0.06	Dirichlet
% showing stable response - Zilucoplan	No	0.90	0.72	1.00	Dirichlet

% showing continued response - Standard of care	No	0.05	0.04	0.06	Dirichlet
% showing loss of response - Standard of care	No	0.05	0.04	0.06	Dirichlet
% showing stable response - Standard of care	No	0.90	0.72	1.00	Dirichlet
Time before MG-ADL response is lost	Yes	1.00	0.80	1.20	Beta
MG-ADL score CFB (continued response)	Yes	6.59	5.27	7.91	Gamma
MG-ADL score CFB (stable response)	Yes	3.40	2.72	4.08	Gamma
Exacerbation annual event rate - uncontrolled	Yes	0.65	0.52	0.78	Beta
Myasthenic crisis annual event rate - uncontrolled	Yes	0.06	0.05	0.07	Beta
Exacerbation annual event rate - responders	Yes	0.24	0.19	0.31	Beta
Myasthenic crisis annual event rate - responders	Yes	0.02	0.01	0.05	Beta
Exacerbation to myasthenic crisis 2 week event rate	Yes	0.18	0.15	0.22	Beta
Exacerbation relative risk - Zilucoplan	No	1.00	0.80	1.20	Lognormal
Myasthenic crisis relative risk - Zilucoplan	No	1.00	0.80	1.20	Lognormal
Exacerbation relative risk - Standard of care	No	1.00	0.80	1.20	Lognormal
Myasthenic crisis relative risk - Standard of care	No	1.00	0.80	1.20	Lognormal
Annual event rate - MG-ADL score 0-4	No	0.14	0.11	0.16	Lognormal
Proportion of clinical events that are exacerbations	No	0.91	0.73	1.10	Normal
Annual event rate - MG-ADL score 4-7	No	0.29	0.23	0.35	Normal
Annual event rate - MG-ADL score 7-10	No	0.04	0.04	0.05	Normal
Annual event rate - MG-ADL score 10-13	No	1.09	0.87	1.31	Normal

Annual event rate - MG-ADL score 13-16	No	2.10	1.68	2.52	Normal
Exacerbation to myasthenic crisis 2 week event rate	No	0.24	0.19	0.29	Normal
Annual event rate - MG-ADL score 16-19	No	4.05	3.24	4.85	Normal
Annual event rate - MG-ADL score 19-22	No	7.80	6.24	9.36	Normal
Annual event rate - MG-ADL score 22+	No	13.48	10.78	16.17	Normal
Uncontrolled/response/exacerbation mortality rate	No	General population mortality	N/a	N/a	Normal
Myasthenic crisis mortality rate	Yes	0.04	0.04	0.05	Beta
Vial sharing	No	Off	N/a	N/a	Gamma
Intravenous administration costs (initial cycles)	Yes	1941.00	1552.80	2329.20	Gamma
Intravenous administration costs (subsequent cycles)	Yes	1941.00	1552.80	2329.20	Gamma
Method of calculation	No	Parameter mean	N/a	N/a	Gamma
Subcutaneous administration costs	Yes	1941.00	1552.80	2329.20	Gamma
Oral administration costs	Yes	0.00	0.00	0.00	Gamma
Patients time cost	Yes	203.00	162.40	243.60	Gamma
Transport cost	Yes	149.20	119.36	179.04	Gamma
IVIg resource use - uncontrolled	Yes	0.00	0.00	0.00	Gamma
IVIg resource use - response	Yes	0.00	0.00	0.00	Gamma
IVIg resource use - exacerbation	Yes	0.40	0.32	0.48	Gamma
IVIg resource use - myasthenic crisis	Yes	0.20	0.16	0.24	Gamma
PLEX resource use - uncontrolled (other costs)	Yes	0.00	0.00	0.00	Gamma
PLEX resource use - response (other costs)	Yes	0.00	0.00	0.00	Gamma
PLEX resource use - exacerbation (other costs)	Yes	0.25	0.20	0.30	Gamma
PLEX resource use - myasthenic crisis (other costs)	Yes	0.40	0.32	0.48	Gamma

GP visits unit costs	Yes	154.98	123.98	185.98	Gamma
GP visits resource use - uncontrolled	Yes	3.00	13.29	13.97	Gamma
GP visits resource use - response	Yes	2.00	9.45	9.61	Gamma
GP visits resource use - exacerbation	Yes	0.80	0.64	0.96	Gamma
GP visits resource use - myasthenic crisis	Yes	0.00	0.00	0.00	Gamma
Visit to other healthcare professionals unit costs	Yes	505.46	404.37	606.55	Gamma
Visit to other healthcare professionals resource use - uncontrolled	Yes	7.00	11.16	11.78	Gamma
Visit to other healthcare professionals resource use - response	Yes	4.00	6.82	6.96	Gamma
Visit to other healthcare professionals resource use - exacerbation	Yes	0.50	0.40	0.60	Gamma
Visit to other healthcare professionals resource use - myasthenic crisis	Yes	0.10	0.08	0.12	Gamma
Outpatient hospital visits unit costs	Yes	1941.00	1552.80	2329.20	Gamma
Outpatient hospital visits resource use - uncontrolled	Yes	5.00	6.86	7.35	Gamma
Outpatient hospital visits resource use - response	Yes	1.00	4.71	4.83	Gamma
Outpatient hospital visits resource use - exacerbation	Yes	0.80	0.64	0.96	Gamma
Outpatient hospital visits resource use - myasthenic crisis	Yes	0.25	0.20	0.30	Gamma
Presenting at emergency room unit costs	Yes	1941.00	1552.80	2329.20	Gamma
Presenting at emergency room resource use - uncontrolled	Yes	0.50	0.38	0.51	Gamma
Presenting at emergency room resource use - response	Yes	0.25	0.31	0.34	Gamma
Presenting at emergency room resource use - exacerbation	Yes	0.25	0.20	0.30	Gamma

Presenting at emergency room resource use - myasthenic crisis	Yes	0.50	0.40	0.60	Gamma
Hospital stay (with ICU, cost per critical care period) unit costs	Yes	37723.00	30178.40	45267.60	Gamma
Hospital stay (with ICU, cost per critical care period) resource use - uncontrolled	Yes	0.10	0.08	0.12	Gamma
Hospital stay (with ICU, cost per critical care period) resource use - response	Yes	0.00	0.00	0.00	Gamma
Hospital stay (with ICU, cost per critical care period) resource use - exacerbation	Yes	0.10	0.08	0.12	Gamma
Hospital stay (with ICU, cost per critical care period) resource use - myasthenic crisis	Yes	1.00	0.80	1.20	Gamma
End of life care costs	Yes	0.00	0.00	0.00	Gamma
Headache - cost per event	No	0.00	0.00	0.00	Gamma
Placeholder - cost per event	No	0.00	0.00	0.00	Gamma
Placeholder - cost per event	No	0.00	0.00	0.00	Gamma
Placeholder - cost per event	No	0.00	0.00	0.00	Gamma
Placeholder - cost per event	No	0.00	0.00	0.00	Normal
Placeholder - cost per event	No	0.00	0.00	0.00	Normal
Placeholder - cost per event	No	0.00	0.00	0.00	Normal
Placeholder - cost per event	No	0.00	0.00	0.00	Normal
Placeholder - cost per event	No	0.00	0.00	0.00	Normal
Placeholder - cost per event	No	0.00	0.00	0.00	Normal
Placeholder - cost per event	No	0.00	0.00	0.00	Normal
Headache - disutility per event	No	0.00	0.00	0.00	Normal
Placeholder - disutility per event	No	0.00	0.00	0.00	Normal
Placeholder - disutility per event	No	0.00	0.00	0.00	Normal

Placeholder - disutility per event	No	0.00	0.00	0.00	Normal
Placeholder - disutility per event	No	0.00	0.00	0.00	Normal
Placeholder - disutility per event	No	0.00	0.00	0.00	Normal
Placeholder - disutility per event	No	0.00	0.00	0.00	Normal
Placeholder - disutility per event	No	0.00	0.00	0.00	Normal
Placeholder - disutility per event	No	0.00	0.00	0.00	Normal
Placeholder - disutility per event	No	0.00	0.00	0.00	Normal
Headache - rate of AE occurrence (Zilucoplan)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Zilucoplan)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Zilucoplan)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Zilucoplan)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Zilucoplan)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Zilucoplan)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Zilucoplan)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Zilucoplan)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Zilucoplan)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Zilucoplan)	No	0.00	0.00	0.00	Normal
Headache - rate of AE occurrence (Standard of care)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Standard of care)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Standard of care)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Standard of care)	No	0.00	0.00	0.00	Normal

Placeholder - rate of AE occurrence (Standard of care)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Standard of care)	No	0.00	0.00	0.00	Normal
Placeholder - rate of AE occurrence (Standard of care)	No	0.00	0.00	0.00	Beta
Placeholder - rate of AE occurrence (Standard of care)	No	0.00	0.00	0.00	Beta
Placeholder - rate of AE occurrence (Standard of care)	No	0.00	0.00	0.00	Beta
Placeholder - rate of AE occurrence (Standard of care)	No	0.00	0.00	0.00	Beta
Baseline EQ-5D (MG0010)	No	0.63	0.51	0.76	Beta
Intercept (MG0010 model)	No	0.65	0.52	0.78	Beta
Coefficient of baseline EQ-5D (MG0010 model)	No	-0.44	-0.35	-0.53	Beta
Coefficient of MG-ADL score (MG0010 model)	No	-0.02	-0.02	-0.03	Beta
Coefficient of BMI (MG0010 model)	No	0.00	0.00	-0.01	Beta
Exacerbation disutility	Yes	-0.20	-0.16	-0.24	Beta
Myasthenic crisis disutility	Yes	-0.39	-0.31	-0.47	Beta
Exacerbation disutility duration	Yes	11.80	9.44	14.16	Beta
Myasthenic crisis disutility duration	Yes	21.00	16.80	25.20	Beta
WTP threshold	No	600000.00	480000.00	720000.00	Gamma
Tablets/vial size split - Zilucoplan 32,4mg	No	1.00	0.80	1.20	Gamma
List price per pack - Zilucoplan 32,4mg	No	11895.10	9516.08	14274.12	Gamma
Zilucoplan - Method of administration	No	SC	N/A	N/A	Gamma
Tablets/vial size split - Standard of care (corticosteroids 10mg)	No	0.63	0.51	0.76	Gamma
List price per pack - Standard of care (corticosteroids 10mg)	No	99.00	79.20	118.80	Gamma

Tablets/vial size split - Standard of care (azathioprine 25mg)	No	0.18	0.14	0.21	Gamma
List price per pack - Standard of care (azathioprine 25mg)	No	60.70	48.56	72.84	Gamma
Tablets/vial size split - Standard of care (mycophenolate mofetil 500 mg)	No	0.19	0.15	0.23	Gamma
List price per pack - Standard of care (mycophenolate mofetil 500 mg)	No	537.00	429.60	644.40	Gamma
Tablets/vial size split - Standard of care (cyclosporine 100mg)	No	0.08	0.06	0.09	Gamma
List price per pack - Standard of care (cyclosporine 100mg)	No	1405.29	1124.23	1686.35	Gamma
Tablets/vial size split - Standard of care (tacrolimus 1 mg)	No	0.06	0.05	0.07	Gamma
List price per pack - Standard of care (tacrolimus 1 mg)	No	856.04	684.83	1027.25	Gamma
Tablets/vial size split - Standard of care (methotrexate 10mg)	No	0.02	0.02	0.03	Gamma
List price per pack - Standard of care (methotrexate 10mg)	No	46.00	36.80	55.20	Gamma
Tablets/vial size split - Standard of care (pyridostigmine 60 mg)	No	0.81	0.64	0.97	Gamma
List price per pack - Standard of care (pyridostigmine 60 mg)	No	129.45	103.56	155.34	Gamma
Standard of care - Method of administration	No	Oral	N/A	N/A	Gamma
Trial results (CFB) week [1] - Zilucoplan	No	1.00	0.80	1.20	Gamma
Trial results (CFB) MG-ADL [1] - Zilucoplan	No	-2.74	-2.19	-3.28	Gamma
Trial results (CFB) week [2] - Zilucoplan	No	2.00	1.60	2.40	Gamma
Trial results (CFB) MG-ADL [2] - Zilucoplan	No	-3.49	-2.79	-4.18	Gamma

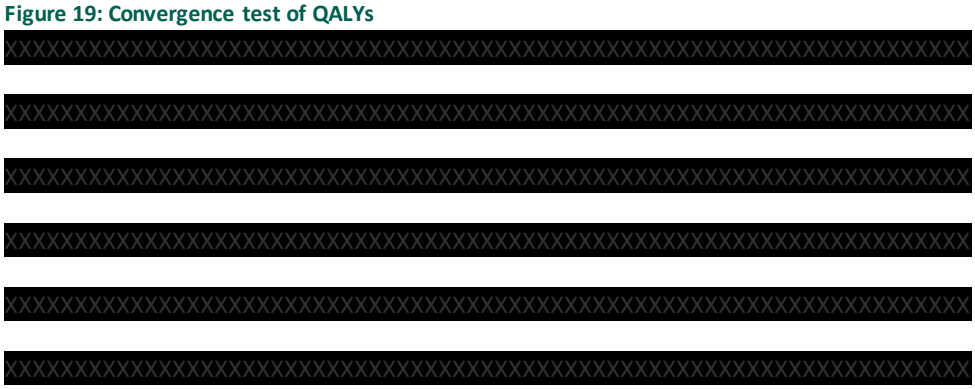
Trial results (CFB) week [3] - Zilucoplan	No	4.00	3.20	4.80	Gamma
Trial results (CFB) MG-ADL [3] - Zilucoplan	No	-4.22	-3.38	-5.07	Gamma
Trial results (CFB) week [4] - Zilucoplan	No	8.00	6.40	9.60	Gamma
Trial results (CFB) MG-ADL [4] - Zilucoplan	No	-4.53	-3.62	-5.43	Gamma
Trial results (CFB) week [5] - Zilucoplan	No	12.00	9.60	14.40	Gamma
Trial results (CFB) MG-ADL [5] - Zilucoplan	No	-4.80	-3.84	-5.76	Gamma
Trial results (CFB) week [6] - Zilucoplan	No	13.00	10.40	15.60	Gamma
Trial results (CFB) MG-ADL [6] - Zilucoplan	No	-4.95	-3.96	-5.94	Gamma
Trial results (CFB) week [7] - Zilucoplan	No	14.00	11.20	16.80	Gamma
Trial results (CFB) MG-ADL [7] - Zilucoplan	No	-5.45	-4.36	-6.54	Gamma
Trial results (CFB) week [8] - Zilucoplan	No	16.00	12.80	19.20	Gamma
Trial results (CFB) MG-ADL [8] - Zilucoplan	No	-5.68	-4.54	-6.81	Gamma
Trial results (CFB) week [9] - Zilucoplan	No	20.00	16.00	24.00	Gamma
Trial results (CFB) MG-ADL [9] - Zilucoplan	No	-6.17	-4.94	-7.41	Gamma
Trial results (CFB) week [10] - Zilucoplan	No	24.00	19.20	28.80	Gamma
Trial results (CFB) MG-ADL [10] - Zilucoplan	No	-6.14	-4.92	-7.37	Gamma
Trial results (CFB) week [1] - Standard of care	No	1.00	0.80	1.20	Gamma
Trial results (CFB) MG-ADL [1] - Standard of care	No	-1.36	-1.09	-1.63	Gamma
Trial results (CFB) week [2] - Standard of care	No	2.00	1.60	2.40	Gamma
Trial results (CFB) MG-ADL [2] - Standard of care	No	-1.75	-1.40	-2.09	Gamma
Trial results (CFB) week [3] - Standard of care	No	4.00	3.20	4.80	Gamma
Trial results (CFB) MG-ADL [3] - Standard of care	No	-1.82	-1.46	-2.19	Gamma

Trial results (CFB) week [4] - Standard of care	No	8.00	6.40	9.60	Gamma
Trial results (CFB) MG-ADL [4] - Standard of care	No	-2.20	-1.76	-2.64	Gamma
Trial results (CFB) week [5] - Standard of care	No	12.00	9.60	14.40	Gamma
Trial results (CFB) MG-ADL [5] - Standard of care	No	-2.31	-1.84	-2.77	Gamma
Trial results (CFB) week [6] - Standard of care	No	0.00	0.00	0.00	Gamma
Trial results (CFB) MG-ADL [6] - Standard of care	No	0.00	0.00	0.00	Gamma
Trial results (CFB) week [7] - Standard of care	No	0.00	0.00	0.00	Gamma
Trial results (CFB) MG-ADL [7] - Standard of care	No	0.00	0.00	0.00	Gamma
Trial results (CFB) week [8] - Standard of care	No	0.00	0.00	0.00	Gamma
Trial results (CFB) MG-ADL [8] - Standard of care	No	0.00	0.00	0.00	Gamma
Trial results (CFB) week [9] - Standard of care	No	0.00	0.00	0.00	Gamma
Trial results (CFB) MG-ADL [9] - Standard of care	No	0.00	0.00	0.00	Gamma
Increase in CFB stable to continued	Yes	0.29	0.23	0.35	Gamma
Proportion of response lost	Yes	1.00	0.80	1.20	Gamma
CFB stable response T0	Yes	3.64	2.91	4.37	Gamma
CFB stable response T6	Yes	1.70	1.36	2.04	Gamma
Steroid disutility stabl.	No	-0.07	-0.06	-0.08	Gamma
Steroid disutility continued	No	0.00	0.00	0.00	Gamma
3 /4 CFB Week 24 T0	No	0.20	0.16	0.24	Gamma
9 /4 CFB Week 24 T6	No	0.44	0.36	0.53	Gamma
< 3 CFB Week 52 T0	No	0.00	0.00	0.00	Gamma
< 3 CFB Week 52 T6	No	0.00	0.00	0.00	Gamma
3/4 CFB Week 52 T0	No	0.20	0.16	0.24	Gamma
3/4 CFB Week 52 T6	No	0.44	0.36	0.53	Gamma
< 3 CFB Week 104 T0	No	0.20	0.16	0.24	Gamma

< 3 CFB Week 104 T6	No	0.05	0.04	0.06	Gamma
3/4 CFB Week 104 T0	No	0.16	0.13	0.19	Gamma
3/4 CFB Week 104 T6	No	0.05	0.04	0.06	Gamma
Cost of steroid uncontrolled	No	306.06	244.85	367.27	Gamma
Cost of steroid stable	No	306.06	244.85	367.27	Gamma
IVIg/PLEX disutility	No	-0.12	-0.10	-0.14	Gamma
Gen gamma parameter 1	No	1.83	1.46	2.19	Gamma
Gen gamma parameter 2	No	-1.09	-0.87	-1.31	Gamma
Gen gamma parameter 3	No	-34.51	-27.61	-41.41	Gamma
Weibull parameter 1	No	0.29	0.23	0.35	Gamma
Weibull parameter 2	No	4.87	3.89	5.84	Gamma
Exponential parameter 1	No	-5.39	-4.32	-6.47	Gamma
Log-log parameter 1	No	0.33	0.27	0.40	Gamma
Log-log parameter 2	No	4.75	3.80	5.70	Gamma
Log-normal parameter 1	No	5.01	4.01	6.02	Gamma
Log-normal parameter 2	No	0.37	0.29	0.44	Gamma
Gompertz parameter 1	No	0.01	0.01	0.01	Gamma
Gompertz parameter 2	No	-5.49	-4.39	-6.59	Gamma
Gamma parameter 1	No	0.37	0.30	0.45	Gamma
Gamma parameter 2	No	-4.49	-3.59	-5.39	Gamma

Figure 18: Convergence test of costs

Figure 19: Convergence test of QALYs



Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

H.1.1.1 Objective

Two SLR's were conducted to support this submission for zilucoplan; One primary SLR with searches conducted on May 1st, 2023, and an SLR update, with searches conducted on January 24th, 2024. The objectives of the clinical SLRs were to

1) identify potential comparators to rozanolixizumab and zilucoplan and
2) retrieve evidence informing on efficacy, safety and tolerability of various interventions used in treatment and management of generalized myasthenia gravis (gMG).

H.1.1.2 Methods

This literature review is based on a reproducible and validated comprehensive search of the evidence.

The SLRs were conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (113) and the methods for systematic reviews as specified by the NICE (114).

A full protocol for the literature review was developed prior to the review for detailing the patient population, interventions, and study designs to be included. The SLR was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (115)

H.1.1.3 Information sources

H.1.1.3.1 Bibliographic databases

The bibliographic databases presented in Table 70 were used to conduct the primary SLR searches, which are in line with recommendations from the Cochrane Collaboration (Higgins et al., 2019) and the NICE (National Institute for Health and Care Excellence (NICE), 2022) guidance.

In the primary SLR searches, MEDLINE® and Embase® were searched using the embase.com interface. Cochrane Central Register of Controlled Trials (CENTRAL) was searched using the Cochrane library interface. MEDLINE® In-Process was searched using the Pubmed.com interface. The detailed search strategies are presented in Table 74, Table 75 and Table 76

Table 70: Bibliographic databases included in the May 2023 literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	From inception to May 1st, 2023	01.05.2023
MEDLINE	Embase.com	From inception to May 1st, 2023	01.05.2023
MEDLINE In-process	Pubmed.com	From inception to May 1st, 2023	01.05.2023
CENTRAL	Cochrane.com	From inception to May 1st, 2023	01.05.2023

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials.

The bibliographic databases in Table 71 were used to conduct the updated SLR searches, which are in line with recommendations from the Cochrane Collaboration (Higgins et al., 2019) and the NICE (NICE, 2022) guidance.

In the updated SLR searches, all databases for MEDLINE® and Embase® and Cochrane were searched using the OVID® platform. The detailed search strategy is presented in Table 78, Table 79 and Table 80.

Table 71: Bibliographic databases included in the January 2024 literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	OVID	From May 1st, 2023, until January 24th, 2024	24.01.2024
MEDLINE*	OVID	From May 1st, 2023, until January 24th, 2024	24.01.2024
EBMR**	OVID	From May 1st, 2023, until January 24th, 2024	24.01.2024

Abbreviations: EBMR = Evidence-Based Medicine Reviews.
Notes: *Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily, **Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects

H.1.1.3.2 Clinical trials and conference proceedings

Conference proceedings were manually searched to retrieve the latest clinical studies that were not published in journals as full-text articles or to supplement results of previously published studies. All the conferences, except those indexed in the Embase® database, were hand searched from the respective conference websites from 2017 to 2023 in the original review and from 2023 to 2024 in the SLR update. A list of the conferences included for the current review is presented in Table 72.

Table 72: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Association of Neuromuscular &	Conference website	Manual search	Detailed in Table 77 and Table 81	01.05.2023 and 24.01.2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Electro diagnostic Medicine				
MGFA National Conference	Conference website	Manual search	Detailed in Table 77 and Table 81	01.05.2023 and 24.01.2024
International Conference on Ophthalmoplegia and Myasthenia Gravis	Conference website	Manual search	Detailed in Table 77 and Table 81	01.05.2023 and 24.01.2024
International Conference on MG and related disorders	Conference website	Manual search	Detailed in Table 77 and Table 81	01.05.2023 and 24.01.2024

Abbreviations: MG = Myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America.

H.1.1.3.3 Other sources

Additionally, bibliographic searching of systematic reviews and meta-analysis was conducted for the identification of any missing studies. Also, clinicaltrials.gov and European Union Clinical Trials Register were searched for information about completed and ongoing trials. The detailed search strategy for clinicaltrials.gov and European Union Clinical Trials Register is presented in Table 77 and Table 81.

Table 73. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinicaltrials.gov	https://clinicaltrials.gov/	See Table 77 and Table 81	01.05.2023 (Original SLR) 24.01.24 (SLR Update)
EUCTR	https://www.clinicaltrialsregister.eu/	See Table 77 and Table 81	01.05.2023 (Original SLR) 24.01.24 (SLR Update)

H.1.2 Search strategies

The systematic literature searches were performed using a pre-defined search strategy to identify eligible studies. The search strategies were developed through the combination of free text words, indexing terms (e.g. medical subject headings [MeSH] terms for Medline and Emtree terms for Embase) and by using Boolean terms (e.g. 'and', 'or') to the terms relevant to disease area and study designs. Outcome measures were not included in the search strategy but rather were incorporated into the eligibility criteria of the SLRs. The search strings were appropriately modified to fit each database-specific syntax. The search strings are presented in Table 70 to Table 81.

The clinical SLR searches were not limited by date or geographical location. The eligibility criteria are specified in Table 82.

H.1.2.1 Primary search

Table 74: Search strategy table for Embase and MEDLINE (01st May 2023)

No.	Query	Results
#1	'myasthenia gravis'/syn OR 'myasthenia' OR myastheni* OR (('acetylcholine receptor antibody' OR 'achr' OR 'muscle specific kinase antibody' OR 'lipoprotein related protein 4' OR 'lrpr4' OR 'seronegative') NEAR/4 ('myasthen*' OR 'myasthenia gravis'))	35,181
#2	'clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomised controlled trial' OR 'randomised controlled trials' OR 'randomised controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR placebo* OR 'prospective study'/de OR allocated NEAR/2 random OR random* NEAR/1 assign* OR random* OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de)	12,335,959
#3	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'intervention study'/exp OR 'survival'/exp OR cohort*:ab,ti OR ((('follow up' OR follow-up) NEXT/1 (study OR studies)):ab,ti) OR ((clinical NEXT/1 trial*):ab,ti) OR 'retrospective study'/exp OR 'case control study'/exp OR ((case* NEXT/1 control*):ab,ti)	11,461,983
#4	#2 OR #3	17,576,112
#5	#1 AND #4	16,598
#6	#5 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)	2,217
#7	#5 AND [animals]/lim NOT ([humans]/lim AND [animals]/lim)	845
#8	#6 OR #7	3,037
#9	#5 NOT #8	13,561
#10	#9 AND [english]/lim	12318

Table 75: Search strategy table for MEDLINE In-process (01st May 2023)

No.	Query	Results
#1	"myasthenia gravis"	20,110
#2	#1 AND (inprocess[sb] OR pubstatusaheadofprint)	615

Table 76: Search strategy table for CENTRAL (01st May 2023)

No.	Query	Results
#1	MeSH descriptor: [myasthenia gravis] explode all trees	331

No.	Query	Results
#2	“myasthenia” OR “myastheni*”	920
#3	(“acetylcholine receptor antibody” OR “achr” OR “muscle specific kinase antibody” OR “lipoprotein related protein 4” OR “lrpr4” OR “seronegative”) NEAR/4 (“myasthen*” OR “myasthenia gravis”)	63
#4	#1 OR #2 OR #3	930
#5	#4 in Trials	492

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials.

Table 77: Search strategy table for clinical trials and conference proceedings

No.	Query	Results
#1	“myasthenia gravis”	84

Abbreviations: NR = Not reported.

H.1.2.2 Updated search

Table 78: Search strategy table for Embase and MEDLINE (January 24th, 2024)

No.	Query	Results
#1	exp myasthenia gravis/	25026
#2	myasthenia gravis.mp.	26937
#3	((acetylcholine receptor antibody or achr or muscle specific kinase antibody or lipoprotein related protein 4 or lrpr4 or seronegative) adj4 (myasthen* or myasthenia gravis)).mp.	916
#4	(myasthenia or myastheni*).mp.	31466
#5	1 or 2 or 3 or 4	31466
#6	Clinical trial/	1067721
#7	Randomised controlled trial/ or controlled clinical trial/ or multicenter study/	1239066
#8	exp Randomization/	99099
#9	Single blind procedure/	53112
#10	Double blind procedure/	211789
#11	Placebo/ or Phase 3 clinical trial/ or Phase 4 clinical trial/ or Crossover Procedure/	506943
#12	Randomi?ed controlled trial$.tw.	335561
#13	Rct.tw.	55805
#14	Random allocation.tw.	2594
#15	Randomly allocated.tw.	46369
#16	Allocated randomly.tw.	2985
#17	(allocat$ adj2 random$).tw.	55732
#18	Single blind$.tw.	32113
#19	Double blind$.tw.	241105
#20	((treble or triple) adj blind$).tw.	1988

No.	Query	Results
#21	Placebo$.tw.	367337
#22	Prospective study/	901404
#23	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	2974956
#24	Case study/	98772
#25	Case report.tw.	545616
#26	Abstract report/ or letter/	1265726
#27	(editorial or letter). pt.	2055034
#28	review.pt.	3141308
#29	note.pt.	974658
#30	24 or 25 or 26 or 27 or 28 or 29	6838770
#31	23 not 30	2547271
#32	Clinical study/ or observational study/ or Case control study/ or Family study/ or Longitudinal study/ or Retrospective Studies/ or Prospective study/ or cross-sectional study/ or Cohort analysis/ or ((cohort or case control or follow up or observational or epidemiologic* or longitudinal or retrospective or prospective or cross sectional) adj (study or studies)).ti,ab. or (Cohort analy$ or Case control or longitudinal or retrospective or cross sectional).tw.	4889770
#33	31 or 32	6289989
#34	5 and 33	5962
#35	limit 34 to yr="2024 -Current"	30
#36	limit 34 to dd=20230501-20240115	203
#37	(May* 2023 or Jun* 2023 or Jul* 2023 or Aug* 2023 or Sep* 2023 or Oct* 2023 or Nov* 2023 or Dec* 2023).dp.	571305
#38	34 and 37	255
#39	35 or 36 or 38	397

Table 79: Search strategy table for MEDLINE databases* (January 24th, 2024)

No.	Query	Results
#1	exp Myasthenia Gravis/	17164
#2	myasthenia gravis.mp.	20588
#3	((acetylcholine receptor antibody or achr or muscle specific kinase antibody or lipoprotein related protein 4 or lrpr4 or seronegative) adj4 (myasthen* or myasthenia gravis)).mp.	617
#4	(myasthenia or myastheni*).mp.	23128
#5	1 or 2 or 3 or 4	23128
#6	Randomised Controlled Trials as Topic/	166428
#7	randomised controlled trial/	607347
#8	Random Allocation/	107058

No.	Query	Results
#9	Double Blind Method/	177287
#10	Single Blind Method/	33199
#11	clinical trial/ or comparative study/	2311855
#12	clinical trial, phase i.pt.	25566
#13	clinical trial, phase ii.pt.	40773
#14	clinical trial, phase iii.pt.	22385
#15	clinical trial, phase iv.pt.	2469
#16	controlled clinical trial.pt.	95539
#17	randomised controlled trial.pt. or crossover study.mp.	614886
#18	multicenter study.pt.	342382
#19	clinical trial.pt.	539343
#20	exp Clinical Trials as topic/	387465
#21	or/6-20	3230327
#22	(clinical adj trial$).tw.	499904
#23	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	202347
#24	PLACEBOS/	35934
#25	placebo$.tw.	252956
#26	randomly allocated.tw.	37791
#27	((allocated adj2 random$) or (random adj1 assign*)).tw.	44599
#28	or/22-27	812635
#29	Epidemiologic studies/ or Clinical study/ or clinical trial/ or observational study/ or exp Case control study/ or Longitudinal study/ or Retrospective Studies/ or Prospective study/ or cross-sectional study/ or exp Cohort analysis/ or ((cohort or case control or follow up or observational or epidemiologic* or longitudinal or retrospective or prospective or cross sectional) adj (study or studies)).ti,ab. or (Cohort analy$ or Case control or longitudinal or retrospective or cross sectional).tw. or intervention study.tw.	4451245
#30	21 or 28 or 29	6784188
#31	case report.tw.	415097
#32	letter/	1241333
#33	historical article/	369396
#34	or/31-33	2006189
#35	30 not 34	6637648
#36	5 and 35	4336
#37	limit 36 to yr="2024 -Current"	32
#38	limit 36 to dt=20230501-20240123	170
#39	(2023 May* or 2023 Jun* or 2023 Jul* or 2023 Aug* or 2023 Sep* or 2023 Oct* or 2023 Nov* or 2023 Dec*).dp.	701443
#40	36 and 39	86

No.	Query	Results
#41	or/37-38,40	195

Notes: *Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily.

Table 80: Search strategy table for EBMR* (January 24th, 2024)

No.	Query	Results
#1	MeSH descriptor: [myasthenia gravis] explode all trees	331
#2	"myasthenia" OR "myastheni*"	920
#3	("acetylcholine receptor antibody" OR "achr" OR "muscle specific kinase antibody" OR "lipoprotein related protein 4" OR "lrpr4" OR "seronegative") NEAR/4 ("myasthen*" OR "myasthenia gravis")	63
#4	#1 OR #2 OR #3	930
#5	#4 in Trials	492

Abbreviations: EBMR = Evidence-Based Medicine Reviews.

Notes: *Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects

Table 81: Search strategy table for clinical trials and conference proceedings (January 24th, 2024)

No.	Query	Results
#1	[intervention] AND/OR "myasthenia gravis"	6

H.1.3 Systematic selection of studies

H.1.3.1 Eligibility criteria

Selection of studies for inclusion was determined using the PICOS framework (113). To be included in this review, trials had to meet the following pre-defined eligibility criteria of clinical review as specified in Table 82. For the 2024 SLR update, the same protocol as the original SLR was followed except for a date restriction for new publications of May 2023 – January 2024. In both SLRs, no country restrictions were applied.

Table 82: Inclusion and exclusion criteria used for assessment of studies (PICOS)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Disease: MG as primary disease • Age: Adult patients (≥18 years) • Gender: Any • Race: Any	Children/adolescents only (<18 years)
Intervention	• Pharmacological interventions • Non-Pharmacological interventions • Surgical interventions/procedures	-

Comparators	• Any of the above listed interventions • Placebo	-
Outcomes	**Efficacy outcomes** • QMG score • MG-ADL score • MGC score • Responders • MG-QoL 15 **Safety and tolerability outcomes** • Any adverse events • Any serious adverse events • Study withdrawals	-
Study design/publication type	• RCTs • nRCTs • Single-arm studies • Observational studies • Case-controlled studies • Cross-sectional studies	Case-series/case-reports
Language restrictions	English language studies were included	Articles published in non-English language

Abbreviations: MG-ADL = Myasthenia gravis activities of daily living; MGC = Myasthenia gravis composite; MG-QoL = Myasthenia gravis quality of life; nRCT = Non-randomised controlled trial; PICOS = Population, Intervention, Comparator, Outcome, Study Design; QMG = Quantitative myasthenia gravis; RCT = Randomised controlled trial.

H.1.3.2 Study selection process

H.1.3.2.1 Global SLR

Initial screening of the retrieved citations was undertaken based on the title and abstract. Citations that did not match the eligibility criteria were excluded at this 'first pass' stage. If there was lack of clarity on whether citations were eligible for the review due to limited information in the abstract, these citations were included for 'second pass' stage. Two independent reviewers screened all citations and full text papers and any discrepancies in their decisions were resolved by a third reviewer. Citation duplicates (due to the overlap in the coverage of the databases) were also excluded at this stage. Upon acceptance during the initial screening, full-text copies of all references that could potentially meet the eligibility criteria were retrieved.

The full-text publications of all citations of potential interest were then screened for inclusion. Two independent reviewers screened all citations and full text papers and any discrepancies in their decisions were resolved by a third reviewer. Citations that did not match the eligibility criteria were excluded at this 'second-pass' stage. At the full text screening stage, if there was lack of clarity on whether the publication met the eligibility criteria, these citations were excluded. Full-text screening was followed by linking of

multiple publications. Studies meeting the eligibility criteria at the second screening stage were extracted.

In the original review (May 2023), the trials evaluating rozanolixizumab and zilucoplan recruited moderate to severe population of gMG patients. Therefore, studies recruiting a comparable patient population among the included RCTs (n = 80) were identified. This was done to generate fairly comparable set of evidence for future relative efficacy assessments of rozanolixizumab and zilucoplan against other interventions. The studies were grouped together into different categories within the gMG population based on type of population enrolled, interventions assessed, and baseline QMG and MG-ADL scores. In total, 47 RCTs were considered to be fairly comparable to the population recruited in rozanolixizumab and zilucoplan trial and were categorised as studies considered evaluating in the gMG population. Among these 47 RCTs considered evaluating gMG population, studies were further grouped into mild to moderate (n=13), mild to severe (n=9), moderate to severe (n=11), severe (n=7), refractory (n=3) and exacerbating (n=4) groups as defined in these individual studies.

H.1.3.2.2 Local adaptation

To inform this submission for zilucoplan in Denmark, the global SLR has been adapted to exclude all studies not relevant in a Danish setting. For this reason, only studies examining the efficacy and safety of zilucoplan is included.

The study selection processes are detailed in the PRISMA flow-charts presented in Figure 20 and Figure 21.

Figure 20: PRISMA flow chart for the primary search

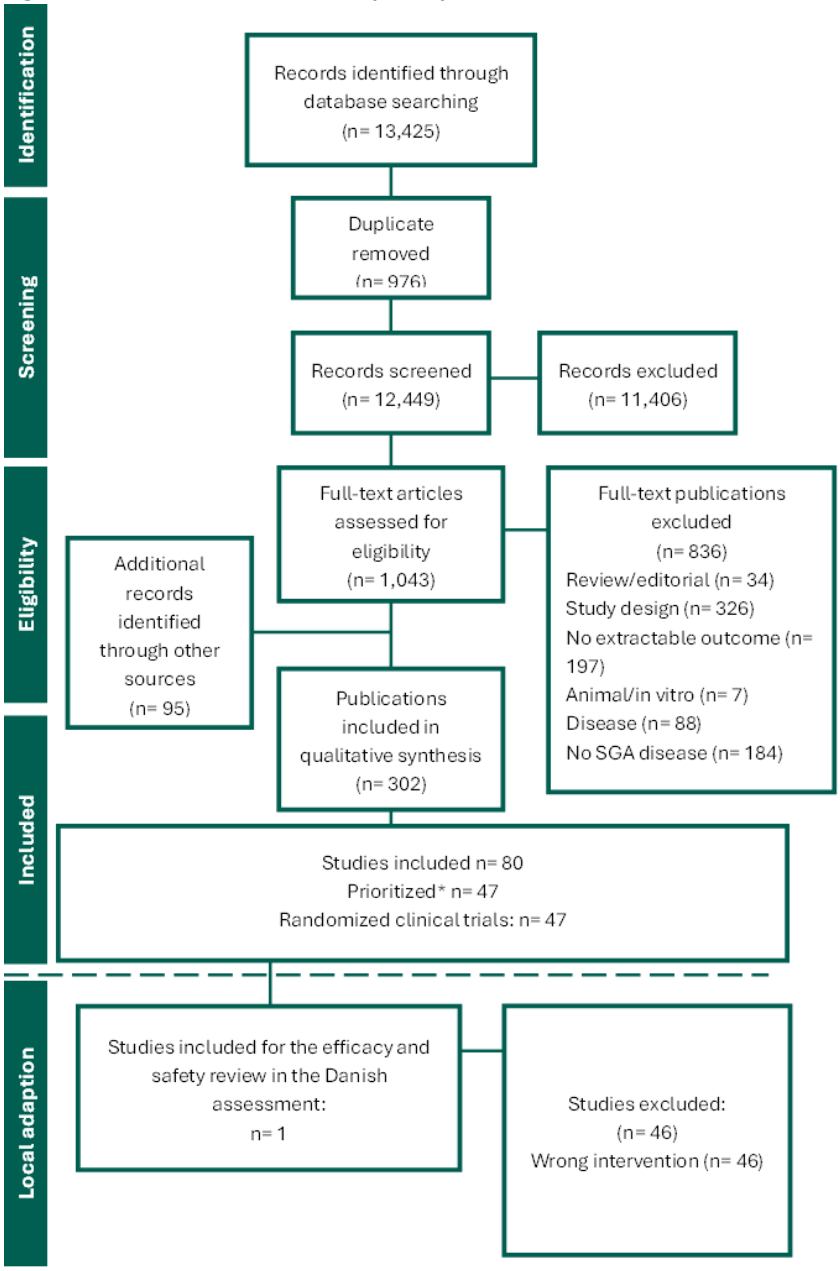
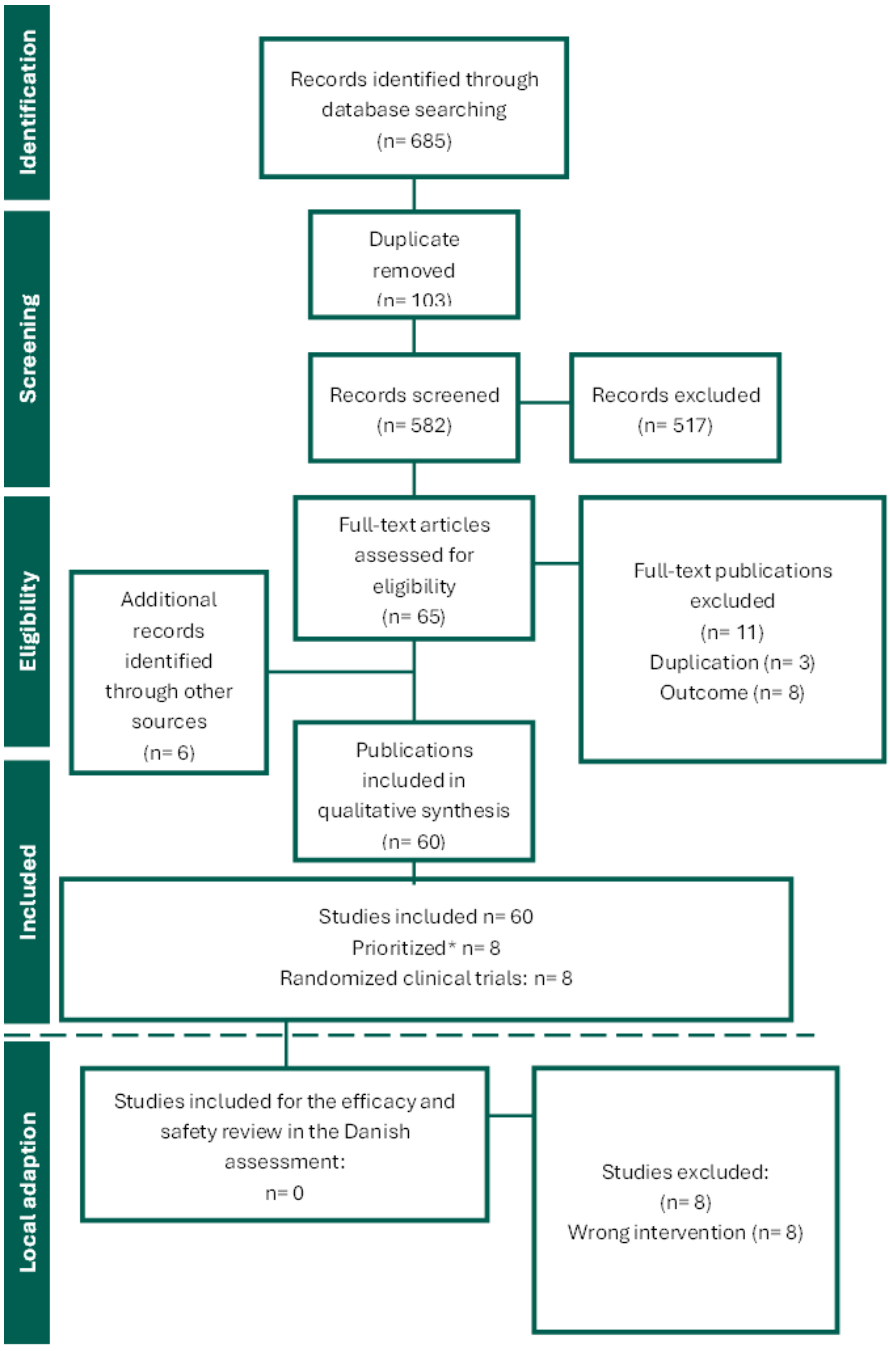


Figure 21: PRISMA flow chart for the secondary search



H.1.3.3 Summary of included studies

In the original review a total of 47 RCTs were deemed to be fit for inclusion in the gMG population. In the 2024 SLR update, 8 RCTs were deemed to be fit for inclusion in the gMG population. 7 of the 8 RCTs identified in the SLR update were previously identified in the original review; a single novel RCT published as a conference abstract was identified in the 2024 SLR update. In the 2024 SLR update, one full text article (10) was identified as the primary publication regarding the RAISE trial, and was included as a substitute for Howard 2022 (116). An overview of all included RCTs (n = 48) across both the primary and the updated review is provided in Table 83.

A summary of included studies in the local adaptation is presented in Table 84.

Table 83: Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population (n)	Interventions	Primary outcome and follow-up period	Secondary outcome and follow-up period
Gamez, 2019 (117)	NR	Double blind	25	IVIg 0.4g/kg/day for 5 days before surgery	Efficacy: Postoperative Myasthenic crisis (4 years)	Efficacy: Length of hospital stays and QMG (4 years)
			22	Placebo for 5 days before surgery		
Howard, 2020 (118)	NR	Double blind	14	Zilucoplan 0.3mg/kg + SOC	Efficacy: CFB in QMG (12 weeks)	Efficacy: CFB in MG-ADL, MGC, MG-QoL 15 (12 weeks)
			15	Zilucoplan 0.1mg/kg + SOC		
			14	Placebo		
Howard, 2019 (119)	NR	Double blind	12	Efgartigimod IV 10 mg/kg + SOC	*Safety, tolerability outcomes (13 weeks)	Efficacy: CFB in MG-ADL, CFB in QMG, CFB in MGC, MG CFB QOL 15 (13 weeks)
			12	Placebo + SOC		
Hewett, 2018 (120)	NR	Double blind	18	Belimumab 10mg/kg + SOC	Efficacy: CFB in QMG (24 weeks)	Efficacy: CFB in MG-ADL at 12, 24 weeks; CFB in MGC at 24 weeks; QMG and MGC response rate; safety outcomes (36 weeks)
			22	Placebo		
Nowak, 2021 (121) [BEAT-MG trial]	NR	Double blind	25	Rituximab (2 cycles; 375 mg/m2 IV weekly x 4 weeks) + background therapy	Efficacy: Steroid sparing effect, CFB in MGC scale (52 weeks)	Efficacy: CFB in QMG, MG-QoL; AChR-Ab levels; safety outcomes (52 weeks)
			27	Placebo + background therapy		
Howard, 2017 (122) [REGAIN trial]	NR	Double blind	62	Eculizumab 900 mg→1200mg# + background therapy	Efficacy: MG-ADL (38 weeks)	Efficacy: QMG, MG-ADL, MGC, Patient reported outcomes: MG-QOL15; safety outcomes
			63	Placebo + background therapy		

Zhou, 2017 (123)	NR	Double blind	45	Tacrolimus 3mg + background therapy	Efficacy: CFB in QMG (24 weeks)	Efficacy: MG-ADL and Manual muscle test scores Proportion of patients with a 4-point reduction from baseline in the QMG total score; safety outcomes (24 weeks)
			38	Placebo + background therapy		
Wolfe, 2016 (124) [MGTX trial]	NR	Single blind	66	Thymectomy + prednisone (alternate day)	Efficacy: QMG scores (3 years)	Efficacy: Average Alternate-day Prednisone Dose (mg) Measured Over 3 Years; SF-36; safety outcomes; MG-ADL (5 years)
			60	Prednisone (alternate day)		
Pasnoor, 2016 (125)	NR	Double blind	25	Methotrexate 20 mg orally qw	Efficacy: 9-month prednisone Area under the dose-time curve	Efficacy: CFB in QMG, CFB Manual muscle test, CFB MG-QOL, CFB MG-ADL, CFB MGC; safety outcomes (12 months)
			25	Placebo		
Zhang, 2014 (126)	NR	NR	20	Double filtration plasmapheresis + Methyl prednisolone	NR (14 days)	Efficacy: Anti-AChR-Ab, relative QMG scores (14 days)
			15	Methyl prednisolone		
Qi, 2013 (127)	NR	Open label	32	Shenqi Fuzheng Injection + Methylprednisolone pulse therapy + pyridostigmine	Efficacy: alleviating the transient worsening induced by steroids (14 days)	Safety outcomes (14 days)
			34	Methylprednisolone pulse therapy + pyridostigmine		
Howard, 2013 (128)	NR	Double blind	7	Eculizumab 600 mg→900 mg## + background therapy	Efficacy: Proportion of patients with a 3-point reduction from baseline in the QMG total score (20 weeks***)	Efficacy: MG-ADL; safety outcomes, Patient reported outcomes: SF-36, MG-QOL15 (20 weeks***)
			7	Placebo		

Heckmann, 2011 (129)	NR	Single blind	16	Methotrexate~17.5 mg weekly	Efficacy: Avg. daily prednisone requirement (2 years)	Efficacy: Minimal manifestation status scores, QMG scores, MG-ADL scores; safety outcomes (2 years)
			15	Azathioprine~2.5-3 mg/kg daily		
Barth, 2011 (130)	NR	Single blind	41	IVIg 1g/kg/day for 2 days	Efficacy: CFB in QMGS (14 days)	Efficacy: CFB in QMGS (21 and 28 days), Post intervention status, AChR titres, post intervention status, safety outcomes (60 days)
			43	Plasma Exchange (5 procedures every 2nd day)		
Kohler, 2011 (131)$	NR	NR	10	Plasma Exchange + background therapy	Efficacy: Change in clinical myasthenia scores, tolerability (6 months)	Efficacy: time to clinically significant improvement, number of relapses; safety outcomes (6 months)
			9	Immunoadsorption + background therapy		
Soliven, 2009 (132)	NR	Double blind	5	Terbutaline	Efficacy: Proportion of patients with a 3-point reduction in QMGS (2 weeks^^)	Efficacy: Functional disability scale, Forced vital capacity, grip strength, AChR-Ab levels and decremental response; safety outcomes (2 weeks^^)
			3	Placebo		
Sanders, 2008 (133)	NR	Double blind	88	Mycophenolate mofetil 2g/day + prednisone	Efficacy: Minimal manifestation (36 weeks)	CFB in QMGS, CFB in MG-ADL, AChR-Ab titre, Patient reported outcomes: SF-36, safety outcomes (36 weeks)
			88	Placebo + prednisone		
Gajdos, 2005 (134)$	NR	Double blind	81	IVIg 1g/kg + background therapy	Efficacy: Minimal manifestation status (15 days)	Efficacy: time to treatment response, response rate 20-point increase in Minimal manifestation status anti-AChR ab levels, safety outcomes (15 days)
			87	IVIg 2g/kg + background therapy		
Gajdos, 1994 (135)$	NR	NR	30	Plasma Exchange (3 procedures every 5 days)	NR (15 days)	Efficacy: Difference in muscular scores, safety outcomes (15 days)
			36	IVIg (0.4g/kg/day for 5 days)		

Gajdos, 1993 (136)	NR	Open label	20	Prednisone (1mg/kg to 0.5mg/kg to 0.25mg/kg) + background therapy	NR (60 months)	Efficacy: time to occurrence of clinical deterioration and treatment failure, AChR titres, Minimal manifestation status, Safety (60 months)
			21	Azathioprine 3mg/kg to 2mg/kg + background therapy		
NCT02565576 (137)	NR	Double blind	22	CFZ533 10 mg/kg+ SOC	Efficacy: CFB in QMG (49 weeks)	CFB in MGC, Proportion of patients with a 3-point improvement or worsening in the QMG total score, intolerant to steroid taper, CFB in MG-ADL, MG QOL-15, week 25 CFB data for QMG response rate, and week 25 CFB data for MGC score, week 25 CFB QMG score (49 weeks)
			22	Placebo + SOC		
NCT02473952 (138)	NR	Double blind	30	IVIG-C 2g/kg→1 g/kg q3w + background therapy	Efficacy: CFB in QMG (24 weeks)	Safety outcomes (24 weeks)
			32	Placebo + background therapy		
Bril, 2021 (139)	NR	Double blind	22	Placebo	Efficacy: CFB in QMG (29 days)	Efficacy: CFB in MGC, CFB in MG-ADL; Safety outcomes (29 days)
			21	UCB7665		
Liu, 2010 (140)	NR	Single blind	15	Double filtration plasmapheresis	NR (14 Days)	Efficacy: CFB in QMG; Clinical efficacy rate; Remission time; Duration of hospital stay; Number of respiratory supports; The titres of acetylcholine receptor antibodies (AChR-ab); Titin-ab, and PrsmR-ab levels, Adverse effects (14 Days)
			10	Immunoadsorption		
			15	IVIg		
Muscle Study Group, 2008 (141)	NR	Double blind	41	Mycophenolate mofetil + prednisone	Efficacy: CFB in QMG (12 week)	Myasthenic Manual muscle test score, MG-ADL score, Forced vital capacity, SF-36v2 scores, CFB in AChR-Ab level, Safety outcomes (12 week)
			39	Placebo + 20 mg/day prednisone		

Zinman, 2007 (142)	NR	Double blind	24	IV immunoglobulin or equivalent volume of IV 5% dextrose in water	Efficacy: CFB in QMG (28 days)	NR
			27	Placebo + 20 mg/day prednisone		
Wolfe, 2002 (143)	NR	Double blind	6	IVIg	Efficacy: CFB in QMG (42 days blinded phase, 6-week open label study)	CFB in MG-ADL (42 days blinded phase, 6-week open label study)
			9	Albumin placebo		
De, 2002 (144)	NR	Double blind	12	Cyclophosphamide	Efficacy: Changes in muscle strength (52 weeks)	Efficacy: steroid and pyridostigmine usage; Safety outcomes (52 weeks)
			11	Placebo		
Palace, 1998 (145)	NR	Double blind	19	Prednisolone + placebo	NR (156 weeks)	Safety outcomes (156 weeks)
			15	Prednisolone + azathioprine		
(Bromberg, 1997 (146)	NR	Unclear	5	Azathioprine	NR (1 year)	Efficacy: Treatment response; MG muscle strength and function score; Side effects (1 year)
			5	Prednisone		
Gajdos, 1997 (147)[$]	NR	Unclear	41	Plasma Exchange	15 days	Efficacy: Minimal manifestation status score; CFB in AChR-Ab titre; Safety outcomes
			46	IVIg		
Tindall, 1993 (148)	NR	Double blind	20	Cyclosporine	Efficacy: QMG score; antireceptor antibody titre; steroid dosage (6 months)	Safety outcomes (6 months)
			19	Placebo		
Tackenberg, 2018 (149)	NR	Double blind	31	Seasonal influenza vaccine (Mutagrip®)	Efficacy: CFB in AChR-ab-titre (12 weeks, 3-year post-study follow-up)	CFB in QMG score; Safety outcomes (12 weeks, 3-year post-study follow-up)
			31	Placebo		

Tindall, 1987 (150)	NR	Double blind	10	Cyclosporine	NR (12 months)	Efficacy: CFB in QMG score; CFB in antireceptor titre; Safety (12 months)
			10	Placebo		
Sharshar et al., 2021 (151)	NR	Single blind	58	Prednisone - Azathioprine slow tapering	Efficacy: Minimal manifestation status (15 months)	Efficacy: MG-ADL response rate, QMG response rate; MGC score, QMG score, MG-ADL score, CFB in MG-ADL score; worsening; Safety outcomes (15 months)
			59	Prednisone - Azathioprine rapid tapering		
NCT03772587 (152)	NR	Double blind	14	Placebo Q2W	Efficacy: CFB in MG-ADL; safety outcomes (20 weeks)	MG-QoL-15r and QMG score; MG-ADL response rate, QMG response rate, QoL MG-QoL-15r total scores (20 weeks)
			14	Nipocalimab 5 mg/kg Q4W		
			13	Nipocalimab 30 mg/kg Q4W		
			13	Nipocalimab 60 mg/kg Single dose		
			14	Nipocalimab 60 mg/kg Q2W		
Vu, 2021 (153)	NR	Double Blind	89	Ravulizumab	Efficacy: CFB in MG-ADL (26 weeks)	Efficacy: QMG, MG-QOL15r, subgroup data (previous IVIG use) for CFB week 26 MG-ADL and QMG (26 weeks)
			89	Placebo		
NCT03304054 (154)	NR	Double Blind	34	Amifampridine Phosphate	Efficacy: CFB in MG-ADL (38 days)	Efficacy: QMG; MG-ADL, MGC, mortality, response rate, safety outcomes (38 days)
			36	Placebo		
Zhao, 2021 (155)	NR	Double Blind	10	Batoclimab 340 mg	NR (52 weeks)	Efficacy: CFB in MG-ADL, MGC; QMG, MG-QoL15, , MG-ADL and QMG response rate; AEs (52 weeks)
			10	Batoclimab 680 mg		
			10	Placebo		
Howard, 2021 (156)	NR	Double Blind	84	Efgartigimod	Efficacy: Clinically Meaningful	Efficacy: CFB in MG-ADL; safety outcomes; QMG responders, subgroup data (patients with <3 years and ≥6 years disease duration) for MG-ADL and
			83	Placebo		

					Improvement (CMI) in MG-ADL Total Score (26 weeks)	QMG subdomains, and for; MG-QOL15r and EQ-5D-5L; % patients achieving response for the subgroup of patients with prior treatment failures; Safety outcomes (26 weeks)
Howard, 2023 (10) [RAISE trial]	NR	Double Blind	86	Zilucoplan 0.3mg/kg	Efficacy: CFB in MG-ADL (12 weeks)	Efficacy: CFB in QMG, MGC, MG-QoL15, QMG responders, MG-ADL responders, EQ-5D, Subgroup data (Japanese patients) for continuous data for MG-ADL, QMG, MGC, MG-QOL-15r; MG-ADL responders, QMG responders, safety data. Subgroup data (baseline MG-ADL: <=9 and >=10; baseline QMG: <=17 and >=18; duration of disease: <5 years and >=5 years) for. Safety outcomes (12 weeks)
			88	Placebo		
Bril, 2022 (157) [MycarinG trial]	NR	Double Blind	66	Rozimab 7mg/kg	Efficacy: CFB in MG-ADL (14 weeks)	Efficacy: subgroup data (new definition of response, for day 8 and day 43) for MG-ADL response rates and QMG response rate. Subgroup data (prior therapy; baseline QMG score, disease duration) for MG-ADL data at day 43, QMG, QMG responders, MG-ADL responders, EQ-5D, MGC, Safety outcomes (14 weeks)
Bril, 2022 (157) [MycarinG trial]	NR	Double Blind	66	Rozimab 7mg/kg	Efficacy: CFB in MG-ADL	Efficacy: subgroup data (new definition of response, for day 8 and day 43) for MG-ADL response
			67	Rozanolixizumab 10mg/kg		

			67	Placebo	(14 weeks)	rates and QMG response rate. Subgroup data (prior therapy; baseline QMG score, disease duration) for MG-ADL data at day 43, QMG, QMG responders, MG-ADL responders, EQ-5D, MGC, Safety outcomes (14 weeks)
Benatar, 2021 (158)	NR	Double Blind	5	Batoclimab 340 mg	NR (6 weeks)	Efficacy: CFB in MG-ADL, QMG, MGC, MG-QOL 15r in levels of total IgG and IgG subclasses, and anti-AChR-IgG, QMG responders, MG-ADL responders, MGC responders, Safety outcomes Safety: safety data added for subgroups (Batoclimab 680 mg qw to 340 mg q2w, Batoclimab 340 mg qw to 340 mg q2w, Batoclimab combined; Placebo qw to 340 mg q2w) (6 weeks)
			6	Batoclimab 680 mg		
			6	Placebo		
Piehl, 2022 (159)	NR	Double Blind	25	Rituximab	NR (175.4 weeks)	Efficacy: CFB in MG-ADL, QMG, MG-QoL, Safety outcomes (175.4 weeks)
			22	Placebo		
Di, 2022 (160)	NR	Open-label, rater-blind	18	Prednisone with Methotrexate	NR (213 weeks)	Efficacy: CFB in MG-ADL and QMG, Safety outcomes (213 weeks)
			17	Prednisone alone		
	NR		12	Placebo	NR	

EuCT2019-003383-47 (161)		Double blind	12 12	Mezagitamab 300 mg Mezagitamab 600 mg	(130 weeks)	Efficacy: CFB in MG-ADL, QMG, MGC, MG-QoL15r, AChR levels, MuSK levels, MG-ADL responders, QMG responders, MGC responders, Safety outcomes (130 weeks)
Bril 2023 (162)	NR	Double blind	30 30	IVIG-C Placebo	NR (45 weeks)	Efficacy: 50% or greater reduction in corticosteroid dose at week 39 from baseline, percent reduction in corticosteroid daily dose and the time to the first episode of MG worsening, Safety outcomes (45 weeks)
Quiroz, 2023 (163)	NR	Double blind	NR NR NR	NMD670 1200mg NMD670 400mg placebo	NR (5h post-dose)	Efficacy: change from baseline vs. placebo for QMG total score; proportion with improvements on QMG of 2 points or more Safety: serious or severe TEAEs (5h post-dose)

Abbreviations: AChR = Acetylcholine receptor; AChR-Ab = Acetylcholine receptor antibody; CFB = Change from baseline; EQ-5D = EuroQol-5 Dimensions; IV = Intravenous; IVIg = Intravenous immunoglobulin; MG = Myasthenia gravis; MG-ADL = Myasthenia gravis activities of daily living; MGC = Myasthenia gravis composite; MGFA = Myasthenia gravis foundation of America; MG-QoL = Myasthenia gravis quality of life; MuSK = Muscle-specific tyrosine kinase; NR = Not reported; QMG = Quantitative myasthenia gravis; SoC = standard of care; TEAEs = Treatment-emergent adverse events.

Notes: *, median (range); ***, Duration before cross-over; after first treatment period a cross over was made and treatment duration was again 16 weeks ^^ excluding cross over; `, from clin trials.gov; Font in bold highlights primary outcome; $,Patients with Myasthenic crisis or MG Exacerbation

Table 84: Overview of study design for studies included in the local adaptation

Study/ID	Aim	Study design	Patient population (n)	Interventions	Primary outcome and follow-up period	Secondary outcome and follow-up period
Howard, 2023 (10, 116) [RAISE trial]	NR	Double Blind	86	Zilucoplan 0.3mg/kg	Efficacy: CFB in MG-ADL (12 weeks)	Efficacy: CFB in QMG, MGC, MG-QoL15, QMG responders, MG-ADL responders, EQ-5D, Subgroup data (Japanese patients) for continuous data for MG-ADL, QMG, MGC, MG-QoL-15r; MG-ADL responders, QMG responders, safety data. Subgroup data (baseline MG-ADL: <=9 and >=10; baseline QMG: <=17 and >=18; duration of disease: <5 years and >=5 years) for. Safety outcomes. (12 weeks)
			88	Placebo		

Abbreviations: CFB = Change from baseline; EQ-5D = EuroQol-5 Dimensions; MG = Myasthenia gravis; MG-ADL = Myasthenia gravis activities of daily living; MGC = Myasthenia gravis composite; MG-QoL = Myasthenia gravis quality of life; NR = Not reported; QMG = Quantitative myasthenia gravis.

Notes: In addition to the RAISE trial, the RAISE-XT trial was included in this submission for zilucoplan. The RAISE-XT trial was not identified in this SLR, as it was published after the SLR update on January 24th, 2024.

H.1.4 Excluded full text references

A list of excluded studies including reason for exclusion is provided in Table 85.

Table 85: Overview of excluded studies

Author	Year	Title	Reason for exclusion
Antonini, A.; Vu, T.; Druzdz, A.; Grosskreutz, J.; Habib, A. A.; Mantegazza, R.; Utsugisawa, K.; Vissing, J.; Lejdstrom, R. B.; Boehnlein, M.; Gasalla, T.; Grimson, F.; Tarancon, T.; Bril, V.	2023	Efficacy of rozanolixizumab in generalised Myasthenia Gravis: subgroup analyses from the randomised Phase 3 MycarinG study	Wrong outcome
Antozzi, C.; Guptill, J.; Bril, V.; Gamez, J.; Meuth, S. G.; Blanco, J. L. M.; Nowak, R. J.; Quan, D.; Sevilla, T.; Szczudlik, A.; Hegarty, B.; Jouvin, M. H.; Jin, J.; Arroyo, S.	2023	VIVACITY-MG: a PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, EFFICACY, PHARMACOKINETICS, PHARMACODYNAMICS, AND IMMUNOGENICITY OF NIPOCALIMAB ADMINISTERED TO ADULTS WITH GENERALIZED MYASTHENIA GRAVIS	Wrong outcome
Bril, V.; Szczudlik, A.; Vaitkus, A.; Rozsa, C.; Kostera-Pruszczyk, A.; Hon, P.; Bednarik, J.; Tyblova, M.; ouml;hler, W.; Toomsoo, T.; Nowak, R. J.; Mozaffar, T.; Freimer, M. L.; Nicolle, M. W.; Magnus, T.; Pulley, M. T.; Rivner, M.; Dimachkie, M. M.; Distad, B. J.; Pascuzzi, R. M.; Babiar, D.; Lin, J.; Querolt Coll, M.; Griffin, R.; Mondou, E.	2023	Randomized Double-Blind Placebo-Controlled Trial of the Corticosteroid-Sparing Effects of Immunoglobulin in Myasthenia Gravis	Duplicate
Gwathmey, K.; Broome, C.; Goebeler, M.; Murai, H.; Bata-Csorgo, Z.; Newland, A.; Ulrichts, P.; Kerstens, R.; Guptill, J.; Agha, S.; Jiang, M.; Howard, J.	2023	Overview of the Safety Profile from Efgartigimod Clinical Trials in Participants with Diverse IgG-Mediated Autoimmune Diseases	Wrong outcome
Hansen, M.; Neilson, L.; Parikh, M.; Katirji, B.0	2023	Greater Number of Plasma Exchanges Does Not Improve Outcome in Myasthenic Crisis	Wrong outcome
Mantegazza, R. E.; Habib, A. A.; Benatar, M.; Vu, T.; Meisel, A.; Attarian, S.; Katsuno, M.; Liao, S.; Beasley, K. N.; Howard, J. F.	2023	Ravulizumab for the treatment of generalized Myasthenia Gravis: timing of response	Duplicate
McGuire, A. L.; Huhyn, C.; Sharma, S.; Vieira, A.; Jain, F.; Lee, D.; Mousa-Doust, D.; Jack, K.; Mezei, M. M.; Chapman, K.; Briemberg, H.; Choi, J. J.; Grant, K.; Yee, J.	2023	P2.20-02 Thymomatous Myasthenia Gravis after Total Thymectomy at a Tertiary-Care Surgical Centre: a 20-Year Retrospective Review	Wrong outcome

Author	Year	Title	Reason for exclusion
Siddiqi, Z.; Howard, J. F.; Bril, V.; Vu, T.; Karam, C.; Pasnoor, M.; Muppidi, S.; Peric, S.; Murai, H.; Ulrichts, P.; T'Joen, C.; Utsugisawa, K.; Verschuuren, J.; Mantegazza, R.	2023	Minimal symptom expression following treatment with efgartigimod in patients with Generalized Myasthenia Gravis	Wrong outcome
Sikorski, P.; Li, Y.; Cheema, M.; Wolfe, G. I.; Kusner, L. L.; Aban, I.; Kaminski, H. J.	2023	Serum metabolomics of treatment response in myasthenia gravis	Wrong outcome
Zubair, A. S.; Rethana, M.; Ma, A.; McAlpine, L. S.; Abulaban, A.; Munro, B. S.; Patwa, H. S.; Nowak, R. J.; Roy, B.	2023	Plasmapheresis Versus Intravenous Immunoglobulin in Patients With Autoimmune Neuromuscular and Neuro-immunological Conditions	Wrong outcome

H.1.5 Quality assessment

The extent to which a review can draw conclusions about the effects of an intervention depends not only on the results available from each of the included studies but also on the methodological quality and risk of bias of said studies. A descriptive appraisal, in terms of risk of bias in trials is presented in Figure 22: Assessment of risk of bias across the included RCTs (gMG population) and Table 86. This quality assessment is performed using the NICE Critical Appraisal Checklist (164).

The first item, 'randomisation', assesses the strength of the randomisation process in preventing selection bias in the assignment of participants to interventions (adequacy of sequence generation and allocation concealment). The method used to generate random allocation sequence was adequately reported in 37 studies. For the remaining 11 studies the risk of selection bias was unclear.

All the studies except for four studies recruited comparable patient populations across the studied interventions. Among these, two studies were published as conference abstracts (135) (163) and one was not published but was available in clinical trial.gov (154) so reported limited information to assess the comparability of baseline characteristics between the studied interventions.

In the 2024 SLR update, a published full-text article that was linked with the clinical trial record was identified (152), which provided additional baseline characteristics to assess. The remaining study (158) was reported in the full publication by Nowak et al. This was a phase 2, RCT assessing the efficacy and safety of subcutaneous batoclimab in patients diagnosed with MG. Patients were randomised to three treatment arms: once-weekly subcutaneous injections of batoclimab 340 mg, batoclimab 680 mg, or matching placebo for 6 weeks. In this study there were some differences between the treatment arms at baseline. The mean age and the proportion of men were higher in the batoclimab 680 mg arm. The mean time since onset of MG was longer in the placebo arm compared to the combined batoclimab arms. Finally, patients in the batoclimab 340 mg arm had higher mean Myasthenia Gravis Composite disease severity score and MG-QOL15r scores than the other arms.

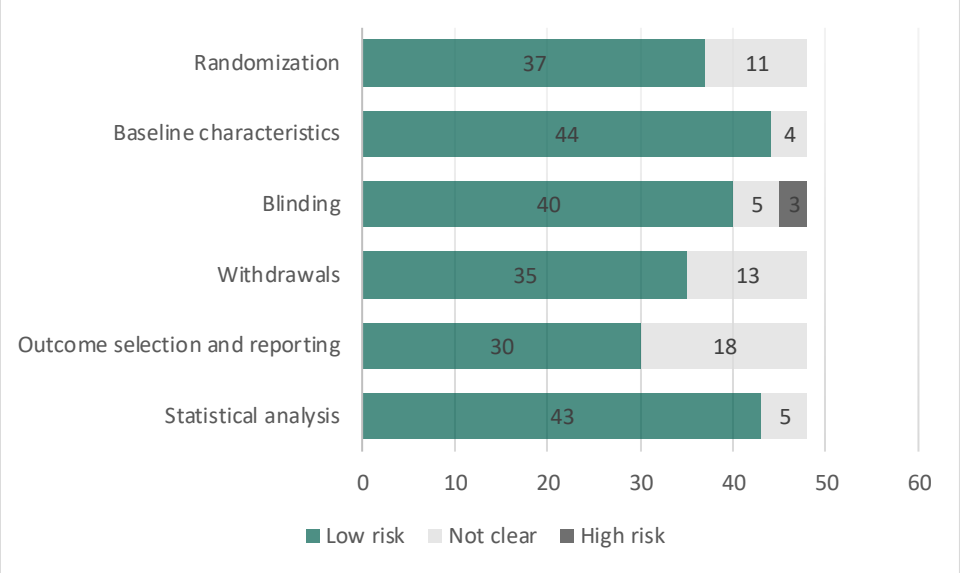
Blinding was assessed in all the included studies to check the influence of performance bias on the study results. Blinding plays a major role in the outcome and reduces the probability of assessment bias. A total of 35 studies were double-blind, five single-blind, and three open-label. Information around blinding was not reported across remaining five studies.

There was no imbalance in the dropouts across the majority of studies (~73 % studies). In these studies, all the patients were taken into consideration during the analysis irrespective of the reason for their exclusion, signifying a low risk of bias. For the remaining 13 studies, such information was not reported across the published studies.

To investigate the selective reporting of the outcomes among the included studies, a clinical trial registry (clinicaltrials.gov) was searched for the published protocols. Evidence on selective reporting could not be determined for 18 studies. In the remaining 30

studies, authors had measured all the outcomes as reported in the protocol and were thus categorised as low risk for outcome selection and reporting. All the studies except five studies reported ITT or mITT and this assessment could not be made because of limited availability of data (126, 127, 146, 150, 163).

Figure 22: Assessment of risk of bias across the included RCTs (gMG population)



Abbreviations: gMG = Generalised Myasthenia gravis; RCT = Randomised controlled trial.

Table 86: Overview of study quality using the NICE checklist for the included RCTs

Study name	Randomisation and allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcomes selection and reporting	Statistical analysis
REGAIN trial	+	+	+	+	+	+
Howard 2013	+	+	+	+	?	+
Gamez 2019	+	+	+	+	?	+
Hewett 2018	+	+	+	+	+	+
Zhou 2017	+	+	+	+	+	+
NCT02473952	?	+	+	?	+	+
Barth 2011	?	+	+	+	+	+
Gajdos 2005	+	+	+	+	?	+
Gajdos 1993	+	+	-	+	?	+
Qi 2013	+	+	-	?	?	?
NCT02565576	+	+	+	+	+	+
Nowak 2018	?	?	+	?	?	?
Nowak 2021	+	+	+	+	+	+
Howard 2020	+	+	+	+	+	+
Sanders 2008	+	+	+	+	?	+
Zhang 2014	?	+	?	?	?	?
Heckmann 2011	+	+	+	+	?	+
Soliven 2009	+	+	+	+	?	+
Pasnoor 2016	+	+	+	+	+	+
Gajdos 1994	?	?	?	?	?	+
Howard 2019	+	+	+	+	+	+
KÃ¶hler 2011	?	+	?	?	?	+
Bril 2021	+	+	+	+	+	+
Liu 2010	?	+	+	?	+	+
Sanders 2008	+	+	+	+	+	+
Zinman 2007	+	+	+	+	+	+
Wolfe 2002	+	+	+	+	+	+
De 2002	?	+	+	+	?	+
Palace 1998	+	+	+	+	?	+
Bromberg 1997	+	+	?	?	+	?
Gajdos 1997	+	+	?	+	?	+
Tindall 1993	+	+	+	+	+	+
Tackenberg	+	+	+	?	?	+
Tindall 1987	+	+	+	?	?	?
Sharshar 2021	+	+	+	+	+	+
NCT03772587	+	+	+	+	+	+
Vu 2021	+	+	+	+	+	+
NCT03304054	+	?	+	?	+	+
Zhao 2021	+	+	+	?	+	+
Howard 2021	+	+	+	+	+	+
Howard 2023	+	+	+	+	+	+
Bril 2022	+	+	+	+	+	+
Benatar 2021	?	?	+	+	+	+
Piehl 2022	?	+	+	?	+	+
Di 2022	+	+	-	+	+	+
2019-003383-47	?	+	+	?	+	+
Bril 2023	+	+	+	+	?	+
Quiroz 2023	?	?	+	+	?	?

Abbreviations: NICE = National Institue for health and care excellence; RCT = Randomised controlled trial.

H.1.6 Unpublished data

Only final results from RAISE-XT will be published at ClinicalTrials.gov. Data from the 11 November 2023 data cut is not planned to be published in a publication or at ClinicalTrials.gov. However, efficacy data and topline safety data from the November 2023 data cut will be published via congress presentations at American Association of Neuromuscular

& Electrodiagnostic Medicine (AANEM) and perhaps also at International Congress on Neuromuscular Diseases (ICNMD) in October 2024.

The unpublished data used in the application is from internal documents describing the methods and results of the RAISE and RAISE-XT studies in detail, and as such is of high quality.

Further, the manuscript by Piehl et al. (2024) (55) will be submitted to a journal end of June 2024. Results on reduction in/discontinuation of use of immunosuppressants (79) have been submitted to be published on a conference.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

An SLR was conducted to identify Health-related quality of life studies from the published literature relevant to the decision problem.

The key biomedical literature databases were searched in accordance with the list of databases suggested by HTA agencies.

Table 87: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		01.05.2023
Medline	Embase.com		01.05.2023
Medline In-Process	Pubmed.com		01.05.2023
EconLit	AEAweb.org		01.05.2023
NHS EED	Centre for Reviews and Dissemination (CRD Database)		01.05.2023

Conference proceedings were manually searched to retrieve the latest clinical studies that were not published in journals as full-text articles or to supplement results of previously published studies. All the conferences, except those indexed in the Embase® database, were hand searched from the respective conference websites for the last seven years (2017–2023).

Table 88: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Association of Neuromuscular & Electro diagnostic Medicine	Conference website	Electronic search		01.05.2023
MGFA National Conference	Conference website	Electronic search		01.05.2023
International Conference on Ophthalmoplegia and Myasthenia Gravis	Conference website	Electronic search		01.05.2023
International Conference on MG and related disorders	Conference website	Electronic search		01.05.2023
ISPOR (all regions)	Conference website	Electronic search		01.05.2023

Additionally, bibliographic searching of included systematic reviews was conducted for the identification of any of any relevant studies.

I.1.1 Search strategies

The search strategy is presented in the tables below. Further below the inclusion criteria can be found.

Table 89: Search strategy for Embase

No.	Query	Results
#1	'myasthenia gravis'/syn OR 'myasthenia' OR myastheni* OR (('acetylcholine receptor antibody' OR 'achr' OR 'muscle specific kinase antibody' OR 'lipoprotein related protein 4' OR 'lrpr4' OR 'seronegative') NEAR/4 ('myasthen*' OR 'myasthenia gravis'))	35181
#2	((utilit* NEAR/2 (measure* OR outcome* OR state* OR health OR score* OR weight* OR analysis)):ab,ti) OR 'health utility index' OR 'hui' OR 'hr QoL ' OR 'h QoL ' OR 'quality of life'/exp OR 'quality of life' OR 'quality-of-life'/exp OR 'quality-of-life' OR QoL OR (utilit* NEXT/1 (score* OR value* OR evaluation*)) OR (health NEXT/2 utilit*) OR (('health'/exp OR 'health') AND (state NEXT/1 utilit*)) OR hui OR ((health NEXT/1 state*) AND (state* NEXT/1 preference*)) OR 'quality adjusted life year'/exp OR 'quality adjusted life year' OR 'quality adjusted life' OR ('quality adjusted' NEXT/1 survival*) OR qaly* OR qald* OR qale* OR qtime* OR 'disability	2954733

No.	Query	Results
	adjusted life' OR daly* OR 'health survey'/exp OR 'health survey' OR hye* OR health*year*equivalent OR (health NEAR/2 utility*) OR 'wellbeing'/exp OR 'wellbeing' OR (quality NEAR/2 well*being) OR qwb OR (willingness NEAR/2 pay) OR (standard NEAR/2 gamble) OR disutili* OR (time NEAR/2 trade*off) OR tto OR ('discrete choice' NEXT/1 experiment*) OR 'short form 36'/exp OR 'short form 36' OR 'sf36' OR 'sf-36' OR 'sf 36' OR 'short form 12'/exp OR 'short form 12' OR 'sf12' OR 'sf-12' OR 'sf 12' OR 'short form 6' OR 'sf6' OR 'sf-6' OR 'sf 6' OR 'euro QoL ' OR euro* QoL OR 'eq5d' OR 'eq-5d' OR 'eq 5d' OR rosser OR ((visual NEXT/1 analog*) AND (analog* NEXT/1 scale*)) OR 'patient reported outcomes' OR pro OR questionnaire OR hrql OR prom OR 'mg- QoL 15' OR 'myasthenia gravis composite scale' OR 'myasthenia gravis-manual muscle testing' OR 'myasthenia gravis impairment index' OR 'mg-adl' OR 'mg- QoL 60' OR 'myasthenia gravis patient reported outcomes' OR 'incb-mg'	
#3	#1 AND #2	2162
#4	#3 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [review]/lim)	408
#5	#3 NOT #4	1755

Table 90: Search strategy for Cochrane

No.	Query	Results
#1	MeSH descriptor: [myasthenia gravis] explode all trees	331
#2	“myasthenia” OR “myastheni*”	920
#3	(“acetylcholine receptor antibody” OR “achr” OR “muscle specific kinase antibody” OR “lipoprotein related protein 4” OR “lrpr4” OR “seronegative”) NEAR/4 (“myasthen*” OR “myasthenia gravis”)	63
#4	#1 OR #2 OR #3	930
#5	utilit* NEAR/2 (measure* or outcome* or state* or health or score* or weight* or analysis)	4308
#6	"health utility index" or “hui”	2403
#7	“hr QoL or h QoL or hrql”	8914
#8	MeSH descriptor: [Quality of Life] explode all trees	43301
#9	“quality of life” or "quality-of-life" or “ QoL ”	152777
#10	utilit* next/1 (score* or value* or evaluation*)	1176
#11	health next/2 utilit* or ('health' and state next/1 utilit*)	1372
#12	"quality adjusted life year" or "quality adjusted life"	6569
#13	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	1934
#14	"quality adjusted" next/1 survival*	241
#15	qaly* or qald* or qale* or qtime*	4996
#16	"disability adjusted life" or daly*	1773
#17	"health survey" or hye* or "health*year*equivalent"	9063
#18	MeSH descriptor: [Health Surveys] explode all trees	36824

#19	health near/2 utility*	950
#20	wellbeing or quality near/2 well*being or qwb	23496
#21	willingness near/2 pay	1940
#22	standard near/2 gamble	96
#23	disutili*	114
#24	time near/2 trade*off or tto	306
#25	“short form 36” or “sf36” or “sf-36” or “sf 36”	18520
#26	“short form 12” or “sf12” or “sf-12” or “sf 12”	4055
#27	“short form 6” or “sf6” or “sf-6” or “sf 6”	282
#28	“euro QoL ” or euro* QoL or “eq5d” or “eq-5d” or “eq 5d”	13351
#29	qlq*	5834
#30	visual analogue scale or (visual analog*) or 'vas'	85035
#31	'mg- QoL 15' OR 'myasthenia gravis composite scale' OR 'myasthenia gravis-manual muscle testing' OR 'myasthenia gravis impairment index' OR 'mg-adl' OR 'mg- QoL 60' OR 'myasthenia gravis patient reported out-comes' OR 'incb-mg'	533
#32	(patient OR self) NEAR/1 (reported OR assessed) OR "patient-reported" NEAR/2 outcome* OR "patient reported" NEAR/2 outcome*	48231
#33	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32	309341
#34	#4 AND #33 in Trials	326

Table 91: Search terms for Pubmed

No.	Query	Results
#1	“myasthenia gravis”	20110
#2	“quality of life” OR “quality of life” OR “quality-of-life” OR “quality-of-life” OR QoL	431318
#3	utilit* AND (score* OR value* OR evaluation* OR health)	140477
#4	health AND state AND utilit*	30108
#5	health AND state* AND preference*	26218
#6	hui OR “quality adjusted life year” OR “quality adjusted life year” OR “quality adjusted life” OR (“quality adjusted” AND survival*)	51041
#7	qaly* OR qald* OR qale* OR qtime* OR “disability adjusted life” OR daly* OR”health survey” OR “health survey” OR hye* OR health*year*equiva-lent OR (health AND utility*)	142948
#8	wellbeing OR (quality AND well*being) OR qwb	144059
#9	(willingness AND pay) OR (standard AND gamble) OR disutili* OR (time AND trade*off) OR tto OR (“discrete choice” AND experiment*)	21336

No.	Query	Results
#10	"short form 36"OR sf36 OR "sf-36" OR "sf 36" OR "short form 12" OR sf12 OR "sf-12" OR "sf 12" OR "short form 6" OR sf6 OR "sf-6" OR "sf 6" OR euro QoL OR euro* QoL OR "eq5d" OR "eq-5d" OR "eq 5d"	54492
#11	visual AND analog* AND scale*	77235
#12	'mg- QoL 15' OR 'myasthenia gravis composite scale' OR 'myasthenia gravis-manual muscle testing' OR 'myasthenia gravis impairment index' OR 'mg-adl' OR 'mg- QoL 60' OR 'myasthenia gravis patient reported outcomes' OR 'incb-mg'	1222
#13	"Patient reported outcome*"	38999
#14	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	884184
#15	#1 AND #14	1482
#16	#15 (inprocess[sb] OR pubstatusaheadofprint)	76

The inclusion criteria for the reviews were developed using the PICOS criteria and a summary for each SLR is provided in Table 92.

Table 92: Predefined eligibility criteria for inclusion of studies in humanistic burden review

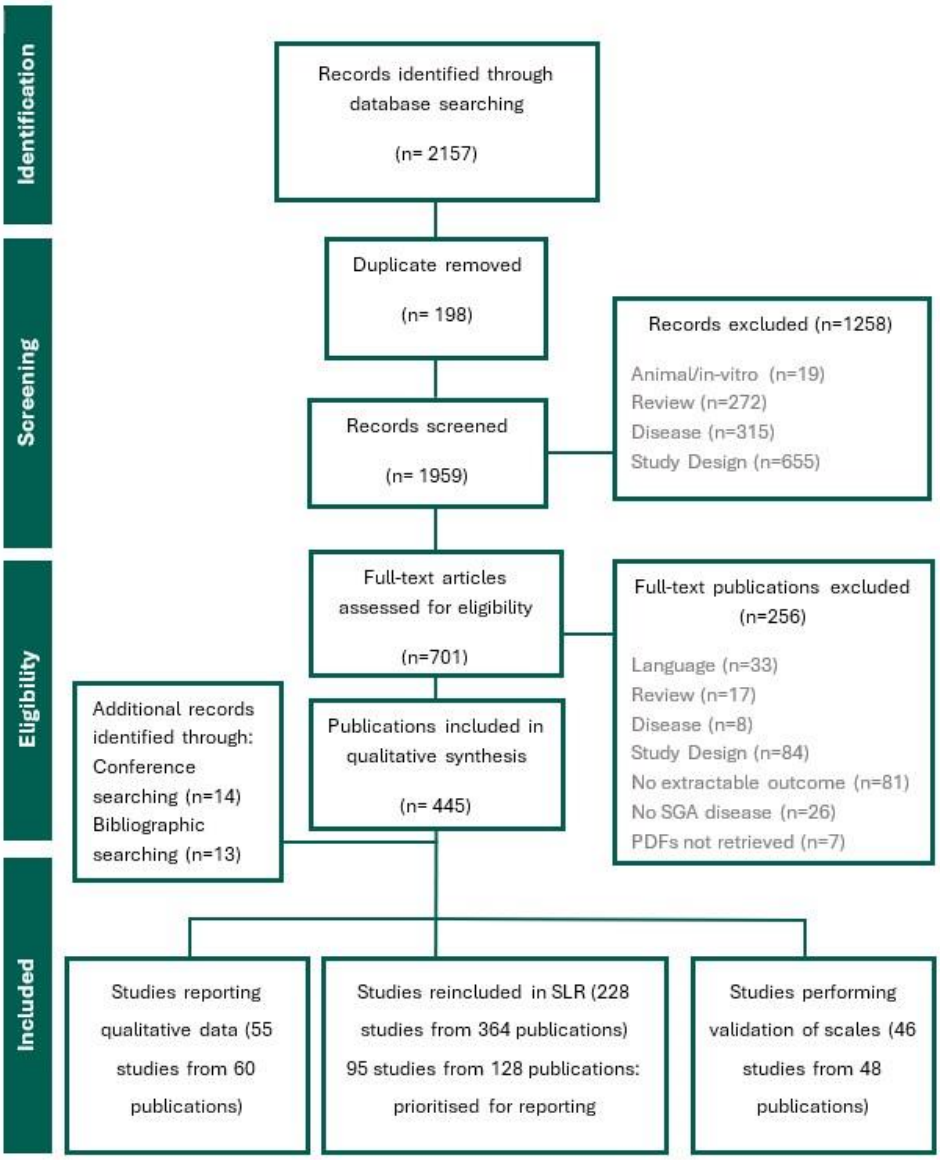
Parameter	Inclusion Criteria
Study design	Controlled studies (both interventional and non-interventional) Cohort studies Patient preference studies Utility mapping studies Economic evaluation study reporting utility data
Population	Age: Adult patients (≥18 years) Gender: Any Race: Any
Disease	MG as primary disease
Intervention	There was no restriction on interventions for humanistic burden review
Comparators	There was no restriction on comparator for humanistic burden review
Language	English language studies were included
Publication time-frame	There was no restriction on publication time frame
Countries	There was no restriction on countries

Abbreviations: MG = Myasthenia gravis.

Searches of literature databases yielded 2,157 separate references. Due to the overlap of coverage between the databases, 198 references were found to be duplicates and were excluded. Following a detailed examination of the remaining 1,959 references, 1,258 references were excluded leading to the inclusion of 701 references for full-text screening. Detailed screening of the references led to the exclusion of 256 references and inclusion of 445 publications. In addition to the references retrieved from the electronic literature databases, 13 publications were identified from hand searching and 14 from conference searching. Following linking of multiple publications of a study, a total of 329 studies from 472 references were included in the current review. 55 studies from 60 publications

reported minimal information around QoL, 46 studies from 48 publications performed validation of various QoL scales, 95 studies from 128 publications reported humanistic burden of the disease and remaining 133 studies from 236 publications assessed impact of intervention Figure 23.

Figure 23: PRISMA diagram for studies in the health-related quality of life SLR



In total, 95 studies reported data pertaining to humanistic burden of MG across various geographies (Table 93). 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.

Overall, the type of MG sub-populations were not reported in most of the studies. Three studies enrolled a refractory population and compared them with a non-refractory population and three other studies described their population as clinically stable. One study each included patients with and without myasthenic crisis, with and without fractures, with and without thymoma, and with restless leg syndrome in MG.

There was a wide variation of sample sizes observed across the included studies, ranging from 16 to 1,815. Of the 95 studies, 19 enrolled fewer than 50 patients; the results of which should be interpreted with caution, as a low sample size is associated with a potential risk of bias. Sixteen studies had a large sample size and included greater than 500 patients with the findings determined to be more reliable and could be extrapolated to real world population. The mean age ranged from 38 to 66.2 years across the studies. Proportion of males enrolled across these studies also has a large range of 16% to 90%.

Table 93: An overview of study and patient characteristics included in the SLR An overview of study and patient characteristics included in the SLR

Study name	Sample size	Population type	Age (years) Mean (SD)	Male (%)	Country	Study design	Study setting
(165)	1,518	MG	56.7 (16.9)	41.4	Germany	Survey based study	NR
(166)	37	MG	55.2 (20.2)	43.2	Germany	Cross-sectional study	Multicentre
(167)	33	MG	52.6 (17.7)	27.2	Germany	Observational study	Single centre
(168)	200	MG	56 (17)	36	Germany	Cross-sectional study	Single centre
(169)	25	Clinically stable MG	45.28 (12.33)	16	Brazil	Cross-sectional study	Single centre
(170)	80	MG	41.89 (14.17)	25	Brazil	Cross-sectional study	Single centre
(171)	69	MG	44.5 (10)	20.3	Brazil	Cross-sectional study	Single centre
(172)	28	MG	48.64 (19.0)	25	Brazil	Cross-sectional study	Single centre
(173)	49	MG	44.1 (18.1)	20.4	Brazil	Cross-sectional study	Single centre
(174)	42	Restless leg syndrome in MG	45 (14.4)	43	Brazil	Cross-sectional study	Single centre
(175)	82	MG	54(16)	39	Norway	Cross-sectional study	Single centre
(176)	78	MG	52.4 (18.5)	41	France	Cross-sectional study	NR
(177)	20	MG	64 (11)	40	Spain	Observational study	NR

(178)	54	Clinically stable MG	66.2 (16.9)	48	Spain	Observational study	NR
(179)	46	MG	50.7	37	Italy	Observational study	NR
(180)	74	MG	48.1 (16.3)	32.4	Italy	Cross-sectional study	Single centre
(181)	91	Ocular MG	70	59.3	Italy	Observational study	Single centre
(182)	773	Refractory (n=56) vs non refractory MG (n=717)	Ref: 48.5 (12.1) Non-Ref: 55.4 (14.6)	Ref:18 Non-Ref: 35	USA	Registry based study	NR
(183)	589	Refractory (Ref) (176) vs non re-fractory MG (Non-Ref) (413)	Ref: 52.3 Non-Ref: 56	Ref: 27.3 Non-Ref: 35.8	USA	Registry based study	NR
(184)	1,140	MG	54.6 (14.8)	33.8	USA	Cross-sectional study	Single centre
(185)	1,315	MG	54.5 (14.76)	37	USA	Registry based study	Single centre
(186)	782	Refractory Ever refractory gMG: 201	51.6 (14.3)	27	USA	Registry based study	Multicentre
		Non-refractory gMG: 581	59.2 (13.9)	43			
(187)	27	MG	56.6 (14.55)	NR	USA	Observational study	NR
(188)	48	MG	NR	NR	USA	Observational study	Single centre
(189)	68	MG	61.5	52.9	USA	Cross-sectional study	NR

(190)	107	MG	64 (13)	NR	UK & USA	Cross-sectional study	NR
(191)	179	MG	22–86	48	Canada	Observational study	NR
(192)	165	MG	47.4 (19.7)	26.83	Australia	Survey based study	NR
(193)	363	MG with and without fractures	57 (16)	32	Japan	Cross-sectional study	Multicentre
(194)	917	MG	57.1 (15.4)	34.8	Japan	Cross-sectional study	Multicentre
(195)	123	Ocular MG	60.5	44	Japan	Cross-sectional study	Multicentre
(196)	102	MG	NR	41	Japan	Survey based study	NR
(197)	640	MG	NR	NR	Japan	Cross-sectional study	Single centre
(198)	102	MG	47.2 (15.7)	31	Japan	Observational study	NR
Suzuki 2019	287	MG	57.5 (17.1)	67.2	Japan	Cross-sectional study	Multicentre
(199)	50	MG	40.74 (17.8)	NR	India	Cross-sectional study	Single centre
(200)	64	Patients with (14) and without myasthenic crisis (MC) (50)	With MC: 47.55 (16) Without MC: 41.7 (19.8)	With MC 85.7 Without MC 54	India	Observational study	Single centre
(201)	71	MG	40.25	20.5	Thailand	Observational study	Multicentre
(202)	188	MG	42.8 (15.8)	50.5	China	Cross-sectional study	NR
(203)	30	MG with and without thymoma	45 (16.9)	NR	South Africa	Cross-sectional study	Single centre

(204)	52	MG	45 (12.6)	26.9	Turkey	Cross-sectional study	Single centre
(205)	19	Clinically stable MG	54 (13)	42	Turkey	Cross-sectional study	NR
(206)	837	MG	60.3 (17.6)	42	Norway and Netherland	Cross-sectional study	NR
(207)	104	MG	38	30.8	Saudi Arabia	Cross-sectional study	NR
(208)	118	MG	38.3 (16.5)	29.5	Saudi Arabia	Survey based study	Multicentre
(209)	73	MuSK MG	NR	24.45	Serbia	Cross-sectional study	Multicentre
(210)	70	MG	53.2 (15.98)	47.1	Serbia	Observational study	NR
(211)	230	MG	55.8 (18.2)	43.9	Serbia	Cross-sectional study	Single centre
(212)	17	MG	49.5 (13.6)	23.5	Austria	Cross-sectional study	Single centre
(213)	73	MG	48.9 (14.8)	24.6	Poland	Observational study	Single centre
(214)	73	MG	45.2 (15)	39	Russia	Observational study	Single centre
(215)	76	MG	51.15	88.3	Sweden & Estonia	Cross-sectional study	NR
(216)	100	MG	61.1 (15.9)	57	NR	Observational study	NR
(217)	55	MG	51.3 (4.5)	36	NR	Observational study	NR
(218)	39	MG	45.4 (16.4)	25.7	NR	Observational study	NR
(219)	120	MG	55.6 (15.90)	60	NR	Survey based study	NR
(220)	16	MG	54	31	NR	Cross-sectional study	Single centre
(221)	58	MG	54.6 (18.1)	46.6	NR	Survey based study	NR
(222)	640	MG	59 (15)	47	NR	Cross-sectional study	NR

(223)	1,815	MG	Female: 39.82 (12.98) Male: 43.44 (13.59)	34	China	Cross-sectional study	Single centre
(224)	69	MG	54.7 (13.7)	62.3	China	Cross-sectional study	Single centre
(225)	137	gMG	NR	NR	Canada	Observational study	Single centre
(226)	56	Ocular and gMG	55.5 (17.7)	25	Russia	Observational study	NR
(227)	1,660	MG	49.3 (19.7)	43.8	Germany	Case-control study	NR
(228)	158	MG	41.82 (10.44)	32.91	China	Cross-sectional study	Single centre
(229)	98	MG	57.33 (12.22)	60	China	Survey based study	Single centre
(230)	100	gMG	60.2 (15.4)	43	Denmark	Cross sectional study	Single centre
(231)	30	MG	58.2 (11.5)	43.3	USA	Observational study	Single centre
(232)	111	MG	60.3 (15.6)	33.3	Australia	Cross sectional study	NR
(233)	196	MG	52.6 (15.34)	NR	NR	Survey based study	NR
(234)	134	MG	44.18 (17.01)	51.5	China	Observational study	Multicentre
(235)	124	MG	61.4 (13.9)	44	Canada	Cross-sectional study	NR
(236)	1,077	MG	64.3 (15.7)	47	Sweden	Cross-sectional study	Multicentre
(237)	420	MG	62.4 (13.9)	46.9	Netherlands	Cross-sectional study	Multicentre
(238)	87	Musk MG	49 (15-68)	30.4	India	Observational study	Single centre
(239)	834	MG	47.4 (14.3)	30	Multiple countries	Observational study	Multicentre

(240)	45	MG	51.5 (13.8)	33.3	Thailand	Cross-sectional study	Single centre
(241)	64	MG	54.1 (16.4)	38.6	Serbia	Cross-sectional study	Single centre
(242)	107	MG	62 (19-88) *	50.5	Denmark	Case control study	Single centre
(243)	340	MG	67#	65.6	USA	Observational study	Single centre
(244)	85	Ocular and gMG	47.7 (15.52)	25.9	NR	Cross-sectional study	NR
(245)	54	MG	NR (8-74) *	NR	India	Observational study	Single centre
(246)	109	MG	75.3 (6.9)	52.3	Canada	Observational study	Single centre
(247)	35	Ocular and gMG	54.34 (16.46)	57.1	Malaysia	Cross-sectional study	Single centre
(248)	113	MG	53.6 (14)	40	USA	Observational study	Multi centre
(249)	188	gMG	AChR MG: 47.4 (7) AChR+LRP4 MG: 49.81 (9.2) AChR+Titin MG: 48.11 (6.5)	AChR MG: 48.5 AChR+LRP4MG: 27.6 AChR+Titin MG: 58.6	China	Observational study	Single centre
(250)	110	MG	51# (31-61.3)	51	China	Cross sectional study	Single centre
(251)	1,399	MG	67# (54-76)	45.6	Germany	Cross sectional study	Multi centre
(252)	520	MG	59.1 (12.9)	43.8	USA	Registry based study	Single centre
(253)	53	Ocular and gMG	48 (13.3)	41.51	Turkey	Observational study	Single centre

(254)	134	MG	52.5# (39-68.8) *	36.57	Germany	Observational study	Single centre
(255)	28	gMG	NR	35.71	USA	Cross sectional study	Single centre
(256)	165	MG	54.4 (18.9)	51.5	Germany	Observational study	Single centre
(257)	1,232	MG	54.2 (16.3)	49.68	Multiple countries	Observational study	Multi centre
(258)	41	MG	44.2 (10.5)	0	France	Cross sectional study	Multi centre

Abbreviations: AChR = acetylcholine receptor; MG = myasthenia gravis; MuSK = Muscle-specific tyrosine kinase; Gmg = generalised myasthenia gravis; NR = not reported; SD = standard deviation; SLR = systematic literature review; UK = United Kingdom; USA = United States of America.

I.1.2 Quality assessment and generalizability of estimates

The quality of the 13 identified studies was assessed using the Downs and Black checklist (323) (Table 94). The studies were evaluated for quality of reporting (10 items), external validity (3 items), internal bias (7 items), and confounding (6 items) using the subscales of the Downs and Black scoring system. Quality scores on the Downs and Black checklist above 20 are considered as good, 11–20 as moderate, and below 11 as poor.

Table 94: Downs and Black checklist

Study name	Reporting										External validity			Internal validity – bias							Internal validity – confounding (selection bias)							Total score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	
Twork S. 2010	1	1	1	0	0	1	1	0	0	0	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	12

Winter Y. 2010	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
Jordan B. 2017	1	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	11
Hoffmann S. 2016	1	1	1	0	2	1	1	0	0	1	1	1	0	0	0	0	0	1	0	1	1	1	0	0	1	0	15
Leonardi 2010	1	1	1	0	0	1	0	0	0	0	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	11
Lee 2017	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Stojanov 2019	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
De 2012	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Stankovic 2018	1	1	1	0	0	1	1	0	0	0	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	12
Farrugia 2014	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
Tascilar 2018	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Basta 2012	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Scott 2006	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	7
Paul 2001	1	1	1	0	2	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	1	0	12
Ataide 2019	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Kulkantrakorn 2010	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Kalita 2014	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13

Happe 2004	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Raggi 2010	1	1	1	0	2	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	1	0	12
Bartel 1995	1	1	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
Sieminski 2012	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Fisher 2003	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	7
Alekseeva 2018	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Bogdan 2019	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Ariatti 2014	1	1	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
Sabre 2017	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Yang 2016	1	1	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
Koopman 2016	1	1	1	0	2	1	1	0	0	1	1	1	0	0	0	0	0	1	0	1	1	1	0	0	1	0	15
Suzuki 2019	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Blum 2015	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Konno 2015	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Cutter 2019	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	14
Braz 2018	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Kumar 2016	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	14

Nagane 2017	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Izaki 2017	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	7
Freeman 2014	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Mourão 2016	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Kotan 2016	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Boldingh 2015	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Suzuki 2014	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Kalbus 2016	1	1	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
Guasch 2009	1	1	1	0	0	1	0	0	0	0	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	11
Ayres 2018	1	1	1	0	0	1	1	0	0	0	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	0	11
Boscoe 2019	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Boscoe 2016	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	0	12
Wang 2017	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	9
Elsais 2013	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Alanazy 2019	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Guy-Coichard 2008	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Masuda 2013	1	1	0	0	1	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	14
De 2006	1	1	1	0	2	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	1	0	13

Padua 2002	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Barnett 2019	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Oliveira 2017	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Dong 2020	1	1	1	0	2	1	1	0	0	0	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	15
Fan 2020	1	1	1	0	2	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	1	0	12
Katzberg 2020	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	7
Kucherova 2021	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	0	0	1	1	1	0	0	0	0	12
Liu 2021	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Mendoza 2020	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Petersson 2021	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Ruiter 2021	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Samal 2020	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Sathirapanya 2020	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Stojanov 2020	1	1	1	0	0	1	1	0	0	0	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	12
Thomsen 2022	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Varon 2019	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	7

Vemuri 2020	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
Vijayan 2021	1	1	1	0	2	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	1	0	13
Wang 2021	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
Xu 2022	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Alanazy 2020	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
Harris 2020	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Vitturi 2021	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	9
Kim 2021	1	1	1	0	2	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	1	0	13
Dewilde 2022	1	1	1	0	2	1	1	0	0	0	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	15
Alsop 2022	1	1	1	0	2	1	1	0	0	0	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	15
Yang 2021	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Andersen 2022	1	1	1	0	2	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	1	0	16
Lehnerer 2022	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Shrubsole 2022	1	1	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	10
Deters 2021	1	1	1	0	0	1	1	0	0	1	1	1	0	0	0	0	0	1	0	1	1	1	0	0	0	0	12
Suppiah 2022	1	1	1	0	2	1	1	0	0	1	1	0	0	0	0	0	0	1	0	1	1	1	0	0	1	0	14
Steyaert 2022	1	1	1	0	0	1	1	0	0	0	1	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	9

Chen 2022	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	0	13
Pesa 2023	1	1	1	0	2	1	1	0	0	0	1	1	0	0	0	0	0	1	0	1	1	1	0	0	1	0	14
Li 2023	1	1	1	0	2	1	1	0	0	1	1	1	0	0	0	0	0	1	0	1	1	1	0	0	1	0	15
Marbin 2022	1	1	1	0	2	1	1	0	0	1	1	1	0	0	0	0	0	1	0	1	1	1	0	0	1	0	15
Lee 2022	1	1	1	0	2	1	1	0	0	1	1	1	0	0	0	0	0	1	0	1	1	1	0	0	1	0	15
Akkan 2022	1	1	1	0	0	1	1	0	0	1	1	1	0	0	0	0	0	1	0	1	1	1	0	0	0	0	12
Stascheit 2023	1	1	1	0	2	1	1	0	0	1	1	1	0	0	0	0	0	1	0	1	1	1	0	0	1	0	15
Jackson 2023	1	1	1	0	0	1	1	0	0	0	1	1	0	0	0	0	0	1	0	1	1	1	0	0	0	0	11
Wilcke 2023	1	1	1	0	0	1	1	0	0	1	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	11
Shrubsole 2021	1	1	1	0	0	1	1	0	0	1	1	1	0	0	0	0	0	1	0	1	1	1	0	0	0	0	12

I.1.3 Unpublished data

Not applicable.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

J.1.1 Systematic search for

Not applicable.

Table 95: Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion

Abbreviations:

J.1.2 Targeted literature search for disutilities and event rates

Which disutilities and clinical event rates have been accepted by the DMC?

Table 96: Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
Medicinrådet	Medicinrådet.dk	Disease: Myastenia gravis	28.05.2024

Only one report was available within the disease area of interest, which was chosen. This was the report of Medicinrådets anbefaling vedr. efgartigimod alfa til behandling af myastenia gravis (259).

Appendix K. Transition probabilities

Week 12 Zilucoplan	Uncontrolled (on initial tx)	Uncontrolled (off initial tx)	≤ 3 CFB MGADL	3-4 CFB MGADL	≥ 5 CFB MGADL	Exacerbation (on initial tx)	Exacerbation (off initial tx)	Myasthenic crisis	Myasthenic crisis death
Uncontrolled (on initial tx)	0.86931	0	0	0.03004	0.07360	0.02468	0	0.00236	0
Uncontrolled (off initial tx)	0	0.97296	0	0	0	0	0.02468	0.00236	0
≤ 3 CFB MGADL	0	0.00000	0.98832	0	0	0.00932	0	0.00236	0
3-4 CFB MGADL	0	0.00000	0	0.98980	0	0.00932	0	0.00089	0
≥ 5 CFB MGADL	0	0.00000	0	0	0.98980	0.00932	0	0.00089	0
Exacerbation (on initial tx)	0	0.35018	0.00000	0.13964	0.34212	0	0	0.16806	0
Exacerbation (off initial tx)	0	0.83194	0	0	0	0	0	0.16806	0
Myasthenic crisis	0	0.99825	0	0	0	0	0	0	0.00175
Myasthenic crisis death	0	0	0	0	0	0	0	0	1.00000

Week 24 Zilucoplan	Uncontrolled (on initial tx)	Uncontrolled (off initial tx)	≤ 3 CFB MGADL	3-4 CFB MGADL	≥ 5 CFB MGADL	Exacerbation (on initial tx)	Exacerbation (off initial tx)	Myasthenic crisis	Myasthenic crisis death

Uncontrolled (on initial tx)	0.86931	0	0.00000	0.02044	0.08321	0.02468	0	0.00236	0
Uncontrolled (off initial tx)	0	0.97296	0	0	0	0	0.02468	0.00236	0
≤ 3 CFB MGADL	0	0.00000	0.98832	0	0	0.00932	0	0.00236	0
3-4 CFB MGADL	0	0.00000	0	0.98980	0	0.00932	0	0.00089	0
≥ 5 CFB MGADL	0	0.00000	0	0	0.98980	0.00932	0	0.00089	0
Exacerbation (on initial tx)	0	0.35018	0.00000	0.09500	0.38677	0	0	0.16806	0
Exacerbation (off initial tx)	0	0.83194	0	0	0	0	0	0.16806	0
Myasthenic crisis	0	0.99825	0	0	0	0	0	0	0.00175
Myasthenic crisis death	0	0	0	0	0	0	0	0	1.00000

Week 12 Standard of care

	Uncontrolled (on initial tx)	Uncontrolled (off initial tx)	≤ 3 CFB MGADL	3-4 CFB MGADL	≥ 5 CFB MGADL	Exacerbation (on initial tx)	Exacerbation (off initial tx)	Myasthenic crisis	Myasthenic crisis death
Uncontrolled (on initial tx)	0.87508	0	0.00000	0.04346	0.05442	0.02468	0	0.00236	0
Uncontrolled (off initial tx)	0	0.97296	0	0	0	0	0.02468	0.00236	0
≤ 3 CFB MGADL	0	0.00000	0.98832	0	0	0.00932	0	0.00236	0

3-4 CFB MGADL	0	0.00000	0	0.98980	0	0.00932	0	0.00089	0
≥ 5 CFB MGADL	0	0.00000	0	0	0.98980	0.00932	0	0.00089	0
Exacerbation (on initial tx)	0	0.35018	0.00000	0.21390	0.26786	0	0	0.16806	0
Exacerbation (off initial tx)	0	0.83194	0	0	0	0	0	0.16806	0
Myasthenic crisis	0	0.99825	0	0	0	0	0	0	0.00175
Myasthenic crisis death	0	0	0	0	0	0	0	0	1.00000

Week 24 Standard of care	**Uncontrolled (on initial tx)**	**Uncontrolled (off initial tx)**	**≤ 3 CFB MGADL**	**3-4 CFB MGADL**	**≥ 5 CFB MGADL**	**Exacerbation (on initial tx)**	**Exacerbation (off initial tx)**	**Myasthenic crisis**	**Myasthenic crisis death**
Uncontrolled (on initial tx)	0.87508	0	0.00000	0.04346	0.05442	0.02468	0	0.00236	0
Uncontrolled (off initial tx)	0	0.97296	0	0	0	0	0.02468	0.00236	0
≤ 3 CFB MGADL	0	0.00000	0.98832	0	0	0.00932	0	0.00236	0
3-4 CFB MGADL	0	0.00000	0	0.98980	0	0.00932	0	0.00089	0
≥ 5 CFB MGADL	0	0.00000	0	0	0.98980	0.00932	0	0.00089	0

Exacerbation (on initial tx)	0	0.35018	0.00000	0.21390	0.26786	0	0	0.16806	0
Exacerbation (off initial tx)	0	0.83194	0	0	0	0	0	0.16806	0
Myasthenic crisis	0	0.99825	0	0	0	0	0	0	0.00175
Myasthenic crisis death	0	0	0	0	0	0	0	0	1.00000

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