Medicinrådet

Bilag til Medicinrådets anbefaling vedr. efgartigimod alfa til behandling af myastenia gravis

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. efgartigimod alfa
2. Forhandlingsnotat fra Amgros vedr. efgartigimod alfa
3. Ansøgers endelige ansøgning vedr. efgartigimod alfa

Attn: Medicinrådet

December 15, 2023

RE: Danish Medicines Council Draft Recommendation for efgartigimod alfa for the treatment of myasthenia gravis

argenx B.V. wishes to thank the Danish Medicines Council (DMC) for its thorough assessment of VYVGART™ (efgartigimod alfa-fcab) and the constructive dialogue during the evaluation process. We appreciate that the DMC recognized and highlighted the debilitating and life-altering nature of generalized myasthenia gravis (gMG) in the Draft Recommendation. However, we were disappointed to discover that the DMC has made substantial changes to our application.

Understanding the limited scope for response permitted in this document, we want to focus on the exclusion of IVIG as maintenance treatment for patients receiving only standard of care, as this: 1) is a critical cost driver in the model we put forth for consideration, and 2) necessarily means that the assessment of Vyvgart was done in relation to a different population than the one we put forward in the application.

- **Exclusion of IVIG from the CEA, as recommended by DMC in the Draft Recommendation, does not align with the intended use for VYVGART.**

  Despite acknowledging that, *"Some patients receive IVIG today due to special circumstances…"* IVIG was completely excluded by the DMC as maintenance treatment in its own analysis, *"as only very few patients receive it in Danish clinical practice"*.

  We disagree with this decision as it excludes the most critical population with the greatest urgency for VYVGART. This is a small group of patients with a significant unmet need; these patients will generally have received maximal doses of steroids and at least two additional therapies, which could include any number of nonsteroidal immunosuppressive therapies (NSISTs) or rituximab. As a result, these patients have few remaining options other than the chronic use of IVIG or plasma exchange (PLEX), which is normally reserved as rescue treatment.[1]

  argenx B.V. considers the following sources of data as evidence that maintenance IVIG is a relevant component of treatment in Denmark for the intended patient population:

  1. Acknowledgement by the DMC in its Draft Recommendation that *"2% of patients in the Danish registry study received IVIG and 1% received plasma replacement"*. According to this survey of Danish citizens with a diagnosis of myasthenia gravis who were registered in the Danish National Registry of Patients, IVIG is used in 4%, and PLEX is used in 1% of the subsample of patients regularly followed by a neurologist, and on active treatment for myasthenia gravis.[2]
  2. Data from the Danish gMG cohort of the prospective, observational, longitudinal MyRealWorld-MG study revealed that 23.7% received IVIG, 15.8% received PLEX, and 2.6% received eculizumab since diagnosis. Conservatively, 8.0% received IVIG, 2.0% received PLEX, and 0.0% received eculizumab in the previous 12 months.[3]
  3. As stated by a gMG clinical expert practicing at the national referral centre in Copenhagen, there are circumstances where gMG patients are dependent on maintenance IVIG, including 1) patients who have B-cell depletion or bone marrow depression as a result of rituximab therapy; 2) patients in whom steroids are contraindicated; and 3) women considering pregnancy or those who are already pregnant (argenx, Data on File).
  4. Other health technology assessment (HTA) agencies acknowledge that maintenance IVIG is used in cases when all standard treatments have failed, and that some patients have come to rely on maintenance therapy as no other treatments have provided sufficient symptom

[1] Andersen H et al. Retningslinjer for myastenibehandlingen i Danmark. 2017 [Myasthenia Gravis – behandling – NNBV].
[2] Andersen LK et al. *Neuromuscul Disord*. 2021;31(8):716-725.
[3] Services in Health Economics. Analysis of MyRealWorld-MG. November 2023. [Available upon request]

relief.[4][5] In one German HTA review, a clinical expert remarked it is not uncommon for patients with gMG to be on IVIG for a long period of time.[6] These findings provide adequate justification to include IVIG as one component of standard-of-care treatment in the comparator arm of the CEA for the intended patient population with high unmet need.

- **A positive recommendation for VYVGART would address a significant unmet need for the eligible patients with gMG in Denmark who have no remaining treatment options.**

  The eligible VYVGART population in Denmark should be those patients with active, uncontrolled disease, with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥5 (>50% of MG-ADL score due to non-ocular symptoms), who have failed, not tolerated, or are ineligible for standard therapy. Standard therapy includes a maximal dose of steroids, and at least two additional therapies, such as NSISTs and rituximab. Thus, the eligible Danish patient population for VYVGART is aligned with the patient population receiving maintenance IVIG and its estimate is in line with what is noted in the DMC Draft Report. These patients are expected to exert a high burden on the healthcare system through the need for costly maintenance IVIG. Furthermore, as IVIG is in chronic short supply in Denmark and globally, it is imperative that healthcare systems take steps to ensure this treatment is reserved for those who have no other options.[7]

- **Listing VYVGART on the Danish formulary will advance health equity for patients with gMG and will be a step forward for patients with other autoimmune diseases for which VYVGART is being evaluated.**

  argenx is willing and prepared to negotiate affordable solutions on reasonable terms to help secure access to VYVGART for Danish patients with gMG who are at greatest need for effective treatment, for whom existing treatments have proven insufficient and where the burden of disease for patients and their families remains high.

  We also view this as the initial step in the path forward for patients with around a dozen other autoimmune diseases for which VYVGART is being evaluated (e.g. chronic inflammatory demyelinating polyneuropathy, bullous pemphigoid, pemphigus vulgaris, idiopathic inflammatory myopathies, primary Sjogren syndrome, and post-COVID postural orthostatic tachycardia syndrome).

  We trust that the information and context presented in this response helps provide a basis for appropriate access to VYVGART for the relevant Danish gMG patients. We look forward to collaborative engagements with the DMC to this end.

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[4] Canadian Agency for Drugs and Technologies in Health (CADTH). Draft reimbursement recommendation: Efgartigimod alfa (VYVGART). 14 Nov 2023.
[5] National Institute for Health and Care Excellence (NICE). Draft guidance consultation: Efgartigimod for treating generalised myasthenia gravis. 1 Sep 2023.
[6] Gemeinsamer Bundesausschuss. Appendix XII: Benefit assessment of ravulizumab. 20 April 2023.
[7] Amgros. Concerted effort to ensure supplies of immunoglobulin. 2019; https://amgros.dk/en/about-amgros/news/concerted-effort-to-ensure-supplies-of-immunoglobulin/.

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15.12.2023
BMC/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	24.01.2024
Leverandør	Argenx BV
Lægemiddel	Vyvgart (Efgartigimod alfa)
Ansøgt indikation	Behandling, som tillæg til standardbehandlingen, af voksne med generaliseret myastenia gravis, som er seropositive for antistoffer over for acetylcholinreceptoren (AChR Ab+)
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Vyvgart (Efgartigimod alfa):

Tabel 1: Forhandlingsresultat betinget af Medicinrådets anbefaling

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Vyvgart	20 mg/ml	20 ml (IV)	57.435,90	[redacted]	[redacted]
Vyvgart	1000 mg	1 stk. (SC)	114.871,80	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Hvis Medicinrådet ikke anbefaler Vyvgart, har Amgros forhandlet følgende pris på Vyvgart:

Tabel 2: Forhandlingsresultat ubetinget af Medicinrådets anbefaling

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Vyvgart	20 mg/ml	20 ml (IV)	57.435,90	[redacted]	[redacted]
Vyvgart	1000 mg	1 stk. (SC)	114.871,80	[redacted]	[redacted]

Aftaleforhold

Amgros har ved forhandling fået ovenstående priser fra leverandøren. Da flere leverandører har udtrykt, at de kan levere Vyvgart har Amgros publiceret et udbud med tilbudsfrist den 31.01.2024. Originalleverandøren byder ind med prisen i tabel 1 i udbuddet, hvis Medicinrådet anbefaler Vyvgart og med prisen fra Tabel 2, hvis Medicinrådet ikke anbefaler Vyvgart.

Aftalen starter den 01.04.2024 og udløber den 31.03.2025 med mulighed for at forlænge 2x6 måneder. Derudover er der mulighed for at lave en præleveringsaftale. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Informationer fra forhandlingen

[redacted]

Den subkutane formulering indgår ikke i Medicinrådets vurderingsrapport, men leverandøren har markedsføringstilladelse til subkutan formulering og har givet et tilbud på denne.

[redacted]

Konkurrencesituationen

På nuværende tidspunkt er der ikke nogen direkte konkurrence, men dette forventes snart at ændre sig. EMA har i november 2023 givet positive opinion til 2 lægemidler Zilbrysq (zilucoplan) og Rystiggo (rozanolixizumab) til samme indikation.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Paknings-størrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Vyvgart	20 mg/ml	20 ml (IV)	10 mg/kg*	[redacted]	[redacted]

*Jf. Medicinrådets vurderingsrapport får patienterne 2,5 hætteglas per behandling
**Jf. Medicinrådet får patienterne i gennemsnit 5 behandlingscykler om året

Status fra andre lande

Tabel 3: Status fra andre lande

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

Konklusion

[redacted]

Application for the assessment of VYVGART™ (efgartigimod alfa-fcab) for adults with anti-AChR antibody positive generalized myasthenia gravis (gMG)

Date: August 2023

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1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	VYVGART®
Generic name	efgartigimod alfa
Marketing authorization holder in Denmark	argenx BV Industrial Park-Zwijnaarde 7 9052 Ghent Belgium
ATC code	L04AA58
Pharmacotherapeutic group	Immunosuppressants, selective immunosuppressants,
Active substance(s)	Each 20 ml vial contains 400 mg of efgartigimod alfa
Pharmaceutical form(s)	Concentrate for solution for infusion (sterile concentrate) Colourless to slightly yellow, clear to slightly opalescent, pH 6.7.
Mechanism of action	Efgartigimod alfa is a human IgG1 antibody fragment engineered for increased affinity to the neonatal Fc Receptor (FcRn). Efgartigimod alfa binds to FcRn, resulting in a reduction in the levels of circulating IgG including pathogenic IgG autoantibodies. Efgartigimod alfa does not affect the levels of other immunoglobulins (IgA, IgD, IgE or IgM), or those of albumin.
Dosage regimen	The recommended dose is 10 mg/kg as a 1-hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks. Subsequent treatment cycles are administered according to clinical evaluation. The frequency of treatment cycles may vary by patient.

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	VYVGART is indicated as an add-on to standard therapy for the treatment of adult patients with generalized Myasthenia Gravis (gMG) who are AChR-Ab+
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	
Packaging – types, sizes/number of units, and concentrations	Each vial of 20 ml contains 400 mg of efgartigimod alfa (20 mg/ml)
Orphan drug designation	On 21 March 2018, orphan designation (EU/3/18/1992) was granted by the European Commission to argenx BV, Belgium, for efgartigimod alfa (also known as ARGX-113) for the treatment of myasthenia gravis. The Committee for Orphan Medicinal Products maintained the orphan designation on 23 June 2022.

2. Abbreviations

Term	Definition
ACh	acetylcholine
AChEi	acetylcholinesterase inhibitor
AChR	acetylcholine receptor
AChR-Ab+ /–	acetylcholine receptor autoantibody-positive/-negative
AE	adverse event
CI	confidence interval
CMI	clinically meaningful improvement
CVD	cardiovascular disease
CS	corticosteroid(s)
FcRn	neonatal FC receptor
gMG	generalized myasthenia gravis
HRQoL	health-related quality of life
IgG	immunoglobulin G
IV	intravenous
IVIg	intravenous immunoglobulin
LOS	length of stay
LRP4	low-density lipoprotein receptor-related protein 4
LRP-Ab+/–	LRP autoantibody-positive/-negative
LY	life years
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living scale
MGC	Myasthenia Gravis Composite scale
MGFA	Myasthenia Gravis Foundation of America
MG-QoL15R	Myasthenia Gravis 15-item Quality of Life scale (revised)
MOA	mechanism of action
MRR	mortality rate ratio

MS	multiple sclerosis
MTX	methotrexate
MuSK	muscle-specific tyrosine kinase
MuSK-Ab+/–	MuSK autoantibody-positive/-negative
NMJ	neuromuscular junction
NSIST	nonsteroidal immunosuppressive therapy
PCS	Physical Component Summary
PLEX	plasma exchange
QALY	quality adjusted life years
QMG	Quantitative Myasthenia Gravis scale
RA	rheumatoid arthritis
SAE	serious adverse event
SD	standard deviation
SF-36	36-Item Short-Form Health Survey
TEAE	treatment-emergent adverse event

3. Tables and Figures

3.1. List of tables

3.2. List of figures

4. Summary

This application is for VYVGART®(efgartigimod alfa), which is indicated as an add-on to standard therapy for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor antibody positive (AChR-Ab+).[1] Generalized myasthenia gravis is a chronic, neuromuscular autoimmune disease mediated by pathogenic immunoglobulin G (IgG) autoantibodies that causes debilitating and potentially life-threatening muscle weakness.[2-8] Exacerbations can result in myasthenic crises wherein the muscles that control breathing are affected, leading to risk of respiratory failure.[9,10] As the disease progresses, muscle weakness becomes more severe, impacting the day-to-day functioning of patients and profoundly impairing their health-related quality of life (HRQoL).[11-13] gMG patients with MGFA class IV have similar mean EQ-5D-5L utility scores as patients with progressive-onset multiple sclerosis.[14-16]

Although gMG is rare, with an incidence in Denmark of approximately 9.2 per million person-years, active surveillance is required by patients and healthcare providers due to its severely disabling and potentially life-threatening nature.[17] The burden of disease is high from a societal aspect due to heavy healthcare resource use (HCRU) and high costs, as well as lost productivity due to patient unemployment.[13, 18-20] There are no curative treatment options for gMG.[21] Conventional therapy in Denmark comprises initial symptomatic treatment with acetylcholinesterase inhibitors (AChEis), followed by corticosteroids and/or nonsteroidal immunosuppressants (NSISTs). In cases of exacerbations or myasthenic crisis, intravenous immunoglobulin (IVIg), plasmapheresis or PLEX are recommended. Amongst them, the most commonly used one is IVIg, therefore, it is also included in the health economic analysis.

Other interventions included in the systematic literature review (SLR), such as rituximab, eculizumab, and the long-term use of both IVIg and PLEX are not of relevant use in Denmark, hence they are not included in the health economic analysis.[22] These therapy options after failure of first-line treatment with an AChEi rely mainly on broadly suppressing the immune system and lack robust supporting clinical data for use in gMG, with many being used off-label. Per Sieb (2014), "*The current standard treatment of MG is hardly proven by controlled studies(…) the choice of treatment modalities seems to rely mainly on institutional preferences and the personal experiences of the respective neurologist.*"[23] With current conventional therapy, many patients with gMG continue to suffer from substantial disease burden, including debilitating symptoms that affect their ability to perform functions of daily life and impair their productivity, treatment-related AEs, and poor HRQoL.[12, 13, 24-27]

Efgartigimod is a first-in-class human IgG1 antibody Fc-fragment that blocks the neonatal Fc receptor (FcRn), leading to the degradation of circulating disease-causing pathogenic IgG autoantibodies.[28] In contrast to conventional therapies for gMG, FcRn blocking does not result in widespread immunosuppression. The phase 3, randomized, double-blind, placebo-controlled, ADAPT trial has demonstrated that treatment with efgartigimod as an add-on to conventional therapy in patients with AChR-Ab+ gMG results in rapid, significant, and clinically meaningful improvements in the physical symptoms of gMG and HRQoL compared with conventional therapy + placebo.[28] This improvement was sustained across multiple treatment cycles as assessed by four MG scales (MG-ADL, QMG, MGC, MG-QoL15R). Efgartigimod was well tolerated, with a lower proportion of AEs and serious AEs reported in patients treated with efgartigimod than in the conventional therapy plus placebo arm. The ADAPT+ study, an ongoing, open-label, single-arm, 3-year extension of ADAPT, has confirmed the reported efficacy and safety results over repeated treatment cycles.

A de-novo Markov model was developed to determine the cost-effectiveness of efgartigimod for the treatment of patients with AChR-Ab+ gMG compared with conventional therapy in Denmark. Over the lifetime horizon, there was a gain of [redacted] QALYs for patients who received efgartigimod

compared with those who received conventional therapy. This is partially attributable to gains in HRQoL, higher utility and lower mortality associated with the efgartigimod arm. In the discounted base-case analysis, the total lifetime cost for a patient treated with efgartigimod was [redacted] vs [redacted] for conventional therapy. The resulting ICER for efgartigimod compared with conventional therapy was DKK [redacted] /QALY. Considering the value offered by efgartigimod as demonstrated in the CEA, the innovative mechanism of action, and the significant and clinically meaningful improvements observed in efgartigimod-treated patients in clinical trials, the availability of efgartigimod would be a paradigm shift for patients and physicians in the treatment of gMG. The introduction of efgartigimod will reduce the clinical burden of gMG. The analysis of budget impact results in a difference (between Future and Current Scenario) of approximately DKK [redacted] at Year 5.

5. The patient population, the intervention and the choice of comparators

5.1. The medical condition and patient population

Generalized myasthenia gravis (gMG) is a rare, chronic, neuromuscular autoimmune disease mediated by pathogenic immunoglobulin G (IgG) autoantibodies that causes debilitating and potentially life-threatening muscle weakness.[2-8]

MG is termed ocular MG when symptoms are exclusive to the eyelids and extraocular muscles, and generalized MG when weakness extends beyond the ocular muscles.[29] gMG is potentially life-threatening due to a complication called myasthenic crisis. A myasthenic crisis is a medical emergency characterized by worsening weakness in the muscles that control breathing, resulting in respiratory failure that requires intubation and mechanical ventilation.[9, 10] Up to 20% of patients with gMG experience a myasthenic crisis at least once in their lifetime.[4, 9]

Initially, patients with MG typically experience fluctuating weakness and fatigue in specific muscle groups.[4, 29] Ocular weakness is the initial symptom in an estimated 85% of patients, including drooping eyelids (ptosis [32%]), double vision (diplopia [14%]), both ptosis and diplopia (36%), or blurred vision (3%).[4] Other frequent initial symptoms include facial muscle weakness that results in problems with talking (dysarthria), chewing and swallowing (dysphagia), or shortness of breath (dyspnoea). Fatigue in the neck, arms, hands, or legs is also common.[4]

Up to 80% of patients with ocular symptoms subsequently develop gMG within 2 years. Patients with gMG experience ongoing debilitating muscle weakness, including difficulties with swallowing, vision, speech, respiratory function, and mobility, with exacerbations that can result in life-threatening myasthenic crises.[4, 9] The symptoms of gMG fluctuate in a day-to-day and diurnal pattern, with weakness usually worse later in the day.[4, 29, 30] There appears to be no gender-related difference in symptoms.[4]

The Myasthenia Gravis Foundation of America (MGFA) clinical classification is used to categorize patients diagnosed with MG based on clinical features and/or disease severity (Table 1).[11] The classification ranges from Class I (ie, ocular weakness only) to Class V (ie, myasthenic crisis). Classes II-V are applicable to gMG. A substantial portion of patients continue to experience debilitating disease symptoms despite treatment.[25, 31, 32]

Table 1. MGFA clinical classification

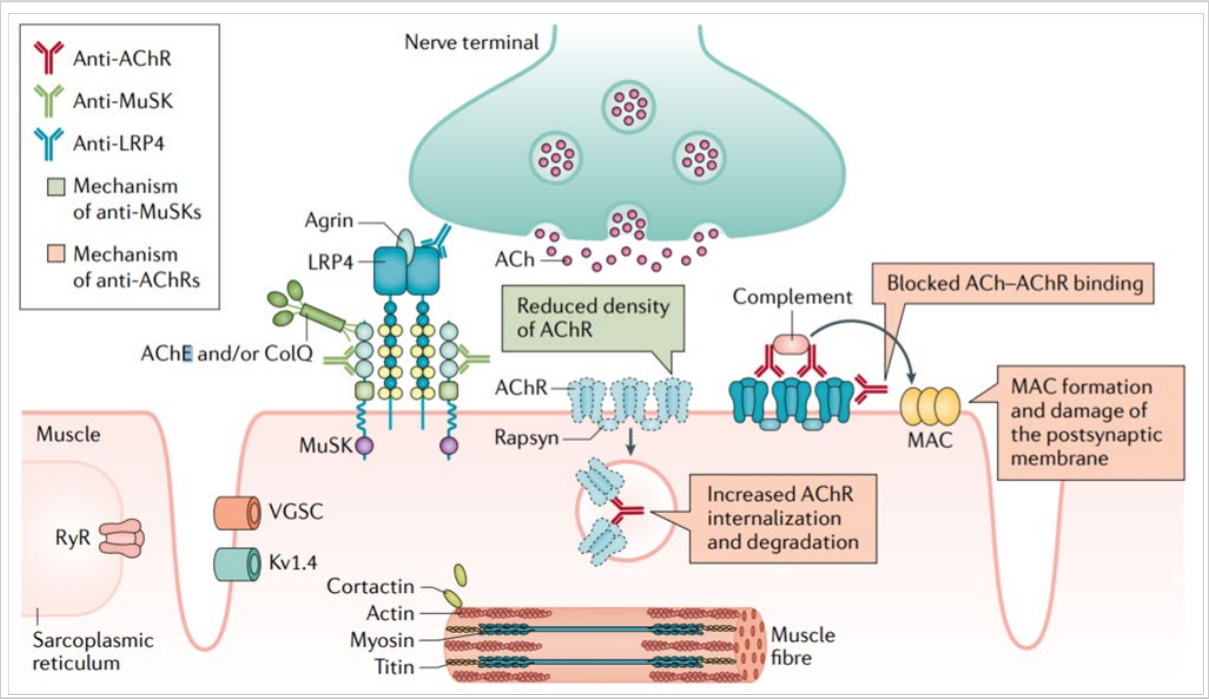
Class	Characteristics
I	Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
II	Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles. IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
III	Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles. IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
IV	Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles. IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

MGFA, Myasthenia Gravis Foundation of America
Source: Jaretzki et al, 2000[11]

5.2. Pathophysiology of gMG

gMG is mediated by pathogenic IgG autoantibodies, causing defective communication at the neuromuscular junction (Figure 1).[2, 5, 29, 33-39] The IgG autoantibodies target acetylcholine receptors (AChRs) and structural components of the neuromuscular junction, impairing neuromuscular transmission, and leading to muscle weakness and fatigue.[29, 33, 40] The neuromuscular junction is the site of transmission between nerve endings and skeletal muscle fibres that controls muscle contractions via the neurotransmitter acetylcholine (ACh).[38, 40] The exact cause of the abnormal immune response in patients with gMG is often unknown, but can be caused by thymoma or thymic dysplasia.[40] Most gMG patients (~85%) have autoantibodies directed against AChRs, which are of the IgG1 and IgG3 subclass. An estimated 1%–10% of patients with MG do not have anti-AChR antibodies but do have IgG4 autoantibodies against the muscle-specific kinase protein (MuSK) or IgG1 autoantibodies against the low-density lipoprotein receptor-related protein 4 (LRP4), which also leads to a decrease in AChRs.[33] Even in patients with no identifiable autoantibodies, MG is considered to be antibody mediated.[39]

Figure 1. Pathophysiology of neuromuscular junction in MG



AChE, acetylcholinesterase; AChR, acetylcholine receptor; ColQ, collagen Q; LRP4, low-density lipoprotein receptor-related protein 4; MAC, membrane attack complex; MuSK, muscle-specific tyrosine kinase; RyR, ryanodine receptor; VGSC, voltage-gated sodium channel
Source: Adapted from Gilhus et al, 2016[33]

5.3. Diagnosis of (g)MG

Physical and neurological examination are the initial step for patients presenting with symptoms of MG.[10] The main diagnostic test for MG is serum anti-AChR antibody testing, as most individuals with MG will have abnormally elevated levels of AChR antibodies.[10, 41] Serum anti-MuSK antibody testing is performed for all patients negative for AChR antibodies in whom MG is strongly suspected. Neurophysiology tests may also help to establish the diagnosis in seronegative patients with suspected MG. In patients with negative serology and neurophysiology, an MRI brain scan may be required to exclude other conditions. All patients with suspected MG, irrespective of type (ocular/generalized) or serology (seropositive/negative), should undergo thymus imaging with CT or MRI to detect thymoma. MG is often associated with thymic abnormalities; thymic lymphoid hyperplasia and thymoma can be found in up to 65% and 15% of patients, respectively.[42]

5.4. Burden of illness

5.4.1. Prognosis

The clinical course of gMG is highly variable and affected by disease-specific characteristics, age, gender, thymectomy, and presence of thymoma.[18, 43-47] An analysis of 1,315 participants in the MGFA registry from 2013 to 2016 found that when compared with men, women with MG were significantly younger (mean age: 50.3 vs. 61.6 years; $p<0.00001$), were significantly younger at symptom onset (39.8 vs. 54.9 years; $p<0.00001$), had experienced a significantly longer delay from symptom onset to diagnosis (5.5 vs. 3.7 years; $p=0.0026$), and had a longer disease duration (10.8 vs. 7.4 years; $p<0.00001$).[18]

Generally, as gMG progresses, muscle weakness and fatigue become more severe, causing physical disability and negatively impacting health-related quality of life (HRQoL). Longitudinal studies of patients with MG have found that initial presenting symptoms, which are ocular in 85% of patients, reach their maximum severity within 1 year in 70% of patients and within 3 years in 85% of patients.[24] Of the 80% of patients who develop gMG after initial ocular presentation, muscular weakness reached maximum severity within 2 years of onset in 82% of patients.[24]

Overall mortality is significantly higher in patients with MG (ie, including gMG and ocular MG) than in the general population. Up to 20% of patients with gMG will experience a potentially life-threatening myasthenic crisis, with respiratory failure requiring mechanical ventilation. The mortality rate of a myasthenic crisis has been estimated at 4% per event.[48]

It has been estimated that up to 80% of patients have disease that fails to achieve remission (ie, the absence of symptoms and signs of gMG).[24] In addition, approximately 10% of patients do not respond adequately to current therapies and are considered treatment refractory.[24] A survey of the German Myasthenia Gravis Foundation in 1,660 patients supports these estimates; despite treatment, only 8% of patients with gMG were in clinical remission (ie, no symptoms of MG for ≥1 year while not taking medication for MG) and 25% were in pharmacological remission (ie, no symptoms while taking medication for MG).[49]

5.4.1.1. Suboptimal care

There is evidence that patients with MG receive suboptimal care from non-specialists, potentially due to a lack of clear guidance and disease awareness.[21] A survey of the German Myasthenia Gravis Foundation in 1,660 patients found that only 8% of patients with gMG were in clinical remission and 25% were in pharmacological remission.[50] More than 20% of respondents reported not benefiting from their medication at all, and 48% experienced treatment-related side effects, with 37% discontinuing therapy as a result.[50]

Suboptimal care was demonstrated in a British study of 108 hospital admissions for 78 patients with MG who were hospitalized due to MG. Upon admission, it was noted that 45% of patients had no change in treatment despite deteriorating in the 50 days prior to hospitalization.[21] Similar treatment patterns were found in another British study, which showed that, in the 4 weeks preceding admission, treatment remained unchanged in 47% of patients despite suffering bulbar symptoms (ie, weakness and fatigue in the neck and jaw, causing dysarthria and dysphagia).

5.4.2. Physical disability

gMG is a disabling and potentially life-threatening condition. Disability mainly arises because of debilitating muscle weakness, including difficulties with vision, swallowing and chewing, speech, respiratory function, and mobility.[12]

A German HRQoL study in 1,518 patients with MG and an average disease duration of 10.2 years found that while most patients (82%) considered their disease stable, 75% had limited mobility due to muscle weakness after physical strain, 71% had weakness in their upper limbs, and 70% had walking problems (Table 2).[13] Problems with swallowing, chewing, defecation, and vision were also common.

Table 2. Proportion of patients experiencing MG-related impairment, based on German survey (N=1,518)

Impairment	Patients (%)
Muscle weakness after physical strain	75.4

Weakness of upper limbs	71.3
Walking problems	69.6
Dysphagia	43.9
Chewing problems	39.1
Defecation problems	38.5
Ptosis	37.8
Diplopia	37.8
Neck weakness	31.6
Speech disorders	28.9
Facial expression disorders	25.9
Urination problems	24.9
Sexual disorders	18.7
Muscle weakness at rest	16.9

MG, myasthenia gravis. Multiple answers possible.
Source: Twork et al, 2010[13]

In addition to muscular weakness, many patients with gMG complain of severe, overwhelming, and constant fatigue that does not disappear with rest.[51] This type of fatigue has a significant impact on patients' HRQoL and activities of daily life.[52] In a survey in 779 patients from the Danish National Registry of Patients with a MG diagnosis (53% women, mean [SD] age 60.8 [15.5]), patients reported high levels of fatigue and low levels of physical activity.[51] Fatigue scores reported by the participants were increased compared with the general population; slightly lower than those found in patients with Parkinson disease, chronic fatigue syndrome, and multiple sclerosis; and similar to fatigue scores in post-stroke patients and patients with other autoimmune diseases.

5.4.3. Cognitive/mental impairment

Cognitive functions such as response fluency (ie, behaviour that occurs smoothly, rapidly, and with little apparent effort), information processing, and verbal and visual learning may be affected by MG.[13] Approximately one-third of patients with gMG exhibit depression, and nearly half exhibit anxiety disorder.[53]

5.4.4. Comorbidities related to treatment

Patients with gMG are at a significantly higher risk of serious infections compared with the general population, mainly due to the chronic immunosuppressant medications used to treat the condition.[12, 26] A Canadian study of 3,823 patients with MG followed over 5 years found MG was associated with a 39% increased infection risk compared with matched controls.[54] Respiratory infections, including bacterial pneumonia, septicaemia, and skin/soft tissue infections were the most common infections reported in the study.

5.4.5. Patient burden: HRQoL

Multiple studies have found that the overall HRQoL for patients with MG is reduced compared with healthy control populations.[12, 13, 47] gMG has a profoundly negative impact on patients' HRQoL due to:

- Debilitating physical impairments caused by muscle weakness[12, 13, 25]
- Poor psychological well-being, including significant fatigue, depression, and anxiety[12, 27, 47, 53, 55]
- Treatment-related side effects, mainly due to the long-term use of immunosuppressive therapies[12, 26]
- Comorbid autoimmune conditions[13, 56]

HRQoL reduction is often greater in female patients with MG compared with men, possibly due to a longer duration of disease.[18] Older age, older age at onset of disease, obesity, lack of employment, low educational attainment, and low physical activity have also been shown to negatively affect HRQoL in MG.[26, 55] A 10-year longitudinal study in 78 MG patients found that even in remission, patients' HRQoL was reduced.[55]

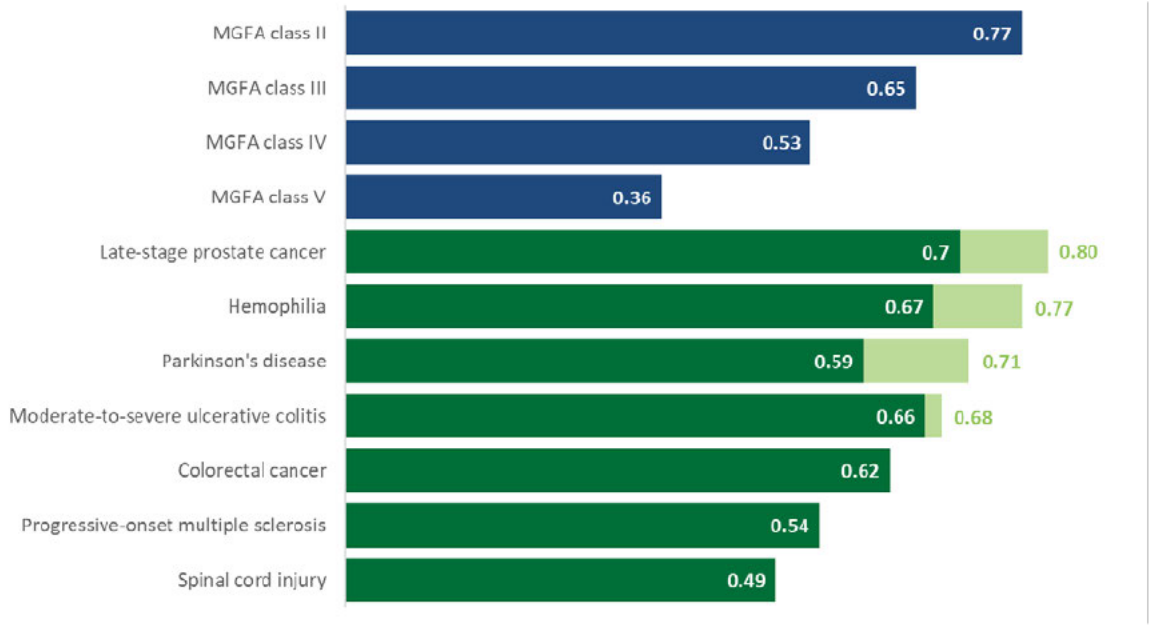
5.4.5.1. General HRQoL disease measures

Compared with the general population, patients with MG experience worse scores in the domains of physical functioning, physical role, general health, social functioning, and mental health.[57]

5.4.5.1.1. EQ-5D-5L

The MyRealWorld MG study is a prospective, observational, longitudinal study aiming to capture the impact of MG from the patient perspective. Based on an interim analysis of responses from 617 patients (70% female, mean age 47 years) from Belgium, Canada, Germany, Italy, Japan, Spain, the UK, and US who completed the EQ-5D-5L at baseline, patients with gMG have lower EQ-5D-5L utility values than the general population of the same age and gender (mean utility: 0.69 vs 0.86).[58] The study also demonstrated that utility was significantly associated with disease severity as defined by MGFA class; utility values significantly declined with higher MGFA class ($p<0.0001$), indicating worsening HRQoL with greater disease severity. These values are similar to, or worse than, those associated with several debilitating diseases (Figure 2).[14-16]

Figure 2. Mean EQ-5D-5L utility scores from the MyRealWorld MG study based on MGFA classification, with comparison across other diseases



MGFA, Myasthenia Gravis Foundation of America
High- and low-end values for other diseases are based on utilities provided in relevant publications identified in a systematic review by Zhou et al.
Sources: Dewilde et al, 2021[58]; Zhou et al, 2021[15]

Utility declines were also significantly associated with worsening in scores on the Myasthenia Gravis Activities of Daily Living (MG-ADL) and Myasthenia Gravis 15-item Quality of Life (MG-QoL15) scales, depression, anxiety, need for caregiver help, and additional comorbidities (Table 3). This indicates that reduced ability to perform activities of daily living, impairment of physical and mental health, and the necessity for a caregiver all significantly diminish the HRQoL of patients with gMG.[58]

Table 3. HRQoL utility decrements in patients with gMG

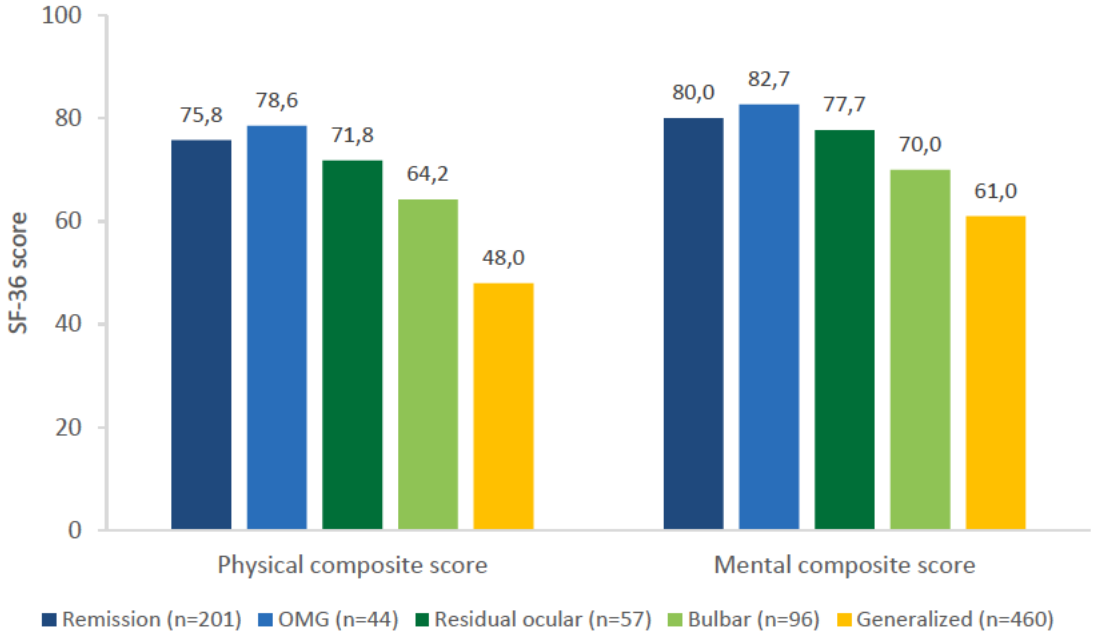
Event	Utility decrement	p value
Worsening in MG-ADL total score (1-point decline)*	0.0375	≤0.0001
Worsening in MG-QoL15 total score (1-point decline)	0.0207	≤0.0001
Depression Mild Moderate Severe	 0.121 0.230 0.408	≤0.0001
Anxiety Mild Moderate Severe	 0.078 0.147 0.252	≤0.0001
Needing caregiver help	0.236	NR
Comorbidities	0.105	≤0.0001

MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MG-QoL15, Myasthenia Gravis 15-item Quality of Life scale; NR, not reported
*The MG-ADL is an eight-item patient-reported scale developed to assess MG symptoms and their effects on daily activities.[59] Responses for each item are given on a 4-point scale, representing normal (0) to severe (3), and the total score ranges from 0 to 24, with higher scores indicating more active MG symptoms.
Source: Dewilde 2021[58]

5.4.5.1.2. SF-36

HRQoL is lower in patients with gMG with more severe symptoms.[26] Achieving remission and/or reducing severe symptoms have been found to improve HRQoL in patients with gMG, emphasizing the need for effective treatments that control symptoms and reduce disease progression.[12, 26] A population-based cross-sectional study in 858 patients with MG found that those with active generalized symptoms had significantly lower HRQoL scores (as measured by the SF-36) than those with OMG, residual ocular symptoms after generalized disease, and those in remission (p<0.001) (Figure 3).[12]

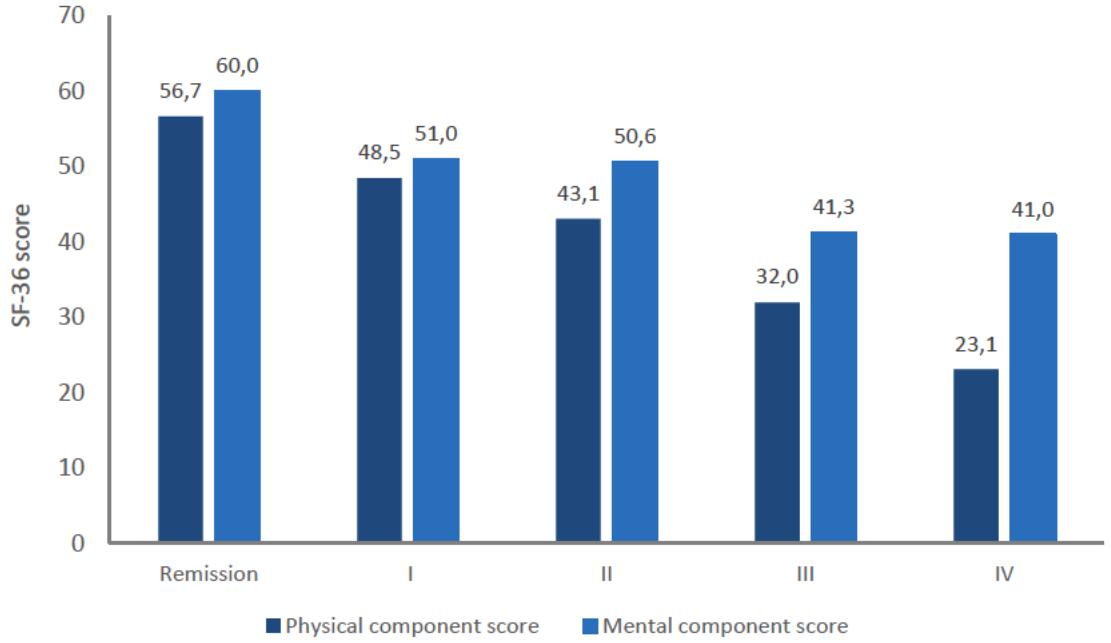
Figure 3. SF-36 scores in patients with MG by disease course



MG, myasthenia gravis; OMG, ocular myasthenia gravis; SF-36, 36-Item Short Form Health Survey
Lower scores on the SF-36 indicate greater disability (0=maximum disability; 100=no disability).
Source: Boldingh et al, 2015[12]

A single-centre study in 339 patients with MG found a significant positive correlation between worsening HRQoL as measured by the SF-36 and higher MGFA classification.[26] While similar HRQoL as assessed by the SF-36 was found between patients with MG classified as I and II on the MGFA scale, as patients' symptoms worsened to MGFA III, significant worsening in HRQoL occurred on both physical and mental component scores of the SF-36 (Figure 4). For the Physical Component Score, there were significant differences between patients in remission and MGFA II, III, or IV; between MGFA I and III or IV; and between MGFA II and III or IV. For the Mental Component Score, significant differences were found between patients in remission and MGFA II and III or IV (all differences p<0.05).

Figure 4. Influence of MGFA classification on SF-36 assessment



Source: Szczudlik et al, 2020[26]

5.4.5.2. Disease-specific HRQoL measures

The MG-QoL15 is a validated HRQoL questionnaire specifically developed for assessing patients with MG[60, 61] and has been found to correlate positively with other clinical measures including the MG-ADL, Myasthenia Gravis Composite scale (MGC), and Quantitative Myasthenia Gravis scale (QMG).[62] The MG-QoL15 evaluates four domains: mobility (nine items), MG symptoms (three items), general contentment (one item), and emotional well-being (two items). Responses for each item are given on a 5-point scale: not at all (0), a little bit (1) somewhat (2), quite a bit (3), and very much (4), and the total score ranges from 0 to 60, with higher scores indicating more severe MG.

Table 4 summarizes five studies reporting MG-QoL15 scores for patients with gMG, ranging from 15.5 to 22.7.[52, 63-66] Overall, patients with gMG report higher MG-QoL15 scores than those without current generalized symptoms. In the studies by Jordan et al, scores in the gMG population (15.7 and 17.0) were significantly worse compared with scores for control populations (3.1 in both; $p<0.05$ for both studies).

Table 4. Summary of MG-QoL15 results in patients with gMG

Reference	Patient population	N	Mean (SD) MG-QoL15 score
Martínez-Lapiscina et al, 2012[66]	gMG	23	19.3 (10.5)
	OMG	6	8.8 (7.4)
	Remission	25	3.6 (5.2)
Hoffmann et al, 2016[52]	gMG (CFQ ≥4)*	110	22.7 (NR)
	OMG (CFQ ≥4)*	110	19.3 (NR)

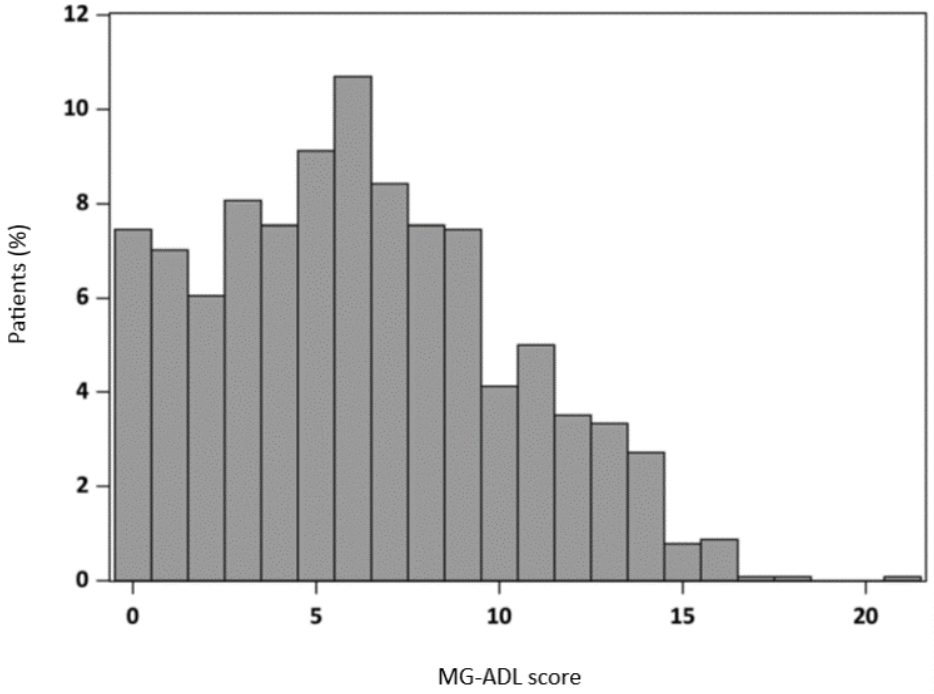
Reference	Patient population	N	Mean (SD) MG-QoL15 score
	MG, remission (CFQ ≥4)*	110	8.6 (NR)
Jordan et al, 2017[64]	gMG	32	17.0 (14.8)
Jordan et al, 2017[65]	gMG	33	15.7 (13.8)
Westerberg et al, 2018[63]	EOMG	40	9.5 (NR)†
	LOMG	17	7 (NR)†
	gMG	5	15.5 (0–42)†
	MG without current generalized symptoms	NR	1.5 (0–11)†‡

CFQ, Chalder Fatigue Questionnaire; EOMG, early-onset myasthenia gravis; gMG, generalized myasthenia gravis; OMG, ocular myasthenia gravis; LOMG, late-onset myasthenia gravis
*Patients with relevant fatigue; †Reported as median (range); ‡p<0.0001 compared with gMG

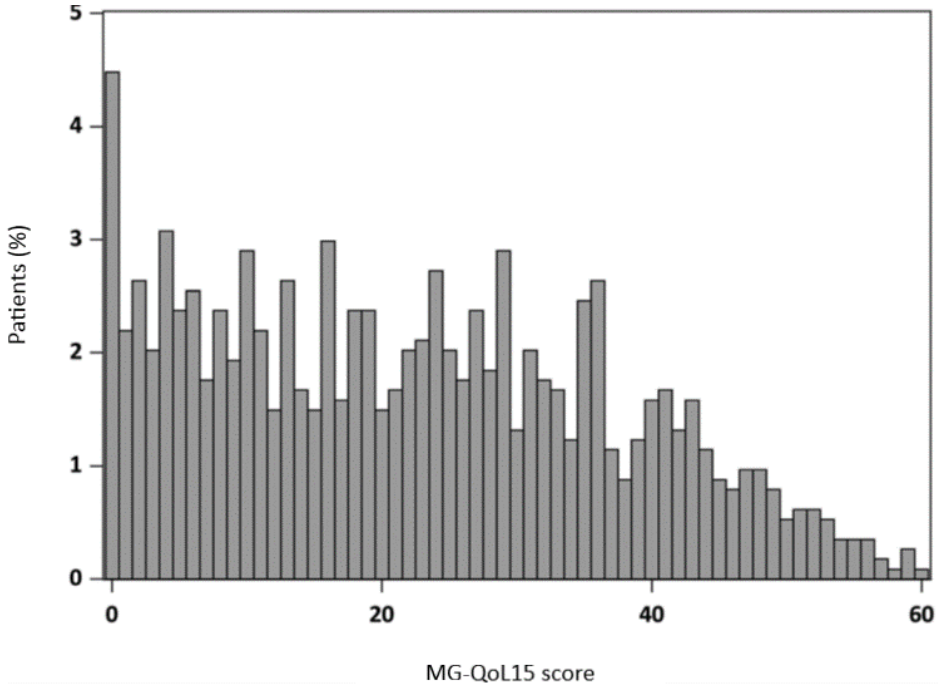
The MG-ADL is an eight-item patient-reported scale developed to assess MG symptoms and their effects on daily activities.[59] Responses for each item are given on a 4-point scale, representing normal (0) to severe (3), and the total score ranges from 0 to 24, with higher scores indicating more active MG symptoms. A registry-based study from 2013 to 2017 of 1,140 patients with MG found that on average, half of patients have moderate to severe symptoms or disability that limit their activities of daily life, based on MG-ADL and MG-QoL15 scores (Figure 5).[25] Mean MG-ADL score was 6.2 (SD 4.0) and mean MG-QoL15 score was 22.2 (SD 15.0). Given that the thresholds for patient-acceptable symptom state (PASS) have been demonstrated as 3 and 8 points for the MG-ADL and MG-QoL15, respectively, these mean scores indicate that most patients had substantial disease burden.[25, 67]

Figure 5. Distribution of (A) MG-ADL (N=1,140) and (B) MG-QoL15 (N=1,138) scale scores based on MGFA patient registry

(A)



(B)



MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MG-QoL15, Myasthenia Gravis Quality of Life 15-item scale; MGFA, Myasthenia Gravis Foundation of America
Source: Cutter et al, 2019[25]

5.4.5.3. HRQoL in Danish patients with gMG

A cross-sectional Danish study conducted in 100 patients with gMG followed at the Copenhagen Neuromuscular Center from October 2019 to June 2020 found one-third of the patients were dissatisfied with their current symptom state.[68] Researchers used MG-specific and generic HRQoL measures, including the QMG, MGC, MG-ADL, Major Depression Inventory, Charlson Comorbidity Index and the EQ-5D-3L, and anchored analyses to the Patient Acceptable Symptom State (PASS). The PASS comprised one yes/no question: 'considering all the ways you are affected by MG, if you had to stay in your current state for the next months, would you say that you are satisfied with your current disease state?'. A total of 33 patients answered 'no' to the PASS question; increasing MG symptoms, fatigue, depression, low MG-related HRQoL, shorter disease duration, and being unemployed or on disability were associated with negative PASS status. The study shows that dissatisfaction with the current symptom level is high in patients with gMG.

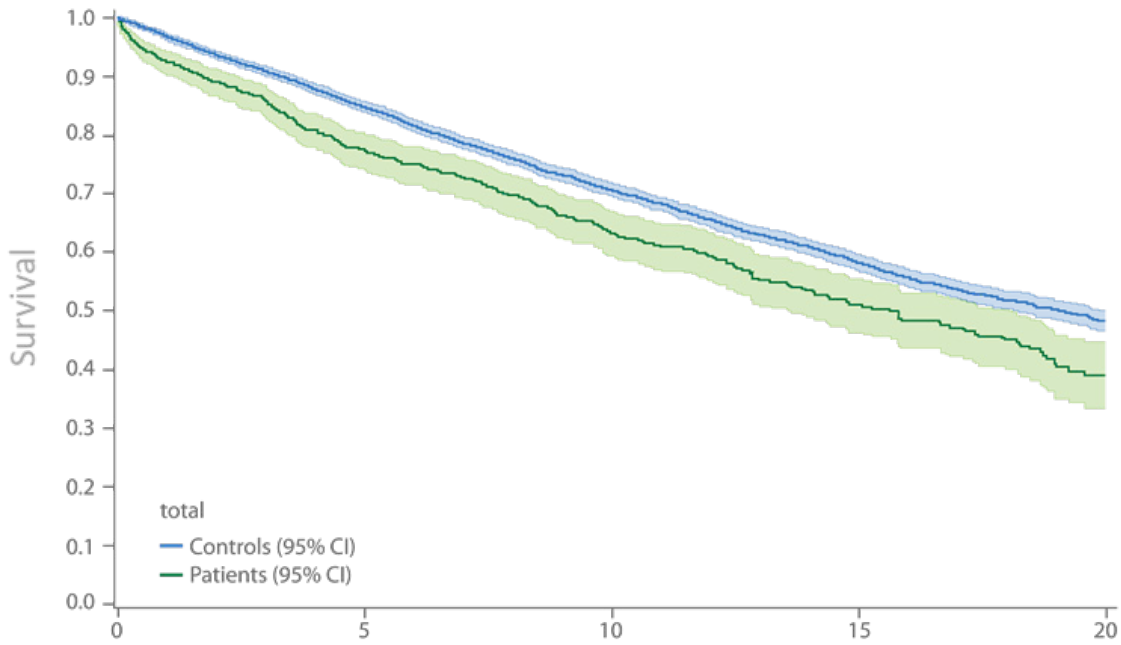
5.4.6. Caregiver burden

Evidence on caregiver burden in MG is limited. A community-based survey of 165 Australian patients with MG found full-time or part-time care was required by 29% of patients at the time of the survey.[56]

5.4.7. Mortality in Denmark

Based on a nationwide study of patients with AChR-Ab+ gMG diagnosed in Denmark between 1985 and 2005, overall mortality is significantly higher in patients with gMG than in the general population (mortality rate ratio [MRR]: 1.4 [95% CI 1.2, 1.6]), particularly within the first 5 years of diagnosis (MRR: 1.7 [95% CI 1.4, 2.0]; Figure 6).[69]

Figure 6. Kaplan–Meier survival curves with 95% CIs for AChR-Ab+ MG patients compared with controls



AChR-Ab+, acetylcholine receptor autoantibody-positive; CI, confidence interval, MG, myasthenia gravis
Source: Hansen et al, 2016[69]

5.5. Epidemiology of gMG in Denmark

gMG is considered a rare disease in the EU, as it affects fewer than 50 people in 100,000.[70] However, epidemiological data for gMG are limited—most evidence is from European studies in a single-centre setting. Incidence, prevalence, and mortality data for Denmark are presented below.

5.5.1. Incidence and prevalence in Denmark

Based on a systematic literature reviewing covering 1980–2007, the incidence of MG is estimated to range from 0.3 to 3.0 per 100,000 persons/year worldwide.[71] The incidence in Denmark has been estimated at 9.2 per million person-years, ranging from 5.8 per million person-years among adults aged 20–29 years to 33.8 per million person-years in adults aged 70–79 years (Table 5).

Table 5. Incidence of MG in Denmark

Age group, years	Incidence per million person-years (95% CI)
20–29	5.8 (4.4–7.6)
30–39	5.1 (3.9–6.6)
40–49	6.7 (5.3–8.5)
50–59	9.7 (7.8–11.8)
60–69	18.1 (15.2–21.5)
70–79	33.4 (28.5–38.8)
80–89	30.8 (24.3–38.3)
90+	13.3 (4.9–28.9)

Source: Pederson et al, 2013[17]

MG is estimated to affect more than 700,000 people worldwide, and around 103,000 people in the EU.[70, 72] Based on studies from 2010 onwards, the prevalence of MG ranges from 11.2 to 33.0 per 100,000 persons.[73, 74]

Recent data for the prevalence of gMG in Denmark are limited. Sørensen & Holm (1989) reported a prevalence rate of 125 per million based on data from Viborg county in Denmark.[75] Christensen et al reported on the epidemiology of MG in western Denmark from 1975 to 1989, basing case identification on records from all hospitals in the survey area. Based on a population of 2.8 million in 1985, the point-prevalence rate (1 January 1990) was 78 per million population. Pedersen et al identified a prevalent population of 1,142 patients in Denmark with gMG based on diagnostic and prescription data from national registers between 1996–2009.[17]

For the health economics analysis, a MG incidence rate of 9.2 per million and a prevalence of 272 per million were considered. [17, 76] Among these patients, 78% were considered gMG patients [77], and 94% of gMG were assumed to be AChR-Ab+. Using a population of 4,041,179 adults [78], this resulted in 811 prevalent patients with a yearly incidence of around 27 patients in Denmark for the current year. Table 6 presents the estimated incidence and prevalence relevant to the analysis over the past 5 years using adult population data from Statistics Denmark. [79]

Table 6.Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	27.0	27.1	27.1	27.2	27
Prevalence in Denmark	799	801	803	804	811

5.5.2. Patient populations relevant for this application

The relevant patient population for this application is adult patients with AChR-Ab+ gMG, in line with the indication for VYVGART®(efgartigimod alfa). Table 7 shows the estimated number of eligible patients in Denmark for the next five years period.

Table 7. Estimated number of patients eligible for treatment

Year	2023	2024	2025	2026	2027
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.6. Current treatment options and choice of comparator

5.6.1. Current treatment options

There is no curative treatment for gMG.[21] Considerable variation exists in the management of gMG, and treatment has yet to be standardized. Available treatments include acetylcholinesterase inhibitors (AChEis), corticosteroids, nonsteroidal immunosuppressants (NSISTs), IVIg, and plasmapheresis or PLEX, rituximab, and eculizumab. The goals for treatment of gMG are for patients to experience normal or near-normal function with little weakness or fatigue due to MG (ie, remission), and no or only mild side effects from medication.[72] However, it has been estimated up to 80% of patients have disease that fails to achieve remission (ie, the absence of symptoms and signs of gMG). In addition, approximately 10% of patients do not respond adequately to current therapies and are considered treatment refractory.[24]

5.6.2. Choice of comparators

In Denmark, patients with gMG are treated by neurologists at four university hospital-based centres.[80] The recommended treatment algorithm is presented in Table 7. Pyridostigmine is considered basic treatment for MG and initiated in all patients. In patients that need additional symptom control, azathioprine is recommended as the first line of NSIST in patients in need of long-term immunosuppression. Physicians are urged to taper corticosteroids to the lowest possible dose and, if possible, phase out treatment, due to significant side effects with long-term treatment. The guidelines note that immunosuppressive therapy should be initiated early in the course of the disease. Rituximab is recommended only in patients with more severe generalized MG where other immunosuppressive therapy has been shown to be ineffective. PLEX and IVIg are mainly considered as treatment for exacerbations or symptoms indicative of myasthenic crisis.

Similar to the Danish treatment guidelines, MGFA International Consensus Guidance recommends initiating treatment of gMG with pyridostigmine, but most patients do not experience an adequate response to this treatment alone and will require further treatment with corticosteroids as well as NSISTs, such as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, or tacrolimus, in an attempt to control their symptoms (Table 8).[13, 57, 72, 81] IVIg, PLEX, rituximab, and eculizumab are generally reserved for refractory patients. The most widely used agents to treat gMG are unlicensed (ie, prescribed off-label) in this indication and are not supported by robust clinical trial data.[23, 41, 82-87]

Table 8. Danish and MGFA International Consensus guidelines for gMG

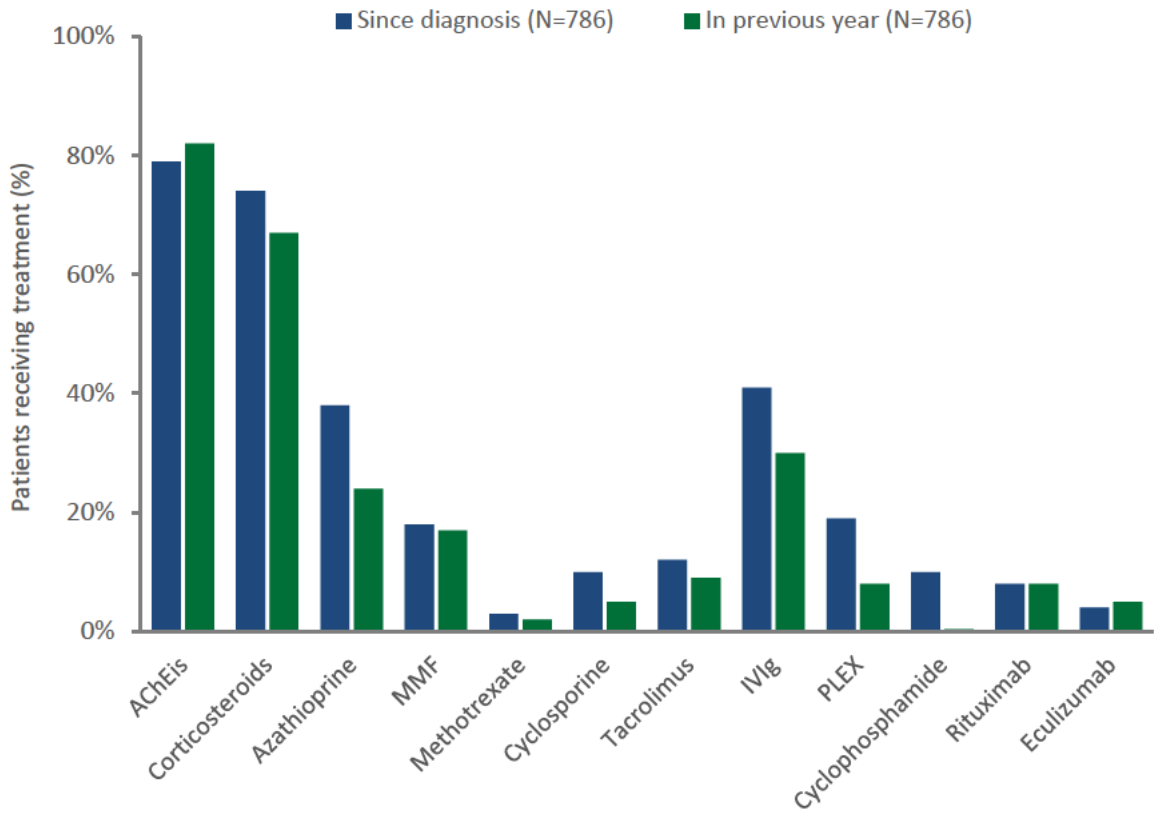
Guideline	Recommended treatment sequence for gMG
Guidelines for myasthenic treatment in Denmark (2017)[22]	1. Pyridostigmine (AChEi) monotherapy 2. Corticosteroid combined with azathioprine. Mycophenolate mofetil or methotrexate can be used as an alternative to azathioprine. 3. Rituximab **or** the addition of cyclosporine or tacrolimus in combination with level 2 treatment. 4. Immunomodulatory therapy (PLEX, IVIg) can be used in case of insufficient response
MGFA International Consensus Guidance (2020)[72, 88]	1. Pyridostigmine (AChEi) 2. Corticosteroids 3. NSISTs (azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus) 4. Chronic IVIg, chronic PLEX, cyclophosphamide, rituximab (refractory patients only) 5. Eculizumab (severe, refractory, AChR-AB+ patients only)

AChEi, acetylcholinesterase inhibitor; IVIg, intravenous immunoglobulin; NSISTs, nonsteroidal immunosuppressants; PLEX, plasmapheresis or plasma exchange

While there is general agreement on treatments that can be useful in managing MG, there is no consensus on the choice and sequence of subsequent immunosuppressive treatment beyond AChEis for patients with uncontrolled gMG.[41, 72, 89] Evidence from registry-based and real-world studies has demonstrated that substantial proportions of patients with gMG receive treatment with corticosteroids and NSISTs, in addition to AChEis.[13, 25, 57, 90, 91]

Figure 7 shows routine treatments for MG taken since diagnosis and in the previous year as reported by patients participating in the ongoing MyRealWorld MG study.[92] The responses show that even though most patients have received an AChEi, this is not adequate to control their symptoms, as evidenced by high utilization of corticosteroids and NSISTs. In the same study, most patients (65%) reported side effects from treatment, including tiredness (53%), weight gain (45%), muscle twitches (44%), diarrhoea (42%), and mood swings (40%).[57] Across all side effects, the most commonly reported AE was infection (10%).[57] Despite ongoing treatment, evidence from multiple studies has demonstrated many patients continue to experience debilitating symptoms and moderate-to-severe HRQoL impairment.[13, 25, 27]

Figure 7. Routine treatments received by participants in the MyRealWorld MG study since diagnosis of MG and in the previous year (N=786)



AChEi, acetylcholinesterase inhibitor; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; PLEX, plasmapheresis or plasma exchange
Source: argenx, data on file[57]

5.6.2.1. AChEis (pyridostigmine)

Pyridostigmine (ATC code: N07AA02) has been used as a treatment for MG for over 50 years.[93] Pyridostigmine inhibits the hydrolysis of the ACh neurotransmitter in the synaptic cleft, increasing the number of interactions between the ACh and the AChR in the neuromuscular junction.[94] The efficacy of AChEis declines with progression of gMG and subsequent damage to the neuromuscular junction.[95] It is administered orally.

A Cochrane systematic review from 2014 found there is effectively no evidence from randomized controlled trials to support the common practice of using AChEis in patients with MG and that studies have failed to establish the optimal dosage and duration of treatment. Recommended dosing schedules are not based on studies but on expert opinion.[81] Pyridostigmine is considered suitable as a long-term treatment in patients with mild gMG, and as an adjunctive therapy in patients with severe disease who are also receiving immunosuppressive therapy.[89, 93] AChEis are short-acting and often need to be taken several times daily.[13, 57, 93] Additionally, the use of AChEis is constrained by the well-defined cholinergic side effects which limit the doses that can be tolerated, and additional treatment is often required to manage adverse effects. Atropine or other anticholinergic drugs may be necessary to counteract the muscarinic effects.[96] Generally, AChEis do not fully control gMG symptoms in most patients, and they must eventually add-on or switch to

long-term immunosuppressive therapies.[13, 57, 93] Pyridostigmine comes in 150 tablets of 60 mg of strength each, with an assumed dose of 720 mg daily for the analysis.

5.6.2.2. Corticosteroids (prednisone)

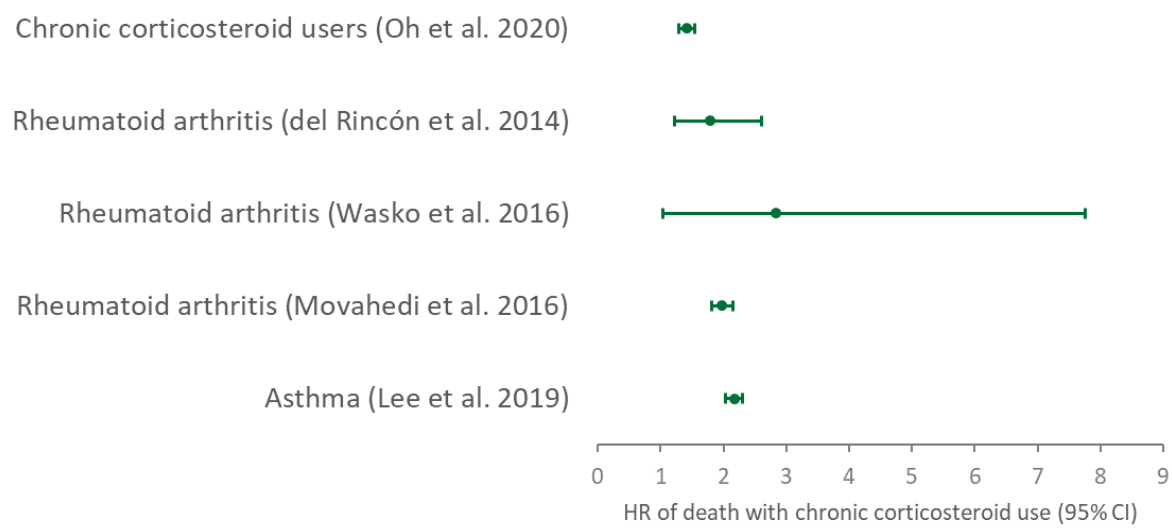
Corticosteroid treatment was the first widely used non-specific immunosuppressive therapy introduced in MG.[94] Corticosteroids are known to have a broad suppressive effect on immune response; however, their exact mechanism of action (MOA) in MG remains unknown.

Patients with gMG and an inadequate response to AChEis are most commonly treated with off-label oral corticosteroids, but their use is mainly based on observational studies and randomized trials with weak statistical power.[13, 57, 97] Limited evidence suggests that corticosteroids offer short-term benefit compared with placebo, and appear to have comparable efficacy to azathioprine and intravenous immunoglobulin (IVIg).[97] Importantly, the optimal dosing in gMG, particularly for long-term treatment has not been established.[94, 98] To mitigate the harmful long-term effects of corticosteroids, treatment strategies in gMG focus on reducing the steroid dose.[32, 89]

A retrospective study in 81 patients with AChR-Ab+ gMG found that daily low-dose prednisone did not provide sufficient disease control for nearly half of patients.[99] A satisfactory response (remission/minimal manifestations) was achieved by 44% of patients after 2 years of chronic, low-dose prednisone monotherapy (<10 mg/day after beginning treatment with 40–60 mg/day); only 59% of patients achieved satisfactory response by year 6. Adding immunosuppressants (azathioprine, methotrexate, or mycophenolate mofetil) to low-dose prednisone did not substantially improve response rates—of patients receiving combination therapy, only 50% achieved satisfactory response at year 2.

In addition to limited efficacy, the number and severity of adverse events (AEs) associated with corticosteroid treatment increases with duration of treatment and cumulative dosage.[89, 94] Studies in gMG patients indicate that the proportion of patients experiencing at least one side effect while on corticosteroid treatment ranges from 67% to 80%.[86, 100] Long-term use of corticosteroids is associated with serious AEs (SAEs) such as osteoporosis and bone fractures, hypothalamic–pituitary–adrenal axis suppression, hyperglycaemia/diabetes, cardiovascular disease and dyslipidaemia, myopathy, cataracts and glaucoma, and psychiatric disturbances.[32, 94, 100-102] In other autoimmune conditions, including rheumatoid arthritis and asthma, the chronic use of systemic corticosteroids has been associated with an increased risk of death and poor HRQoL (Figure 8).[103-106] The corticosteroid used in the analysis is Prednisolone (ATC code: S02BA03). It is administered by mouth, with 40 mg daily doses. It is provided in the form of 100 tablets of 5mg each.

Figure 8. Chronic use of systemic corticosteroids is associated with increased risk of death in patients with chronic diseases



HR, hazard ratio; CI, confidence interval
Sources: Oh, 2020;del Rincon, 2014; Wasko, 2016; Movahedi, 2016; Lee, 2019[103-107]

5.6.2.3. NSISTs

NSISTs are non-specific, systemic treatments that work in MG via broad immunosuppressive mechanisms.[108] Commonly prescribed NSISTs for gMG include azathioprine (ATC code: L04AX01), mycophenolate mofetil (ATC code: L04AA06), methotrexate (ATC code: L04AX03), cyclosporine (ATC code: L04AD01), and tacrolimus (ATC code: L04AD02).[41, 72, 88, 89] Only Jayempi (azathioprine) 10 mg/ml oral suspension has been approved in the EU for the treatment of gMG, but azathioprine tablets have not been approved.[109]

In prospective clinical trials, NSISTs have failed to show efficacy in patients with gMG.[82-87] Specifically, the addition of NSISTs failed to reduce corticosteroid dosages required to maintain disease control, and mycophenolate mofetil, tacrolimus, and methotrexate failed to show significant improvement vs placebo in QMG or MG-ADL.[82, 84, 85] In RCTs, the duration of remission with azathioprine was not significantly different from the control group.[86, 87, 110] A small study has also reported that azathioprine can take up to 3 years to demonstrate a significant steroid-sparing effect.[87]

Long-term studies of AEs associated with NSISTs are lacking in MG.[88, 98] Long-term use of NSISTs may be associated with SAEs including liver and bone marrow toxicities, malignancies, and increased risk for infection.[72, 98, 110, 111] According to guidelines, most patients require life-long immunosuppressive treatment, which predisposes patients to opportunistic infections, an increased risk of cancer, and other severe treatment-related side effects.[72, 89, 112, 113] Treatment with NSISTs also leads to impaired physical HRQoL, as revealed by significantly lower scores on the SF-36 Physical Component Scale, independent of disease activity ($p<0.05$).[12] Table 9 presents the NSITs included in the health economics analysis.

Table 9. NTSIs included in the analysis

NSTI	Method of administration	Strength	Size (units per pack)	Dose assumed in the analysis
Azatioprin (Mylan)	Oral	25	50	2.5 mg/kg daily
Methotrexat (Ebewe)	Oral	2.5	100	7.5mg once weekly
Ciclosporin (Ciqorin)	Oral	25	50	3mg/kg daily
Tacrolimus (Envarsus)	Oral	1	90	3 mg/day
Mycophenolate (Myfenax Teva)	Oral	500	100	1 g/day
Cyclophosphamide (Cyclophosphamid 2care4)	Oral	50	100	2 mg/kg daily

5.6.2.4. Intravenous immunoglobulin (IVIg)

IVIg is an effective therapy in other autoimmune diseases and has been used in gMG for treatment of acute exacerbations in refractory patients and for myasthenic crisis.[114] The IVIg used for the health economic analysis is Privigen (ATC code: J06BA02). It is provided in a vial with 20000 mg strength, with a dose used of 1000 mg/kg.

A Cochrane review of IVIg for gMG found that in three randomized, controlled trials, one showed some evidence of efficacy for IVIg versus placebo and two did not show a significant difference between IVIg and plasma exchange.[114] Another trial showed no significant difference between IVIg and oral methylprednisolone. Overall, there was insufficient evidence from RCTs to determine whether IVIg is efficacious.

IVIg therapy is burdensome for patients and healthcare systems. The treatment requires hospitalization; IVIg is administered slowly over several hours and may require a series of infusions over 3–5 days.[115] IVIg use also requires substantial premedication with antihistamines, corticosteroids, or nonsteroidal anti-inflammatory drugs to avoid IVIg-induced AEs, including neutropaenia.[116] IVIg is associated with the risk of acute renal failure and thromboembolic events, including stroke and myocardial infarction; caution must be exercised when administering IVIg to patients with risk factors.[117]

As a blood-derived product, IVIg may be subject to periodic supply issues, necessitating altered dosing schedules, including postponed infusions, increased intervals between doses, decreased dosages, and substitution of alternative therapy.[118]

5.7. Unmet medical need

Despite current treatments, many patients with gMG suffer substantial disease burden, including physical and mental symptoms that negatively impact their activities of daily living and HRQoL.[13, 25, 27, 31]

The muscle weakness experienced by patients with gMG severely impacts their day-to-day functioning, which can lead to difficulties with swallowing, vision, speech, breathing, and mobility, as well as extreme fatigue.[2-4, 27] Up to 20% of patients with gMG experience a myasthenic crisis, affecting the muscles that control breathing and resulting in life-threatening respiratory impairment.[4, 9] gMG has a profoundly negative impact on patients' HRQoL due to the debilitating physical impairments caused by muscle weakness[12, 13, 25], poor psychological well-being,

including significant depression, and anxiety[12, 27, 47, 53, 55], comorbid autoimmune conditions[13, 56], and treatment-related side effects, mainly due to the long-term use of immunosuppressive therapies.[12, 26]

There is no curative treatment for gMG[21] but patients who achieve clinical remission (ie, experiencing minimal symptoms) have HRQoL in line with healthy controls.[12] However, current treatment options are not satisfactory in many patients, are often used off-label, and carry the risk of significant adverse events.[49] According to a survey of 1,660 German patients with MG, only 8% of patients were in clinical remission and 25% were in pharmacological remission, more than 20% did not benefit from their medication at all, and 48% experienced treatment-related side effects, with 37% discontinuing therapy as a result.[49]

Even with ongoing treatment, patients continue to experience debilitating symptoms that profoundly impact their activities of daily living.[13, 25, 27, 31] Initial treatment of gMG is with AChEi monotherapy, but many patients do not achieve an adequate response, and most require another treatment during their disease.[13, 72, 81] Corticosteroids and NSISTs are used off label for treatment of gMG, without evidence from controlled studies. Broad immune suppression with these agents frequently yields burdensome adverse events and insufficient symptom relief.[12, 32, 81, 98, 111, 119] Long-term use of NSISTs puts patients at risk for serious adverse events that can include liver and bone marrow toxicities, malignancies, and increased risk for infection,[98, 110, 111] while long-term immunosuppression predisposes patients to opportunistic infections, lymphoma, and other severe treatment-related side effects.[72, 89]

There is an urgent unmet need for more effective, well-tolerated treatments for gMG that target the disease process to control symptoms with few side effects to improve each patient's quality of life.

Specifically, patients who respond inadequately to current treatments need options that:

- Have proven efficacy supported by well designed, randomized controlled trials
- Provide more control of symptoms and better tolerability than corticosteroids and NSISTs
- Target the underlying disease pathophysiology rather than broadly suppressing the immune system
- Can be used in the broader gMG population, including those who are non-refractory but insufficiently controlled on currently available treatment options.

5.8. The intervention

Efgartigimod (ATC code: L04AA58) is a first-in-class human IgG1 antibody Fc-fragment that blocks the neonatal Fc receptor (FcRn).[28] FcRn has a specific role in IgG homeostasis by recycling IgG, rescuing it from lysosomal degradation.[120] Recycling by FcRn is why IgGs, including pathogenic IgG autoantibodies, have a longer half-life and higher concentration than other immunoglobulins that are not recycled by FcRn.[120, 121] By blocking FcRn, treatment with efgartigimod leads to the degradation of circulating disease-causing pathogenic IgG autoantibodies without impacting other immunoglobulins that are not recycled by FcRn[120-122] Therefore, FcRn blocking does not result in widespread immunosuppression, in contrast to many therapies in routine clinical use for the treatment of gMG.[121, 122] Efgartigimod reduces all IgG subtypes; allowing treatment of a broad gMG patient population, including those who are AChR-Ab+, MuSK-Ab+, and LRP-Ab+.[123]

The recommended dose of efgartigimod is 10 mg/kg as a 1-hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks. Subsequent treatment cycles are administered according to clinical response and evaluation. Some patients experience an extended

clinical benefit, which could result in fewer treatment cycles per year.[28] It is available in vials of 400 mg strength each.

6. Literature search and identification of efficacy and safety studies

6.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical and non-clinical evidence (eg, economic evaluations, healthcare resource use [HCRU], costs, and utilities) for the use of efgartigimod and other interventions of interest in the treatment of adult patients with gMG. The clinical searches identified randomized controlled trials (RCTs) and open-label extensions (OLEs) of RCTs that assessed and reported the clinical efficacy of relevant gMG treatments. Adverse event (AE) data from these clinical trials was also captured. In addition to published cost-effectiveness (CE) analyses, the non-clinical searches identified studies that reported healthcare cost, resource utilization estimates, and utilities pertinent to gMG. Among those studies, there were four non-clinical full publications and one conference abstract. Only one record reported an economic evaluation, but the data informing the analysis were from only six patients treated with rituximab at a single centre. Therefore, no economic information was usable in the CE analysis. Some of the identified studies reported information on QoL utilities, but this was not included in the cost-effectiveness analysis due to the availability of EQ-5D data directly from the ADAPT study. The literature search was conducted systematically and transparently and in accordance with international standards,[124] per the DMC Methods Guide for Assessing New Pharmaceuticals.[125] The process of study identification and de-duplication is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.[126] Databases and search strategy.

For details of the search strategies, see Appendix A: Systematic literature review: Treatment of gMG.

6.2. List of relevant studies

The process for identifying and selecting relevant studies is detailed in Appendix A: Systematic literature review: Treatment of gMG.
ADAPT is the only included trial considered relevant to this submission because it compares efgartigimod add-on therapy plus standard of care (corticosteroids and NSISTs) with placebo plus standard of care (Table 10). Other interventions included in the SLR (rituximab, eculizumab, and long-term use of IVIG and PLEX) are not relevant to the clinical question because their use is limited in Denmark and/or the treatments are not included in the treatment guidelines. The characteristics of the ADAPT trial are presented in Appendix B: Main characteristics of included studies.

Table 10. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question

Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial (Howard JF, et al. Lancet Neurol 2021; 20: 526–36)[28, 127]	ADAPT	NCT03669588	Study completed (September 2018–April 2020)	Efgartigimod vs SOC [28, 127]
A Long-Term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Trial of ARGX-113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness [128]	ADAPT+	NCT03770403	Actual Study Start Date March 1, 2019 Actual Primary Completion Date: June 23, 2022 Actual Study Completion Date: June 30, 2022	Safety and Tolerability as measured by the incidence of treatment emergent (serious) adverse events in the AChR-positive population[128]

7. Efficacy and Safety

7.1. Efficacy and safety of efgartigimod compared to SoC in the treatment of adult patients with anti AChR+ gMG.

7.1.1. Relevant studies

The proof of concept for efgartigimod as a treatment for gMG was established in an exploratory phase 2 study in 24 patients with gMG.[123] The clinical development program for efgartigimod in gMG includes five phase 3 studies: ADAPT, ADAPT+, ADAPT SC, ADAPT SC+, and ADAPT NXT (Table 11).

Results from ADAPT and interim results from ADAPT+ are relevant for this application. Data are presented for patients with AChR-Ab+ gMG treated with efgartigimod IV during the ADAPT and ADAPT+ studies since these are the phase 3 RCTs providing data relevant to the currently approved indication and formulation of efgartigimod.

Table 11. Summary of clinical trial program for efgartigimod in gMG

Study argenx study no. (Clinical trials ID)	N	Study type	Efgartigimod formulation	Primary endpoint
Efgartigimod in gMG ARGX-113-1602 (NCT02965573)	24	Phase 2, randomized, double-blind, placebo-controlled, multicentre	IV	Safety & tolerability

Study argenx study no. (Clinical trials ID)	N	Study type	Efgartigimod formulation	Primary endpoint
ADAPT ARGX-113-1704 (NCT03669588)	167	Phase 3, randomized, double-blind, placebo-controlled, multicentre	IV	Efficacy, MG-ADL responders in AChR-Ab+ patients
ADAPT+ ARGX-113-1705 (NCT03770403)	151	Phase 3, long-term, single-arm, open-label, multicentre	IV	Safety & tolerability in AChR-Ab+ patients
ADAPT SC ARGX-113-2001 (NCT04735432)	111	Phase 3, randomized, open-label, parallel-group, multicentre	SC vs IV	Change (%) from baseline in total IgG levels (SC vs IV)
ADAPT SC+ ARGX-113-2002 (NCT04818671)	201	Phase 3, long-term, single-arm, open-label, multicentre	SC	Long-term safety & tolerability
ADAPT NXT ARGX-113-2003 (NCT04980495)	72	Phase 3b, randomized, open-label, parallel-group, multicentre	IV (different dosing regimens)	Efficacy, MG-ADL total score change from baseline
Efgartigimod IV in children with MG ARGX-113-2006 (NCT04833894)	12	Phase 2/3, open-label uncontrolled (children 2–<18 years old), multicentre	IV	Pharmacokinetics, pharmacodynamics, safety

AChR-Ab+, acetylcholine receptor autoantibody positive; IgG, immunoglobulin G; MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Source: ClinicalTrials.gov, 2022

7.1.2. Overview of ADAPT

7.1.2.1. Study design

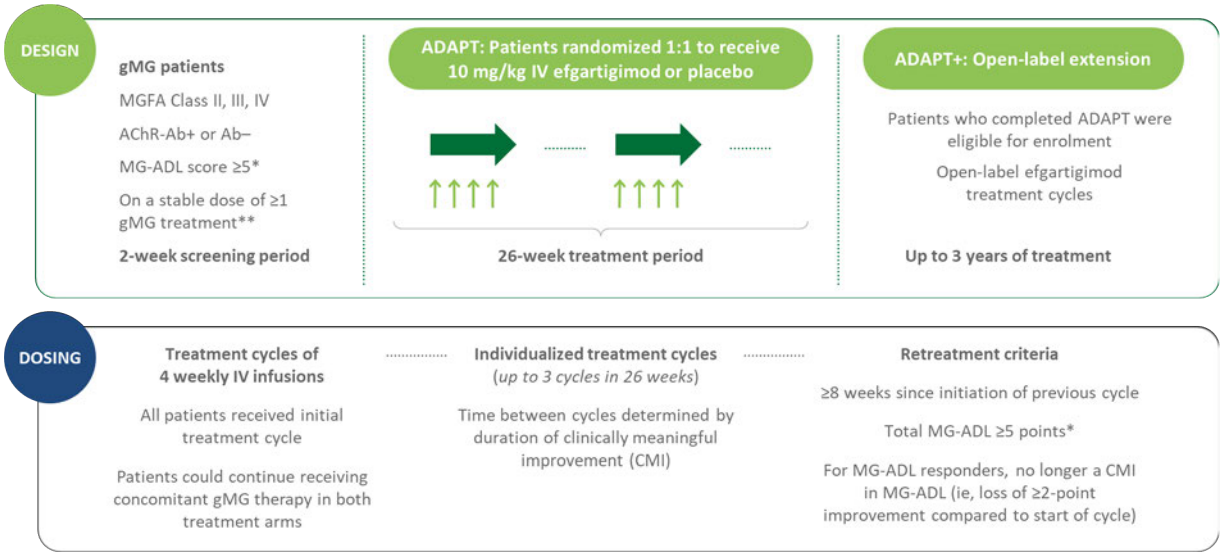
ADAPT was a randomized, double-blind, placebo-controlled, multicentre, phase 3 trial designed to evaluate the efficacy, safety, and tolerability, of efgartigimod, as well as impact on quality of life and normal daily activities, in patients with gMG.[28]

Patients were recruited from 56 centres in Europe, North America, and Japan.[28] After a 2-week screening period, patients were randomized in a 1:1 ratio to receive 4 infusions of efgartigimod 10 mg/kg or matching placebo administered at weekly intervals, starting at baseline (Figure 9).[28] All patients received an initial cycle; subsequent cycles were administered over a 26-week treatment period according to individual clinical response and no sooner than 8 weeks after the start of the previous cycle. Therefore, a maximum of three cycles were possible in the 26-week study.

Patients were considered eligible for another cycle when their MG-ADL score was ≥5 (with >50% of the MG-ADL score due to non-ocular symptoms) and, if the patient was an MG-ADL responder, when they no longer had a clinically meaningful decrease (≥2-point improvement in total MG-ADL score) compared with baseline.[28] Patients who completed the study or could not complete a cycle before

study end (retreatment after day 126) were able to roll over to the open-label extension study ADAPT+ (see Section 7.1.6).

Figure 9. ADAPT study design



AChR-Ab+/–, acetylcholine receptor autoantibody positive/negative; gMG, generalized myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGFA, Myasthenia Gravis Foundation of America
*50% of the score attributed to non-ocular items

7.1.2.2. Patient eligibility

Adult patients (≥18 years old) diagnosed with gMG were eligible for enrolment in ADAPT if their disease was categorized as Myasthenia Gravis Foundation of America (MGFA) class II to IV and they had an MG-ADL score of ≥5, with 50% of the score caused by non-ocular symptoms.[28] All serotypes of gMG were eligible for enrolment, including AChR-Ab+, AChR-Ab-, and MuSK (only the efficacy results from the AChR-Ab+ population are presented in line with the approved indication). Patients were required to be on a stable dose of at least one concomitant therapy for gMG before screening and throughout the trial, but there was no requirement to have received or discontinued use of any specific therapy (no dose change for 2 weeks prior to screening), steroids (at least 3 months of treatment, no dose change for 1 month), or NSISTs (at least 6 months of treatment, no dose change for 3 months) were allowed alone or in combination.

Key exclusion criteria included:

- Treatment with IVIg or PLEX within 1 month of screening
- Treatment with rituximab or eculizumab in the 6 months before screening
- Thymectomy in 3 months before screening
- MGFA Class I and V patients
- Active hepatitis B or C, HIV, severe infections, or malignancies
- Low IgG serum levels (<6 g/L) at screening
- Pregnancy
- History of autoimmune disease other than MG that would interfere with an accurate assessment of clinical symptoms

7.1.2.3. Assessments

Efficacy and HRQoL were assessed via multiple validated physician- and patient-reported instruments for MG, as detailed in Table 12. Minimal clinically important differences (MCID) for the scales, which were used to define responders in the efficacy analyses for ADAPT and ADAPT+, are noted in the table.

The generic EQ-5D-5L visual analogue scale (VAS) was also completed by patients. The EQ VAS records a patient's self-rated health on a vertical VAS, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS is a quantitative measure of health outcomes that reflects the patient's own judgement; higher scores indicate better HRQoL.

Efficacy assessments were done weekly for 8 weeks after the initiation of each cycle and then every 2 weeks, for up to 26 weeks.[28, 127]

Table 12. Summary of MG assessment scales and MCID used in ADAPT to evaluate efficacy and HRQoL

Scale	No. items	Score range	Interpretation	MCID	Outcomes measured
MG-ADL (patient reported, physician recorded)	8	0–24	Higher scores indicate worse functioning and disability, more severe disease	≥2 point reduction	• Talking • Chewing • Swallowing • Breathing • Impairment of ability to brush teeth or comb hair • Impairment of ability to arise from a chair • Double vision • Eyelid droop
QMG (physician assessed, requires spirometer and dynamometer)	13	0–39	Higher scores indicate worse functioning and disability, more severe disease	≥3 point reduction	• Double vision • Ptosis • Facial muscles • Swallowing • Speech • Right/left arm outstretched • Forced vital capacity • Right/left hand grip • Head lift • Right/left leg outstretched

Scale	No. items	Score range	Interpretation	MCID	Outcomes measured
MGC (patient and physician assessed)	10	0–50	Higher scores indicate worse functioning and disability, more severe disease	≥3 point reduction	• Ptosis • Double vision • Eye closure • Talking • Chewing • Swallowing • Breathing • Neck flexion or extension • Shoulder abduction • Hip flexion
MG-QoLR (patient completed)	15	0–30	Higher scores indicate worse HRQoL, more severe disease	Depends on disease severity	• Frustration • Vision • Eating • Social activities • Hobbies and fun activities • Family • Spontaneity • Work performance • Speech • Personal independence • Depression • Walking • Mobility in public places • Feeling overwhelmed • Personal grooming

HRQoL, health-related quality of life; MCID, minimally clinical important difference; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite scale; MG-QoL15R, Myasthenia Gravis 15-item Quality of Life revised scale; QMG, Quantitative Myasthenia Gravis
Source: Barnett et al, 2018[129]; Thomsen et al, 2020[30]

7.1.2.4. Outcomes

The primary efficacy endpoint of ADAPT was the proportion of AChR-Ab+ patients who were MG-ADL responders in the first treatment cycle.[28] An MG-ADL responder was defined as a patient with a ≥2-point improvement (ie, reduction) in MG-ADL score that lasted for at least 4 consecutive weeks, with the first improvement occurring by week 4 of the first cycle (ie, 1 week after the fourth infusion). Further details concerning the secondary endpoints are described in Appendix D: Efficacy and safety results per study.

Secondary endpoints were assessed in hierarchical order as follows:[28, 127]

1. Proportion of QMG responders in the AChR-Ab+ population, defined as a ≥3-point improvement in the total QMG score for at least 4 consecutive weeks, with the first improvement occurring by week 4 of cycle 1.

2. Proportion of MG-ADL responders in the overall population (ie, AChR-Ab+ and AChR-Ab- patients) in the first treatment cycle. *These results are not shown in the application as this population includes AChR-Ab- patients.*
3. Proportion of time AChR-Ab+ patients showed a clinically meaningful improvement (CMI) in MG-ADL score, up to day 126.
4. Time from day 28 to qualify for retreatment in the AChR-Ab+ population, defined as the patient having a <2-point reduction in the MG-ADL total score and a MG-ADL total score of ≥5 points, with >50% of the total score due to non-ocular symptoms.
5. Proportion of early MG-ADL responders in the AChR-Ab+ population in the first treatment cycle, defined as MG-ADL responders with first MG-ADL improvement of ≥2 points occurring by week 2.

The efficacy of efgartigimod was assessed in additional exploratory analyses of MG-ADL, QMG and MGC scores, and HRQoL via the generic EQ-5D-5L and the disease-specific MG-QoL15R. Predefined exploratory endpoints assessed time to onset of effect; magnitude of effect, including proportion of patients achieving minimal symptom expression (defined as MG-ADL score of 0 or 1) and the proportion of patients with increasing levels of MG-ADL and QMG improvement in each cycle; duration of response in MG-ADL responders; efficacy of second treatment cycle; and the change in MGC and MG-QoL15R scores.[28]

Safety was assessed through incidence of AEs and changes in clinical laboratory values and vital signs.[28] Tertiary endpoints included pharmacodynamics and immunogenicity.[28]

7.1.2.5. Statistical analyses

Efficacy analyses were performed in the modified intention-to-treat (ITT) population, which included all randomized patients who had a valid baseline MG-ADL assessment and at least one post-baseline MG-ADL assessment.[28] Safety analyses were evaluated in all patients who received at least one dose or part of a dose of study treatment.[28, 127]

The primary endpoint was tested using a two-sided exact test using a logistic regression model with baseline MG-ADL total score as a covariate and the following three stratification factors as variables: AChR-Ab status (positive vs negative), NSISTs (taking vs not taking), and Japanese nationality (yes vs no).[28] The treatment effect is presented as an odds ratio (OR) with 95% confidence interval (CI) and two-sided p value. If the primary endpoint met significance at the 5% two-sided α level, secondary endpoints were tested at a 5% two-sided significance level in hierarchical order using a fixed sequence approach.[28, 127]

7.1.3. Overview of ADAPT+

7.1.3.1. Study design

ADAPT+ is an ongoing, open-label, single-arm, multicentre, 3-year extension of ADAPT designed to evaluate the long-term safety, tolerability, and efficacy of efgartigimod for the treatment of gMG.[128] Study results presented in this dossier include safety and efficacy analyses from the last data cut-off of 31 Jan2022.

ADAPT+ follows the dose regimen of ADAPT; patients received 4 doses of efgartigimod 10 mg/kg administered at weekly intervals.[128] After the fourth infusion (first cycle), patients were monitored for safety and efficacy. Subsequent treatment cycles were implemented according to clinical response, with an interval of at least 4 weeks from the last infusion. For each patient, the first visit of ADAPT+ was intended to coincide with the last visit of ADAPT.

7.1.3.2. Patient eligibility

Patients who completed ADAPT or patients who required retreatment but could not complete a treatment cycle within the timeframe of ADAPT were eligible for enrolment in ADAPT+.[128] Patients who discontinued ADAPT for reasons other than pregnancy, rescue therapy or an AE or SAE were also potentially eligible to enter ADAPT+, or patients who had a temporary treatment interruption. Patients were required to be on a stable dose of their concomitant gMG treatment (ie, AChEis, steroids, and NSISTs) prior to study entry.

7.1.3.3. Outcomes

The primary and secondary objectives of ADAPT+ are to evaluate the long-term safety and tolerability of efgartigimod 10 mg/kg in AChR-Ab+ patients and in the overall population (ie, AChR-Ab+ and AChR-Ab- patients), respectively, via the incidence and severity of AEs, serious AEs, vital signs, electrocardiograms (ECGs), and laboratory assessments throughout the study.[128] Exploratory objectives include evaluation of efficacy via the MG-ADL and QMG, pharmacodynamics, and immunogenicity. Exploratory efficacy endpoints were assessed over 1 year via:

- Total MG-ADL score changes at each cycle compared with baseline of the first cycle in AChR-Ab+ patients and in the overall population (AChR-Ab+ and AChR-Ab- patients)
- Total QMG score changes at each cycle compared with baseline of the first cycle in AChR-Ab+ patients and in the overall population (AChR-Ab+ and AChR-Ab- patients)

7.1.3.4. Statistical analysis

Safety analyses were evaluated in all patients who received at least one dose or part of a dose of study treatment.[128] As with ADAPT, the efficacy of efgartigimod has been assessed in ADAPT+ by mean changes in MG-ADL and QMG score, each compared with the corresponding cycle baseline in the AChR-Ab+ population, the AChR-Ab- population, and the overall population.

7.1.4. Efficacy and safety - ADAPT

7.1.4.1. Baseline patient demographics and disposition

A total of 167 patients were enrolled and randomized to receive efgartigimod (n=84) or placebo (n=83); 152 (91%) patients completed treatment and 156 (93.4%) completed the study.[28, 127] The majority of patients who discontinued from treatment did so in cycle 1. Four (2.4%) patients discontinued treatment in cycle 1 and continued to participate in follow-up study visits and completed the study: 1 (1.2%) patient in the efgartigimod group and 3 (3.6%) patients in the placebo group.[127]

Further details are listed in Appendix C: Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

7.1.4.2. Primary endpoint: MG-ADL responders in cycle 1 (AChR-Ab+ population)

MG-ADL responders were defined as having a ≥2-point improvement for at least 4 consecutive weeks during the first treatment cycle. The MCID for the MG-ADL has been validated in previous studies as a 2-point change.[30]

The primary endpoint in ADAPT was met. A statistically significantly higher proportion of AChR-Ab+ patients in the efgartigimod group were MG-ADL responders during cycle 1 compared with the placebo group (67.7% [44/65) vs 29.7% [19/64]; OR 4.95 [95% CI 2.21, 11.53]; p<0.0001; Figure 10).[28, 127]

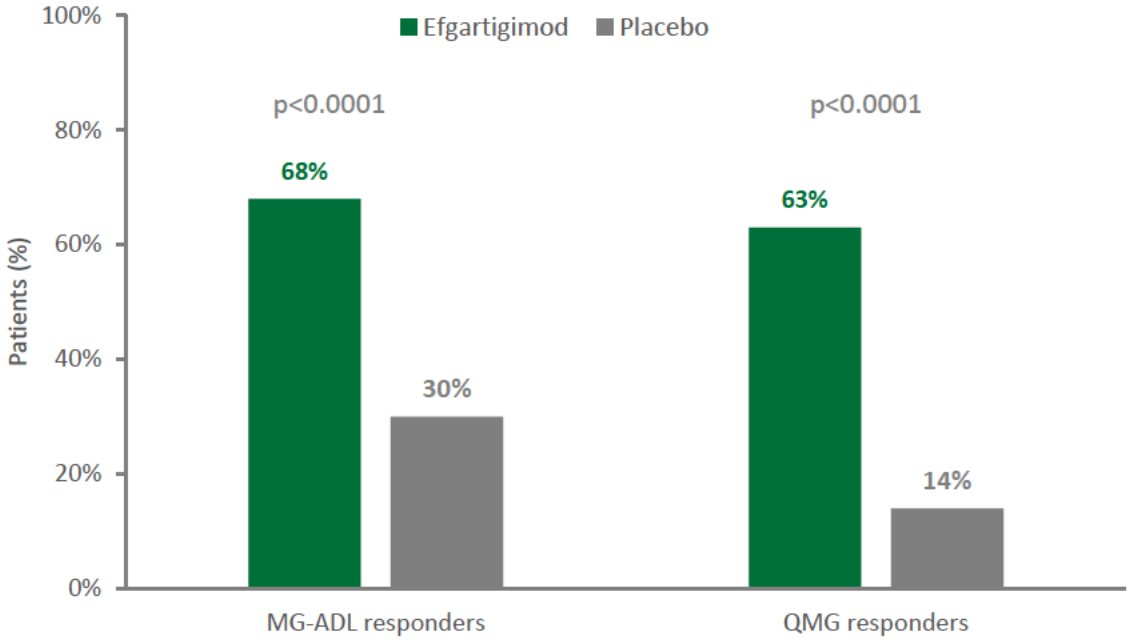
7.1.4.3. QMG responders in cycle 1 (AChR-Ab+ population)

QMG responders were defined as having a ≥3-point improvement for at least 4 consecutive weeks during the first cycle. The MCID for the QMG has been validated in previous studies as a 3-point change.[30]

A statistically significantly higher proportion of AChR-Ab+ patients in the efgartigimod group were QMG responders during cycle 1 compared with the placebo group (63.1% [41/65] vs 14.1% [9/64]; OR 10.84 [95% CI 4.18, 31.20]; p<0.0001; Figure 10).[28, 127]

The higher proportion of both MG-ADL and QMG responders in the efgartigimod treatment group during cycle 1 demonstrates a consistency of improvement across different scales that measure the manifestations of gMG. The MG-ADL is a patient-reported outcome (PRO) questionnaire focused on gMG symptoms and impairment of bodily functions, while the QMG is assessed quantitatively by a physician using a dynamometer and spirometer and aims to measure disease severity via muscle strength and fatigue (Table 12). MG-ADL and QMG scores have shown correlation with each other.[129]

Figure 10. Proportion of MG-ADL and QMG responders, AChR-Ab+ population, cycle 1



AChR-Ab+, acetylcholine receptor autoantibody positive; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QMG, Quantitative Myasthenia Gravis scale
Source: Howard et al, 2021[28]; argenx, 2020[127]

7.1.4.4. ADAPT: safety and tolerability

The safety population included all patients who received at least one dose or part of a dose of study treatment.[28, 127] Overall, 252 AEs in 65 (77.4%) patients in the efgartigimod group and 270 AEs in 70 (84.3%) patients in the placebo group were reported.

7.1.4.4.1. Treatment-emergent AEs

The most common TEAEs are presented in Table 13 by system organ class.[127] Overall, 65 (77%) of 84 patients in the efgartigimod group and 70 (84%) of 83 in the placebo group had TEAEs.[28] The most frequently reported TEAEs in the efgartigimod group were headache (29%), nasopharyngitis

(12%), nausea (8%), diarrhoea (7%), upper respiratory tract infections (11%), and urinary tract infections (10%). Most AEs were mild or moderate in severity; nine (11%) and eight (10%) patients in the efgartigimod and the placebo groups, respectively, experienced severe events (grade ≥3). There were no clinically meaningful changes in haematology or chemistry parameters, including albumin, electrocardiograms, or vital signs in either group.[28]

Few patients discontinued treatment due to a TEAE: 3 (3.6%) patients in the efgartigimod group and 2 (2.4%) patients in the placebo group.[127] Administration of rescue therapy resulted in the discontinuation of treatment in 1 (1.2%) patient in the efgartigimod group and 2 (2.4%) patients in the placebo group.[127] Further details concerning the emergence of serious adverse events are presented in Appendix E: Safety data for intervention and comparator(s).

Table 13. Common (≥5% in any group) TEAEs by system organ class and preferred term, n (%)

TEAE	Efgartigimod (n=84)	Placebo (n=83)
≥1 TEAE	65 (77.4)	70 (84.3)
Infections and infestations	39 (46.4)	31 (37.3)
Bronchitis	5 (6.0)	2 (2.4)
Nasopharyngitis	10 (11.9)	15 (18.1)
Upper respiratory tract infection	9 (10.7)	4 (4.8)
Urinary tract infection	8 (9.5)	4 (4.8)
Nervous system disorders	29 (34.5)	32 (38.6)
Dizziness	3 (3.6)	5 (6.0)
Headache	24 (28.6)	23 (27.7)
Gastrointestinal disorders	19 (22.6)	20 (24.1)
Diarrhoea	6 (7.1)	9 (10.8)
Nausea	7 (8.3)	9 (10.8)
Musculoskeletal and connective tissue disorders	17 (20.2)	18 (21.7)
Injury, poisoning, and procedural complications	10 (11.9)	12 (14.5)
Skin and subcutaneous tissue disorders	9 (10.7)	8 (9.6)
General disorders and administration site conditions	8 (9.5)	13 (15.7)
Respiratory, thoracic, and mediastinal disorders	7 (8.3)	13 (15.7)
Cough	3 (3.6)	5 (6.0)
Oropharyngeal pain	3 (3.6)	7 (8.4)

TEAE	Efgartigimod (n=84)	Placebo (n=83)
Eye disorders	7 (8.3)	4 (4.8)
Vascular disorders	7 (8.3)	6 (7.2)
Hypertension	3 (3.6)	6 (7.2)

Source: Howard et al, 2021 [28]; argenx, 2020[127]

7.1.4.4.2. Exposure

The mean (SD) duration in the study (ie, period starting from the first dose until end of study) was 151.5 (22.4) days in the efgartigimod group and 151.7 (29.6) days in the placebo group. The cumulative duration of treatment exposure was 34.9 patient-years for the efgartigimod group and 34.5 patient-years for the placebo group.

Overall, 606 efgartigimod infusions were administered over 154 cycles compared with 562 placebo infusions administered over 143 cycles. Patients in either group received a maximum of 3 cycles. In the efgartigimod group 21 patients received 1 cycle, 56 patients received 2 cycles, and 7 patients received 3 cycles. In the placebo group, 27 patients received 1 cycle, 54 patients received 2 cycles, and 3 patients received 3 cycles.

7.1.5. ADAPT: Summary

ADAPT was designed to assess the efficacy and safety of efgartigimod in a broad population of gMG patients. The patient population enrolled in the study is representative of the gMG patient population in terms of age, gender, and prior and ongoing use of gMG therapies. Overall, there were no notable differences between treatment arms in patient demographics, baseline characteristics, disease characteristics, or medical history. As shown by the MG-ADL and QMG scores at baseline, all participants were symptomatic despite their current treatment for gMG.

The efficacy analyses used in ADAPT are validated clinical outcome scales and the endpoints were stringent, combining the accepted thresholds of MCID with the requirement for improvement to be sustained for at least 4 consecutive weeks. Results in AChR-Ab+ patients show clinically meaningful and sustained improvements in clinical symptoms and HRQoL across multiple treatment cycles, as assessed by four MG scales (MG-ADL, QMG, MGC, MG-QoL15R). Additional analyses in AChR-Ab+ patients demonstrated a quick onset of response, which occurred mostly within 2 weeks of starting treatment with efgartigimod, and a substantial magnitude of effect, with more patients achieving increasing thresholds of MG-ADL and QMG improvement in the efgartigimod group than the placebo group. Efgartigimod's individualized patient-dosing approach allowed patients with ongoing clinical benefit to extend the time to initiation of the next cycle. Around one-third of AChR-Ab+ patients experienced an extended clinical benefit, which could result in fewer treatment cycles per year.

Efgartigimod was well tolerated, with a lower proportion of AEs reported in patients treated with efgartigimod than with placebo. Most TEAEs were mild-to-moderate in severity. Notably, serious AEs were reported in a lower proportion of patients in the efgartigimod group compared with the placebo group.

Overall, results from ADAPT have demonstrated that efgartigimod is effective in AChR-Ab+ gMG patients, providing significant, rapid, and durable clinical benefit. Efgartigimod was efficacious regardless of concomitant gMG therapy and meets the current unmet need for patients with gMG who have an inadequate response to AChEis, corticosteroids, and/or NSISTs.

7.1.6. Efficacy and safety -ADAPT+

7.1.6.1. Baseline patient demographics and disposition

Overall, 151 patients from ADAPT rolled over into ADAPT+, and 145 patients have received at least 1 dose of efgartigimod as of the January 2022 data cutoff date: 77 patients were from the efgartigimod group (ie, efgartigimod-efgartigimod cohort), and 68 patients were from the placebo group (ie, placebo-efgartigimod cohort).[128] A total of 111 patients were AChR-Ab+ and 34 patients were AChR-Ab-.

Baseline patient demographics and characteristics are summarized in Appendix C: Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety (Table 44.[128]).

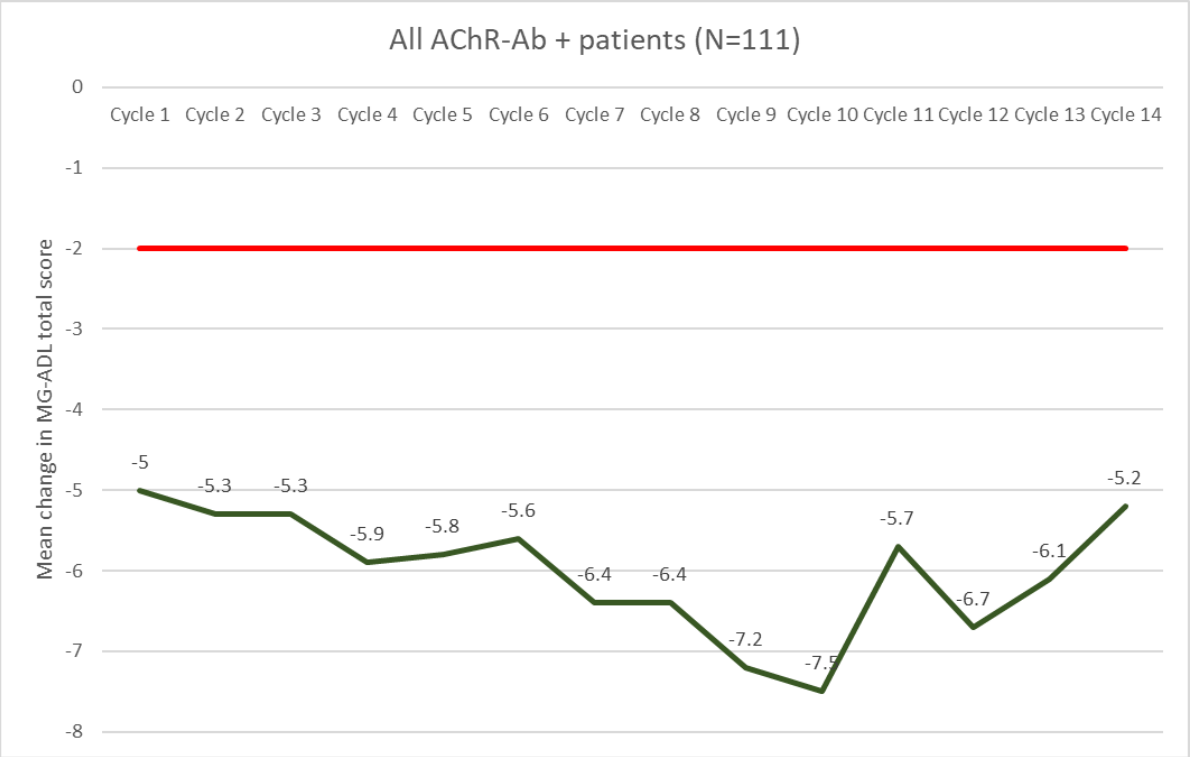
7.1.6.2. Treatment duration

At data cutoff, the mean (SD) total duration of treatment and follow up was 548.0 (231.79) days, resulting in 217.55 patient-years of observation.[128] The median (range) duration of treatment combined with follow-up was 588 (40–924) days. Treatment combined with follow-up was: <6 months for 14 (9.7%) patients; 6 to <12 months for 18 (12.4%) patients; 12 to <18 months for 23 (15.9%) patients; 18 to <24 months for 49 (5.033.8%) patients; 24 to <30 months for 38 (26.2%) patients, and 30 to <36 months for 3 (2.1) patients.

7.1.6.3. Mean change in MG-ADL total score

The mean change from baseline in MG-ADL total score at week 3 of cycles 1 through 9 in the efgartigimod AChR-Ab+ population is shown in Figure 11.[128] The week-3 time point was selected due to the limited number of scheduled visits (ie, no visits were scheduled at weeks 4, 5, and 6). The mean (SE) change from cycle baseline in the MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 was −5.0 (0.33) in C1, −5.3 (0.36) in C2, −5.3 (0.37) in C3, −5.9 (0.42) in C4, −5.8 (0.40) in C5, −5.6 (0.43) in C6, −6.4 (0.48) in C7, −6.4 (0.50) in C8, −7.2 (0.49) in C9, −7.5 (0.65) in C10, -5.7 (0.88) in C11, -6.7 (0.72) in C12, -6.1 (0.94) in C13, and -5.2 (1.08) in C14 . The number of total patients (N) slightly differs from the number of participants for whom the observation occurred (n). For all cycles (except cycle 11), >90% and 50% of patients in the AChR-Ab+ population had a minimum point improvement from cycle baseline in the MG-ADL total score of 2 and 5 points, respectively.

Figure 11. ADAPT+: Mean change from cycle baseline in MG-ADL total score in AChR-Ab+ and AChR-Ab- patients



No. patients for each received cycle (n):

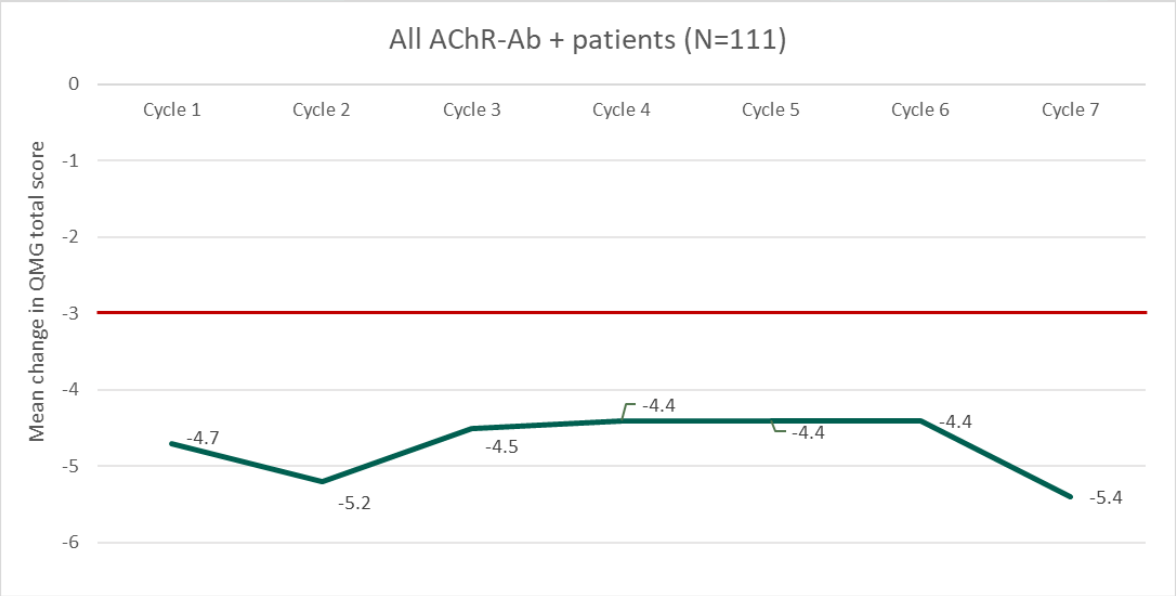
108	97	89	80	74	71	58	53	45	36	23	19	15	13

MG-ADL, Myasthenia Gravis Activities of Daily Living scale
Red line at –2 represents the clinically meaningful decrease (≥2-point improvement in total MG-ADL score). N=number of participants in the analysis set; n=number of participants for whom the observation occurred.
Source: argenx, 2022[128]

7.1.6.4. Mean change in QMG score

The mean change from baseline in QMG score at week 3 of cycles 1 through 7 in the efgartigimod AChR-Ab+ population is shown in Figure 12.[128] The mean (SE) change from cycle baseline in the QMG total score in the total efgartigimod AChR-Ab+ population at week 3 was −4.7 (0.41) in C1, −5.2 (0.42) in C2, −4.5 (0.52) in C3, −4.4 (0.60) in C4, −4.4 (0.56) in C5, −4.4 (0.77) in C6, and −5.4 (0.70) in C7. The mean change from baseline in QMG score was numerically greater, for the first 5 cycles, in AChR-Ab+ patients with prior exposure to efgartigimod in ADAPT (data not shown).

Figure 12. Mean change from cycle baseline in QMG total score in AChR-Ab+ patients



No. patients for each cycle (n):

					100		90				73	57	45	34	23
					71	58	53	45	36	23	19	15	13		

QMG, Quantitative Myasthenia Gravis scale
Red line at –3 represents the clinically meaningful decrease (≥3-point improvement in total QMG score). N=number of participants in the analysis set; n=number of participants for whom the observation occurred.
Source: argenx, 2022 [128]

7.1.6.5. Safety and tolerability: ADAPT+

In the following section, the safety data for the ADAPT+ study are presented. Further details are shown in Appendix E: Safety data for intervention and comparator(s).

7.1.6.5.1. Exposure

A total of 145 patients received at least 1 dose (or part of a dose) of efgartigimod by the interim cut-off date of Jan 2022.[128] The maximum number of cycles completed at the cutoff date was 17. Median cycle durations between cycle 1 and cycle 16 ranged from 50.0 and 70.0 days in AchR-Ab+ patients.

7.1.6.5.2. Treatment-emergent AEs

A summary of the frequently reported TEAEs (≥3 patients) by system organ class is provided in Table 14.[128] The most commonly reported TEAEs were headache in 14 (9.7%) patients, nausea herpes zoster and infusion related reaction in 4 (2.8%) patients each. TEAEs of severity grade ≥3 occurred in 38 (26.2%) patients: 21 (27.3%) patients in the efgartigimod-efgartigimod cohort and 17 (25.0%) patients in the placebo efgartigimod cohort. Events with severity grade ≥3 reported in ≥2 patients in either cohort were COVID-19 pneumonia, pneumonia, urinary tract infection, headache, and MG.

Table 14. Frequently reported TEAEs (≥3 patients in any group) by system organ class in ADAPT+, n (%)

TEAE	EFG-EFG (N=77)	PBO-EFG (N=68)	Total EFG (N=145)
≥1 TEAE	69 (89.6)	54 (79.4)	123 (84.8)
Blood and lymphatic system disorders	5 (6.5)	4 (5.9)	9 (6.2)
Anaemia	3 (3.9)	1 (1.5)	4 (2.8)
Gastrointestinal disorders	19 (24.7)	15 (22.1)	34 (23.4)
Abdominal pain upper	1 (1.3)	2 (2.9)	3 (2.1)
Diarrhoea	7 (9.1)	7 (10.3)	14 (9.7)
Nausea	6 (7.8)	3 (4.4)	9 (6.2)
Toothache	2 (2.6)	2 (2.9)	4 (2.8)
Vomiting	4 (5.2)	3 (4.4)	7 (4.8)
General disorders and administration site conditions	16 (20.8)	15 (22.1)	31 (21.4)
Asthenia	1 (1.3)	3 (4.4)	4 (2.8)
Influenza like illness	3 (3.9)	0	3 (2.1)
Pyrexia	5 (6.5)	6 (8.8)	11 (7.6)
Infections and infestations	41 (53.2)	39 (57.4)	80 (55.2)
Bronchitis	4 (5.2)	0	4 (2.8)
COVID-19	12 (15.6)	6 (8.8)	18 (12.4)
COVID- 19 pneumonia	2 (2.6)	1 (1.5)	3 (2.1)
Cystitis	1 (1.3)	2 (2.9)	3 (2.1)
Herpes zoster	6 (7.8)	1 (1.5)	7 (4.8)
Nasopharyngitis	8 (10.4)	12 (17.6)	20 (13.8)
Oral herpes	3 (3.9)	0	3 (2.1)
Pharyngitis	1 (1.3)	2 (2.9)	3 (2.1)
Pneumonia	0	3 (4.4)	3 (2.1)
Respiratory tract infection	1 (1.3)	2 (2.9)	3 (2.1)
Upper respiratory tract infection	3 (3.9)	3 (4.4)	6 (4.1)

TEAE	EFG-EFG (N=77)	PBO-EFG (N=68)	Total EFG (N=145)
Urinary tract infection	8 (1().4)	5 (7.4)	13 (9.0)
Injury, poisoning and procedural complications	12 (15.6)	903.2)	21 (14.5)
Contusion	1 (1.3)	2 (2.9)	3 (2.1)
Fall	0	3 (4.4)	3 (2.1)
Infusion related reaction	3 (3.9)	1 (1.5)	4 (2.8)
Joint dislocation	2 (2.6)	1 (1.5)	3 (2.1)
Procedural pain	2 (2.6)	2 (2.9)	4 (2.8)
Vaccination complication	2 (2.6)	1 (1.5)	3 (2.1)
Investigations	7(9.1)	11 (16.2)	18 (12.4)
Lymphocyte count decreased	2 (2.6)	1 (1.5)	3 (2.1)
Musculoskeletal and connective tissue disorders	14(18.2)	17 (25.0)	31 (21.4)
Arthralgia	5 (6.5)	7 (10.3)	12 (8.3)
Back pain	4 (5.2)	3 (4.4)	7 (4.8)
Muscle spasms	2 (2.6)	1 (1.5)	3 (2.1)
Myalgia	3 (3.9)	1 (1.5)	4 (2.8)
pain in extremity	0	4 (5.9)	4 (2.8)
Nervous system disorders	32 (41.6)	28 (41.2)	60 (41.4)
Dizziness	5 (6.5)	2 (2.9)	7 (4.8)
Headache	15 (19.5)	21 (30.9)	36 (24.8)
Hypoaesthesia	1 (1.3)	2 (2.9)	3 12.1)
Migraine	4 (5.2)	1 (1.5)	5 (3.4)
Myasthenia gravis	5 (6.5)	3 (4.4)	8 (5.5)
Somnolence	1 (1.3)	2 (2.9)	3 (2.1)
Respiratory, thoracic and mediastinal disorders	10(13.0)	10 (14.7)	20 (13.8)
Cough	2 (2.6)	2 (2.9)	4 (2.8)
Oropharyngeal pain	2 (2.6)	6 (8.8)	8 (5.5)
Skin and subcutaneous tissue disorders	12 (15.6)	10 (14.7)	22 (15.2)

TEAE	EFG-EFG (N=77)	PBO-EFG (N=68)	Total EFG (N=145)
Rash	3 (3.9)	3 (4.4)	6 (4.1)
Vascular disorders	9 (1 1.7)	5 (7.4)	14 (9.7)
Hypertension	4 (5.2)	4 (5.9)	8 (5.5)

EFG, efgartigimod; PBO, placebo
Source: argenx, 2022[128]

7.1.6.5.3. Deaths and neoplasm malignancies

Five patients have died in ADAPT+; a summary is presented in Table 15. No deaths were considered related to treatment with efgartigimod. Though there is no clear mechanism of action, it is noted that as of the clinical cut-off date, overall, 11 events of neoplasms have been reported in efgartigimod-treated gMG patients at the intended dose (one in ADAPT and 10 in 7 patients in study ADAPT+) and only one case has been reported in the placebo group. Of these, 6 events were considered serious in 5 efgartigimod treated patients and none in placebo-treated patients. Even though a correlation couldn't be found, it is noteworthy that 11 events have been reported in efgartigimod treated patients and only one case in the placebo group.[130]

Table 15. Patient deaths in ADAPT+

Cohort	Preferred term	Event date (cycle)	Last infusion date/Total received	Relationship to efgartigimod
PBO-EFG	Acute myocardial infarction	25 Jul 20 (4)	02 Jul 20/ 16 infusions	Not related
EFG-EFG	Septic shock	03 Nov 20 (4)	27 Aug 20/ 16 infusions	Unlikely related
EFG-EFG	MG crisis	16 Mar 20 – 09 Apr 20 (1)	22 Jan 20/ 4 infusions	Not related
EFG-EFG	Lung neoplasm malignant	01 Jul 20 – 09 Aug 20 (2)	11 Jan 20/ 8 infusions	Not related
EFG-EFG	Death	15 Dec 19 (3)	12 Dec 19/ 9 infusions	Not related

EFG, efgartigimod; PBO, placebo; MG, myasthenia gravis

7.1.7. ADAPT+: Summary

The safety and tolerability of efgartigimod in patients with gMG have been further characterized in ADAPT+, confirming that efgartigimod continues to be well tolerated with repeated treatment cycles. The safety profile is similar to that reported in the randomized, placebo-controlled ADAPT study. Few SAEs or TEAEs have led to discontinuation. Importantly, increases in the number of treatment cycles received by patients did not result in an increased incidence of new events, or more frequent occurrences, or greater severity, of previously reported events. Efficacy results from ADAPT+ are in line with those observed in ADAPT study. Reductions in mean MG-ADL and QMG

scores in the AChR-Ab+ population have been repeated with further cycles of efgartigimod, showing CMIs from baseline.

7.2. Comparative analyses

No comparative analyses were conducted.

8. Health economic analysis

A pharmacoeconomic model was developed to assess the cost-effectiveness of efgartigimod in the treatment of patients with AChR-Ab+ gMG vs conventional therapy in Denmark. Efgartigimod is approved in Europe as an add-on to standard therapy for the treatment of adult patients with AChR-Ab+ gMG.[1] The health economic analysis developed for this submission is aligned with the standard analysis recommended in the Danish guidelines.[125] This section summarizes results from the cost-effectiveness model (CEM) developed in Microsoft Excel named 'CEM efga in gMG_Denmark)_ v6.06'.

The pharmacoeconomic model is a de-novo Markov simulation that uses a cost-effectiveness approach to compare costs and benefits of efgartigimod vs conventional therapy in adult patients with AChR-Ab+ gMG. The model has been designed to capture the benefit of efgartigimod treatment in:

- Improving direct consequences of gMG (both ongoing muscular/respiratory impairment and acute events)
- Improving indirect consequences of gMG caused by currently used therapies

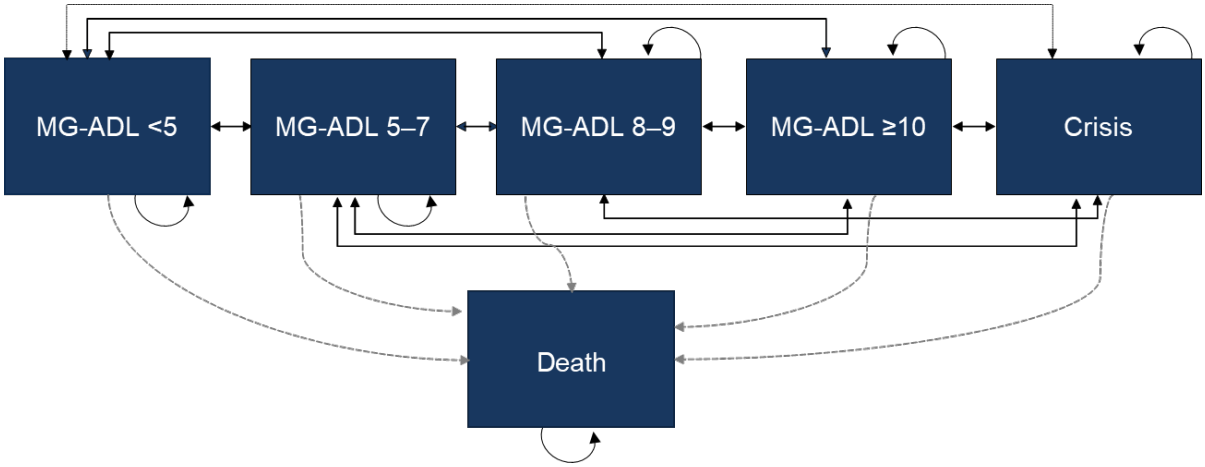
The effectiveness outcome of interest is quality-adjusted life-years (QALYs; ie, the CEA adopts a cost-utility analysis approach), with the ultimate results being expressed in terms of incremental cost per QALY gained over the model's time horizon; ie, the incremental cost-effectiveness ratio (ICER), as calculated in the following formula:

$$ICER = \frac{Cost\ New\ pharmaceutical - Cost\ Comparator}{QALYs\ New\ pharmaceutical - QALYs\ Comparator}$$

8.1. Model

The de novo Markov model comprises six health states that capture the levels of disease activity, based on the MG-ADL scale: MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9, MG-ADL ≥10, crisis, or death (Figure 13). Within each of the alive health states, the model considers acute events (gMG and treatment related) and adverse impact of chronic corticosteroid use on mortality, QoL, and costs. The model also considers temporary and permanent treatment interruptions to represent the management of patients more accurately in clinical practice. Patients enter the model in the MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health state based on the proportion of AChR-Ab+ patients in each of these categories at baseline of ADAPT. Transitions between health states are based on observed effect during cycles in the ADAPT and ADAPT+ studies.[28, 128] See Section 8.2.2.4.3 for details on the transition probabilities used in the model. Additional information on the distribution of the health states in the model are provided in Appendix P: Health state distribution over time.

Figure 13. Markov model structure



8.1.1. Justification of the chosen structure in line with the clinical pathway of care

An estimated 80% of patients with gMG continue to experience debilitating symptoms despite receiving current standard of care (ie, conventional therapy).[24] The model aims to capture the highly variable nature of gMG, including fluctuating symptoms and the rapid transition between health states as patients experience disease exacerbations or myasthenic crisis.

Health states in the model were defined based on MG-ADL score for two reasons: (1) this was the primary endpoint of ADAPT, allowing for more streamlined use of the RCT data in the model, and (2) health states based on MG-ADL are aligned with the trial entry criteria requiring patients to have an MG-ADL score of ≥5. MGFA class was an alternative option for defining the health states as it is a classification system for MG. However, MGFA was not used to define health states in this model because MGFA data were not collected throughout the ADAPT trial (MGFA class was recorded only at screening), which means that there was insufficient information on transitions between MGFA class over the treatment period. Further, an analysis of MGFA and MG-ADL data at screening in ADAPT did not show a sufficiently strong correlation that could support mapping between the two measures (ie, transforming MG-ADL scores into MGFA classes).

MG-ADL score is a continuous scoring system that is based on a patient's own assessment of their condition. PROs are preferred as primary outcomes in MG trials due to the fluctuating nature of the disease and because objective physical assessments may not fully reflect the burden of symptoms experienced by patients.[30] The MG-ADL scale comprises questions examining disease activity; eight questions assess ocular function, speech, chewing, swallowing, respiratory function, and strength of proximal upper and lower extremities. Each item is scored from 0 to 3, resulting in a total score of 0–24 points; higher scores are indicative of more active disease (ie, more symptoms).

There are no established MG-ADL cut-offs to define levels of disease activity in gMG. The health-states MG-ADL cut-offs were defined based on the following rationale:

- MG-ADL<5 health-state: likely to represent a minimally symptomatic disease stage, as defined by the clinical expert involved in the validation of the model. This is supported by the MG-ADL cut-off used to define the population in the current cost-effectiveness analysis, i.e., MG-ADL of at least 5, which is also the main criteria to define eligibility for re-treatment with efgartigimod (in line with ADAPT study and its open label extension).
- MG-ADL 5-7, MG-ADL 8-9 and MG-ADL ≥10 health-states: likely to represent considerably symptomatic disease, as suggested by the clinical expert involved in the validation of the model. The MG-ADL cut-offs for these 3 health-states were defined in line with the

subgroup analysis conducted for the ADAPT study as listed in the associated Statistical Analysis Plan [131]. Moreover, clustering (a machine learning technique) was used to identify appropriate categorical groupings based on the MG-ADL score and HRQoL data from ADAPT (EQ-5D an MG-QoL15):

  - The objective was to create homogeneous groups out of heterogeneous observations. This is achieved by minimising the intra-cluster distance and maximising the inter-cluster distance.
  - Specifically, the K-means clustering approach was used where each record is assigned to the cluster based on the distance from each cluster by averaging of the data.
  - Both the analysis on EQ-5D and the MG-QoL as a quality of life measure supported a MG-ADL threshold of 10 to define the cohort with the most considerable disease activity.

- A 2-point improvement in the MG-ADL score is a threshold that optimally (in terms of best sensitivity and specificity when referenced to Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15)) indicates clinical improvement at the level of the individual for patients with MG [129, 132, 133] . Given this minimum that indicates clinical improvement, the category from 5-9 was divided into two sub-categories: 5-7 and 8-9 in order to further differentiate disease severity using these separate health states.

8.1.2. Perspective

The current base-case version of the model was developed using a restricted societal perspective, as recommended in Danish guidelines. The model incorporates resource and cost inputs relevant to this perspective, including direct medical costs and the costs incurred by public health services to treat MG-related hospitalizations and manage treatment-related adverse events. Transportation costs and patient and caregiver use of time costs related to ongoing treatment and treatment of MG exacerbations and crises have been included in the base case.

8.1.3. Discount rate

Both costs and outcomes (life-years [LYs] and QALYs) were discounted in a time-dependent manner: 3.5% annually for the first 35 years, 2.5% for 36–70 years, and 1.5% for >70 years, in line with Danish guidelines[125] and the current socio-economic discount rates set forth by the Danish Ministry of Finance.[134]

8.1.4. Time horizon and model cycle

The base case analysis adopts a ‘lifetime' horizon of approximately 53.07 years. This is considered long enough to capture the lifetime of patients in this setting (mean starting age for patients in the model is 46.93 years). The time horizon is implemented by tracking patients up to the model cycle where they die or reach the age of 100 years. This is an appropriate time scale given that gMG is a lifelong medical condition.[5] The model cycle length was selected to match the duration of the treatment cycles used in ADAPT,[28] a key source of data for the model. The model includes half-cycle correction implemented by applying the trapezoidal rule.

8.2. Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1. Presentation of input data used in the model and how they were obtained

Below in Table 16 a summary of the inputs for the analysis, with the relevant sources, is described. Additional information on transition probabilities is presented in Appendix K: Transition probabilities.

Table 16. Input data used in the model

Parameters	Input used in the model	Source
Health-states	MG-ADL<5,MG-ADL 5-7, MG-ADL 8-9, MG-ADL ≥10, Crises and Death	ADAPT
Population	AChR+ gMG patients with MG-ADL≥5 despite use of conventional therapy	ADAPT & ADAPT+
Intervention	Efgartigimod 10mg/kg per infusion (4 weekly infusions and 8 weeks tx interval) + conventional therapy	ADAPT & ADAPT+
Comparator	Conventional therapy (with 50% IVIG in MG-ADL8-9 and 100% IVIG in MG-ADL>=10)	ADAPT & ADAPT+
Efgartigimod positive stopping rule	The cohort with MG-ADL<5 after a cycle of 4 weekly infusions, remains off-treatment for a minimum of 8 weeks or until it worsens to MG-ADL 5-7, MG-ADL 8-9 and MG-ADL>=10. The probability from MG-ADL<5 to other health-states is estimated based on observations in the inter-treatment cycle of cycle 1 in ADAPT efgartigimod arm and conventional therapy (pooled).	Assumption based on ADAPT
Negative stopping rule (all treatments)	Cohort on crisis stop treatment and receives rescue therapy. Treatment is started again once the cohort transit out of the crises HS.	ADAPT
Non responders stopping rule	The cohort not responding to 2 consecutive cycles (based on response definition in ADAPT) is excluded from treatment with efgartigimod and is thereafter assumed to receive conventional therapy treatment. The costs, effects and HRQoL of conventional therapy are therefore applied to this proportion of the cohort excluded from treatment with efgartigimod.	Assumption based on ADAPT

Parameters	Input used in the model	Source
Transition probabilities in efgartigimod arm	• On treatment cycle: Change in MG-ADL from baseline to week 4 of each treatment cycle* based on ADAPT and ADAPT + reconstructed data (efgartigimod arm) • Off treatment cycle(s) in MG-ADL≥5 at week 4: MG-ADL change from week 4 to week 8 and week 8 to week 12 of cycle 1 in ADAPT (efgartigimod arm). ADAPT + is not used because observations off treatment beyond week 8 of each cycle are few and data are at week 12 are not reported. Off treatment cycle(s) in MG-ADL<5 at week 4: MG-ADL change from week 4 to week 12 (8 weeks) in cycle 1 of ADAPT (pooled arms) and from week 12 to week 16 (4 weeks). Beyond 16 weeks too few data are available, so transitions at week 16 are recycled.	Calculation based on ADAPT & ADAPT+
Treatment effect extrapolation efgartigimod	Average of observed transition probabilities from cycle 2 are applied for the entire cohort at any cycle for the entire time-horizon of the analysis	Calculation based on ADAPT
Transition probabilities in conventional therapy arm	Considering temporal change in MG-ADL every 4 weeks in ADAPT, placebo arm. Beyond ADAPT observations the cohort returns towards baseline health-state distribution to remain in the same health state unless a crisis or death occurs	Assumption based on ADAPT
Maintenance Ig	• 50% in conventional therapy arm in MG-ADL 8-9 • 100% in conventional therapy arm in MG-ADL ≥10 • Maintenance Ig is assigned also to efgartigimod cohort who discontinue treatment 100% IV, 0% SC	ADAPT
Corticosteroid (CS) use	High-dose definition: >5mg/day. Cohort on CS = 75.2% based on ADAPT at baseline • All arms: ○ % on CS in MG-ADL<5 =0% % on CS in MGADL 5-7, MG-ADL 8-9 and MG-ADL ≥10 = SoC (75.2%, of whom 91% on high-dose)	ADAPT
Health-state utilities	• EQ-5D-5L Danish value sets • Regression on utilities, health-state and treatment based on ADAPT data (mixed model) Utilities are adjusted for relative decrement associated with ageing of the cohort	Calculation based on ADAPT

Parameters	Input used in the model	Source
Caregiver disutility	• Not considered.	Assumption
Adverse Event – efgartigimod frequencies		
Infection	0.44%	ADAPT
Asthenia (fatigue)	0.00%	
Cardiovascular disorders (incl. thrombosis)	0.00%	
Eyelid disorders	0.00%	
Myalgia	0.22%	
Headache or procedural pain	0.22%	
Gatrointestinal	0.22%	
Other	0.89%	
Adverse Event – SoC frequencies		
Infection	0.22%	ADAPT
Asthenia (fatigue)	0.22%	
Cardiovascular disorders (incl. thrombosis)	0.22%	
Eyelid disorders	0.22%	
Myalgia	0.00%	
Headache or procedural pain	0.22%	
Gatrointestinal	0.00%	
Other	0.66%	

8.2.2. Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1. Patient population

The base-case population considered in the model—adult patients with AChR-Ab+ gMG—is consistent with the expected EMA-licensed population for efgartigimod.[1] The characteristics of the simulated patient cohort at model entry are based on the baseline characteristics of the AChR-Ab+ population (n=129) in ADAPT, and include patients with an MG-ADL score ≥5 with at least 50% non-

ocular scores despite receiving conventional therapy (Table 17).[76, 127] No relevant subgroups were identified for the analysis. These are assumed to be in line with the Danish population.

Table 17. Baseline model cohort characteristics

Characteristic	Clinical documentation	Used in the model	Danish clinical practice
Initial age (years)	46.9 [76, 127]	46.9	Assumed to be the same
Female population (%)	66.7 [76, 127]	66.7	Assumed to be the same
Weight (kg)	80.6 [76, 127]	80.6	Assumed to be the same
MG-ADL 5-7 (%)	26.4 [76, 127]	26.4	Assumed to be the same
MG-ADL 8-9 (%)	41.9 [76, 127]	41.9	Assumed to be the same
MG-ADL ≥10 (%)	31.8 [76, 127]	31.8	Assumed to be the same

Sources: argenx, data on file[76, 127]

8.2.2.2. Intervention

The intervention in the analysis is intravenous efgartigimod 10 mg/kg per infusion, administered in 4 weekly infusions within 8-week treatment cycles*. This is in line with the expected Danish clinical practice, and with the ADAPT clinical trial. The main characteristics of the intervention are presented in Table 18.

Table 18. Intervention clinical data and model inputs

Intervention	Clinical documentation (ADAPT)	Used in the model	Expected Danish clinical practice
Posology	10 mg/kg as a 1-hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks	10 mg/kg per infusion, administered in 4 weekly infusions within 8-week treatment cycles	Assumed to be in line with ADAPT
Length of treatment (time on treatment) (mean/median)	Median duration: 10 weeks	Median duration: 10 weeks	Median duration: 10 weeks
Criteria for discontinuation	The cohort with MG-ADL<5 after a cycle of 4 weekly infusions, remains off-treatment for a minimum of 8 weeks or until it worsens to MG-ADL 5-7, MG-ADL 8-9 and MG-ADL>=10. In case of exacerbations or crisis, or lack of responses after 2 cycles, the treatment is stopped.	The cohort with MG-ADL<5 after a cycle of 4 weekly infusions, remains off-treatment for a minimum of 8 weeks or until it worsens to MG-ADL 5-7, MG-ADL 8-9 and MG-ADL>=10. In case of exacerbations or crisis, or lack of responses after 2	The cohort with MG-ADL<5 after a cycle of 4 weekly infusions, remains off-treatment for a minimum of 8 weeks or until it worsens to MG-ADL 5-7, MG-ADL 8-9 and MG-ADL>=10. In case of exacerbations or crisis, or lack of responses after 2

* Per study protocol a Cycle is defined as the 'Treatment Period' or TP (i.e. 4 once weekly infusions) + the 'Intertreatment Period' or ITP (which was a 5 week FU time, total duration was 8 weeks). In the model, 4 weeks are considered for the duration of a cycle.

Intervention	Clinical documentation (ADAPT)	Used in the model	Expected Danish clinical practice
		cycles, the treatment is stopped.	cycles, the treatment is stopped.
The pharmaceutical's position in Danish clinical practice	Add-on to standard therapy for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor antibody positive (AChR-Ab+)	Add-on to standard therapy for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor antibody positive (AChR-Ab+)	Add-on to standard therapy for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor antibody positive (AChR-Ab+)

8.2.2.3. Comparators

As agreed in pre-submission discussions with the DMC, the comparator in the analysis for Denmark is conventional therapy, comprising the standard treatments used in Danish clinical practice to manage gMG. This includes IVIg, corticosteroids, AChEis, and NSISTs (azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide). The model considers the use of maintenance IVIg only for a proportion of the gMG population with more severe disease. Based on clinical practice as described by a Danish clinical expert[†] who treats patients with gMG, rituximab is used in only a small number of patients in Denmark and its use is not supported by strong evidence; therefore, this comparator is not included in model. In addition, PLEX is generally only used in resolving myasthenic crises and therefore not included. A summary of the comparators included in the health economics analysis are presented in Table 19.

Table 19. Comparators clinical data and model input

Comparators	Clinical documentation (ADAPT)	Used in the model	Expected Danish clinical practice (including source)
Posology	Relevant information on the posology of all the comparators are listed in Section 5.6.2	Posology of all the comparators used in the model is presented in Section 5.6.2	Posology of all the comparators and sources used in the model is presented in Section 5.6.2
Length of treatment	Median duration: 10 weeks	Median duration: 10 weeks	Median duration: 10 weeks
The comparator's position in the Danish clinical practice	Standard of care	Standard of care	Standard of care

[†] Professor John Vissing at the Department of Clinical Medicine, University of Copenhagen, provided expert clinical opinion on the treatment of gMG in Denmark and the appropriateness of the CEM developed by argenx bv.

8.2.2.4. Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation is based on ADAPT, which relies on changes in MG-ADL and QMG score, each compared with the corresponding cycle baseline in the AChR-Ab+ population, the AChR-Ab- population, and the overall population. However, only the MG-ADL score was implemented in the analysis. The transition probabilities were based on responders excluding the non-responders during the first two treatment cycles to reflect an accurate representation of the response to treatment. By study protocol, responders were defined as a patient who had at least a 2-point improvement (reduction) in MG-ADL score. The study documentation is relevant for the Danish clinical practice since these endpoints are established efficacy outcomes in the treatment of gMG. In the health economic analysis, relative treatment effect is modelled as changes in MG-ADL score. Reduced MG-ADL score is also modelled with a lower probability of MG crises (ie, the probability of having a crisis is higher in health states with greater disease activity). A summary of relative efficacy outcomes values and relevance is presented in Table 20 and Table 21.

Table 20. Summary of efficacy outcomes regarding value

Clinical efficacy outcome	Clinical documentation (ADAPT)	Used in the model (value)
Mean changes in MG-ADL score	AChR-Ab+ patients in the efgartigimod group, MG-ADL responders during cycle 1: 67.7% (44/65) Placebo group: 29.7% (19/64)	AChR-Ab+ patients in the efgartigimod group, MG-ADL responders during cycle 1: 67.7% (44/65) Placebo group: 29.7% (19/64)

Table 21. Summary of efficacy outcomes regarding relevance

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Mean changes in MG-ADL score	MG-ADL responder was defined as a patient who had at least a 2-point improvement (reduction) in MG-ADL score, sustained for at least 4 consecutive weeks, with the first improvement occurring by week 4 of the cycle (1 week after the fourth infusion)	MG-ADL score is relevant as this was one of the primary endpoint of ADAPT	Relevant

8.2.2.4.1. Pooling treatment cycle data and reconstruction of the ADAPT+ observations to define transition probabilities in the efgartigimod arm

The patients included in ADAPT were allowed to rollover into ADAPT+ (NCT03770403) and receive additional treatment cycles with efgartigimod. An analysis of the change in the MG-ADL score between baseline and week 4 of each treatment cycle in ADAPT+ showed that the change from cycle baseline to week 4 of each cycle is constant over time. Thus, the data suggest that at every subsequent treatment cycle, the effect of treatment is similar to the effect of treatment in the previous cycle. This allowed for the model to consider the treatment cycles of ADAPT+ as consecutive to those in ADAPT, which meant that the number of treatment cycles could be counted progressively from baseline in ADAPT to the ADAPT+ study cut-off date. In addition, data could be pooled for patients in the same treatment cycle regardless of which trial they were in (eg, a patient who started treatment cycle 2 while in ADAPT would be in the same model cohort as a patient who started cycle 2 in ADAPT+).

The main obstacle encountered by pooling treatment cycle data in the two studies is related to the timing of the study visits. In ADAPT+, visits for each treatment cycle were conducted weekly only until third week and then monthly thereafter. In ADAPT, visits for each treatment cycle were conducted weekly until the eighth week and then bi-weekly thereafter. This generates two issues:

1) In ADAPT+, the observations do not follow the same 4-week pattern observed in ADAPT, since after the third week the subsequent visits are conducted at uneven timepoints (third week, seventh week, eleventh week, etc). This poses a challenge both because of the resulting misalignment with the observations in ADAPT,[28] which are conducted at even timepoints (fourth week, eighth week, twelfth week, etc), and because of the resulting misalignment with the 4-week cycles adopted in the Markov model.
2) The last infusion of efgartigimod is administered at the end of the third week of each treatment cycle. Therefore, the visit at the fourth week of each treatment cycle allows the full treatment effect of efgartigimod to be captured. In ADAPT, this is demonstrated by the average MG-ADL score at the fourth week being the lowest in each treatment cycle, making week 4 the maximum improvement timepoint. The lack of the 4-week visit in ADAPT+ is therefore a major limitation in the ability to fully capture the effect of efgartigimod.

To overcome these issues, the fourth week of ADAPT+ was reconstructed based on the difference between the fourth and the third week observed in ADAPT.[28] The MG-ADL scores at the fourth week of the first treatment cycle in ADAPT were regressed on the MG-ADL scores at the third week using a linear regression model. A cross-validation technique was used to identify the best least-square estimators of the regression coefficients.[57] The coefficients were then used to predict the values of the fourth week of each treatment cycle in ADAPT+.

The approach described above allows for the observations of the ADAPT and ADAPT+ studies up to the fourth week of each treatment cycle to be pooled. The maximum number of treatment cycles obtained by pooling the two trials is 13. However, due to low patient numbers, only the first 8 cycles from the baseline of ADAPT were used to inform the model.

8.2.2.4.2. 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 ADAPT and the ADAPT+ studies, shifted 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 probabilities matrices that are then applied over the time horizon of the analysis in the efgartigimod and conventional therapy arms of the model.

Further details on how the transition matrices are calculated and applied in the model are presented in Appendix K: Transition probabilities.

8.2.2.4.3. gMG exacerbations

The CE analysis only considers gMG exacerbations that require hospitalization since exacerbations not requiring inpatient treatment are expected to have minimal impact on costs and quality of life. gMG exacerbations are included in the analysis as acute events requiring in hospital care, which may occur in any health state except crisis and death. At the occurrence of exacerbation, the corresponding cost and utility reduction are applied in the model. The rate of MG exacerbation is modelled as treatment specific; however an analysis of MyRealWorld MG study data on exacerbations is ongoing with the aim to derive MG exacerbation rates by health states which would then be applied independently of the treatment arm of the analysis.

The rate of MG exacerbations was obtained by treatment arm in ADAPT. The mITT population was considered instead of the AChR-Ab+ population to allow for a larger sample size given the small number of events occurring. During ADAPT, a total of two patients in the conventional therapy arm and one in the efgartigimod arm had an MG exacerbation. Considering a total follow-up period of 3,052 and 3,061 weeks in the conventional therapy and efgartigimod arms respectively, the resulting model cycle (ie, 4 weeks) rate of MG exacerbation was 0.003 for the cohort in the conventional therapy arm and 0.001 in the efgartigimod arm.

8.2.2.4.4. Probability of transitioning into or out of MG crisis

gMG crisis is modelled as a health state rather than as an event (as in the case of exacerbations) because crises are long in duration, carry the potential for death, and involve an interruption of maintenance treatment in order for rescue therapy to be administered along with ICU-specific treatment algorithms. The probability of transition to the crisis health state was based on the literature and assumed to apply to MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states only.[135] The percentage of MG patients that present with myasthenic crisis is variable among studies, ranging from 5.6%[136] to 9.6% [137]. Based on the incidence of myasthenic crisis in MG patients reported in the literature, a cycle probability of transitioning to crisis of 0.09% from MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states was estimated, independent of baseline treatment. Further evidence to populate the probability of crises is expected from the MyRealWorld MG study data, when available.

The probability of transitioning out of the crisis (the worst health state possible in terms of disease severity and the need for constant monitoring in the ICU and ventilatory support) is assumed to be 100%—that is, the cohort remains in the crisis health state for only 1 cycle. Such an assumption was taken due to lack of evidence on which proportion of crisis patients would remain in MG crisis longer than 4 weeks (ie, beyond the cycle length). This assumption can be considered conservative given that a greater proportion of the cohort in the comparator arm than in the efgartigimod arm experience a crisis. The probability of crisis was based on data from Liu et al 2019, from which probability of crises per cycle is estimated at 0.049% and therefore a probability of being without crises is 99.66%.[136] It was assumed in the model that all patients transition from crisis to the MG-ADL ≥10 health state, considering that after an ICU stay patients require specific in-hospital treatments and rehabilitation programs in order to achieve full recovery. After an episode of myasthenic crisis, patients could require mechanical ventilation at discharge or inpatient rehabilitation/discharge to rehabilitation centres.

In line with clinical practice, ongoing treatments for gMG are suspended when patients enter the crisis health state. Rescue therapy is administered, and treatment is resumed once the cohort transitions out of the crisis health state.

8.2.2.5. Treatment-emergent adverse events

In the model, only grade ≥3 treatment-emergent adverse events (AEs) are considered since these events are expected to have measurable impact on costs and QoL. Likewise, treatment-emergent AEs were included in the model as acute events, and specifically by treatment administered. At any cycle, AEs may occur for the proportion of the cohort in a specific treatment arm.

Based on the number of grade ≥3 AEs reported for efgartigimod and placebo arms in ADAPT, the incidence of treatment-emergent AEs was implemented in the model (Table 22). In addition to acute AEs, the model considers the chronic impact of corticosteroid use on mortality, HRQoL, and costs.

Table 22. Treatment-emergent grade ≥3 AEs (overall population; safety analysis set)

AE	N events		Cycle rate	
	Placebo	Efgartigimod	Placebo	Efgartigimod
Infection	1	2	0.002	0.004
Asthenia (fatigue)	1	0	0.002	0.000
Cardiovascular disorders (incl. thrombosis)	1	0	0.002	0.000
Eyelid disorders	1	0	0.002	0.000
Myalgia	0	1	0.000	0.002
Headache or procedural pain	1	1	0.002	0.002
Gastrointestinal	0	1	0.000	0.002
Neutropenia	0	0	0.000	0.000
Other	3	4	0.007	0.009

Source: ADAPT CSR, Table 14.3.1.6.2

8.2.2.6. Mortality

8.2.2.6.1. Mortality in MG

The mortality rate in MG reported in the literature is around 0.06 to 0.89 deaths per million person years.[138] However, the natural, untreated course of MG has been associated with high mortality and persistence of symptoms in most patients.[139] In 1960, mortality rates were as high as 50%–80%,[136] but due to faster recognition of crises and improvements in rescue treatments, the mortality rate has fallen over time. Currently, myasthenic crisis (as the main cause of MG-related deaths) is reported to be fatal in less than 5% of cases[138]; however, reports on mortality are heterogeneous, and this proportion changes across studies, usually ranging from 5%–22%.[140] This reduction in mortality is related to the improvement of intensive respiratory care and the introduction of immunosuppressive treatments.

8.2.2.6.2. *Mortality by health state*

Evidence of mortality related to MG-ADL, independent of crises and complications due to corticosteroids, is scarce. Therefore, in the model it is assumed that the mortality in each health state is the same as the general population (ie, HR = 1 is assumed), except in crisis.

8.2.2.6.3. *Probability of death in MG crisis*

A targeted literature review (TLR) was conducted (June 2021) to look for available literature that reported the probability of death due to myasthenic crises. The following search strategy was implemented in PubMed:

- ((((("myasthenia gravis"[Title] OR "myasthenic crisis"[All Fields]) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading]))))) NOT (("perioperative"[All Fields]) OR ("anesthesia"[All Fields]) OR ("COVID"[All Fields]) OR ("pregnant"[All Fields]) OR ("pediatric"[All Fields]) OR ("thymoma"[Title])OR ("ocular"[Title]) OR ("thymectomy"[Title]) OR ("preoperative"[Title]) OR ("animal"[Title]))

Retrieved publications (a total of 249 studies) were subjected to title and abstract screening to determine relevance. Pertinent outcome data from selected records (including probability of death related to myasthenic crisis and length of hospitalization), were summarized in data extraction tables. Based on multiple publications, a 0.12% probability of death during myasthenic crisis was implemented in the model.[135, 136, 140-144]

8.2.2.6.4. *Mortality associated with chronic corticosteroid use*

An SLR was conducted to estimate the impact of chronic corticosteroid (CS) use on mortality, HRQoL, and costs. For mortality, European studies retrieved from the SLR were used to calculate average HRs for mortality based on high- and low-dose CS use (Table 23). Although the information available in the literature is variable, 5mg/day was found to be a common threshold to distinguish between high and low dose [145]. The association between mortality and CS dose was also supported by the evidence from the SLR, showing a strong relationship between higher CS doses and risk of death.

Results of the modelling show that there between risks of death and chronic CS use compared to non-CS users among chronic diseases. And although a heterogeneous threshold among the evaluated studies to define CS high dose was not clear, the dose-dependent trend between CS dose and all-cause mortality was demonstrated.

The SLR conducted to evaluate the clinical and economic impact of chronic CS use is available in Appendix N: Systematic literature review: Clinical and economic impact of chronic use of corticosteroids.

Table 23. Average hazard ratios for mortality based on high- and low-dose CS use

	HR of death vs no CS use
High dose (>5 mg/day)	2.03
Low dose (<5 mg/day)	1.01

8.3. Extrapolation of relative efficacy

The treatment effect is modelled as changes in MG-ADL score. Reduced MG-ADL score is also modelled with a lower probability of MG crises (ie, the probability of having a crisis is higher in

health states with greater disease activity). Thus, changes in MG-ADL score also impact the probability of transitioning to the crisis health state. The analysis also considers the effect of treatment on the incidence of MG exacerbations.

Changes in MG-ADL from baseline to 4 weeks and every 4 weeks thereafter from ADAPT[28] and ADAPT+ (NCT03770403) were used to define the cycle transition probabilities in the efgartigimod and conventional therapy arms of the model. ADAPT provides the data for comparison of efgartigimod as an add-on to conventional therapy with placebo (conventional therapy alone). Using the placebo arm of ADAPT allows for conventional gMG therapy to be modelled—patients in both arms of ADAPT were treated with conventional therapy, with the only difference being the addition of efgartigimod or placebo to each treatment arm. Data on the effect of efgartigimod are also available from ADAPT+, but no data on the conventional therapy arm alone are available from that trial since all patients who received placebo in the ADAPT and rolled over into ADAPT+ started receiving efgartigimod treatment as add-on to conventional therapy.

To be fully aligned with the approved indication for efgartigimod, only AChR-Ab+ patients were used to inform the effectiveness of efgartigimod in the model. In addition, the patients in ADAPT who did not respond to two consecutive cycles were not included in the population used to estimate the effectiveness of efgartigimod; this approach was confirmed by a Danish clinical expert. This is also aligned with the stopping rule implemented in the model (see Section 10.12) whereby the proportion of the efgartigimod cohort that does not respond to efgartigimod within two cycles stops treatment and shifts to the conventional therapy group.

From the total of 65 patients in the efgartigimod group, 21 were not MG-ADL responders during cycle 1. From those 21 patients, 2 were not treated and 19 were retreated. From the 19 patients treated in these two consecutive cycles, seven (37%) of those were MG-ADL responders in cycle 2 (considered non-responders in the first cycle) and 12 (18%) were considered non-responders in two consecutive cycles. So it was considered that 18% of patients would be defined as non-responders. Since only the responders remain on treatment, the effect for the responders only was modelled by estimating transition probabilities excluding the observations of the 12 patients who did not respond to two consecutive cycles. The proportion of the cohort defined as non-responders and who therefore permanently discontinued treatment with efgartigimod are applied the transitions as in the SoC arm of the model.

8.3.1. Definition of the time-points in ADAPT and ADAPT+ used to derive the transition probabilities in efgartigimod and conventional therapy arms of the model

The efgartigimod cohort in the CEA is assumed to receive a cycle of treatment (4 weekly infusions) and to remain off treatment for 4 weeks, which represents the average duration of the treatment interval in ADAPT.[28] The only exception is the cohort in the MG-ADL <5 health state, which is assumed to remain off treatment for a minimum of 4 weeks or until progression to the MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health states (ie, by treatment eligibility criteria, patients would not receive a treatment cycle unless they have an MG-ADL score >5). During the off-treatment period, the efgartigimod cohort is assumed to be treated with conventional therapy alone, in line with ADAPT and ADAPT+.[28, 128]

To obtain transition probabilities that adequately describe the effect observed during the efgartigimod on-treatment period (ie, while patients receive the 4 weekly infusions) and off-treatment period, each treatment cycle in ADAPT and ADAPT+ was considered in isolation. Patient-level changes in MG-ADL scores from baseline to week 4 of each treatment cycle in ADAPT and ADAPT+ were used to estimate the transition probabilities during the on-treatment periods. The transition probabilities in the off-treatment model cycles were informed by observations in the

efgartigimod arm of ADAPT. For the cohort in the MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health states at the end of the on-treatment model cycle, the off-treatment transitions were based on patient-level changes in MG-ADL from week 4 to week 8. For the cohort in MG-ADL<5 health-state at the end of the on-treatment model cycle, the off-treatment transitions were based on patient-level changes in MG-ADL every 4 weeks from week 4 (the last week of the 4 weekly infusions), following patients who maintained MG-ADL<5 over-time. Since a subsequent treatment cycle in ADAPT was not initiated unless the MG-ADL score was ≥5, the number of off-treatment model cycles in the MG-ADL <5 health state was indefinite (i.e., efgartigimod treatment was only recommenced upon transitioning to one of the health states with MG-ADL ≥5).

Health-state changes from the start of each treatment cycle in ADAPT and ADAPT+ were considered independently of chronological time from study entry because of challenges posed by the innovative design of the trial, which permitted efgartigimod dosing in a highly individualised manner. In each treatment cycle, patients in ADAPT and ADAPT+ were treated with 4 weekly infusions of efgartigimod or placebo. In ADAPT, patients were then allowed to start another treatment cycle after week 8 from the start of the cycle, provided that they met specific criteria, requiring an MG-ADL total score of ≥5 points, with >50% of the total score attributed to non-ocular symptoms. Thus, due to the individualized nature of the subsequent-criteria, the duration of this off-treatment period varied from patient to patient and, for each patient, from period to period. This posed a challenge in modelling because after the eighth week from baseline, the efgartigimod cohort comprised a mixture of patients in on- and off-treatment states. If the time periods used to estimate the treatment effect were based only on the chronological distance of each timepoint from baseline, the treatment effect on the transition probabilities would be impossible to isolate beyond the first 8 weeks due to the mixed nature of the cohort after this timepoint.

In contrast, there is no need to isolate the treatment effect in the context of the placebo arm since the conventional therapy is administered constantly over time and only the placebo is administered intermittently. Therefore, it is possible to use the conventional therapy data from ADAPT based on chronological distance from the baseline and to disregard the corresponding treatment cycles. Indeed, even if the cohort comprises a mixture of patients on-(placebo) treatment and off-(placebo) treatment after the eighth week, this has no influence on the effect of the conventional therapy. ADAPT was used to inform the transition matrices for the conventional therapy arm because there is no control arm in ADAPT+.

8.3.2. Discontinuation due to unplanned reasons

In both ADAPT and ADAPT+,[28, 128] patients could stop ongoing efgartigimod treatment due to unplanned reasons. In the clinical trials, discontinuation due to unplanned reasons was recorded if any of the following events occurred:

- Serious AEs
- Pregnancy
- Prohibited medication taken
- Treatment with rescue therapy required

Moreover, patients could discontinue treatment if there was clinical evidence of bacterial, viral, or fungal disease, or any other significant disease which could confound the results of the trial or put the patient at undue risk. To inform the per-cycle probability of discontinuing the efgartigimod treatment due to unplanned reasons, the treatment duration during the pooled ADAPT and ADAPT+ studies was used.[28, 128]

The time between the date of first treatment exposure in ADAPT and the date of the last observation in either ADAPT or ADAPT+ was calculated for each patient and used to produce a

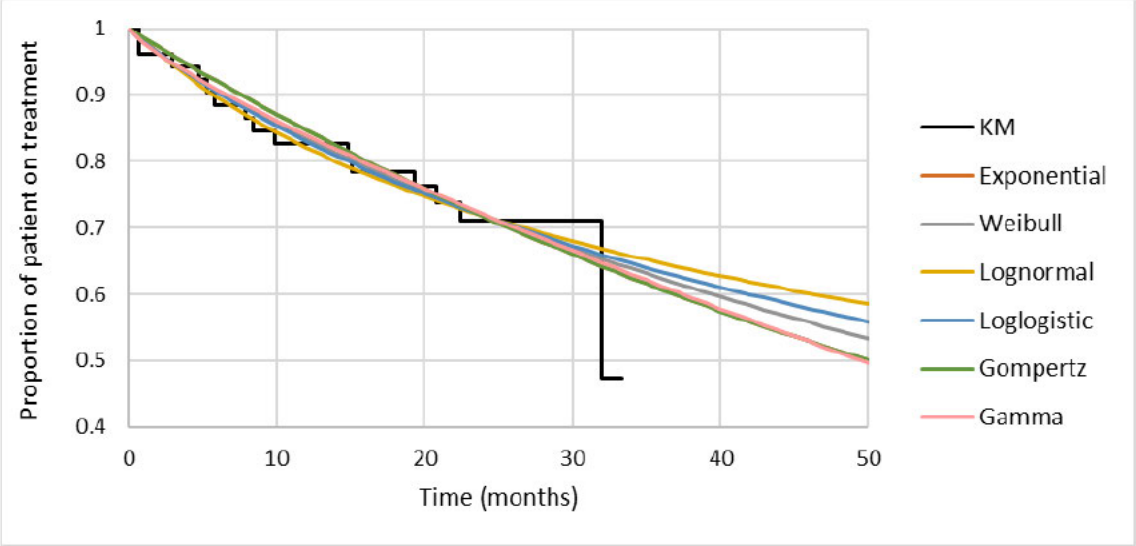
Kaplan-Meier (KM) curve of the time-on-treatment (ToT). Only the AChR+ patients who were in the efgartigimod arm of ADAPT were considered for the analyses. The patients who did not discontinue efgartigimod treatment by the last time point available were censored.

The KM ToT curve covers a time horizon that is smaller than the model time horizon; therefore, extrapolation is needed. Parametric fitting of KM curves was performed to extrapolate beyond the observation period using the following distributions: Exponential, Weibull, Log-Normal, Log-Logistic, Gompertz, and Gamma. The parametric function was pre-selected based on AIC/BIC, visual inspection, and internal and external validity. In the base case, a piecewise approach is used where the KM points are used to define the probability of discontinuations until available data (i.e., 33 months) and thereafter, the best-fitting parametric model is applied. The Exponential parametric function was selected since it is the best-fitting curve based on AIC/BIC values. Table 24 summarizes the AIC/BIC values associated with each parametric function. Figure 14 shows the parametric functions fitted on the ToT KM curve.

Table 24. AIC/BIC values of each parametric function

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Gamma
AIC+BIC	203.41	208.73	208.67	208.76	328.80	214.79
AIC	100.72	102.39	102.36	102.41	162.40	104.44
BIC	102.69	106.34	106.31	106.35	166.40	110.35

Figure 14. Parametric fitting of the ToT curve (AChR-Ab+)



The cohort in the efgartigimod arm post permanent discontinuation is assumed to worsen towards baseline health-states distribution, i.e. disease activity recorded at trial entry in ADAPT study. The distribution between health-states observed at baseline in the ADAPT study is overall representative of the expected population level distribution of disease activity in gMG patients with MG-ADL of at least 5 despite treatment with Standard of Care. This assumption is in line with the long-term simulation of effect in the Standard of Care arm and it is supported by clinical experts involved in the model validation.

It was assumed that most patients return to their baseline health states gradually over 6 months from time of permanent treatment discontinuation. For the remaining patients a residual effect of efgartigimod was assumed, allowing them to remain in the MG-ADL <5. This assumption is based on three different pieces of evidence that, although based on small sample sizes, all point towards a residual treatment effect after permanent discontinuation of efgartigimod.

8.3.2.1. ADAPT and ADAPT+

When considering the ADAPT+ population n=13 out of n=145 pts received only one cycle of efgartigimod for the entire duration of the study (3 years), suggesting a long-lasting treatment effect after the first infusions [ADAPT+ CSR]. Therefore, it seems plausible to consider that a similar proportion of long-responders would apply in the cohort of those who discontinue the treatment due to adverse events or intolerance. Based on this concept, we analysed the available MG-ADL data post permanent discontinuation in both ADAPT and ADAPT+.

In the ADAPT trial, of the five patients who discontinued treatment with efgartigimod, two had an MG-ADL score <5 on the last exposure time point and one remained at an MG-ADL score <5 after 154 days [Figure 2].

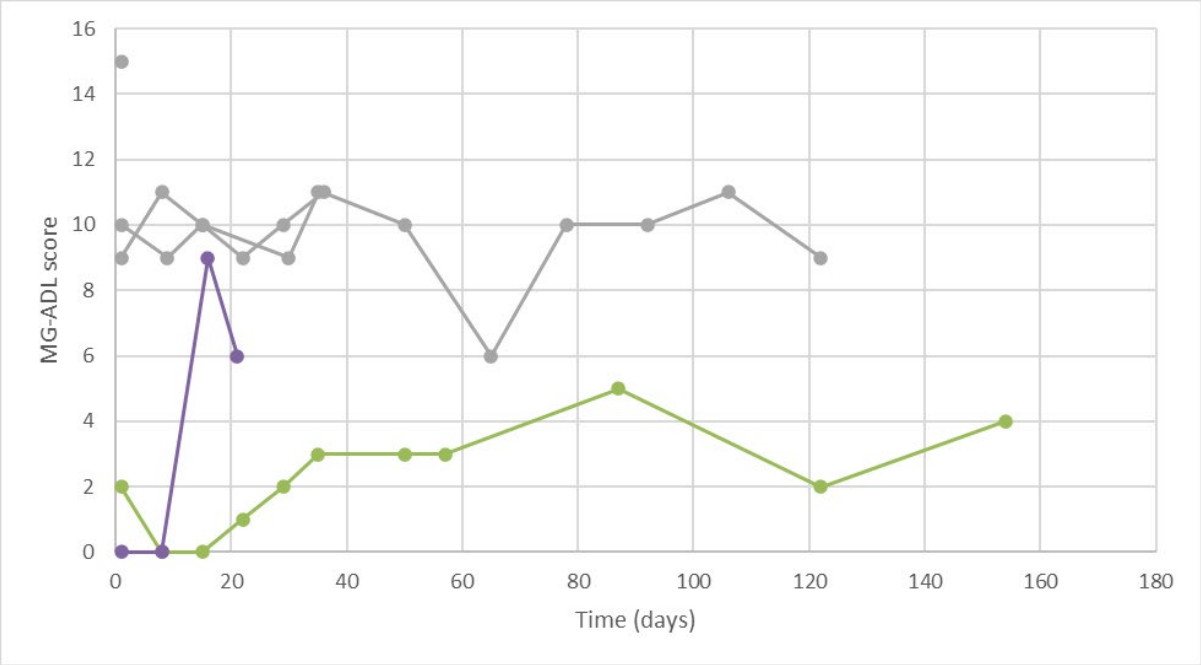


Figure 15. MG-ADL trajectories following permanent discontinuation for patients discontinuing efgartigimod treatment in ADAPT

In the ADAPT+ trial, of the 39 patients who permanently discontinued treatment with efgartigimod, ten had an MG-ADL score <5 at the last exposure time point, and six remained at an MG-ADL score <5, with the last MG-ADL measurement recorded between 80 and 260 days after the last efgartigimod exposure (mean: 155 days) [Figure 3].

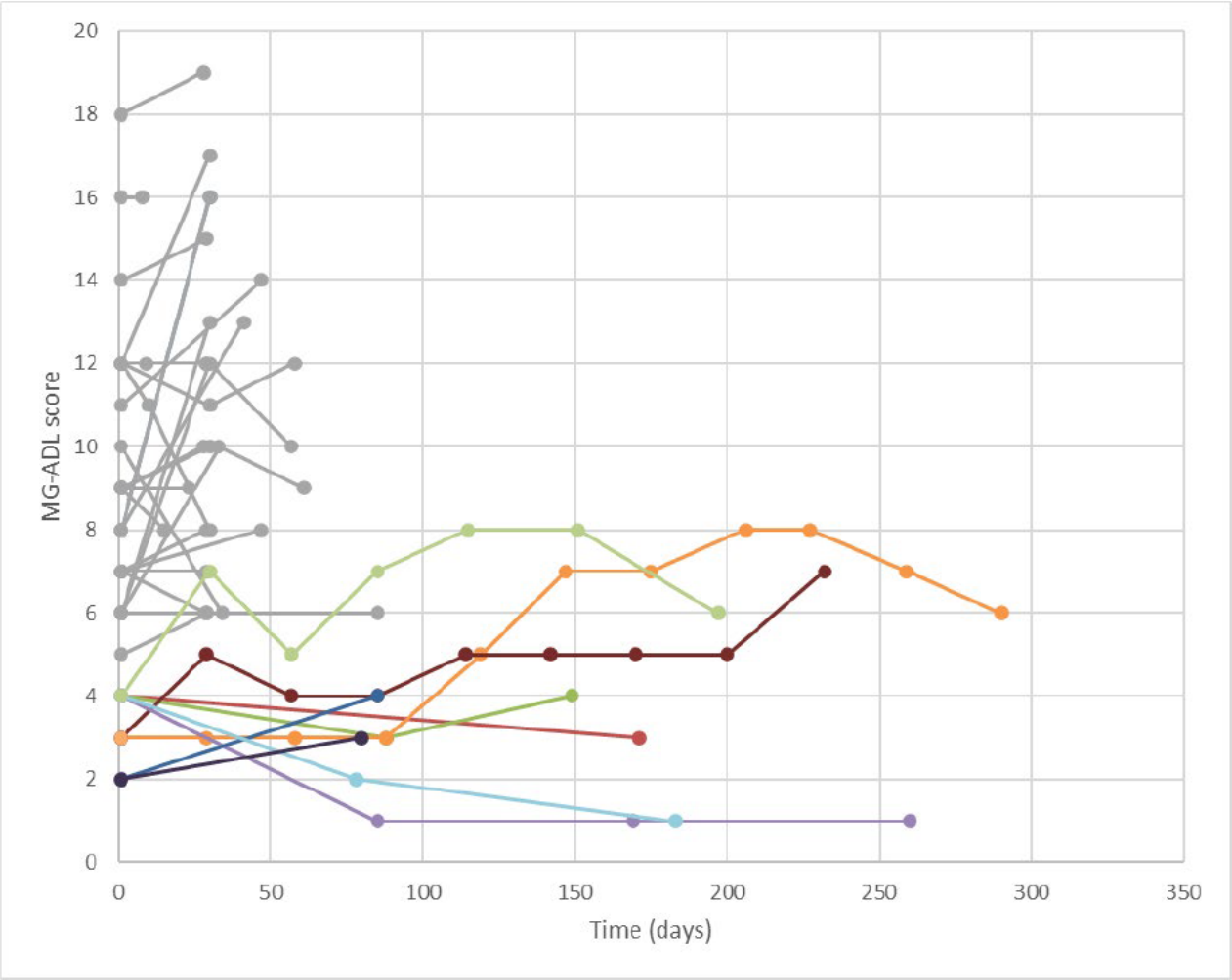


Figure 16. MG-ADL trajectories following permanent discontinuation for patients discontinuing efgartigimod treatment in ADAPT +

Table 3 summarizes the number of patients who maintained an MG-ADL score <5 after permanent efgartigimod discontinuation based on ADAPT and ADAPT+ trials and the respective mean and range of follow-up.

Table 25. Summary of number of patients keeping the MG-ADL score below 5 after the permanent efgartigimod discontinuation based on ADAPT and ADAPT+ trials

Clinical trial	Number of patients with MG-ADL score < 5 after the last infusion	Number of patients with MG-ADL score < 5 in the last measurement who had MG-ADL score < 5 after the last infusion	Follow-up (days) Median (range)
ADAPT	2	1	154 (NA)
ADAPT+	10	6	155 (80; 260)

Overall, more than half patients who had MG-ADL scores <5 at the time of permanent treatment discontinuation maintained the residual efgartigimod effect for an average of 5 months after the last treatment exposure.

8.3.2.2. Real-world evidence from US patients who received efgartigimod

In addition to the data from ADAPT and ADAPT+, an additional analysis has been performed, using data from real-world evidence (RWE) from the US, which confirmed the findings from ADAPT and ADAPT+. In this analysis, 70-75% of patients who had an MG-ADL score <5 at time of permanent treatment discontinuation, still had MG-ADL<5 at the time of their latest MG-ADL measure, which was on average more than four months after their last infusion [146].

8.3.2.3. Evidence from efgartigimod in other indications

To further supplement the data in gMG from ADAPT/ADAPT+, signals of ongoing efgartigimod treatment effect following permanent discontinuation have also been observed in both our Immune Thrombocytopenic Purpura (ITP) & Pemphigus Vulgaris/ Pemphigus Foliaceus (PV/PF) efgartigimod clinical development programmes [147, 148].

8.3.2.3.1. Immune Thrombocytopenic Purpura [147]

In the Phase II study of efgartigimod in adult patients with primary immune thrombocytopenia (ITP), patients were randomly assigned in a 1:1:1 ratio to receive four weekly doses of either placebo, efgartigimod at a dose of 5 mg/kg body weight, or efgartigimod at a dose of 10 mg/kg body weight, administered as an intravenous infusion. The patients were then followed for up to 21 weeks.

Whilst most patients who responded to efgartigimod had a transient increase in platelet counts, with counts returning to baseline levels in the treatment-free follow-up period, at least 3 of 26 (11.5%) efgartigimod-treated patients (two newly diagnosed; one chronic) with ITP remained in remission throughout the follow-up period.

8.3.2.3.2. Pemphigus Vulgaris/ Pemphigus Foliaceus [148]

In the Phase II study of efgartigimod in PV/PF, an open-label, multicenter study aimed to determine the optimal dose and posology, efgartigimod as hypothesized, demonstrated a reduction in total IgG levels. However, unlike total IgG, which returned to baseline levels after discontinuation of efgartigimod treatment (with a 10-week treatment-free follow-up), autoreactive antibody levels remained low in several study participants. This suggests a sustained reduction in autoantibody levels during efgartigimod treatment and indicates potential disease modification in peripheral lymphocytes in some patients even after treatment cessation.

Furthermore, argenx were recently informed by a German Phase II efgartigimod PV/PF study investigator, that two patients currently on minimal dose levels of steroids only (5 mg/day and 2.5 mg every other day, respectively), remain in clinical remission following their last efgartigimod dose in 2020.

argenx plans to explore this further in Phase III trials, to in part, help us understand if efgartigimod has the potential to modify disease course in certain patients.

8.3.2.4. Proportion assumed to remain in MG-ADL <5 health state

Based on the evidence presented above, the company believes that it is reasonable to assume that 15% of patients remain at MG-ADL<5 after six months following permanent discontinuation from efgartigimod. Given that the discontinuation data presented indicate a potential for 50–70% of patients to have residual treatment benefits, the company believes assuming 15% remain in the least severe health state to be a reasonable assumption.

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

8.4.1.1. General population utility values

The gender- and age-specific utility of the general population was used to adjust the utility values for aging of the cohort over the time horizon of the analysis (Table 25). The utility in the Danish general population by age was obtained from the values reported in the DMC MethodsGuide.[146]

Table 26. Coefficients of the linear and mixed models

Age range of the general population	Utility value
18–29	0.87
30–39	0.85
40–49	0.83
50–59	0.82
60–69	0.81
70+	0.72

8.4.1.2. Health-state utility values

The utility values in MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states were obtained from observations in ADAPT. The non-clinical SLR identified four full publications and one conference abstract, but only one record reported an economic evaluation. Moreover, the data were deemed insufficient as they were sourced from only six patients treated with rituximab at a single centre. Few of the identified studies reported information on QoL utilities, nonetheless this was not included in the submitted CE due to the availability of EQ-5D data from ADAPT. In ADAPT, EQ-5D-5L data were collected at 1-week intervals while patients were on-treatment and at 2-week intervals while patients were off-treatment (Table 26). The Danish EQ-5D-5L value sets were applied to obtain utility values specific for the Danish population.[147]

Table 27. Number of EQ-5D respondents by visit

Analysis visit	Efgartigimod (N=65)	Placebo (N=64)
Cycle 1		
Cycle Baseline	65	64
Week 1	65	61
Week 2	65	63
Week 3	64	63
Week 4	64	63
Week 5	61	59
Week 6	63	62
Week 7	62	62
Week 8	71	62

Week 10	55	59
Week 12	26	17
Week 14	16	17
Week 16	14	15
Week 18	12	13
Week 20	9	11
Week 22	6	11
Week 24	5	9
Week 26	4	8
Week 28	0	1
Cycle 2		
Cycle Baseline	51	43
Week 1	51	42
Week 2	51	43
Week 3	50	42
Week 4	47	42
Week 5	49	42
Week 6	47	42
Week 7	48	42
Week 8	51	41
Week 10	44	38
Week 12	8	7
Week 14	2	5
Week 16	0	3
Week 18	0	3
Cycle 3		
Cycle Baseline	7	1
Week 1	6	1
Week 2	6	1
Week 3	6	1
Week 4	6	1
Week 5	6	1
Week 6	6	1
Week 7	6	1
Week 8	10	2
Week 10	1	0

Utility values in MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 were estimated by regressing the EQ-5D utilities on the health state and the treatment arm. From a theoretical point of view, health states in a Markov model are meant to fully capture discrete disease stages, including their associated QoL utility, and therefore a treatment effect is generally not considered appropriate. However, in the current case, the treatment effect is a statistically significant variable in the regression analysis for EQ-5D, indicating that MG-ADL is not fully capturing the effect of efgartigimod on gMG patients. Therefore, if the treatment effect were to be neglected and utilities estimated only based on health-state effect, the benefit of efgartigimod would likely be underestimated.

The fact that treatment effect is a statistically significant variable indicates that within each of the MG-ADL ranges defining the model health-states, there are additional differences between efgartigimod and SoC which by themselves may explain part of the variation in the HRQoL of patients. When a treatment effect is present and significant in the regression, this can be considered in two ways:

- The health states are not granular enough, i.e., two patients in the same health state can have a different utility because the health state is too broad. If this is the case, when health states are redefined to offer greater granularity, the treatment effect disappears from the regression.
- If the treatment effect does not disappear, it means that the instrument used to define health states, in this case, MG-ADL is not capturing something that is instead captured by EQ-5D or vice versa. In the absence of being able to redefine the health states, the use of a treatment effect may be acceptable.

The regression was implemented using a mixed model with both fixed and random effects (Table 27). The analysis was based on the AChR-Ab+ population, in line with the cohort simulated in the model.

The mixed model is an extension of the linear model and is used to analyse longitudinal data from multiple patients. With longitudinal data, the EQ-5D observations belonging to the same patient have a higher correlation. Because of that, the results of a linear model could be misleading as they may reflect a pattern that is only observable in the aggregate data, but different from what would be observed if the data from a single patient were considered. The mixed model addresses this issue by acknowledging that the longitudinal EQ-5D observations from each patient may have a different pattern. Thus, the parameters of the model, which refer to the entire population and not to a specific patient, are subject to a certain degree of uncertainty and vary randomly within a certain range. A fixed and a random term are introduced in the model for each parameter assumed to differ between patients. The fixed term represents the expected value of the parameter in the entire sample, while the random term represents its variability.

The model considers health state and treatment as fixed effect, and a subject-level random effect with unstructured covariance matrix. That is, a random term for the intercept is introduced, meaning that the average EQ-5D utility of the entire sample is assumed to vary among the patients. The EQ-5D utility in the MG-ADL <5 health state in the efgartigimod arm is used as reference (model intercept). All other values by health state and treatment arm are coefficients representing the difference in EQ-5D utility vs the reference value. The resulting utility values are presented in Table 29.

Table 28. Coefficients of the mixed model used to derive utility values by health state (ADAPT data, AChR-Ab+)

Variable	Mixed model

	Coefficient	SE	p value
Intercept (MG-ADL<5)	0.914	0.0164	0.00000
MG-ADL 5–7	-0.044	0.0065	0.00000
MG-ADL 8–9	-0.104	0.0078	0.00000
MG-ADL ≥10	-0.175	0.0105	0.00000
Conventional therapy	-0.083	0.0230	0.00043

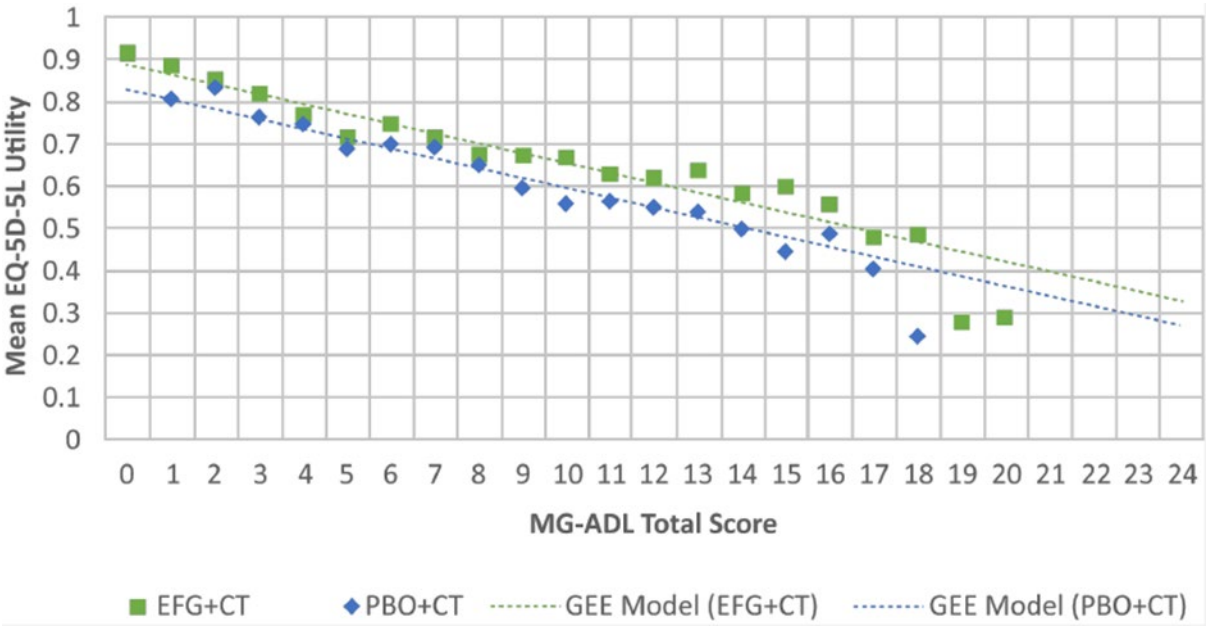
Additional evidence supporting treatment effect on HRQoL for each MG-ADL score

The efgartigimod effect on the HRQoL was confirmed in a recently published regression analysis [148] of data from ADAPT (entire population of AChR-Ab- and AChR-Ab+ patients), where MG-ADL is treated as a continuous variable, showing the existence of a treatment effect (Figure 15). A normal ID regression estimated the association between utility and the eight domains of the MG-ADL from the ADAPT study. A Generalized Estimating Equations model was then estimated to predict utility based on the patient's total MG-ADL score and treatment received by considering MG-ADL score and treatment as independent variables.

Results of the modelling presented in the publication show that there is a statistically significant lower utility value for conventional care compared with efgartigimod treatment for the same health states. Efgartigimod+CT-treated patients experienced an additional improvement in utility for the same MG-ADL score, in line with what was observed in the mixed model regression estimated to derive utility values by health-state.

Thus, this additional evidence, on the HRQoL difference between efgartigimod and placebo at each MG-ADL point, supports the inclusion of treatment effect in the calculation of utilities, to fully capture the benefit provided by the treatment.

Figure 17 Association between MG-ADL total score and EQ-5D-5L utility values by treatment (UK utilities value set)



Note: Regression results on utility from the GEE model are represented by the dashed lines.

Alternative approach to model health-state utilities in the analysis

In addition, the model includes the flexibility to run the analysis using utility values estimated based on averages of observed data by health state. In this case, the model uses a mixed model regression with data from the MyRealWorld MG (ARG-MG-2019-01) study, with MG-ADL<5 as the reference (ie, intercept).[76] The coefficients for this regression analysis are reported in Table 28. The resulting utility values by health state are applied to both the efgartigimod and conventional therapy arms of the model (Table 29). The impact of this alternative option is explored in a scenario analysis.

Table 29. Coefficients of the mixed model regression using the ARG-MG-2019-01 study data to derive utility values by health state

Variable	Coefficient	SE	p value
Intercept (MG-ADL<5)	0.870	0.008	0.00000
MG-ADL 5–7	-0.110	0.010	0.00000
MG-ADL 8–9	-0.170	0.012	0.00000
MG-ADL ≥10	-0.313	0.012	0.00000

Table 30. Overview of utility values by health state (MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10) – base case and alternative scenario (Danish utilities value set)

	Mixed model regression on ADAPT data		Mixed model regression on ARG-MG-2019-01 data
	Efgartigimod	Conventional therapy	All patients
MG-ADL <5	0.91	0.83	0.87
MG-ADL 5–7	0.87	0.79	0.76
MG-ADL 8–9	0.81	0.73	0.70
MG-ADL ≥10	0.74	0.66	0.56

Since no patient had a crisis during the ADAPT time horizon, data from the ARG-MG-2019-01 study were used to inform the utility in the crisis health state. In the ARG-MG-2019-01 study, EQ-5D-5L data were collected at 1-month intervals. To calculate the HRQoL related to crises, all the timepoints were pooled and the observations were stratified by their baseline MGFA class. The average utility of the MGFA Class V of 0.41 was used in the model as proxy for the HRQoL value during crisis.[76]

8.4.1.3. Utility decrements

8.4.1.3.1. Corticosteroid-related utility decrements

Despite the fact that normally the effect on utility values of a therapy used during a trial would be captured in the overall EQ-5D-data collected during that trial, it was decided to include the disutility of corticosteroid use in the model separately, in this case the effect of corticosteroids has been accounted for separately in the model for the following two reasons:

- By using data solely based on the ADAPT clinical trial it is not certain for how long patients are on corticosteroid and this may not be reflective of long-term systemic use. This is of particular relevance in the case of the current model, given that the time horizon is the lifetime of the patient;
- Additionally, it allows the potential differentiation as a consequence of steroid-sparing strategies. Essentially, by adding an additional layer of disutility to both treatment arms this allows the observation of the impact of lower steroid use on quality of life that is not directly observable from the clinical trial. This is likely due to differences in high and low corticosteroid use as a consequence of distinct disease progression in the two treatment arms.

Among the available immunosuppressive therapies, oral CS remain a first-line treatment option and are still the most common agents used for long-term immunosuppression for the management of MG.[152] CS have been widely prescribed in several chronic conditions for their immunosuppressant and anti-inflammatory effects, but evidence regarding the impact of CS on HRQoL is scarce. CS-related AEs, particularly in patients on high-dose and/or long-term regimens, can have a negative impact on patient quality of life.[153]

A systematic literature review on the humanistic and economic burden of gMG was conducted (see Appendix N: Systematic literature review: Clinical and economic impact of chronic use of corticosteroids). No studies were identified that reported the impact of CS on QoL in gMG patients, but evidence on the impact of CS use in other chronic diseases was found. Considering only studies that reported utility values by CS dose, two studies were identified for inclusion in order to define the utility decrements associated with high-dose and low-dose systemic CS use compared with no CS treatment. Bexelius et al[154] conducted a Swedish study that evaluated the impact of CS use on QoL and costs in systemic lupus erythematosus (SLE) patients. CS dosage was a statistically significant predictor for total costs and HRQoL, with a lower HRQoL reported in the high-dose and low-dose groups (EQ-5D 0.61) vs the no-CS group (0.70). The study by Sullivan et al[155] was conducted in US and UK cohorts and explored the impact of systemic CS use on HRQoL on a range of chronic conditions. CS use appeared to be associated with a significantly lower EQ-5D score compared to no exposure, and the greatest adverse impact was reported for patients on high-dose CS.

Based on the evidence retrieved from the literature, the current model includes a utility decrement related to CS use differentiated by dose (high vs low dose), estimated by averaging the utility decrements obtained from the two studies noted earlier (Table 31).

Table 31. Utility decrements associated with systemic CS use

Systemic corticosteroid use	Utility decrement
High-dose corticosteroid use	-0.18
Low-dose corticosteroid use	-0.07

8.4.1.3.2. Utility decrements due to exacerbations

Exacerbations are associated with a temporary reduction of HRQoL. This is reflected in the model by introducing a utility decrement at the occurrence of each exacerbation (Table 30). The disutility is applied for each exacerbation for an average duration of 14 days. The disutility per exacerbation was derived from Van Wilder et al,[149] assuming severe allergic rhinitis as a proxy since both conditions require use of high-dose corticosteroids and hospitalisation.

A TLR (June 2021) was conducted to identify available literature reporting the impact on quality of life in terms of utility decrement associated to myasthenia gravis exacerbation and myasthenic crisis. The following search strategy was implemented in PubMed:

- ("myasthenia gravis"[All Fields] OR "myasthenia gravis exacerbation"[All Fields] OR "myasthenia gravis crisis"[All Fields]) AND ("eq5d"[All Fields] OR "utility value"[All Fields]).

Three publications were retrieved and subjected to full text screening to determine relevance (Mendoza et al. 2020, de Meel et al. 2020, Winter et al. 2010). However, the impact of exacerbations or crisis in quality of life were not reported. Due to the lack of available evidence, in the model, the utility decrement of severe allergic rhinitis derived from Van Wilder et al, is used as a proxy, considering that both diseases require hospitalization as part of their management, and the prescription of high-dose corticosteroids is a common clinical decision to treat acute worsening of both conditions.

Based on the TLR strategy described above, an average hospitalization number of days for patients diagnosed with acute MG exacerbation and myasthenic crisis were obtained. In order to collect all relevant studies published, an additional search strategy was created on PubMed (June 2021) to identify relevant sources reporting the average hospitalization days for patients during an acute exacerbation of the disease with the following terms:

- ("myasthenia gravis"[All Fields] AND "exacerbations"[All Fields] AND "hospitalization"[All Fields])

A total of 5 publications were retrieved, but only one study (Gummi et al. 2019) mentioned the outcome of interest.

Table 32. Temporary HRQoL decrement per exacerbation

	Value in the model	Source
Disutility of exacerbation	-0.16	Van Wilder et al, 2019 (assuming severe allergic rhinitis as a proxy)[149]
Average exacerbation duration (days)	20.73	Gummi et al, 2018[150]; Sakaguchi et al, 2012[151]; Mandawat et al, 2010[143]; Alshekhlee et al, 2009[144]

8.4.1.3.3. Caregiver utility decrements

The base case does not include the effects (utility and disutility/utility decrements) for caregivers into the model. However, the impact of these effects was explored in one of the scenario analyses and the results are reported in Section 8.7.3.

No studies were identified reporting caregiver disutility in gMG. Therefore, an ad hoc search was conducted to identify caregiver disutility in conditions characterised by progressive disability (disease worsening), with stages of severity that could be linked to the gMG disease activity scale (MG-ADL) used in the current analysis. Caregiver disutility at different severity stages of multiple sclerosis (MS) as measured using the Patient Determined Disease Steps (PDDS) scale was therefore used as a proxy for caregiver disutility in the different gMG health states in the conventional therapy arm, based on caregiver HRQoL data reported in the MS study by Acaster et al., 2013 [156]. No difference in caregiver disutility between treatment arms was assumed for a given health state (Table 32). This means that the higher utility value of the cohort in the efgartigimod arm resulted in a lower caregiver disutility.

Table 33. Caregiver disutility values by health state

	Efgartigimod arm	Conventional therapy arm
MG-ADL <5	0.00	-0.02
MG-ADL 5–7	0.00	-0.07
MG-ADL 8–9	-0.04	-0.13
MG-ADL ≥10	-0.10	-0.19
Crises	-0.28	-0.28

8.5. Resource use and costs

The following costs were considered in the analysis:

- Drug acquisition and administration
- Costs related to reduction in CS use
- Cost of patient monitoring
- Cost of complications associated with the chronic use of corticosteroids
- Cost of rescue treatments
- Cost of treatment-emergent AEs
- Cost of transportation
- Cost of the use of time of patients and caregivers

The current analysis was developed with the aim of including costs that would closely represent the actual costs of treatment in Denmark. Conservative estimates of the least expensive medications were used instead of a weighted average based on sales data. Where needed, costs were updated to 2022 prices using the Consumer Price Index (CPI) published by Statistics Denmark, with the 2022 value set as the average CPI from 2017 to 2021.[157]

All the relevant inputs are listed in Appendix L: Costs inputs.

8.6. Results

8.6.1. Base case overview

A summary overview of base-case settings for the CEA is presented in Table 33.

Table 34. Base-case model settings

Model settings	Description
Population	AChR+ gMG patients with MG-ADL ≥5 despite use of conventional therapy
Age at start and % female	46.9 years; 66.7% female
Health states	MG-ADL<5,MG-ADL 5-7, MG-ADL 8-9, MG-ADL ≥10, crisis, and death
Time horizon	Lifetime
Cycle length	4 weeks

Model settings	Description
Intervention	Efgartigimod 10 mg/kg per infusion + conventional therapy
Comparator	Conventional therapy
Perspective	Restricted societal perspective in Denmark
Discount rate (costs and outcomes)	3.5% (0–35 years), 2.5% (36–70 years), and 1.5% (>70 years)
Health state utilities	• EQ-5D-5L Danish value sets • Regression on utilities, health state, and treatment, based on ADAPT data (mixed model) • Utilities are adjusted for relative decrement associated with ageing of the cohort
Caregiver disutility	Not included in base case, just considered in scenario analysis. Based on mapping of Duchenne muscular dystrophy severity to gMG disease activity; adjusted to align with relative differences in patient utilities between efgartigimod and conventional therapy[158]
Transportation cost	Cost applied for drug administration, exacerbations, crises, and adverse events, based on the average kilometres (km) per visit to the hospital and the cost per km

8.6.2. Cost-effectiveness results

Table 34 presents summary results of the base-case CEA for efgartigimod vs conventional therapy, from the payer perspective in Denmark. Over the lifetime time horizon, there was a substantial gain in QALYs for patients who received efgartigimod [redacted]44) compared with those who received conventional therapy. This is partially attributable to gains in HRQoL in the efgartigimod arm as a result of more years spent in the least active health state (ie, MG-ADL <5), the higher utility associated with efgartigimod, and the lower mortality associated with a decrease in the CS dose.

Table 35. Pairwise comparison of costs (DKK), LYs, and QALYs between efgartigimod and conventional therapy

	Costs	Disc Costs	LY	Disc LY	QALY	Disc QALY
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efgartigimod vs conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LY, life years; QALY, quality adjusted life-years

Table 35 and Table 36 present the disaggregated undiscounted and discounted costs, respectively, across the time horizon in the efgartigimod and conventional therapy arms. Increased total costs with efgartigimod are almost entirely attributable to drug acquisition cost. The cost components that are notably higher in the conventional therapy arm are costs associated with treatment administration, disease monitoring, CS-related chronic complications, crises, AEs, and use of time (patient and caregiver). The total discounted lifetime cost in the efgartigimod arm was [redacted] than in the conventional therapy arm.

Table 36. Undiscounted cost (DKK) breakdown by category

	Drug acquisition	Drug admin	Disease monitoring	Exacerbations	CS related chronic complications	Crises	AEs	Transport. cost	Use of time	TOTAL
Efgartigimod	[redacted]									
Conventional therapy	[redacted]									
Efgartigimod vs conventional therapy	[redacted]									

Table 37. Discounted cost (DKK) breakdown by category

	Drug acquisition	Drug admin	Disease monitoring	Exacerbations	CS related chronic complications	Crises	AEs	Transport. cost	Use of time	TOTAL
Efgartigimod	[redacted]									
Conventional therapy	[redacted]									

Efgartigimod vs conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Considering the incremental gain with efgartigimod of [redacted] QALYs at an increased cost of DKK [redacted] he CEA yielded an ICER of DKK [redacted] /QALY for efgartigimod vs conventional therapy (Table 37).

Table 38. Incremental cost-effectiveness ratios (ICER) for efgartigimod vs conventional therapy

	Incr Cost (DKK)/ Incr LYs	Incr Cost (DKK)/ Incr QALYs	Discounted Incr Cost (DKK)/ Incr LYs	Discounted Incr Cost (DKK)/ Incr QALYs
Efgartigimod vs conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]

8.7. Sensitivity analysis

8.7.1. Deterministic sensitivity analysis

In the one-way sensitivity analysis, the variables with the greatest influence on the ICER were the average weight (kg), efgartigimod RDI and administration cost of IVIg (Figure 16). Other influential variables were the proportion of patients on IVIg in the MG-ADL>=10 health-states on SoC, the proportion of patients MG-ADL>=10 health-states on SoC. Results are presented in Table 38.

[redacted]

Table 39. Detailed results of the one-way sensitivity analysis

Parameter	ICER (DKK/QALY)	
	Lower	Upper
Base-case	[redacted]	

Average weight, kg	[redacted]	[redacted]
Discount rate costs, 0-35 years in model	[redacted]	[redacted]
Administration costs - Hospital administration, IVIG	[redacted]	[redacted]
Efgartigimod RDI	[redacted]	[redacted]
Immunoglobulin in MG-ADL≥ 10 SoC cohort (%)	[redacted]	[redacted]
% of patients in MG-ADL ≥10 health state	[redacted]	[redacted]
Immunoglobulin in MG-ADL8-9 SoC cohort (%)	[redacted]	[redacted]
% of patients in MG-ADL 5-7 health state	[redacted]	[redacted]

8.7.2. Probabilistic sensitivity analysis

In the PSA, [redacted] of iterations are in the North-East quadrant (Figure 17) of the cost-effectiveness plane (ie, positive incremental benefit and higher incremental cost)), being the remaining [redacted] of the simulations in the South-East quadrant (i.e., positive incremental benefit and savings in terms of costs), resulting in [redacted] of simulations indicating that efgartigimod could be dominating. The base-case ICER and the PSA mean ICER were similar, confirming the overall robustness of the model results (Table 39). The cost-effectiveness acceptability curve is presented in Figure 18.

[redacted]

Table 40. Comparison of the base case and PSA results

	Cost (DKK)			QALYs			ICER (DKK/QALY)
	EFG	Conv Tx	Incr	EFG	Conv Tx	Incr	
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PSA 95%CI lower	[redacted]						
PSA 95%CI upper	[redacted]						

EFG, efgartigimod; Conv Tx, conventional therapy; Incr, incremental

[redacted]

[redacted]

8.7.3. Scenario analyses

Results of the scenario analyses are shown in Table 40. Except the scenarios related to the administration cost of IVIg and the percentage of patients remaining in the MG-ADL<5 after the permanent efgartigimod discontinuation, variation in the source of evidence to model the extrapolation of efgartigimod effect does not appear to impact the results importantly, thus supporting the current modelling approach.

Regarding the scenario analyses related to the IVIg administration costs it is important to note that a Danish neurologist was consulted about the best DRG code to consider for IVIg administration and the opinion received was that 01MP08 (139,891 DKK) is the most appropriate, as it refers to "treatment with high dose immunoglobulin for disease in nervous system" and also that the 01MA18 DRG code was not so appropriate because it is a general cost referred to "observation for disease in the nervous system". This feedback supports our base case approach. The assumption of assuming the 01MA18 for all the health states could be also considered unreasonable because that does not account for the difference in resources between acute and chronic patients, which is large.

About the proportion of patients in MG-ADL<5, the company believes that percentages below 15% are unreasonable since the ADAPT and ADAPT+ trials showed an important proportion of patients where efgartigimod had a residual effect, meaning they remained in MG-ADL<5 even though it was based on a small sample size.

Table 41. Scenario analyses for efgartigimod vs conventional therapy

Scenario description	Efgartigimod vs conventional therapy			
	Incr Cost (DKK)	Incr QALYs	ICER DKK/QALY	ICER % change
Base case	[redacted]	[redacted]	[redacted]	[redacted]
1. CS high-dose threshold of 10 mg/day	[redacted]	[redacted]	[redacted]	[redacted]
2. Low-dose CS in MG-ADL <5 cohort	[redacted]	[redacted]	[redacted]	[redacted]
3. Utilities from mixed model regression using MyRealWorld MG data	[redacted]	[redacted]	[redacted]	[redacted]
4. Allow vial sharing	[redacted]	[redacted]	[redacted]	[redacted]
5. Loss of exclusivity discount of 24% after 10 years	[redacted]	[redacted]	[redacted]	[redacted]
6. Efgartigimod extrapolations based only on ADAPT trial	[redacted]	[redacted]	[redacted]	[redacted]
7. Include caregivers utility decrements	[redacted]	[redacted]	[redacted]	[redacted]
8. Equal adverse events incidence in both treatment arms	[redacted]	[redacted]	[redacted]	[redacted]
9. Assume 01MA18 (24,572 DKK) only for IVIg admin cost	[redacted]	[redacted]	[redacted]	[redacted]
10. Assume 01MA18 (24,572 DKK) for all health states, and no separate admin costs	[redacted]	[redacted]	[redacted]	[redacted]
11. Assume that 5% of patients remain in MG-ADL <5 after permanent discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
12. Assume that 10% of patients remain in MG-ADL <5 after permanent discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

CS, corticosteroids.

Table 41 and Figure 19 show the relationship between the value of the discount applied to the efgartigimod price (ranging from 0 to 40%) and the resulting incremental cost-effectiveness ratio (ICER).

[redacted]

Table 42. Relationship between discount rate (% reduction) of efgartigimod price and ICER

Efgartigimod price		ICER (Kr/QALY)
% change on price	Price per vial (Kr)	Efgartigimod vs Standard of Care
[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]

9. Budget impact analysis

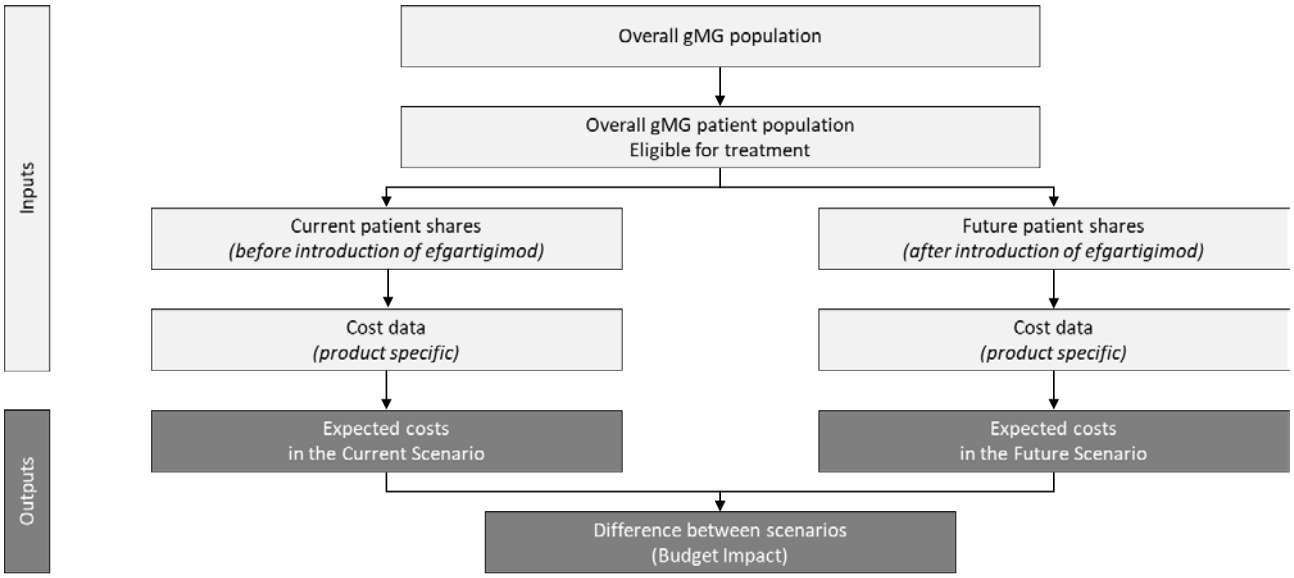
9.1. Study objective and overview of analysis

The aim of this analysis is to estimate the budget impact for the introduction and use of efgartigimod as an add on to conventional therapy in the treatment of adult patients with AChR+ gMG in Denmark. The analysis has been developed within the cost-effectiveness model.

The BIM is population-based and estimates the budgetary impact of reimbursing efgartigimod. Figure 20 provides an overview of the model structure. The following two scenarios are compared:

- Scenario without efgartigimod (or Current Scenario), where efgartigimod is not available as an option for the treatment of gMG.
- Scenario with efgartigimod (or Future Scenario), where efgartigimod is available and used as an add-on option for the treatment of gMG (in addition to conventional therapy) in a proportion of patients between 0% and 100%.

Figure 22. Overview of the BIM structure



The base case was developed using a restricted societal perspective and covers a 5-year time horizon. Resource and cost inputs relevant to this perspective, including direct medical costs and the costs incurred by public health services to treat gMG-related hospitalizations and manage treatment-related adverse events have been included. From an economic perspective, this analysis evaluates whether the cost of treating patients with efgartigimod can be offset by savings due to improved patient outcomes and/or a reduction in other drug costs and healthcare resource utilization. Given the relatively short time horizon, outcomes and costs are not discounted.

9.1.1. Treatments included in the BIM

This BIM is directly derived from the CEM developed by argenx. Data inputs are therefore aligned with the CEM. Consistent with the current treatment pathway of gMG in Denmark, the following treatment options are included in the analysis:

- Efgartigimod (only in the Future Scenario). Efgartigimod is administered in addition to conventional therapy.

- Conventional therapy alone (in both Current and Future Scenarios). This includes CS, AChEis, and NSISTs. The model considers use of maintenance IVIg only for a proportion of cohort with more severe disease.
- Chronic Ig therapy (in both Current and Future Scenarios).

9.1.2. Estimation of efgartigimod-eligible population

The cohort entering the model is the adult population in Denmark affected by gMG. The population eligible for efgartigimod comprises all patients affected by gMG who are also AChR-Ab+ (Table 42).

Table 43. Estimation of efgartigimod-eligible population

Population type	Estimate	N of prevalent patients	N of incidence patients	Source
Country population – adults (N)	-	4,041,719		[78]
MG prevalence (N per 100,000 subjects)	27.2	1,100	-	[17, 76]
MG incidence (N per 100,000 subjects)	0.9	-	37	[17]
Proportion of patients with generalized MG (%)	78%	859	29	[77]
Proportion of patients with AChR-Ab+ gMG	94%	811	27	[68]

An estimated [redacted] patients ([redacted] prevalent patients + [redacted] incident patients) would be considered eligible for efgartigimod treatment during the first year of introduction of efgartigimod. Based on this initial Y1 estimate and the yearly incidence, there would be [redacted] patients eligible for treatment with efgartigimod in Y2, Y3, Y4 and Y5, respectively, following the introduction of efgartigimod (Table 43).

Table 44. Cumulative estimations of efgartigimod-eligible population

Population type	Year 1	Year 2	Year 3	Year 4	Year 5
Efgartigimod-eligible population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.1.3. Estimation of efgartigimod-treated population

The distribution of patients by treatment received in the Current and Future Scenarios has been estimated internally by argenx based on market data and expert opinion (Table 44).

Table 45. Estimation of the efgartigimod-treated population and relative market shares

Scenario without efgartigimod							**Scenario with efgartigimod**						
Patients (n)							**Patients (n)**						
Treatment	***Y1***	***Y2***	***Y3***	***Y4***	***Y5***		***Treatment***	***Y1***	***Y2***	***Y3***	***Y4***	***Y5***
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic Ig	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Chronic Ig	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share (%)							**Market share (%)**						
Treatment	***Y1***	***Y2***	***Y3***	***Y4***	***Y5***		***Treatment***	***Y1***	***Y2***	***Y3***	***Y4***	***Y5***
Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Efgartigimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Conventional therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic Ig	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Chronic Ig	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual patient numbers are rounded and therefore totals for each year may differ slightly.

9.2. Results

The results of the budget impact analysis show that the introduction and progressive utilization of efgartigimod will result in an increase in overall costs of approximately [redacted] by Year 5 (Table 45). The expected efgartigimod expenditure will increase from around [redacted] in Year 1 to around [redacted] at Year 5 (Figure 21). Additional details concerning the BIM are provided in Appendix O: Efgartigimod budget impact analysis: technical report.

[redacted]

Figure 23. Expected efgartigimod expenditure

[redacted]

In this budget impact analysis to estimate the potential cost impact for Denmark using a restricted societal perspective, the introduction of efgartigimod in the market is expected to [redacted] pharmacological expenditure by DKK [redacted] over the 5-year forecast. This increase [redacted] Treatment with efgartigimod brings provides a relevant health benefit for patients, who achieve better disease control, in terms of reduced frequency of crises and exacerbations, and reduced CS use, in addition to a substantial improvement in HRQoL. Therefore, the benefits realized by the publicly funded healthcare payer are even greater.

10. Discussion on the submitted documentation

A pharmacoeconomic model has been developed in which health-state transitions and associated costs for patients with AChR-Ab+ gMG are compared between efgartigimod and conventional therapy. The model incorporates key clinical data from the ADAPT RCT and ADAPT+, the open-label extension of ADAPT, and is customized to the Danish healthcare setting. Key model parameters were validated by clinical experts.

Over the lifetime horizon, there was a gain of [redacted] QALYs for patients who received efgartigimod compared with those who received conventional therapy. This is partially attributable to gains in HRQoL in the efgartigimod arm as a result of more years spent in the least advanced health state (ie, MG-ADL <5), the higher utility associated with efgartigimod, and the lower mortality associated with a decrease in the CS dose.

In the discounted base-case analysis, the total lifetime cost for a patient treated with efgartigimod was [redacted] which is DKK [redacted] more than the lifetime costs incurred by a patient treated with conventional therapy [redacted]. The resulting ICER for efgartigimod compared with conventional therapy was DKK [redacted] /QALY.

Interpretation of the results of this CEA should consider the value of a clinically efficacious drug treating a small and well-defined group of patients who have a serious chronic disease that has thus far lacked clinically proven treatment options. Moreover, management is suboptimal, with physicians resorting to several off-label products. Therefore, efgartigimod should be viewed as a cost-effective breakthrough to reduce the burden of gMG on patients, caregivers, and society.

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Appendix A: Systematic literature review: Treatment of gMG

The objective of the SLR was to inform the Danish Vyvgart™ (efgartigimod) HTA submission for the treatment of gMG. The SLR was designed to identify all relevant clinical and non-clinical evidence (eg, economic evaluations, healthcare resource use [HCRU], costs, and utilities) for the use of efgartigimod and other interventions of interest in the treatment of adult patients with active gMG. The clinical searches identified randomized controlled trials (RCTs) and open-label extensions (OLEs) of RCTs that assessed and reported the clinical efficacy of relevant gMG treatments. Adverse event (AE) data from these clinical trials was also captured. In addition to published economic analyses, the non-clinical searches sought to identify studies that reported healthcare cost, resource utilization estimates, and utilities pertinent to gMG.

11.1. Clinical SLR

The process of study identification was divided into searches of bibliographic databases to identify published studies and non-database search methods to identify in-process, unpublished, or grey literature.

Literature searching

Electronic databases

Bibliographic databases were searched from database inception using predefined search strategies. The search strategy for the Clinical SLR was designed as follows:

- **Clinical:** ((search terms and synonyms for gMG) AND (search filters for: randomized or controlled studies))

The Clinical searches were not limited by language or date and were not specific to any interventions to ensure that publications with non-standard terminology for the interventions of interest are captured.

The following bibliographic databases were searched for the Clinical SLR:

- MEDLINE®, 1946 to present (OVID)
- MEDLINE In-Process & Other Non-Indexed Citations (OVID)
- MEDLINE Epub Ahead of Print (OVID)
- Embase, 1980 to present (OVID)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- PubMed (NLM)—e-publications only
- Database of Abstracts of Reviews of Effects (DARE) (CRD)
- Health Technology Assessment (HTA) database (CRD)
- International HTA (INAHTA) database
- Conference Proceedings Citation Index-Science (CPCI-S), 1990 to present (Web of Science, Clarivate Analytics)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Presentations Database

Manual searches

In addition to bibliographic databases, several non-database sources were searched for relevant clinical study data, including the following trial registries:

- ClinicalTrials.gov
- EU Clinical Trials Register
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)

Hand-searching of conference abstracts from the past two years (2020–2022) from the following proceedings was conducted:

- European Academy of Neurology (EAN) Congress
- American Academy of Neurology (AAN) Annual Meeting
- Peripheral Nerve Society (PNS) Annual Meeting

To supplement this search, conference abstracts from proceedings that are indexed in Embase or CPCI-S were identified in the database search. The database search was conducted from 2020 to align with the timeframe of the manual search.

Bibliographies of relevant systematic reviews or meta-analyses identified via a targeted search were hand-searched for applicable clinical studies.

Processing the searches

Search results were exported to EndNote X9 (Clarivate Analytics, Philadelphia, PA; available at: www.endnote.com) where a file for each database or resource searched was saved. De-duplication was undertaken in Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; available at: www.covidence.org). The process of study identification, and de-duplication, was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.

Study selection

Two levels of screening (title–abstract and full-text screening) using predefined Population, Intervention, Comparator, Outcome, and Study design (PICOS) criteria was performed during study selection. PICOS criteria for the Clinical SLR are listed in Table A1.

Title–abstract screening was conducted independently by two researchers using Covidence systematic review software. At the onset of the screening phase, the two researchers pilot-tested the inclusion criteria on a subset of citations to ensure consistency between researchers and reliability of study selection. The Covidence software offers the option of “yes/no/maybe” for article inclusion. Articles that are designated as “Yes” or "Maybe" at the title–abstract screening stage are advanced to full-text screening. Articles were advanced to full-text screening in case of doubt by either researcher or in case of disagreement not remedied through discussion. No study was excluded at title–abstract screening due to insufficient information.

The full-text publications of citations that progress through title–abstract screening were retrieved for further review. As with title–abstract screening, screening of full-text publications was conducted by two independent researchers using Covidence systematic review software. The same inclusion and exclusion criteria used in title–abstract screening was applied during full-text screening.

Disagreements were resolved through discussion or, if necessary, by consulting a third researcher. Studies were excluded if they did not meet the inclusion criteria; if preliminary results were presented in abstract form only; or if they were duplicate publications, narrative reviews, editorials, or letters. The study selection results are presented in the PRISMA flow chart format.

Although the searches were not limited by language, publications in a language other than English were screened out at full-text review with the exclusion criterion "Language other than English" for simplified retrieval at a later date.

Table A47. Study selection (PICOS) criteria for identifying clinical evidence

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with gMG	• Children (<18 years) • Patients with ocular MG only • Mixed populations (eg, adults and children, gMG and MG/ocular MG, etc) if data for target population are not reported separately
Intervention	• Eculizumab • Efgartigimod • Immunoglobulin therapy (IV and SC) • Plasmapheresis • Rituximab	• Any intervention other than those listed for inclusion
Comparators	• Placebo • Standard of care with or without placebo and/or background medication • Active intervention (ie, head-to-head trials)	• No comparator (ie, single-arm trials; except for OLEs of RCTs where no comparator is permitted) • Non-pharmacologic therapies, other than plasmapheresis (eg, physiotherapy)

Criteria	Inclusion criteria	Exclusion criteria
Outcomes	**Efficacy/HRQoL** • MG-ADL response/change from baseline/proportion of responders • QMG response/change from baseline/proportion of responders • MGC response/change from baseline/proportion of responders • MGQoL15 response/change from baseline/proportion of responders • Change in corticosteroid dose **Safety** • Incidence of any AEs, TEAEs, and SAEs • Mortality, including treatment-related mortality • Discontinuation due to AEs	• Pharmacodynamic/ pharmacokinetic outcomes • Non-clinical outcomes (eg, gene or protein expression outcomes) • General laboratory measures, unless reported as a safety outcome (eg, ALT, AST, etc)

Criteria	Inclusion criteria	Exclusion criteria
Study design	• RCTs (phases I–IV) • Randomized crossover trials • Long-term follow-up studies (eg, open-label follow-up studies with continuation of treatment)	• Non-randomized trials (except OLEs of RCTs are included) • Single-arm trials • Dose-finding studies that do not include a control arm • Studies reporting pooled data from >1 trial • Studies with sample size of ≤10 patients • Observational studies (retrospective and prospective) • Case-control studies • Preclinical studies • Animal studies • Prognostic studies • Case reports • Commentaries and letters • Consensus reports • Systematic and non-systematic reviews*
Limits	• Conference presentations published on or after March 1, 2020 • English language†	• Conference presentations published before March 1, 2020

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; gMG, generalized myasthenia gravis; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite scale; MG-QOL15, Myasthenia Gravis 15-item Quality of Life scale; OLE, open-label extension; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis scale; RCT, randomized controlled trial; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event.
*Relevant systematic reviews were searched for studies but not included.
†Publications in languages other than English were tagged during screening for record-keeping purposes, but were not included.

11.2. Non-Clinical SLR

Literature searching

Electronic databases

Bibliographic databases were searched from database inception using predefined search strategies. The search strategy for the Non-Clinical SLR was designed as follows:

- **Non-clinical:** ((search terms and synonyms for gMG) AND (search filters for: economics/costs/resource use OR health-related quality of life OR utility questionnaires))

The non-clinical searches were not limited by language and were not specific to any interventions to ensure that publications with non-standard terminology for the interventions of interest were captured. A 10-year date limit was applied to the non-clinical searches to capture more recent cost data.

The following bibliographic databases were searched for relevant non-clinical evidence:

- MEDLINE®, 1946 to present (OVID)
- MEDLINE In-Process & Other Non-Indexed Citations (OVID)
- MEDLINE Epub Ahead of Print (OVID)
- Embase, 1980 to present (OVID)
- PubMed (NLM)—e-publications only
- Database of Abstracts of Reviews of Effects (DARE) (CRD)
- Health Technology Assessment (HTA) database (CRD)
- International HTA (INAHTA) database
- Conference Proceedings Citation Index-Science (CPCI-S), 1990 to present (Web of Science, Clarivate Analytics)
- Econlit, 1886 to present (EBSCOhost)
- National Health Service (NHS) Economic Evaluation Database (EED)
- ScHARR Health Utilities Database (HUD)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Presentations Database

Manual searches

In addition to bibliographic databases, the following HTA websites were searched for relevant technology appraisals:

- The National Institute for Health and Care Excellence (NICE)
- Scottish Medicine Consortium (SMC)
- Pharmaceutical Benefits Advisory Committee (PBAC)
- Institute for Quality and Efficiency in Healthcare (IQWiG)
- Canadian Agency for Drugs and Technologies in Health (CADTH)

Conference proceedings searched in the Clinical SLR were also screened using the Non-Clinical SLR PICOS criteria.

Processing the searches

Searches were processed as summarized in the methods for the Clinical SLR.

Study selection

Non-clinical evidence (economic analyses, HCRU/cost, utilities) was assessed for relevance using the predefined PICOS criteria outlined in Table A2 using the same process as for the Clinical SLR.

Economic analyses, and cost and HCRU data, were included if associated with an intervention of interest as noted in Table A2. Utility evidence was not restricted to the interventions of interest to enable identification of disease-specific utilities.

Although the searches were not limited by language, publications in a language other than English were screened out at full-text review with the exclusion criterion "Language other than English" for simplified retrieval at a later date.

Records published prior to 2012 were excluded at the screening stage with the rationale that costing and HCRU data are expected to have evolved substantially over 10 years, minimizing the relevance of older costing/HCRU data.

The Non-Clinical SLR searches were designed to identify economic analyses, HCRU, and cost evidence regardless of region. Studies with no UK or European data were screened out with the exclusion criterion "Cost data - non-UK/Europe" at the full-text screening stage. The restriction to the UK/European region did not apply to utility evidence.

Table A48. Study selection (PICOS) criteria for identifying non-clinical evidence

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adults (≥18 years) with gMG	• Children (<18 years) • Patients with ocular MG only • Mixed populations (eg, adults and children, gMG and MG/ocular MG, etc) if data for target population are not reported separately
Interventions	Economic analyses, cost, HCRU evidence: • Eculizumab • Efgartigimod • Immunoglobulin therapy (IV and SC) • Plasmapheresis • Rituximab Utility evidence: • No interventions (disease-specific utilities)	Economic analyses, cost, HCRU evidence: • Any intervention other than those listed for inclusion Utility evidence: • None

Criteria	Inclusion criteria	Exclusion criteria
Comparators	• All	• None

Outcomes	• Economic evaluation outcomes
	  • ICERs
	  • QALYs
	  • LYs
	  • DALYs
	• Direct costs/HCRU:
	  • Medication costs
	  • Outpatient visits
	  • Hospitalization costs (emergency room or hospital visits)
	  • Laboratory costs
	  • Diagnostic costs
	  • Physician costs
	  • Resource-use estimates
	  • Cost per treatment success, per remission, or per QALY
	  • Costs of AEs
	  • Cost of concomitant therapies
	• Indirect costs/productivity loss:
	  • Productivity loss costs (wages lost because of travel or absences from work)
	  • Out-of-pocket expenses
	  • Travel costs for patients and caregivers
	  • WPAI
	• Utilities:
	  • EQ-5D
	  • HUI
	  • TTO
	  • SG
	  • DCE
		• None

Study design	• Economic analyses (cost-effectiveness, cost-utility, cost-benefit, cost-minimization analyses) • Prospective or retrospective studies reporting costs, resource utilization, or utilities (including mapping studies)	• Commentaries and letters • Consensus reports • Systematic and non-systematic reviews* • Articles reporting cost estimates not based on data (eg, publications making general reference to cost burden)

Criteria	Inclusion criteria	Exclusion criteria
Limits	• Publication on or after January 1, 2012 • Conference presentations published on or after March 1, 2020 • English language† • CEA/cost/HCRU publications reporting any relevant UK/European data‡	• Publication prior to January 1, 2012 • Conference presentations published before March 1, 2020 • CEA/cost/HCRU publications not reporting any UK/European data‡

DALY, disability-adjusted life year; DCE, discrete choice experiment; HCRU, healthcare resource use; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; IV, intravenous; LY, life year; MRI, magnetic resonance imaging; QALY, quality-adjusted life year; SC, subcutaneous; SG, standard gamble; TTO, time trade-off; WPAI, Work Productivity and Activity Index.
*Relevant systematic reviews were searched for studies but not included.
†Publications in languages other than English were tagged during screening for record-keeping purposes, but were not included.
‡The SLR searches identified economic analyses, HCRU, and cost evidence regardless of region. At the full-text screening stage, studies with no UK or European data were excluded with a reason (ie, non-UK/European data).

11.3. Results

A total of 3,136 unique records were identified for the Clinical and Non-Clinical SLR, of which 323 full-text publications were screened using predefined PICOS criteria, resulting in inclusion of 54 records across both reviews (Figure A1). These included:

- 50 records included in the Clinical SLR, representing 21 unique studies
- 5 records included in the Non-Clinical SLR, one of which was also included in the Clinical SLR

A total of 30 full reports, 9 conference abstracts, and 16 trial registry entries were included across five different interventions: eculizumab, efgartigimod, immunoglobulin, plasmapheresis, and rituximab. As data on rituximab, eculizumab, long-term use of immunoglobulin and plasmapheresis were not deemed relevant to the Danish setting, studies investigating these interventions have not been presented in the application. Focus on the Danish treatment landscape resulted in only one clinical study being included in the application: the ADAPT RCT, which compared efgartigimod add-on therapy plus standard of care (corticosteroids and NSISTs) with placebo plus standard of care.

Of the five records included in the Non-Clinical SLR, only one reported an economic evaluation. The study was a retrospective analysis of rituximab at a single centre that also reported costs (in Euros) and QALYs. The other four records reported on HCRU or utilities in patients with myasthenia gravis. Three of these records, all of which focused on quality of life, were cited in the application (Andersen et al. 2021; Barnett et al. 2019; Dewilde et al. 2021).

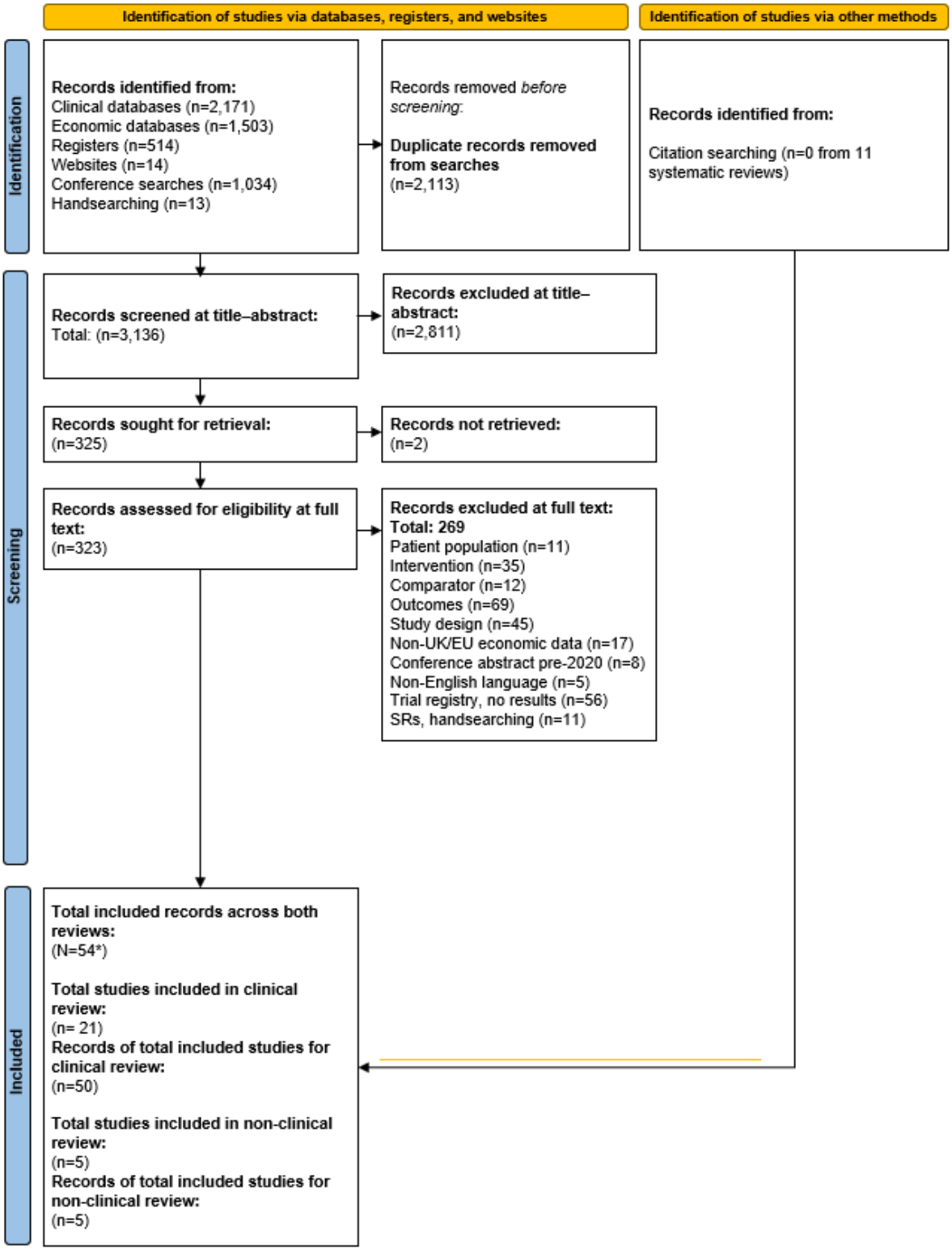

Figure A24. PRISMA flow chart

*One record was identified for inclusion in both the Clinical and Non-Clinical SLRs

11.4. List of included records

1. Alipour-Faz A, Shojaei M, Peyvandi H, et al. A comparison between IVIG and plasma exchange as preparations before thymectomy in myasthenia gravis patients. *Acta Neurol Belg.* 2017;117(1):245-249.
2. Andersen LK, Jakobsson AS, Revsbech KL, Vissing J. Causes of symptom dissatisfaction in patients with generalized myasthenia gravis. *J Neurol.* 2021;21:21.
3. Barnett C, Bril V, Bayoumi AM. EQ-5D-5L and SF-6D health utility index scores in patients with myasthenia gravis. *Eur J Neurol.* 2019;26(3):452-459.
4. Barnett C, Wilson G, Barth D, Katzberg HD, Bril V. Changes in quality of life scores with intravenous immunoglobulin or plasmapheresis in patients with myasthenia gravis. *J Neurol Neurosurg Psychiatry.* 2013;84(1):94-97.
5. Barth D, Nabavi Nouri M, Ng E, Nwe P, Bril V. Comparison of IVIg and PLEX in patients with myasthenia gravis. *Neurology.* 2011;76(23):2017-2023.
6. Bril V, Murai H, Vu T, et al. Analysis of efgartigimod efficacy across patient populations and myasthenia gravis specific scales: Results of the phase 3 ADAPT study. *Ann Neurol.* 2021;90(SUPPL 27):S28.
7. ClinicalTrials.gov. Safety and Efficacy Study of Eculizumab in Patients With Refractory Generalized Myasthenia Gravis (NCT00727194). 2008; https://clinicaltrials.gov/show/NCT00727194. Accessed June 27, 2022.
8. ClinicalTrials.gov. Safety and Efficacy of Eculizumab in Refractory Generalized Myasthenia Gravis (REGAIN Study) (NCT01997229). 2013; https://clinicaltrials.gov/show/NCT01997229. Accessed June 27, 2022.
9. ClinicalTrials.gov. BeatMG: Phase II Trial of Rituximab In Myasthenia Gravis (NCT02110706). *https://clinicaltrials.gov/show/NCT02110706* 2014; https://clinicaltrials.gov/show/NCT02110706. Accessed June 27, 2022.
10. ClinicalTrials.gov. Extension Study of ECU-MG-301 to Evaluate Safety and Efficacy of Eculizumab in Refractory Generalized Myasthenia Gravis (NCT02301624). 2014; https://ClinicalTrials.gov/show/NCT02301624. Accessed June 27, 2022.
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13. ClinicalTrials.gov. A Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of ARGX-113 in Patients With Myasthenia Gravis Who Have Generalized Muscle Weakness. 2016; https://clinicaltrials.gov/show/NCT02965573. Accessed June 27, 2022.
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16. EU Clinical Trials Register. A Randomized, Double-Blind, Placebo-Controlled, Cross-Over, Multi-Center Study of Eculizumab in Patients with Generalized Myasthenia Gravis (gMG) Who Have Moderate to Severe Muscle Weakness Despite Treatment with Immunosuppressants. - C08-001. 2009; https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-014669-13. Accessed June 27, 2022.
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https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002191-41. Accessed June 27, 2022.
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21. EU Clinical Trials Register. A Study of the Safety and Effectiveness of ARGX-113 in Patients with Myasthenia Gravis who Have Generalized Muscle Weakness. 2016; https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-002938-73.
22. EU Clinical Trials Register. A Randomized, Double-Blind, Placebo-Controlled Multicenter Trial to Evaluate the Safety and Efficacy of Rituximab (Mabthera) in Subjects With New Onset Myasthenia Gravis: The Rinomax Study 2016; https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-005749-30. Accessed June 27, 2022.
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26. Howard J, Bril V, Vu T, et al. Long-term safety, tolerability, and efficacy of efgartigimod in patients with generalized myasthenia gravis: Interim results of the ADAPT+ study. Presented at: American Academy of Neurology Annual Meeting; April 2-7, 2022; Seattle, WA.
27. Howard J, Bril V, Mantegazza R, et al. Additional analyses of the phase 2 efgartigimod study in myasthenia gravis. *Neurology.* 2020;94(15).
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41. Mantegazza R, O'Brien FL, Yountz M, Howard JF. Consistent improvement with eculizumab across muscle groups in myasthenia gravis. *Ann Clin Transl Neurol.* 2020;7(8):1327-1339.
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53. Yeh JH, Chiu HC. Plasmapheresis in myasthenia gravis. A comparative study of daily versus alternately daily schedule. *Acta Neurol Scand.* 1999;99(3):147-151.
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11.5. List of excluded records

Record	Reason for exclusion
A randomized, doubleblind, placebo-controlled multicenter trial to evaluate the safety and efficacy of rituximab (Mabthera) in subjects with new onset myasthenia gravis; the RINOMAX study.	Population
Aldrich J, Pundole X, Tummala S, et al. Immune checkpoint inhibitor-related myositis: A retrospective cohort study. *Annals of the Rheumatic Diseases.* 2020;79(SUPPL 1):399.	Population
Alsop T, Williams K, Gomersall S. Physical Activity and Sedentary Behaviour in People with Myasthenia Gravis: A Cross-Sectional Study. *Journal of neuromuscular diseases.* 2022;9(1):137-146.	Population
De Meel RHP, Barnett C, Bril V, Tannemaat MR, Verschuuren JJGM. Myasthenia Gravis Impairment Index: Sensitivity for Change in Generalized Muscle Weakness. *Journal of Neuromuscular Diseases.* 2020;7(3):297-300.	Population
Howard FM, Jr., Duane DD, Lambert EH, Daube JR. Alternate-day prednisone: preliminary report of a double-blind controlled study. *Annals of the New York Academy of Sciences.* 1976;274:596-607.	Population
Mantegazza R, Antozzi C, Peluchetti D, Sghirlanzoni A, Cornelio F. Azathioprine as a single drug or in combination with steroids in the treatment of myasthenia gravis. *Journal of Neurology.* 1988;235(8):449-453.	Population
Mendoza M, Tran C, Bril V, Katzberg HD, Barnett C. Patient-acceptable symptom states in myasthenia gravis. *Neurology.* 2020;95(12):e1617-e1628.	Population
Nagane Y, Utsugisawa K, Obara D, Kondoh R, Terayama Y. Efficacy of low-dose FK506 in the treatment of Myasthenia gravis--a randomized pilot study. European Neurology. 2005;53(3):146-150.	Population
Nct. The Efficacy and Safety of Leflunomide or Azathioprine Therapy in Myasthenia Gravis Patients After Expand Thymectomy. *https://clinicaltrials.gov/show/NCT01727193.* 2012.	Population
Sieb JP, Kohler W. Benefits from sustained-release pyridostigmine bromide in myasthenia gravis: results of a prospective multicenter open-label trial. Clinical Neurology & Neurosurgery. 2010;112(9):781-784.	Population
Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. *Neurology.* 2007;68(11):837-841.	Population

Fang W, Li Y, Mo R, et al. Hospital and healthcare insurance system record-based epidemiological study of myasthenia gravis in southern and northern China. *Neurological Sciences.* 2020;41(5):1211-1223.	Intervention
Harris L, Graham S, MacLachlan S, Exuzides A, Jacob S. Healthcare resource utilization by patients with treatment-refractory myasthenia gravis in England. *Journal of Medical Economics.* 2019;22(7):691-697.	Intervention
Ignatova V, Kostadinov K, Vassileva E, et al. Socio-Economic Burden of Myasthenia Gravis: A Cost-of-Illness Study in Bulgaria. *Frontiers in Public Health.* 2022;10:822909.	Intervention
Zhang Q et al. Real-World Resource Utilization and Productivity Loss among Patients with Myasthenia Gravis in Sweden: A Nationwide Population-based Study. 2022.	Intervention
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Ravulizumab in Complement-Inhibitor-Naïve Adult Patients With Generalized Myasthenihttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-003243-39.	Intervention
Bril V, Benatar M, Andersen H, et al. Efficacy and Safety of Rozanolixizumab in Moderate to Severe Generalized Myasthenia Gravis: A Phase 2 Randomized Control Trial. *Neurology.* 2021;96(6):e853-e865.	Intervention
De Feo LG, Schottlender J, Martelli NA, Molfino NA. Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. *Muscle & Nerve.* 2002;26(1):31-36.	Intervention
Di L, Shen F, Wen X, et al. A Randomized Open-Labeled Trial of Methotrexate as a Steroid-Sparing Agent for Patients With Generalized Myasthenia Gravis. *Frontiers in Immunology.* 2022;13:839075.	Intervention
Euctr CZ. A prospective, randomized, double-blind, placebo controlled, parallel group, multicenter, 36-weeks trial to assess the efficacy and safety of adjunct mycophenolate mofetil (MMF) to maintain or improve symptoms control with reduced corticosteroids in subje. 2005.	Intervention
Euctr DE. An optional continuation of double-blind treatment for subjects who have achieved good symptom control with stable prednisone dosing and who have completed Protocol WX17798 (A prospective, randomized, double-blind, placebo-controlled, parallel group, mult. 2005.	Intervention
Euctr DE. Study to test the safety, tolerability and efficacy of UCB7665 in subjects with moderate to severe myasthenia gravis.&#x0D. 2016.	Intervention
Gajdos P, Elkharrat D, Chevret S, et al. A randomised clinical trial comparing prednisone and azathioprine in myasthenia gravis. Results of the second interim analysis. *Journal of Neurology Neurosurgery and Psychiatry.* 1993;56(11):1157-1163.	Intervention
Heckmann JM, Rawoot A, Bateman K, Renison R, Badri M. A single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in generalized myasthenia gravis. *BMC Neurology.* 2011;11:97.	Intervention
Howard JF, Nowak RJ, Wolfe GI, et al. Clinical Effects of the Self-administered Subcutaneous Complement Inhibitor Zilucoplan in Patients with Moderate to Severe Generalized Myasthenia Gravis: Results of a Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial. *JAMA Neurology.* 2020;77(5):582-592.	Intervention
Howard JF, et al. Long-term Efficacy and Safety of Ravulizumab, a Long-acting Terminal Complement Inhibitor, in Adults with Anti-Acetylcholine	Intervention

Receptor Antibody-Positive Generalized Myasthenia Gravis: Results from the Phase 3 CHAMPION MG Open-label Extension. 2022.	
Lindberg C, Andersen O, Lefvert AK. Treatment of myasthenia gravis with methylprednisolone pulse: a double blind study. *Acta Neurologica Scandinavica.* 1998;97(6):370-373.	Intervention
Meriggioli MN, Rowin J. Single fiber EMG as an outcome measure in myasthenia gravis: results from a double-blind, placebo-controlled trial. *Journal of Clinical Neurophysiology.* 2003;20(5):382-385.	Intervention
Meriggioli MN, Rowin J, Richman JG, Leurgans S. Mycophenolate mofetil for myasthenia gravis: a double-blind, placebo-controlled pilot study. *Annals of the New York Academy of Sciences.* 2003;998:494-499.	Intervention
Nct. Efficacy of Methotrexate in Myasthenia Gravis. https://clinicaltrials.gov/show/NCT00814138. 2008.	Intervention
Nct. Study to Test the Safety, Tolerability and Efficacy of UCB7665 in Subjects With Moderate to Severe Myasthenia Gravis. 2017.	Intervention
Nct. Safety and Efficacy Study of RA101495 in Subjects With Generalized Myasthenia Gravis. https://clinicaltrials.gov/show/NCT03315130. 2017.	Intervention
Nct. Safety and Efficacy Study of Ravulizumab in Adults With Generalized Myasthenia Gravis. https://clinicaltrials.gov/show/NCT03920293. 2019.	Intervention
Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. *Neurology.* 1998;50(6):1778-1783.	Intervention
Pasnoor M, He J, Herbelin L, et al. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. *Neurology.* 2016;87(1):57-64.	Intervention
Sanders DB. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. *Neurology.* 2008;71(6):394-399.	Intervention
Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. *Neurology.* 2008;71(6):400-406.	Intervention
Sharshar T, Porcher R, Demeret S, et al. Comparison of Corticosteroid Tapering Regimens in Myasthenia Gravis: A Randomized Clinical Trial. *JAMA Neurology.* 2021;78(4):426-433.	Intervention
Tindall RS, Phillips JT, Rollins JA, Greenlee RG, Wells L, Belendiuk G. Ciclosporin in the treatment of myasthenia gravis. *Monographs in Allergy.* 1988;25:135-147.	Intervention
Tindall RS, Phillips JT, Rollins JA, Wells L, Hall K. A clinical therapeutic trial of cyclosporine in myasthenia gravis. *Annals of the New York Academy of Sciences.* 1993;681:539-551.	Intervention
Tindall RS, Rollins JA, Phillips JT, Greenlee RG, Wells L, Belendiuk G. Preliminary results of a double-blind, randomized, placebo-controlled trial of cyclosporine in myasthenia gravis. *New England Journal of Medicine.* 1987;316(12):719-724.	Intervention
Tindall RSA, Rollins JA, Phillips JT, Greenlee RG, Belendiuk G. A double-blind randomized placebo-controlled trial to assess the safety and efficacy of cyclosporin A in the treatment of myasthenia gravis. *Annals of the New York Academy of Sciences.* 1987;505:854-856.	Intervention
Tuan Vu et al. Efficacy and Safety of Ravulizumab, a Long-acting Terminal Complement Inhibitor, in Adults with Anti-Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis: Results from the Phase 3 CHAMPION MG Study. 2022.	Intervention

Yoshikawa H, Kiuchi T, Saida T, Takamori M. Randomised, double-blind, placebo-controlled study of tacrolimus in myasthenia gravis. *Journal of Neurology, Neurosurgery & Psychiatry.* 2011;82(9):970-977.	Intervention
Zang WJ. Clinical study of ia in the treatment of generalized myasthenia gravis. *China Foreign Med Treat.* 2015;29:7-8.	Intervention
Zhou L, Liu W, Li W, et al. Tacrolimus in the treatment of myasthenia gravis in patients with an inadequate response to glucocorticoid therapy: Randomized, double-blind, placebo-controlled study conducted in China. *Therapeutic Advances in Neurological Disorders.* 2017;10(9):315-325.	Intervention
A Phase 3, Randomized, Open-Label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of… https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-004085-19.	Comparator
Euctr ES. An open-label study to investigate the clinical efficacy of different dosing regimens of efgartigimod IV in patients with generalized myasthenia gravis. 2021.	Comparator
Euctr HU. Evaluating the Pharmacodynamic Noninferiority of Efgartigimod PH20 Administered Subcutaneously as Compared to Efgartigimod Administered Intravenously in Patients With Generalized Myasthenia Gravis. 2020.	Comparator
Euctr IT. A Phase 3b, Randomized, Open-label, Parallel-Group Study to Evaluate Different Dosing Regimens of Intravenous Efgartigimod to Maximize and Maintain Clinical Benefit in Patients With Generalized Myasthenia Gravis (gMG). 2021.	Comparator
Euctr NL. Evaluating the Pharmacodynamic Noninferiority of Efgartigimod PH20 Administered Subcutaneously as Compared to Efgartigimod Administered Intravenously in Patients With Generalized Myasthenia Gravis. *https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2020-004085-19-NL.* 2021.	Comparator
Gajdos P, Tranchant C, Clair B, et al. Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: A randomized double-blind clinical trial. *Archives of Neurology.* 2005;62(11):1689-1693.	Comparator
jRct J. A Phase 3 study of Efgartigimod PH20 SC in patient with Generalized Myasthenia Gravis. 2021.	Comparator
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Ephedrine as add-on therapy for patients with myasthenia gravis.	Outcomes
Long term safety study of amifampridine phosphate in patients with MuSK antibody positive and AChR antibody positive myasthenia gravis patients.	Outcomes
A Multi-center, Randomised, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy of Subcutaneous Injections of the Myasthenia Gravis Active Targeted Immunotherapy CV-MG0.	Outcomes
A multi-center, randomized, double-blind, placebo-controlled, parallel group study to preliminarily evaluate the safety, tolerability, pharmacokinetics and efficacy of CFZ533 in patients with moder.	Outcomes
A multicenter, prospective, open-label, non-controlled clinical trial to assess the efficacy and safety of Immune Globuline (Human), 10% Caprylate/Chromatography Purified (IGIV-C) in patients with.	Outcomes
An Open-label Extension Study of MOM-M281-004 to Evaluate the Safety, Tolerability, and Efficacy of M281 Administered to Patients with Generalized Myasthenia Gravis.	Outcomes
A phase 2 clinical trial assessing the efficacy and safety of adding cladribine for treatment modifying course of seropositive myasthenia gravis.	Outcomes
A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics and Pharmacodynamics of M281 Administered to Adults with.	Outcomes
A Phase 2, Randomized, Double Blind, Placebo Controlled Multicenter Study to Evaluate the Efficacy and Safety of ALXN2050 in Adult Participants with Generalized Myasthenia Gravis.	Outcomes
Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Nipocalimab Administered to Adults with Generali.	Outcomes
A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of tolebrutinib (SAR442168) in adults with generalized myasthenia gravis (MG).	Outcomes
A Phase 3b, Randomized, Open-label, Parallel-Group Study to Evaluate Different Dosing Regimens of Intravenous Efgartigimod to Maximize and Maintain Clinical Benefit in Patients With Generalized Mya.	Outcomes
A Phase II Double Blind, Cross-Over Study to Compare the Safety and Efficacy of 10, 20 and 40 mg Monarsen (EN101) administered to Patients with Myasthenia Gravis.	Outcomes
A Phase Iii, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Satralizumab in Patients with Generalized Myasth.	Outcomes
A Randomized, Double-Blind, Multicenter, Placebo-Controlled Phase 3 Study with Open-Label Period to Evaluate the Efficacy and Safety of Inebilizumab in Adults with Myasthenia Gravis.	Outcomes
A Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacodynamics of Belimumab in Subjects with Generalized Myasthenia Gravis (MG).	Outcomes
A Randomized, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Amifampridine Phosphate in Patients with MuSK Antibody Positive Myasthenia Gravis, and a Sample of AChR Antibody Pos.	Outcomes

A Randomized, Placebo-Controlled, Pilot Crossover Study to Evaluate the Effect of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with MuSK Antibody Positive Myasthenia Gravis.	Outcomes
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Dogra A, Rana K, Rathod C, Prakash S. Outcome of therapeutic plasma exchange in Myasthenia gravis patients. *Journal of Family Medicine & Primary Care.* 2020;9(12):5971-5975.	Non-UK/European economic data
Furlan JC, Barth D, Barnett C, Bril V. Cost-minimization analysis comparing intravenous immunoglobulin with plasma exchange in the management of patients with myasthenia gravis. *Muscle & Nerve.* 2016;53(6):872-876.	Non-UK/European economic data
Guptill JT, Sharma BK, Marano A, Soucy A, Krueger A, Sanders DB. Estimated cost of treating myasthenia gravis in an insured U.S. population. *Muscle & Nerve.* 2012;45(3):363-366.	Non-UK/European economic data
Kataoka H, Kiriyama T, Kawaguchi T, et al. Preoperative low-dose steroid can prevent respiratory insufficiency after thymectomy in generalized myasthenia gravis. *European neurology.* 2014;72:228-233.	Non-UK/European economic data
Kermode A, Lee Y. PND10 Assessing the Cost of Treatment for Myasthenia Gravis Crisis Patients in Australia. *Value in Health Regional Issues.* 2020;22(Supplement):S76.	Non-UK/European economic data

Kumar R, Birinder SP, Gupta S, Singh G, Kaur A. Therapeutic plasma exchange in the treatment of myasthenia gravis. *Indian J Crit Care Med*. 2015;19(1):9-13.	Non-UK/European economic data
Lean PL, Loo LK, Rajakumar S, et al. PMD13 Estimating the Cost of Treating Myasthenia Gravis Patient in a Single Public Hospital. *Value in Health Regional Issues.* 2020;22(Supplement):S61.	Non-UK/European economic data
Pei-Wen Lien et al. Cost-Effectiveness of Eculizumab and Efgartigimod for the Treatment of generalized Myasthenia Gravis. 2022.	Non-UK/European economic data
Phillips G, Abreu C, Goyal A, et al. Real-World Healthcare Resource Utilization and Cost Burden Assessment for Adults With Generalized Myasthenia Gravis in the United States. *Frontiers in neurology [electronic resource].* 2021;12:809999.	Non-UK/European economic data
Qi C et al. Hospitalization and Exacerbation Estimates of Efgartigimod Vs. Conventional Therapy in Generalized Myasthenia Gravis Patients: A Post-Hoc Analysis of the Phase 3 ADAPT Study. 2022.	Non-UK/European economic data
Qi C et al. Real-World Usage Patterns and Costs of IVIG Treatment in Adults with Generalized Myasthenia Gravis in the United States. 2022.	Non-UK/European economic data
Qi C et al. Numbers Needed to Treat and Costs per Improved Outcome Among Treatments for Myasthenia Gravis. 2022.	Non-UK/European economic data
Tice JA, Touchette DR, Lien PW, Agboola F, Nikitin D, Pearson SD. The effectiveness and value of eculizumab and efgartigimod for generalized myasthenia gravis. *Journal of Managed Care & Specialty Pharmacy.* 2022;28(1):119-124.	Non-UK/European economic data
Wolfe GI, Kaminski HJ, Cutter GR. Randomized Trial of Thymectomy in Myasthenia Gravis. *New England Journal of Medicine.* 2016;375(20):2006-2007.	Non-UK/European economic data
Effect of pyridostigmine (Mestinon®) on muscle strength in Myasthenia Gravishttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002599-15.	Trial registry record with no results posted
A Long-Term, Single-Arm, Open-label, Multicenter Phase 3 Study to Evaluate the Safety and Tolerability of Multiple Subcutaneous Injections of Efgartigimod PH20 SC in Patients With Generalized Myasthttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-004086-38.	Trial registry record with no results posted
A Long-Term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Trial of ARGX-113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis having Generalizedhttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-002133-37.	Trial registry record with no results posted
An Open-Label Extension Study to Evaluate Rozanolixizumab in Study Participants With Generalized Myasthenia Gravishttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-003230-20.	Trial registry record with no results posted
A Phase 2, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of TAK-079 in Patients With Generalized Myasthenia Gravishttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-003383-47.	Trial registry record with no results posted
A Phase 3, Multicenter, Open-Label Extension Study of Zilucoplan in Subjects with Generalized Myasthenia Gravishttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-001565-33.	Trial registry record with no results posted

A Phase 3, Multicenter, Randomized, Double Blind, Placebo-Controlled Study to Confirm the Safety, Tolerability, and Efficacy of Zilucoplan in Subjects with Generalized Myasthenia Gravishttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-001564-30.	Trial registry record with no results posted
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Efficacy and Safety of Rozanolixizumab in Adult Patients With Generalized Myasthenia Gravishttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-000968-18.	Trial registry record with no results posted
A Randomized, Open-Label Extension Study to Investigate the Long-Term Safety, Tolerability, and Efficacy of Rozanolixizumab in Adult Patients With Generalized Myasthenia Gravishttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-000969-21.	Trial registry record with no results posted
Single-Cell Deep Phenotyping of B Lymphocytes to Personalize Immunotherapy in Patients with Myasthenia Gravis: Clinical Trial to Evaluate the Efficacy and Safety of Ritxuximab in Generalized Achr-Ahttps://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-005619-35.	Trial registry record with no results posted
Chi CI. A prospective study of combined use of prednisone and methotrexate for the treatment of myasthenia gravis. 2015.	Trial registry record with no results posted
Chi CI. A prospective study of combined use of small doses of hormones and methotrexate for the treatment of myasthenia gravis. *https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR-IPR-15006081.* 2015.	Trial registry record with no results posted
ChiCtr. Different doses of methylprednisolone in the treatment of myasthenia gravis. *https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR1800018623.* 2018.	Trial registry record with no results posted
ChiCtr. Comparison of the efficacy of azathioprine and cyclosporine in myasthenia gravis immune modification. 2019.	Trial registry record with no results posted
Euctr DE. A Study to Confirm the Safety, Tolerability, and Efficacy of Zilucoplan in Patients with Generalized Myasthenia Gravis. 2019.	Trial registry record with no results posted
Euctr DE. Study to evaluate the safety and efficacy of ravulizumab in adult patients with generalized Myasthenia Gravis who have never been treated with a complement inhibitor. 2019.	Trial registry record with no results posted
Euctr DK. Effect of pyridostigmine (Mestinon®) on muscle strength in Myasthenia Gravis. 2017.	Trial registry record with no results posted
Euctr DK. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Efficacy and Safety of Rozanolixizumab in Adult Patients With Generalized Myasthenia Gravis. - MycarinGstudy. 2019.	Trial registry record with no results posted
Euctr ES. Intravenous immunoglobulin for preparing myasthenia gravis patients for thymectomy and other surgical procedures preventing myasthenic crisis. 2012.	Trial registry record with no results posted
Euctr ES. A study to investigate the long-term safety, tolerability, and efficacy of rozanolixizumab in adult patients with generalized myasthenia gravis. *https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2019-000969-21-ES.* 2019.	Trial registry record with no results posted
Euctr ES. Open-Label Extension Study of Zilucoplan in Subjects with Generalized Myasthenia Gravis. 2020.	Trial registry record with no results posted
Euctr GB. Open-Label Extension Study of Zilucoplan in Subjects with Generalized Myasthenia Gravis. 2019.	Trial registry record with no results posted
Euctr GB. A study to test efficacy and safety of rozanolixizumab in adult patients with generalized myasthenia gravis. 2019.	Trial registry record with no results posted

Euctr GB. A study to evaluate rozanolixizumab in study participants with generalized myasthenia gravis. 2020.	Trial registry record with no results posted
Euctr HU. Evaluating the Long-term Safety and Tolerability of Efgartigimod PH20 SC Administered Subcutaneously in Patients With Generalized Myasthenia Gravis. 2021.	Trial registry record with no results posted
Euctr IT. Single-Cell Deep Phenotyping Of B Lymphocytes To Personalize Immunotherapy In Patients With Myasthenia Gravis: Clinical Trial To Evaluate The Efficacy And Safety Of Ritxuximab In Generalized AChR-Antibody Positive Myasthenia Gravis. 2021.	Trial registry record with no results posted
Euctr NL. A safety and tolerability study of ARGX-113 in patients with myasthenia gravis who have generalized muscle weakness. 2018.	Trial registry record with no results posted
Irct20190205042629N. Comparison of the effect and Complications of Failure to do Plasmapheresis in Patients with Myasthenia Gravis. 2019.	Trial registry record with no results posted
JapicCti J. A study to test efficacy and safety of rozanolixizumab in adult patients with generalized myasthenia gravis. 2020.	Trial registry record with no results posted
Jprn U. Randomized comparative study on efficacy and safety of reduced-dose steroid combined with tacrolimus vs conventional-dose steroid in late- or elderly-onset myasthenia gravis patients. *https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-UMIN000007671.* 2012.	Trial registry record with no results posted
jRcts J. Prospective multi-center study on pathophysiological features of generalized myasthenia gravis(MG)patients treated with eculizumab. 2019.	Trial registry record with no results posted
Nct. Randomized Study of Intravenous Immunoglobulin in Patients With Mild or Moderate Myasthenia Gravis. *https://clinicaltrials.gov/show/NCT00004682.* 2000.	Trial registry record with no results posted
Nct. Randomized Study of Intravenous Immunoglobulin in Patients With Mild or Moderate Myasthenia Gravis <Scientific_title/> <Acronym/>. 2000.	Trial registry record with no results posted
Nct. FK506 Phase 3 Study: a Study for Steroid Non-resistant Myasthenia Gravis (MG) Patients. *https://clinicaltrials.gov/show/NCT00309088.* 2006.	Trial registry record with no results posted
Nct. Intravenous Immune Globulin Treatment Compared to Placebo in Patients With Myasthenia Gravis. *https://clinicaltrials.gov/show/NCT00306033.* 2006.	Trial registry record with no results posted
Nct. Mycophenolate Mofetil in Myasthenia Gravis. *https://clinicaltrials.gov/show/NCT00285350.* 2006.	Trial registry record with no results posted
Nct. Efficacy and Safety Study of GB-0998 for Treatment of Generalized Myasthenia Gravis. *https://clinicaltrials.gov/show/NCT00515450.* 2007.	Trial registry record with no results posted
Nct. A Study to Assess the Effect of CellCept (Mycophenolate Mofetil) and Reduced Corticosteroids in Controlling Symptoms of Myasthenia Gravis. 2008.	Trial registry record with no results posted
Nct. Trial of Mycophenolic Acid Versus Azathioprine in the Treatment of Corticosteroid-refractory Myasthenia Gravis. 2009.	Trial registry record with no results posted
Nct. Intravenous Immunoglobulin and Plasma Exchange in Myasthenia Gravis. *https://clinicaltrials.gov/show/NCT01179893.* 2010.	Trial registry record with no results posted
Nct. A Study to Compare the Efficacy and Safety of Tacrolimus Capsules in Patient With Myasthenia Gravis. 2011.	Trial registry record with no results posted
Nct. A Pilot Trial To Assess The Feasibility And Efficacy Of SCIG In Patients With MG Exacerbation (SCIG-MG). 2015.	Trial registry record with no results posted
Nct. A Study Evaluating the Safety and Efficacy of Rituximab in Patients With Myasthenia Gravis. 2016.	Trial registry record with no results posted
Nct. Effect of Pyridostigmine (Mestinon) on Muscle Strength in Myasthenia Gravis. *https://clinicaltrials.gov/show/NCT03510546.* 2018.	Trial registry record with no results posted

Nct. The Curative Effect of Extended Thymectomy Performed Through Subxiphoid-right VATS Approach With Elevation of Sternum. 2018.	Trial registry record with no results posted
Nct. The Impact of Myasthenia Gravis in the Real World. 2019.	Trial registry record with no results posted
Nct. Open-Label Extension of Zilucoplan in Subjects With Generalized Myasthenia Gravis. 2019.	Trial registry record with no results posted
Nct. A Phase 3 Study to Confirm the Safety, Tolerability, and Efficacy of Zilucoplan in Subjects With Generalized Myasthenia Gravis. *https://clinicaltrials.gov/show/NCT04115293.* 2019.	Trial registry record with no results posted
Nct. Safety, Tolerability, and Efficacy of Zilucoplan in Subjects With Generalized Myasthenia Gravis. 2019.	Trial registry record with no results posted
Nct. A Study to Investigate the Long-term Safety, Tolerability, and Efficacy of Rozanolixizumab in Adult Patients With Generalized Myasthenia Gravis. 2019.	Trial registry record with no results posted
Nct. A Study to Test Efficacy and Safety of Rozanolixizumab in Adult Patients With Generalized Myasthenia Gravis. 2019.	Trial registry record with no results posted
Nct. A Study to Evaluate Rozanolixizumab in Study Participants With Generalized Myasthenia Gravis. 2020.	Trial registry record with no results posted
Nct. Evaluating the Long-Term Safety and Tolerability of Efgartigimod PH20 SC Administered Subcutaneously in Patients With Generalized Myasthenia Gravis. 2021.	Trial registry record with no results posted
Nct. A Study of Nipocalimab Administered to Adults With Generalized Myasthenia Gravis. 2021.	Trial registry record with no results posted
Nice. [GID-TA10986] Efgartigimod for treating generalised myasthenia gravis [ID4003]. 2022.	Trial registry record with no results posted
Nice. [GID-TA10987] Ravulizumab for treating refractory antibody positive generalised myasthenia gravis [ID4019]. 2022.	Trial registry record with no results posted
Banerjee S, Adcock L. *Canadian Agency for Drugs and Technologies in Health. CADTH Rapid Response Reports.* 2018;08:14.	SR handsearched
Cadth. Rituximab for the Treatment of Myasthenia Gravis: A 2021 Update. 2021.	SR handsearched
Cahoon Jr WD, Kockler DR. Mycophenolate mofetil treatment of myasthenia gravis. *Annals of Pharmacotherapy.* 2006;40(2):295-298.	SR handsearched
Chen R, Zhang N, Gao L, et al. Quantitative evaluation of drug efficacy in the treatment of myasthenia gravis. *Expert Opinion on Investigational Drugs.* 2021;30(12):1231-1240.	SR handsearched
Di Stefano V, Lupica A, Rispoli MG, Di Muzio A, Brighina F, Rodolico C. Rituximab in AChR subtype of myasthenia gravis: systematic review. *Journal of Neurology, Neurosurgery & Psychiatry.* 2020;91(4):392-395.	SR handsearched
Feng X, Song Z, Wu M, et al. Efficacy and Safety of Immunotherapies in Refractory Myasthenia Gravis: A Systematic Review and Meta-Analysis. *Frontiers in neurology [electronic resource].* 2021;12:725700.	SR handsearched
Garzón-Orjuela N, van der Werf L, Prieto-Pinto LC, Lasalvia P, Castañeda-Cardona C, Rosselli D. Quality of life in refractory generalized myasthenia gravis: A rapid review of the literature. *Intractable Rare Dis Res.* 2019;8(4):231-238.	SR handsearched
Hart K, Sharshar T, Sathasivam S. Immunosuppressant drugs for myasthenia gravis. *Journal of Neurology, Neurosurgery and Psychiatry.* 2009;80(1):5-6.	SR handsearched
Wang L, Huan X, Xi JY, et al. Immunosuppressive and monoclonal antibody treatment for myasthenia gravis: A network meta-analysis. *CNS Neuroscience and Therapeutics.* 2019;25(5):647-658.	SR handsearched

Wang L, Xi J, Zhang S, et al. Effectiveness and safety of tacrolimus therapy for myasthenia gravis: A single arm meta-analysis. *Journal of Clinical Neuroscience.* 2019;63:160-167.	SR handsearched
Wang L, Zhang S, Xi J, et al. Efficacy and safety of tacrolimus for myasthenia gravis: a systematic review and meta-analysis. *Journal of Neurology.* 2017;264(11):2191-2200.	SR handsearched

11.6. Search strategies – Clinical SLR

Databases

Database	N
MEDALL	618
Embase	727
Cochrane CENTRAL	721
Cochrane CDSR	10
PubMed – e-publications only	57
DARE (CRD)	24
HTA (CRD)	5
International HTA (INAHTA) database	9
Total	**2171**

MEDLINE

Database: MEDALL

Host: Ovid

Data parameters: 1946 to April 06, 2022

Date of search: 7 April 2022

Search strategy	Search narrative
1 exp myasthenia gravis/ (16377) 2 ((myasthen$ adj3 gravis) or gMG).ti,ab,kw,kf. (16047) 3 "erb goldflam disease".ti,ab,kw,kf. (16) 4 1 or 2 or 3 (20080)	Lines 1-3 set out the condition terms. Line 1 is the controlled indexing (MeSH) term. Lines 2 and 3 capture free-text for the condition. These lines search in the following fields: * ti = title * ab = abstract * kw = keyword * kf = author indicated keyword

5	randomized controlled trial.pt. (563745)	Lines 5-9 are the Cochrane Highly Sensitive Search Strategy (HSSS) for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format.[84]
6	controlled clinical trial.pt. (94796)	
7	random$.af. (1551698)	
8	clinical trials as topic.sh. (199657)	
9	(trial or trail).ti. (265754)	
10	("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw,kf. (76895)	We have modified this strategy at line 7 following the guidance of Royle and Waugh[85] (which also accounts for US/UK spelling of randomisation since the truncation at M means both the s or z would be captured), line 9 where we include a misspelling for trial, and lines 10 and 11 where we follow the guidance of Cooper et al,[86] as referenced in the Cochrane Handbook technical supplement.[87] These modifications seek to improve the sensitivity of the strategy.
11	("Phase 2" or "phase2" or "phase II" or P2 or "PII").ti,ab,kw,kf. (118237)	
12	5 or 6 or 7 or 8 or 9 or 10 or 11 (1952339)	
13	4 and 12 (648)	Line 13 combines the condition terms with the search filter for randomized trials. Randomized trials focused on animals are removed at line 15, which also completes the search.
14	exp animals/ not humans.sh. (4985821)	
15	13 not 14 (618)	
		This search is not limited by date, language, or by interventions. The latter, specifically, seeks to improve the sensitivity of the searches.

Embase

Database: Embase

Host: Ovid

Data parameters: 1980 to 2022 Week 13

Date of search: 7 April 2022

#	Searches	Results
1	exp *myasthenia gravis/	13889
2	((myasthen$ adj3 gravis) or gMG).ti,ab,kw,kf.	18486
3	"erb goldflam disease".ti,ab,kw,kf.	1
4	1 or 2 or 3	19936
5	random*.af.	2004222
6	(trial or trail).ti.	356029
7	Randomized controlled trial/	699060

8	factorial*.ti,ab,kw,kf.	43430
9	(crossover* or cross over*).ti,ab,kw,kf.	115018
10	((doubl* or singl*) adj blind*).ti,ab,kw,kf.	248374
11	(assign* or allocat* or volunteer* or placebo*).ti,ab,kw,kf.	1146377
12	crossover procedure/	69754
13	single blind procedure/	45681
14	double blind procedure/	190736
15	("Phase 2" or "phase2" or "phase II" or P2 or "PII").ti,ab,kw,kf.	192124
16	("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw,kf.	141926
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	3002426
18	4 and 17	1192
19	(Conference abstract or Conference review or Conference paper).pt.	5139026
20	18 not 19	781
21	exp animal/ not human/	4611166
22	20 not 21	727

Cochrane CENTRAL

Database: Cochrane CENTRAL

Host: Wiley interface

Data parameters: Issue 3 of 12, March 2022

Date of search: 7 April 2022

ID Search Hits

#1MeSH descriptor: [Myasthenia Gravis] explode all trees 238

#2((myasthen* NEAR/3 gravis) or (gMG)):ti,ab,kw722

#3"erb goldflam disease":ti,ab,kw 0

#4#1 or #2 or #3 734

NB: The Cochrane databases aggregate search returns from CDSR, CENTRAL, and Methods. The total N at line #4 is for the whole search (N=734) of which 721 records from CENTRAL were relevant to this search. The 721 records identified in CENTRAL were downloaded.

Cochrane Database of Systematic Reviews (CDSR)

Database: Cochrane CDSR

Host: Wiley interface

Data parameters: Issue 4 of 12, April 2022

Date of search: 7 April 2022

ID Search Hits

#1MeSH descriptor: [Myasthenia Gravis] explode all trees 238

#2((myasthen* NEAR/3 gravis) or (gMG)):ti,ab,kw722

#3"erb goldflam disease":ti,ab,kw 0

#4#1 or #2 or #3 734

NB: The Cochrane databases aggregate search returns from CDSR, CENTRAL, and Methods. The total N at line #4 is for the whole search (N=734) of which 10 records from CDSR were relevant to this search. The 10 records identified in CDSR were downloaded.

PubMed

Database: PubMed

Host: NLM interface

Date of search: 7 April 2022

Searcher location: London, UK

Search number	Query	Sort By	Filters	Search Details	Results
1	"myasthenia gravis"[Title/Abstract]			"myasthenia gravis"[Title/Abstract]	15,835
2	random*[Title/Abstract]			"random*"[Title/Abstract]	1,308,582
3	(((((((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]))))))))			"pubstatusaheadofprint"[All Fields] OR "publisher"[Filter] OR "pubmednotmedline"[Filter]	4,607,588
4	(#1 AND #2 AND #3)			"myasthenia gravis"[Title/Abstract] AND "random*"[Title/Abstract] AND ("pubstatusaheadofprint"[All Fields] OR "publisher"[Filter] OR "pubmednotmedline"[Filter])	57

CRD DARE database

Database: CRD DARE database

Host: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp

Date of search: 7 April 2022

Searcher location: London, UK

Retrieved records: 24

Search term: myasthenia gravis (any field)

CRD HTA database

Database: CRD HTA database

Host: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp

Date of search: 7 April 2022

Searcher location: London, UK

Retrieved records: 5

Search term: myasthenia gravis (any field)

International HTA database

Database: International HTA database

Host: https://database.inahta.org/

Date of search: 7 April 2022

Searcher location: London, UK

Retrieved records: 9

Search term: myasthenia gravis

Trial Registers

Registry	N
ClinicalTrials.gov	193
EU Clinical Trials Register	61
WHO ICTRP	260
Total	**514**

ClinicalTrials.gov

Interface / URL: https://clinicaltrials.gov/

Date of search: 9 April 2022

Retrieved records: 193

The search was run in expert search using the following search string. The results were downloaded and imported into EndNote.

Search strategy: "myasthenia gravis" OR gMG OR "erb goldflam disease"

EU Clinical Trials Register

Interface / URL: https://www.clinicaltrialsregister.eu/ctr-search/search

Date of search: 9 April 2022

Retrieved records: 61

The following search strings were run separately in the basic search box. Any duplicates retrieved across the search results from these search strings were removed when importing the individual search results into EndNote.

Search strategy: "myasthenia gravis" OR gMG OR "erb goldflam disease"

International Clinical Trials Registry Platform (ICTRP)

Interface / URL: https://trialsearch.who.int/

Date of search: 9 April 2022

Retrieved records: 411 records for 260 trials

The following search strings were run separately in the basic search box. Any duplicates retrieved across the search results from these search strings were removed when importing the individual search results into EndNote.

Search strategy: "myasthenia gravis" OR gMG OR "erb goldflam disease"

Conferences

Conference	N
European Academy of Neurology (EAN) Congress	78
American Academy of Neurology (AAN) Annual Meeting	92
Peripheral Nerve Society (PNS) Annual Meeting	3
Embase	658
CPCI-S	190
ISPOR	13
Total	**1034**

Conference hand-searching

The following conferences were hand-searched for this SLR.

European Academy of Neurology (EAN) Congress

A hand-search was undertaken followed by a keyword search for the interventions under review.

Hand-search of EAN Congress, 2022

Searched via: N/A; Conference taking place on June 25-28, 2022

Not searched as out of scope for this update

Hand-search of EAN Congress, 2021

Searched via: https://onlinelibrary.wiley.com/toc/14681331/2021/28/S1

Searched on 5 April 2022

Records retrieved: 40

Hand-search of EAN Congress, 2020

Searched via: https://onlinelibrary.wiley.com/toc/14681331/2020/27/S1

Searched on 5 April 2022

Records retrieved: 38

American Academy of Neurology (AAN) Annual Meeting

A hand-search was undertaken followed by a keyword search for the interventions under review.

Hand-search of AAN Meeting, 2022

Searched via: https://index.mirasmart.com/aan2022/

Searched on 6 April 2022

Records retrieved: 54

Hand-search of AAN Meeting, 2021

Searched via: https://index.mirasmart.com/AAN2021/

Searched on 6 April 2022

Records retrieved: 38

Hand-search of AAN Meeting, 2020

Searched via: N/A; Cancelled due to COVID

Peripheral Nerve Society Annual Meeting

A hand-search was undertaken followed by a keyword search for the interventions under review.

Hand-search of PNS Meeting, 2022

Searched via: N/A; Conference taking place in May 2022

Hand-search of PNS Meeting, 2021

Searched via: https://onlinelibrary.wiley.com/doi/10.1111/jns.12460

Searched on: 9 April 2022

Records retrieved: 2

Hand-search of PNS Meeting, 2020

Searched via: https://onlinelibrary.wiley.com/doi/10.1111/jns.12416

Searched on: 9 April 2022

Records retrieved: 1

Embase

Database: Embase

Host: Ovid

Data parameters: 1980 to 2022 Week 13

Date of search: 7 April 2022

#	Searches	Results
1	exp *myasthenia gravis/	13889
2	((myasthen$ adj3 gravis) or gMG).ti,ab,kw,kf.	18486
3	"erb goldflam disease".ti,ab,kw,kf.	1
4	1 or 2 or 3	19936
5	(Conference abstract or Conference review or Conference paper).pt.	5139026
6	(2020* or 2021* or 2022*).yr.	4055094
7	4 and 5 and 6	658

CPCI-S

Database: CPCI-S

Host: Ovid

Data parameters: 1980 to 2022 Week 13

Date of search: 7 April 2022

Retrieved records: 190

Search strategy: ((myasthenia gravis) or ("erb goldflam disease")) (Topic)

ISPOR

Database: ISPOR

Host: https://www.ispor.org/heor-resources/presentations-database/search

Date of search: 10 April 2022

Retrieved records by search strategy:

"myasthenia gravis" = 13

"erb goldflam disease" = 0

11.7. Search strategies – Non-Clinical SLR

Databases

Database	N
MEDALL	649
Embase	754
PubMed – e-publications only	57
Econlit	2
NHS EED	3
ScHARR HUD	0
DARE (CRD)	24
HTA (CRD)	5
International HTA (INAHTA) database	9
ISPOR*	13
CPCI-S*	190
Total	**1503**

*Search performed once but clinical and non-clinical PICOS applied to results; n = 203 counted only once in Clinical SLR tally (conferences)

MEDLINE

Database: MEDALL

Host: Ovid

Data parameters: 1946 to April 07, 2022

Date of search: 8 April 2022

Search strategy	Search narrative
1 exp myasthenia gravis/ (16381) 2 ((myasthen$ adj3 gravis) or gMG).ti,ab,kw,kf. (16050) 3 "erb goldflam disease".ti,ab,kw,kf. (16) 4 1 or 2 or 3 (20083)	Lines 1-3 set out the condition terms. Line 1 is the controlled indexing (MeSH) term. Lines 2 and 3 capture free-text for the condition. These lines search in the following fields: * ti = title * ab = abstract * kw = keyword * kf = author indicated keyword

5 economics/ (27438) 6 exp "Costs and Cost Analysis"/ (256706) 7 economics, dental/ (1920) 8 exp Economics, Hospital/ or Financial management, hospital/ (32811) 9 Economics, Medical/ (9193) 10 economics, nursing/ (4013) 11 economics, pharmaceutical/ (3060) 12 (economic* or cost or costs or costly or costing or expense or expenses or price or prices or pricing or pharmacoeconomic* or CEA or CUA or CBA or CMA).ti,ab,kf,kw. (1024099) 13 exp "fees and charges"/ (31091) 14 exp budgets/ (13987) 15 (resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw. (228815) 16 (expenditure* not energy).ti,ab,kw. (33976) 17 (value adj1 money).ti,ab,kw. (37) 18 (budget* or fiscal or funding or financial or finance*).ti,ab,kw. (207604) 19 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 (1465972)	Lines 5-18 are a modified version of the unpublished NHS-EEDs search filter.
20 (15D or 15-D or 15 dimension).ti,ab,kw. (5786) 21 (eq-5d or eq5d or eq-5 or eq5 or EQ-5D-Y or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol or EQ-5D-3L).ti,ab,ot,hw,kw. (14745) 22 (sf6 or sf 6 or SF-6D or short form 6 or short-form 6 or short-form six or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot,hw,kw. (3159)	Lines 20-46 are a modified version of the Paisley and Booth Quality of Life filter.

23 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or shortform

eight).ti,ab,ot,hw,kw. (687)

24 (sf10 or sf 10 or short form 10 or short-form 10 or short-form ten or shortform 10 or sf ten or sften or

shortform ten or short form ten).ti,ab,ot,hw,kw. (151)

25 (sf12 or sf 12 or short form 12 or short-form 12 or short-form twelve or shortform 12 or sf twelve of sftwelve or

shortform twelve or short form twelve).ti,ab,ot,hw,kw. (6883)

26 (sf16 or sf 16 or short form 16 or short-form 16 or short-form sixteen or shortform 16 or sf sixteen or sfsixteen

or shortform sixteen or short form sixteen).ti,ab,ot,hw,kw. (36)

27 (sf20 or sf 20 or short form 20 or short-form 20 or short-form twenty or shortform 20 or sf twenty of sftwenty or

shortform twenty of short form twenty).ti,ab,ot,hw,kw. (425)

28 (sf36 or sf 36 or short form 36 or short-form 36 or short-form thirty six or shortform 36 or sf thirtysix or sf

thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short

form thirty six).ti,ab,ot,hw,kw. (28578)

29 (health utilities index* or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or

hui-3)).ti,ab,ot,hw,kw. (2056)

30 ("Child Health Utility 9D Index" or "Child Health Utility 9D" or CHU9D or "CHU 9D" or

"CHU-9D").ti,ab,ot,hw,kw,kf. (99)

31 ("time trade off" or "time tradeoff" or "time trade-off" or TTO).ti,ab,ot,hw,kw. (2123)

32 (standard gamble* or SG).ti,ab,ot,hw,kw. (12687)

33 ("discrete choice" or DCE).ti,ab,ot,hw,kw. (8671)

34 (AQoL or "Assessment of Quality of Life").ti,ab,ot,hw,kw. (2143)

35 Quality-Adjusted Life Years/ (14583)

36 (HRQoL or HRQL or HQL or HQOL or H QoL or hr QoL or QoL or (quality adj3 life) or quality time or HYE or HYES or

(health* adj3 equivalent*)).ti,ab,ot,hw,kw. (409420)

37 quality of life/ (237578)

38 value of life/ (5782)

39 uncertainty/ (15692)

40 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years

of healthy life" or healthy years equivalent or "years of potential life lost" or "years of healthlife

lost").ti,ab,ot,kw. (5106)

41 (HSUV* or health state* value* or health state* preference* or HSPV*).ti,ab,ot,kw. (497)

42 (uncertain* or wellbeing or "well being" or "quality of wellbeing" or "index of wellbeing" or "index of well

being" or rosser or "willingness to pay").ti,ab,kw. (318188)

43 (utility* or disutili*).ti,ab,kw. (234526)

44 (illness state*1 or health state* or health status or Quality adjusted life year* or QALY or QALD or DALY* or

HALY* or YHL or HYES or YPLL or YHLL or qale or qtime or AQoL* or life year* or ICER or "incremental

cost").ti,ab,ot,hw,kw. (206205)

45 (burden and (disease or illness or caregiver or home)).ti,ab,kw. (115474)

46 (lost adj2 (productivity or work or employment or earnings)).ti,ab,kw. (3208)

47 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 or 33 or 34 or 35 or 36 or 37 or 38 or

39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 (1184769)

48 ("Myasthenia Gravis Quality of Life scale" or "MG-QOL15" or "MG-QOL" or "MGQOL MGQOL15*" or "MG-QOL 15" or "MG-QOL 15-J").ti,ab,kw,kf. (64)	Lines 48-51 represent a search for condition-specific Quality of Life instruments. These search lines were developed based on scoping searches and reviews of studies which evaluate QoL.[88-93]

49 ("Italian Myasthenia Gravis Questionnaire" or IMGQ).ti,ab,kw,kf. (1)

50 ("Myasthenia Gravis Activities of Daily Living Scale" or "MG-ADL").ti,ab,kw,kf. (95)

51 ("Quantitative Myasthenia Gravis" or QMG).ti,ab,kw,kf. (220)

52 48 or 49 or 50 or 51 (301)

53 47 or 52 (1184965) 54 19 or 53 (2456246) 55 4 and 54 (970) 56 (2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022*).dt,dp,ed,ep,yr. (13112631) 57 55 and 56 (649)	Line 53 combines the Paisley and Booth filters OR the condition-specific hedge developed for this search. Line 54 combines the search for economic/costs data OR the QoL searches. Line 55 combines the condition search terms AND the economic/costs OR QoL terms. Line 56 is a limit to the last ten years of records. The search is limited by date and completed at line 57.

Embase

Database: Embase

Host: Ovid

Data parameters: 1980 to 2022 Week 13

Date of search: 7 April 2022

#	Searches	Results
1	exp *myasthenia gravis/	13889
2	((myasthen$ adj3 gravis) or gMG).ti,ab,kw,kf.	18486
3	"erb goldflam disease".ti,ab,kw,kf.	1
4	1 or 2 or 3	19936
5	exp economic evaluation/	329008
6	health economics/	30127
7	socioeconomics/	146211

8	exp health-care-cost/	313505
9	exp pharmacoeconomics/	212672
10	(economic* or cost or costs or costly or costing or expense or expenses or price or prices or pricing or pharmacoeconomic* or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1289323
11	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	302377
12	(expenditure* not energy).ti,ab,kw.	44796
13	(value adj1 money).ti,ab,kw.	35
14	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	288220
15	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	2123995
16	(15D or 15-D or 15 dimension).ti,ab,kw.	7208
17	(eq-5d or eq5d or eq-5 or eq5 or EQ-5D-Y or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol or EQ-5D-3L).ti,ab,ot,hw,kw.	28636
18	(sf6 or sf 6 or SF-6D or short form 6 or short-form 6 or short-form six or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot,hw,kw.	4062
19	(sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or shortform eight).ti,ab,ot,hw,kw.	1258
20	(sf10 or sf 10 or short form 10 or short-form 10 or short-form ten or shortform 10 or sf ten or sften or shortform ten or short form ten).ti,ab,ot,hw,kw.	235
21	(sf12 or sf 12 or short form 12 or short-form 12 or short-form twelve or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab,ot,hw,kw.	13159
22	(sf16 or sf 16 or short form 16 or short-form 16 or short-form sixteen or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,ot,hw,kw.	66
23	(sf20 or sf 20 or short form 20 or short-form 20 or short-form twenty or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab,ot,hw,kw.	538
24	(sf36 or sf 36 or short form 36 or short-form 36 or short-form thirty six or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot,hw,kw.	54756
25	(health utilities index* or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)).ti,ab,ot,hw,kw.	3879
26	("Child Health Utility 9D Index" or "Child Health Utility 9D" or CHU9D or "CHU 9D" or "CHU-9D").ti,ab,ot,hw,kw,kf.	139

27	("time trade off" or "time tradeoff" or "time trade-off" or TTO).ti,ab,ot,hw,kw.	3163
28	(standard gamble* or SG).ti,ab,ot,hw,kw.	18768
29	("discrete choice" or DCE).ti,ab,ot,hw,kw.	12647
30	(AQoL or "Assessment of Quality of Life").ti,ab,ot,hw,kw.	3501
31	quality adjusted life year/	31127
32	(HRQoL or HRQL or HQL or HQOL or H QoL or hr QoL or QoL or (quality adj3 life) or quality time or HYE or HYES or (health* adj3 equivalent*)).ti,ab,ot,hw,kw.	710010
33	"quality of life"/	547654
34	uncertainty/	40176
35	(Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of healthlife lost").ti,ab,ot,kw.	6074
36	(HSUV* or health state* value* or health state* preference* or HSPV*).ti,ab,ot,kw.	752
37	(uncertain* or wellbeing or "well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being" or rosser or "willingness to pay").ti,ab,kw.	402135
38	(utility* or disutili*).ti,ab,kw.	323061
39	(illness state*1 or health state* or health status or Quality adjusted life year* or QALY or QALD or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qale or qtime or AQoL* or life year* or ICER or "incremental cost").ti,ab,ot,hw,kw.	233278
40	(burden and (disease or illness or caregiver or home)).ti,ab,kw.	188581
41	(lost adj2 (productivity or work or employment or earnings)).ti,ab,kw.	4686
42	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 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41	1711920
43	("Myasthenia Gravis Quality of Life scale" or "MG-QOL15" or "MG-QOL" or "MGQOL MGQOL15*" or "MG-QOL 15" or "MG-QOL 15-J").ti,ab,kw,kf.	137
44	("Italian Myasthenia Gravis Questionnaire" or IMGQ).ti,ab,kw,kf.	2
45	("Myasthenia Gravis Activities of Daily Living Scale" or "MG-ADL").ti,ab,kw,kf.	228
46	("Quantitative Myasthenia Gravis" or QMG).ti,ab,kw,kf.	397
47	43 or 44 or 45 or 46	577
48	42 or 47	1712278
49	15 or 48	3523044
50	4 and 49	1859

51	(Conference abstract or Conference review or Conference paper).pt.	5139026
52	50 not 51	1148
53	(2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022*).yr.	16140640
54	52 and 53	754

PubMed

Database: PubMed

Host: NLM interface

Date of search: 7 April 2022

Searcher location: London, UK

Search number	Query	Sort By	Filters	Search Details	Results
1	"myasthenia gravis"[Title/Abstract]			"myasthenia gravis"[Title/Abstract]	15,835
2	random*[Title/Abstract]			"random*"[Title/Abstract]	1,308,582
3	(((((((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]))))))))			"pubstatusaheadofprint"[All Fields] OR "publisher"[Filter] OR "pubmednotmedline"[Filter]	4,607,588
4	(#1 AND #2 AND #3)			"myasthenia gravis"[Title/Abstract] AND "random*"[Title/Abstract] AND ("pubstatusaheadofprint"[All Fields] OR "publisher"[Filter] OR "pubmednotmedline"[Filter])	57

EconLit

Database: EconLit

Host: EBSCOhost

Date of search: 8 April 2022

#	Query	Limiters/Expanders	Last Run Via	Results

S1	TI (((myasthen* N2 gravis) or gMG)) OR AB (((myasthen* N2 gravis) or gMG))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	2
S2	TI ("erb goldflam disease") OR AB ("erb goldflam disease")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0

CRD NHS EED database

Database: CRD DARE database

Host: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp

Date of search: 8 April 2022

Searcher location: London, UK

Retrieved records: 3

Search term: myasthenia gravis (any field)

ScHARR HUD

Database: ScHARR HUD

Host: https://www.scharrhud.org/index.php?recordsN1&m=search

Date of search: 9 April 2022

Searcher location: London, UK

Retrieved records: 0

Search term: "myasthenia gravis" (any field)

Web searches

Website	N
NICE	5
SMC	1
PBAC	0
IQWiG	0
CADTH	8 downloaded from 14 results
Total	**14**

National Institute for Health and Care Excellence (NICE)

Date of search: 9 April 20222

Searcher location: London, UK.

Searched via: https://www.nice.org.uk/

Retrieved records: 5; all records downloaded; none included company submissions

Search terms: "myasthenia gravis", limited to guidance

Scottish Medicine Consortium (SMC)

Date of search: 9 April 20222

Searcher location: London, UK.

Searched via: https://www.scottishmedicines.org.uk/

Retrieved records: 1

Search terms: "myasthenia gravis"

Pharmaceutical Benefits Advisory Committee (PBAC)

Date of search: 9 April 20222

Searcher location: London, UK.

Searched via: https://www.pbs.gov.au/pbs/home

Retrieved records: 0

Search terms: "myasthenia gravis"

Institute for Quality and Efficiency in Healthcare (IQWiG)

Date of search: 9 April 20222

Searcher location: London, UK.

Searched via: https://www.iqwig.de/en/projects/projects-results/#searchQuery=query=*&page=1&rows=10&sortBy=score&sortOrder=desc&facet.filter.language=en

Retrieved records: 0

Search terms: "myasthenia gravis"

Canadian Agency for Drugs and Technologies in Health (CADTH)

Date of search: 9 April 20222

Searcher location: London, UK.

Searched via: https://www.cadth.ca/

Retrieved records: 14; 8 downloaded*

Search terms: "myasthenia gravis"

*All search results other than “new at CADTH” were downloaded. “New at CADTH” records were not downloaded as they do not contain data on trials, submissions, or clinical data.

Appendix B: Main characteristics of included studies

Table 49. Main study characteristics of ADAPT

ADAPT	
Trial name	ADAPT (A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness)
Abstract	Background: There is an unmet need for treatment options for generalised myasthenia gravis that are effective, targeted, well tolerated, and can be used in a broad population of patients. We aimed to assess the safety and efficacy of efgartigimod (ARGX-113), a human IgG1 antibody Fc fragment engineered to reduce pathogenic IgG autoantibody levels, in patients with generalised myasthenia gravis. Methods: ADAPT was a randomised, double-blind, placebo-controlled, phase 3 trial done at 56 neuromuscular academic and community centres in 15 countries in North America, Europe, and Japan. Patients aged at least 18 years with generalised myasthenia gravis were eligible to participate in the study, regardless of anti-acetylcholine receptor antibody status, if they had a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 5 (>50% non-ocular), and were on a stable dose of at least one treatment for generalised myasthenia gravis. Patients were randomly assigned by interactive response technology (1:1) to efgartigimod (10 mg/kg) or matching placebo, administered as four infusions per cycle (one infusion per week), repeated as needed depending on clinical response no sooner than 8 weeks after initiation of the previous cycle. Patients, investigators, and clinical site staff were all masked to treatment allocation. The primary endpoint was proportion of acetylcholine receptor antibody-positive patients who were MG-ADL responders (≥2-point MG-ADL improvement sustained for ≥4 weeks) in the first treatment cycle. The primary analysis was done in the modified intention-to-treat population of all acetylcholine receptor antibody-positive patients who had a valid baseline MG-ADL assessment and at least one post-baseline MG-ADL assessment. The safety analysis included all randomly assigned patients who received at least one dose or part dose of efgartigimod or placebo. This trial is registered at ClinicalTrials.gov (NCT03669588); an open-label extension is ongoing (ADAPT+, NCT03770403). Results: Between Sept 5, 2018, and Nov 26, 2019, 167 patients (84 in the efgartigimod group and 83 in the placebo group) were enrolled, randomly assigned, and treated. 129 (77%) were acetylcholine receptor antibody-positive. Of these patients, more of those in the efgartigimod group were MG-ADL responders (44 [68%] of 65) in cycle 1 than in the placebo group (19 [30%] of 64), with an odds ratio of 4·95 (95% CI 2·21–11·53, p<0·0001). 65 (77%) of 84 patients in the efgartigimod group and 70 (84%) of 83 in the placebo group had treatment-emergent adverse events, with the most frequent being headache (efgartigimod 24 [29%] *vs* placebo 23 [28%]) and nasopharyngitis (efgartigimod ten [12%] *vs* placebo 15 [18%]). Four (5%) efgartigimod-treated patients and seven (8%) patients in the placebo group had a serious adverse event. Three patients in each

ADAPT	
	treatment group (4%) discontinued treatment during the study. There were no deaths. Conclusion: Efgartigimod was well tolerated and efficacious in patients with generalised myasthenia gravis. The individualised dosing based on clinical response was a unique feature of ADAPT, and translation to clinical practice with longer term safety and efficacy data will be further informed by the ongoing open-label extension.
NCT number	NCT03669588
Objective	This randomized, double-blinded, placebo-controlled, multicenter, phase 3 study was conducted to evaluate the efficacy, safety, tolerability, quality of life, and impact on normal daily activities in patients with gMG treated with efgartigimod.
Publications – title, author, journal, year	Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial (Howard JF, et al. Lancet Neurol 2021; 20: 526–36) doi: https://doi.org/10.1016/S1474-4422(21)00159-9
Study type and design	ADAPT was a randomised, double-blind, placebo-controlled, phase 3 trial. Patients were randomly assigned 1:1 using interactive response technology, using both web and voice systems, by an independent company. No crossover was allowed. The investigators, patients, and sponsor were masked to treatment assignment.
Follow-up time	26-week study; patients who completed ADAPT were eligible to rollover into ADAPT+
Population (inclusion and exclusion criteria)	Inclusion criteria: • Ability to understand the requirements of the trial, provide written informed consent, and comply with the trial protocol procedures. • Male or female patients aged ≥ 18 years. • Diagnosis of MG with generalized muscle weakness meeting the clinical criteria for diagnosis of MG as defined by the MGFA class II, III, IVa and IVb. Exclusion criteria: • Pregnant and lactating women, and those intending to become pregnant during the trial or within 90 days after the last dosing. • Male patients who are sexually active and do not intend to use effective methods of contraception during the trial or within 90 days after the last dosing or male patients who plan to donate sperm during the trial or within 90 days after the last dosing. • MGFA Class I and V patients. • Patients with worsening muscle weakness secondary to concurrent infections or medications. • Patients with known seropositivity or who test positive for an active viral infection at Screening with: HBV (except patients who are seropositive because of HBV vaccination), HCV, HIV

ADAPT	
Intervention	Efgartigimod (10 mg/kg) or matching placebo was administered as four infusions per cycle (one infusion per week). All patients received an initial cycle, with subsequent cycles administered according to individual clinical response when MG-ADL score was ≥5, with >50% non-ocular symptoms. If the patient was an MG-ADL responder, subsequent cycles were administered when the patient no longer had a clinically meaningful decrease (≥2-point improvement in total MG-ADL score compared with baseline). Subsequent cycles could commence no sooner than 8 weeks from initiation of the previous cycle; a maximum of three cycles were possible in the 26-week study.
Baseline characteristics	In the overall population, median age (range) was 45 (19–78) years and 46 (19–81) years in the efgartigimod and placebo groups, respectively, with most patients in the 18 to <65 years age category (87% efgartigimod, 83% placebo). Most patients were female (75%/66%), and white (82%/87%). Most patients were AChR-Ab+ (77%) and were receiving immunosuppressive treatment (either corticosteroids or NSISTs, alone or in combination) at baseline, although approximately 30% of patients had never received NSISTs. MGFA class III was the most frequently reported, indicating a patient population with generalized disease and moderate muscle weakness. The overall mean time since diagnosis of gMG was 9.5 years.
Primary and secondary endpoints	The primary efficacy endpoint was the proportion of AChR-Ab+ patients who were MG-ADL responders in the first treatment cycle. Secondary endpoints were as follows: (1) proportion of QMG responders (defined as a ≥3 point improvement in the total QMG score for ≥4 consecutive weeks with the first improvement occurring by week 4 of cycle 1) in the AChR-Ab+ population; (2) percentage of MG-ADL responders in cycle 1 in the overall population (ie, AChR-Ab+ patients and AChR-Ab- patients); (3) proportion of time patients showed a CMI in MG-ADL score in the AChR-Ab+ population, up to day 126; (4) time from day 28 to not having CMI in the AChR-Ab+ population; and (5) proportion of early MG-ADL responders in cycle 1 (defined as having an MG-ADL improvement of ≥2 points occurring by week 2) in the AChR-Ab+ population.
Method of analysis	Efficacy analyses were performed in the modified ITT population, which included all randomized patients who had a valid baseline MG-ADL assessment and at least one post-baseline MG-ADL assessment. Safety analyses were evaluated in all patients who received at least one dose or part of a dose of study treatment. The primary endpoint was tested using a two-sided exact test using a logistic regression model with baseline MG-ADL total score as a covariate and the following three stratification factors as variables: AChR-Ab status (positive vs negative), NSISTs (taking vs not taking), and Japanese nationality (yes vs no). The treatment effect is presented as an odds ratio (OR) with 95% confidence interval (CI) and two-sided p value. If the primary endpoint met significance at the 5% two-sided α level, secondary endpoints were tested at a 5% two-sided significance level in hierarchical order using a fixed sequence approach.

ADAPT	
Subgroup analyses	No subgroup analyses were performed.

Table 50. Main study characteristics of ADAPT+

ADAPT+	
Trial name	ADAPT+ (A Long-term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Study of ARGX 113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness)
Abstract	Background: Efgartigimod is a human IgG1 antibody Fc-fragment that blocks neonatal Fc receptor. In the ADAPT study, treatment with efgartigimod resulted in clinically meaningful improvement (CMI) in generalised myasthenia gravis (gMG)-specific outcome measures. All patients completing ADAPT were eligible to enroll in its ongoing open-label, 3-year extension, ADAPT+. This study aimed to evaluate the safety, tolerability, and efficacy of efgartigimod in patients with gMG enrolled in ADAPT+. Methods: Efgartigimod 10 mg/kg was administered intravenously in cycles of once-weekly infusions for 4 weeks, with subsequent cycles initiated based on clinical response. Efficacy was assessed during each cycle utilising MG-ADL and QMG scales, in addition to other secondary analyses. Results: 90% of ADAPT patients (151/167) entered ADAPT+. As of February 2021, 106 AChR-Ab+/33 AChRAb- patients had received ≥1 dose of open-label efgartigimod (including 66 ADAPT placebo patients). The mean (SD) study duration was 363 (114) days, resulting in 138 patient-years of observation. The most common adverse events in the overall safety population (n=139) were headache (22.3%; n=31), nasopharyngitis (10.8%; n=15), and diarrhoea (8.6%; n=12), which were mostly mild or moderate. In cycle 1, CMI was observed in the overall population with a mean change (mean [SE]) of -5.1 (0.32) in MG-ADL and -4.8 (0.36) in QMG, and this magnitude of improvement occurred during each cycle for up to 10 cycles. Clinical improvements correlated with reductions in total IgG and AChR antibodies across all cycles. Additional analyses will be presented. Conclusion: The results of these analyses suggest longterm treatment with efgartigimod was well tolerated and efficacious
NCT number	NCT03770403
Objective	ADAPT+ is a follow-on study to ADAP to evaluate the long-term safety and tolerability of efgartigimod in patients with gMG
Publications – title, author, journal, year	Long-term safety and efficacy of efgartigimod in patients with generalised myasthenia gravis (Meisel A, et al. Eur J Neurol 2022; 29 (Suppl 1): 62 (abs OPR-021). Available at: https://www.ean.org/congress2022/abstracts/important-information/ean-2022-book-of-abstracts

ADAPT+	
Study type and design	Long-term, single-arm, open-label phase 3 follow-on trial of the ADAPT study to evaluate the safety and tolerability of efgartigimod in patients with gMG
Follow-up time	3 years (currently ongoing)
Population (inclusion and exclusion criteria)	Inclusion criteria: • Ability to understand the requirements of the trial, provide written informed consent, and comply with the trial protocol procedures. • Patients who participated in trial ARGX-113-1704 (ADAPT) and are eligible for roll over, as specified in the protocol. Exclusion criteria: • Patients who discontinued early from trial ARGX-113-1704 or patients who discontinued early from randomized treatment for pregnancy or rescue reasons or an (S)AE that might jeopardize the safety of the patient in that trial. • Pregnant and lactating women, and those intending to become pregnant during the trial or within 90 days after the last dosing. • Male patients who are sexually active and do not intend to use effective methods of contraception during the trial or within 90 days after the last dosing or male patients who plan to donate sperm during the trial or within 90 days after the last dosing. • Patients with known seropositivity for HBV, HCV, HIV
Intervention	Patients received efgartigimod IV in cycles, comprising 10 mg/kg infused every 7 days for 4 infusions, followed by an observation period, with subsequent cycles initiated according to clinical response.
Baseline characteristics	As of February 2021, 151 patients from ADAPT rolled over into ADAPT+, and 145 patients have received at least 1 dose of efgartigimod. Median age is 47 years; 85.5% of patients are in the 18–<65 years age category. Most patients are white (86.9%) and female (71%).
Primary and secondary endpoints	Primary endpoint is safety and tolerability as measured by the incidence of treatment-emergent (serious) AEs in the AChR-Ab+ population. Secondary endpoints include safety and tolerability as measured by the incidence of treatment emergent (serious) AEs in the overall population (AChR-Ab+ patients and AChR-Ab- patients)
Method of analysis	This study is designed to collect additional safety data on efgartigimod and provide continued treatment to patients who completed ADAPT. The primary and secondary endpoints were summarized in the safety analysis set by descriptive statistics. Frequency tables were prepared for all binary variables by cycle and overall. Summary statistics were provided for the continuous endpoints in terms of absolute values and changes from baseline.
Subgroup analyses	No subgroup analyses were performed.

Appendix C: Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Overall, patient characteristics were representative of the gMG population and well balanced between treatment groups, with the exception that more patients receiving efgartigimod had received thymectomy (Table 48). Most patients were AChR-Ab+, <65 years old, and were receiving immunosuppressive treatment (either corticosteroids or NSISTs, alone or in combination) at baseline, although approximately 30% of patients had never received NSISTs. MGFA class III was the most frequently reported, indicating a patient population with generalized disease and moderate muscle weakness. The overall mean time since diagnosis of gMG was 9.5 years. Baseline MG-ADL and QMG scores indicate an ongoing substantial disease burden for patients, despite receiving treatment.[28]

Table 51. ADAPT: Baseline demographics and clinical characteristics

	All patients		AChR-Ab+	
	Efgartigimod (n=84)	Placebo (n=83)	Efgartigimod (n=65)	Placebo (n=64)
Mean age (SD), years	45.9 (14.4)	48.2 (15)	44.7 (15)	49.2 (15.5)
Age category, n (%)				
18–<65 years	73 (86.9)	69 (83.1)	57 (87.7)	51 (79.7)
≥65 years	11 (13.1)	14 (16.9)	8 (12.3)	13 (20.3)
Sex, n (%)				
Female	63 (75.0)	55 (66.3)	46 (70.8)	40 (62.5)
Male	21 (25.0)	28 (33.7)	19 (29.2)	24 (37.5)
Race, n (%)				
Asian	9 (10.7)	7 (8.4)	7 (10.8)	4 (6.3)
Black or African American	3 (3.6)	3 (3.6)	1 (1.5)	3 (4.7)

	All patients		AChR-Ab+	
White	69 (82.1)	72 (86.7)	54 (83.1)	56 (87.5)
Other*	3 (3.6)	1 (1.2)	3 (4.6)	1 (1.6)
Mean time (SD) since diagnosis, years	10.1 (9.0)	8.8 (7.6)	9.7 (8.3)	8.9 (8.2)
Previous thymectomy, n (%)	59 (70.2)	36 (43.4)	45 (69.2)	30 (46.9)
MGFA class at screening, n (%)				
II	38 (40.4)	31 (37.4)	28 (43.1)	25 (39.1)
III	47 (55.9)	49 (59.0)	35 (53.8)	36 (56.3)
IV	3 (3.6)	3 (3.6)	2 (3.1)	3 (4.7)
Total MG-ADL score				
Mean (SD)	9.2 (2.6)	8.8 (2.3)	9.0 (2.5)	8.6 (2.1)
Median (range)	9.0 (5–17)	9.0 (5–16)	9.0 (5–15)	8.0 (5–16)
Total QMG score				
Mean (SD)	16.2 (5.0)	15.5 (4.6)	16.0 (5.1)	15.2 (4.4)
Median (range)	17.0 (4–28)	16.0 (6–27)	16.0 (4–28)	15.5 (6–24)
Total MGC score				

	All patients		AChR-Ab+	
Mean (SD)	18.8 (6.1)	18.3 (5.5)	18.6 (6.1)	18.1 (5.2)
Median (range)	19.0 (3–33)	18.0 (4–29)	19.0 (3–33)	18.0 (8–29)
Total MG-QoL15R score				
Mean (95% CI)	16.1 (14.7, 17.5)	16.8 (15.5, 18)	15.7 (14.2, 17.3)	16.6 (15.3, 18)
Median (range)	16.5 (3–29)	17 (4–30)	16 (3–29)	17 (4–27)
Concomitant gMG therapy at baseline				
At least one previous NSIST	47 (72.3)	43 (67.2)	62 (73.8)	57 (68.7)
Any steroid	60 (71.4)	67 (80.7)	46 (70.8)	51 (79.7)
Any NSIST	51 (60.7)	51 (61.4)	40 (61.5)	37 (57.8)
Steroid + NSIST	43 (51.2)	44 (53.0)	34 (52.3)	31 (48.4)
No steroid or NSIST	16 (19.1)	7 (8.4)	13 (20.0)	6 (9.4)

AChR-Ab+, acetylcholine receptor autoantibody positive; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite scale; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15R, Myasthenia Gravis Quality of Life; NA, not available; NSIST, non-steroidal immunosuppressant therapy; QMG, Quantitative Myasthenia Gravis; SD, standard deviation

Ranges of the clinical outcome assessments are as follows: MG-ADL total score 0-24, QMG score 0-39, MGC 0-50, and MG-QoL15R 0-30; for each instrument, higher scores are indicative of more severe disease.

*Includes American Indian or Alaska Native, multiple reported, or not reported.

Source: Howard et al, 2021[28]; argenx, 2020[127]

For ADAPt+, the baseline characteristics are illustrated in Table 49. The mean (SD) and the median age were 47.1 (14.90) years and 45.0 years, respectively, with 86% of patients in the 18–<65 years age category. Most patients were white (88%) and female (71%). The demography of the AChR-Ab+ population was similar to that of the overall population.

Table 52. ADAPT+: Baseline patient demographics and characteristics

Characteristic	AChR-Ab+ (n=111)	All patients (n=145)
Mean age (SD, years)	47.1 (15.52)	47.0 (14.76)
18–<65 years	93 (83.8)	124 (85.5)
≥65 years	18 (16.2)	21 (14.5)
Female	75 (67.6)	103 (71.0)
Male	36 (32.4)	42 (29.0)
American Indian or Alaska Native	2 (1.8)	2 (1.4)
Asian	8 (7.2)	11 (7.6)
Black or African American	3 (2.7)	5 (3.4)
White	97 (87.4)	126 (86.9)
Multiple	1 (0.9)	1 (0.7)
Mean time since diagnosis (SD), years	9.68 (7.933)	9.72 (8.2)
Mean MG-ADL score (SD)	9.5 (3.09)	9.8 (3.19)
Total MG-ADL score category, n (%)		
<5	1 (0.9)	1 (0.7)
5-7	32 (28.8)	39 (26.9)
8-9	24 (21.6)	30 (20.7)
≥10	54 (48.6)	75 (51.7)
Mean QMG score (SD)	15.3 (5.65)	15.4 (5.71)

Concomitant gMG treatment, n (%)		
NSIDs	67 (60.4)	89 (61.4)
No NSIDs	44 (39.6)	56 (38.6)

AChR-Ab+, acetylcholine receptor autoantibody-positive; NSIST, non-steroidal immunosuppressive therapy; PBO, placebo; SD, standard deviation
Source: argenx, 2021[128]

Appendix D: Efficacy and safety results per study

Table 53. Summary of primary and secondary endpoints from the ADAPT trial (AChR-Ab+ population only)

ADAPT								
Trial name:	ADAPT (A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness)							
NCT number:	NCT03669588							
Outcome (AChR-Ab+ population)	**Study arm**	**N**	**Result**	**Estimated relative difference in effect (Odds ratio)**			**Description of methods used for estimation**	**Reference**
MG-ADL responders in cycle 1, % (primary endpoint)	Efgartigimod	65	44/65 (68%)	4.95	2.21–11.53	<0.0001	Two-sided exact test using a logistic regression mode	Howard et al, 2021[28]
	Placebo	64	19/64 (30%)					
QMG responders in cycle 1, % (secondary endpoint)	Efgartigimod	65	41/65 (63%)	10.84	4.18–31.20	<0.0001		
	Placebo	64	9/64 (14%)					
Time patients showed a CMI in MG-ADL score to day 126, % (secondary endpoint)	Efgartigimod	65	48.7%	–	–	0.0001		
	Placebo	64	26.6%					
Median time from day 28 to not having CMI, days (range) (secondary endpoint)	Efgartigimod	65	35 (18–71)	–	–	0.26		
	Placebo	64	8 (1–57)					

ADAPT								
Early MG-ADL responders in cycle 1, % (secondary endpoint)	Efgartigimod	65	37/65 (57%)	–	–	Not assessed*		
	Placebo	64	16/64 (25%)					

*Secondary endpoints were tested in hierarchical order. The fifth secondary endpoint was not assessed because the fourth secondary endpoint was not significant.

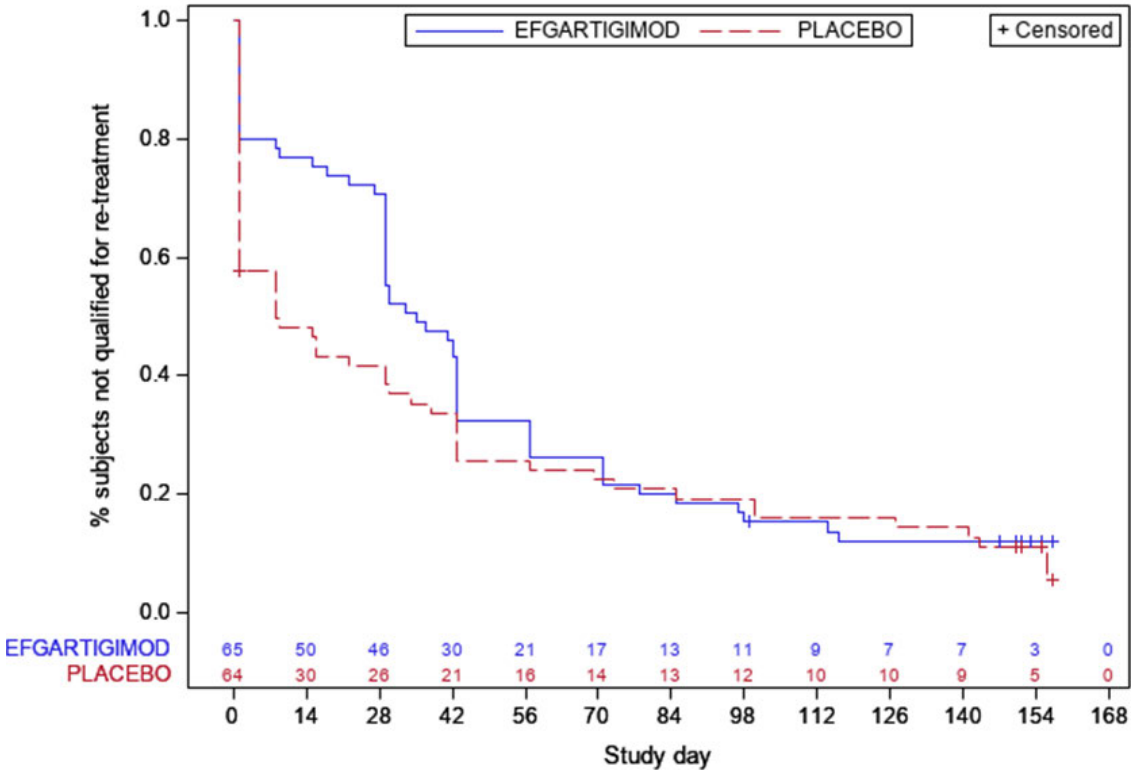
11.8. Time with CMI (AChR-Ab+ population)

A CMI was defined as reduction of ≥2 points compared with baseline in MG-ADL total score (in line with the MCID for the MG-ADL measure). AChR-Ab+ patients treated with efgartigimod showed a CMI in MG-ADL score for a significantly longer mean percentage of time during the study compared with placebo-treated patients (48.7% [95% CI 36.5, 60.9] vs 26.6% [14.2, 39.2]; p=0.0001).[127]

11.9. Time to qualify for retreatment in AChR-Ab+ patients

Qualifying for retreatment in the AChR Ab+ population was defined as the patient having a <2-point reduction in the MG-ADL total score and a MG-ADL total score of ≥5 points, with >50% of the total score due to non-ocular symptoms. The median time from day 28 to qualification for retreatment was longer in AChR-Ab+ patients receiving efgartigimod compared with patients receiving placebo (35 days vs 8 days) (Figure 19), therefore 50% of subjects in the PBO arm were meeting the criteria for retreatment at day 8, substantially earlier than Efgartigimod (35 days). Although a log-rank test did not identify this difference as being statistically significant (p=0.26), a Wilcoxon test done post hoc found a significant difference (p=0.013).[28, 127]

Figure 25. Time to not qualify for retreatment in the AChR-Ab+ population



Note: Time to not qualify for re-treatment means failing to meet the criteria for a next treatment cycle thus having more than 2 points reduction in MG-ADL total score and having a MG-ADL total score below 5.
AChR-Ab+, acetylcholine receptor autoantibody positive
Source: argenx, 2020[127]

11.10. Early MG-ADL responders in cycle 1 (AChR-Ab+ population)

MG-ADL responders with first MG-ADL improvement of ≥2 points occurring by week 2 of the first treatment cycle were considered early responders.[28, 127] A higher proportion of AChR-Ab+ patients treated with efgartigimod were early MG-ADL responders compared with patients receiving placebo (56.9% [37/65] vs 25.0% [16/64]), but this was not tested for significance because a statistically significant difference between the efgartigimod and placebo groups was not attained in the previous endpoint in the hierarchy (See Section 7.1.2.5, Statistical analyses).

11.11. ADAPT: Summary of secondary endpoints

A summary of secondary efficacy endpoints and results from ADAPT (AChR-Ab+ patients only) is shown in Table 51.

Table 54. Summary of secondary endpoints and results from ADAPT

Secondary endpoint type	Measure	Population	Time	Efgartigimod	Placebo	p value
Response	QMG responder	AChR-Ab+	Cycle 1	63% (41/65)	14% (9/64)	<0.0001 OR (95% CI): 10.84 (4.18, 31.20)
Duration	Time (%) with CMI in MG-ADL	AChR-Ab+	Until day 126*	48.7%	26.6%	0.0001
Duration	Time from day 28 until no CMI	AChR-Ab+	Full study	Median 35 days, (IQR 18-71 days)	Median 8 days (IQR 1-57 days)	0.26
Onset	Early MG-ADL responder (onset by week 2)	AChR-Ab+	Cycle 1	57% (37/65)	25% (16/64)	Not tested**

AChR-Ab+, acetylcholine receptor autoantibody positive; CI, confidence interval; CMI, clinically meaningful improvement; IQR, interquartile range; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; OR, odds ratio; QMG, Quantitative Myasthenia Gravis scale

*Day 126 was the last day on which it was possible to start and complete a retreatment cycle within the study. **Secondary endpoints were tested in hierarchical order. The fifth secondary endpoint was not tested as the fourth secondary endpoint did not achieve statistical significance.

Source: Howard et al, 2021[28]; argenx, 2020[127]

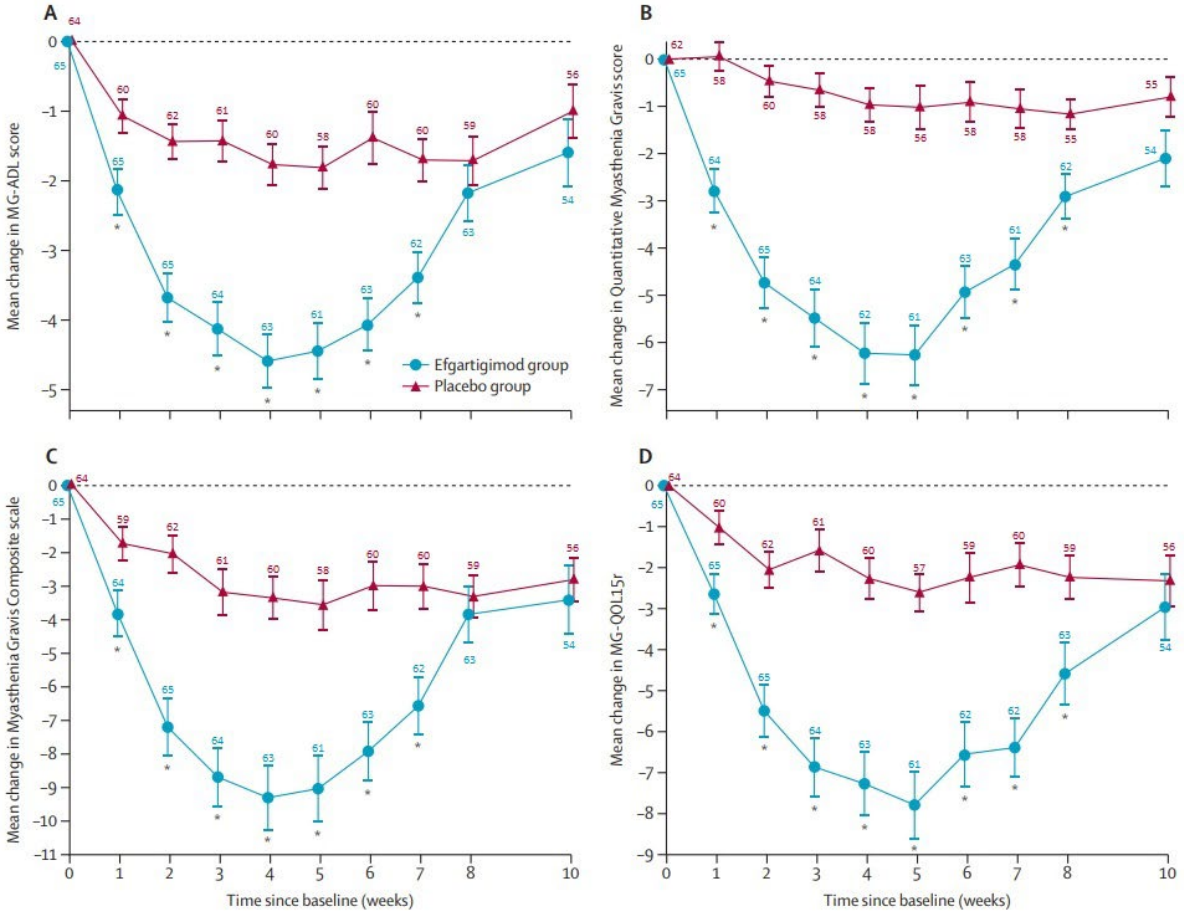
11.12. ADAPT: exploratory analyses (AChR-Ab+ population)

11.12.1. MG-ADL, QMG, MGC, MG-QoL15R: Change from baseline in total mean score

In the AChR-Ab+ population, patients treated with efgartigimod had greater improvements in MG-ADL, QMG, MGC, and MG-QoL15R total mean scores in cycle 1, and statistically significant differences from baseline observed from week 1 and sustained through week 7 across all measures.[28, 127].

The CMI has been established as a reduction of ≥2 points for the MG-ADL, and a reduction of ≥3 points for the QMG and MGC.[129] The magnitude of change required to indicate improvement or worsening on the MG-QoL15R is variable and depends on disease severity.[159] The maximum improvement for efgartigimod-treated patients occurred at week 4 for the MG-ADL, QMG, and MGC, and week 5 for the MG-QoL15R.

Figure 26. Mean change in total scores from baseline for MG-ADL (A), QMG (B), MGC (C), and MG-QoL15R (D) during cycle 1, AChR-Ab+ patients.



AChR-Ab+, acetylcholine receptor autoantibody positive; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite scale; MG-QoL15R, Myasthenia Gravis 15-item Quality of Life revised scale QMG, Quantitative Myasthenia Gravis. Patients' numbers measured at the different timepoints are listed in the figure. Error bars show standard error. *p<0.05
Source: Howard et al, 2021[28]

A summary of mixed model for repeated measures (MMRM) analyses conducted for the change from baseline in total mean scores across efficacy and HRQoL scales is shown in Table 52. The maximum improvement from SEB in the QMG total score occurred at week 4 during the first cycle in the AChR-Ab+ population. In the MMRM analysis, the mean (95% CI) change from SEB in the QMG score was -5.769 (-7.024; -4.513) points in the efgartigimod group and -0.543 (-1.852; 0.766) points in the placebo group, therefore a mean difference larger than 5 points. The difference in the change in the MG-QoL15r total score between the efgartigimod and placebo groups at week 4 is 5 points in favor of efgartigimod. The pooled SD for the population is 5.31. The effect size, calculated as the difference between groups/SD, is 0.94.

Table 55. Summary of MMRM analyses for MG-ADL, QMG, MGC, and MG-QoL15R

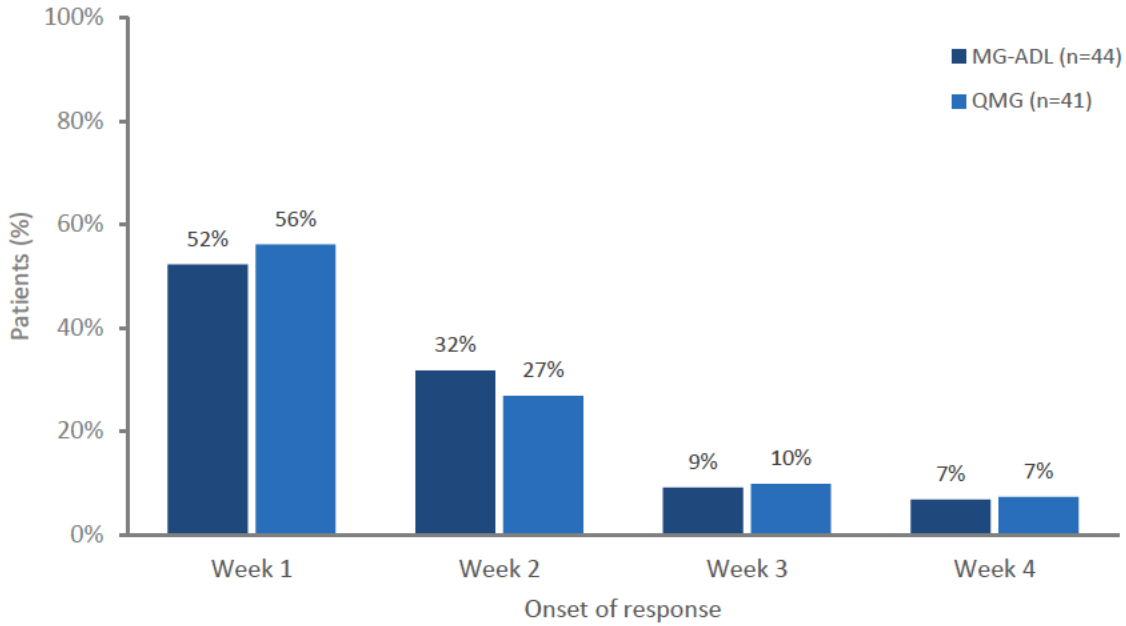
Scale	Max improvement timepoint	Mean change from baseline (95% CI)		LS mean difference (SE)	p value
		Efgartigimod	Placebo		
MG-ADL	Week 4, cycle 1	-4.10 (-5.01; -3.20)	-1.27 (-2.20; -0.34)	-2.84 (0.49)	p<0.0001 W1–W7
QMG	Week 4, cycle 1	-5.77 (-7.02; -4.51)	-0.54 (-1.85, 0.77)	-5.23 (0.71)	p<0.0001 W1–W7
MGC	Week 4, cycle 1	-8.91 (SE: 0.97)	-2.87 (SE: 1.01)	na	p<0.0001
MG-QoL15R	Weeks 3	-6.685 (SE:0.777)	-1.208 (SE:0.796)	-5.477 (SE:0.47) Effect size: 0.94*	p<0.0001
	Week 4	-7.213 (SE:0.801)	-1.759 (SE:0.822)	-5.453 (SE:0.893) Effect size: 0.94*	p<0.0001
	Week 5	-7.340 (SE:0.799)	-2.005 (SE:0.822)	-5.335 (SE:0.891) Effect size: 0.94*	p<0.0001

LS, least squares; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite scale; MG-QoL15R, Myasthenia Gravis 15-item Quality of Life revised scale; MMRM, mixed model for repeated measures; na, not applicable; QMG, Quantitative Myasthenia Gravis scale; SE, standard error
*An effect size >0.8 is considered a large effect size
Source: argenx, 2020[127]

11.12.2. MG-ADL and QMG responders: Onset and duration of response

Among AChR-Ab+ patients who were MG-ADL and QMG responders to efgartigimod in cycle 1, 84% and 83%, respectively, experienced an onset of response by week 2 of the treatment cycle (Figure 24).

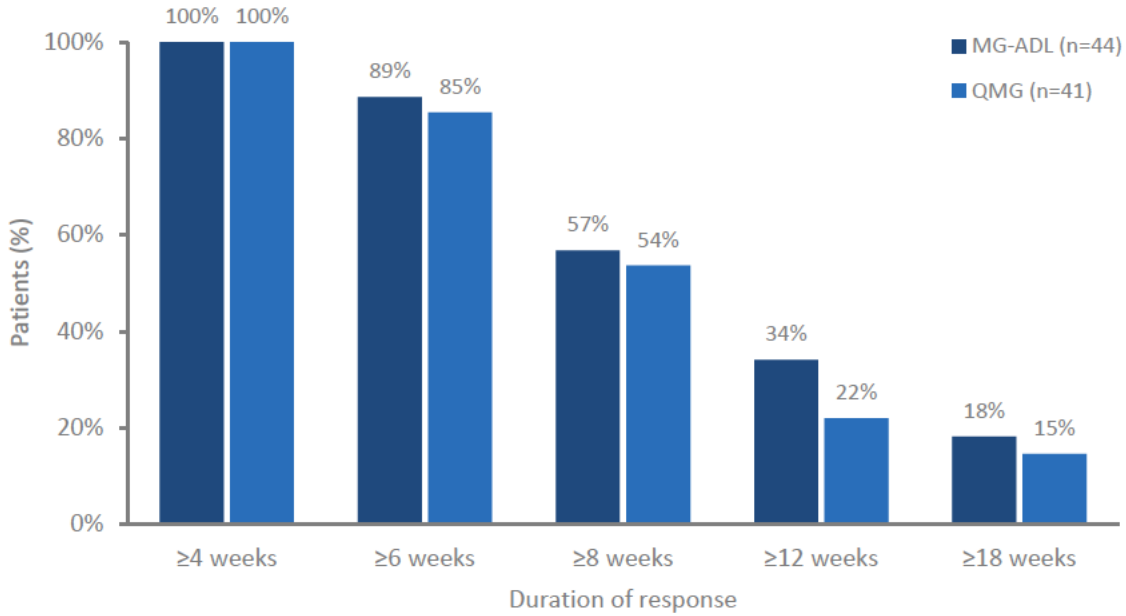
Figure 27. MG-ADL and QMG responders (%) by week of onset of response during cycle 1



MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QMG, Quantitative Myasthenia Gravis scale
Source: argenx, 2020[127]

For AChR-Ab+ patients who responded to efgartigimod during cycle 1, the proportion of patients with a given duration of response, defined as the period over which a CMI was maintained, is presented in Figure 25. All patients responded for at least 4 weeks. For the MG-ADL, the duration of response was at least 6 weeks in 89% of responders, at least 8 weeks in 57% of responders, and at least 12 weeks in 34% of responders The duration of QMG response was at least 6 weeks in 85% of responders, at least 8 weeks in 54% of responders, and at least 12 weeks in 22% of responders. The 8- and 12-week response results for both the MG-ADL and QMG scales demonstrate that a substantial proportion of patients have extended clinical benefit during treatment with efgartigimod.

Figure 28. Duration of responses for MG-ADL and QMG responders from cycle 1



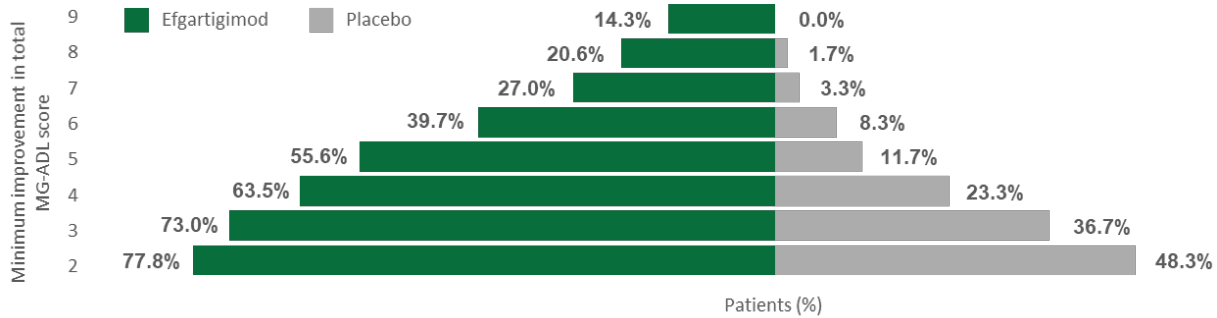
MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QMG, Quantitative Myasthenia Gravis scale
Source: argenx, 2020[127]

11.12.3. MG-ADL and QMG: Minimum point improvement in total score

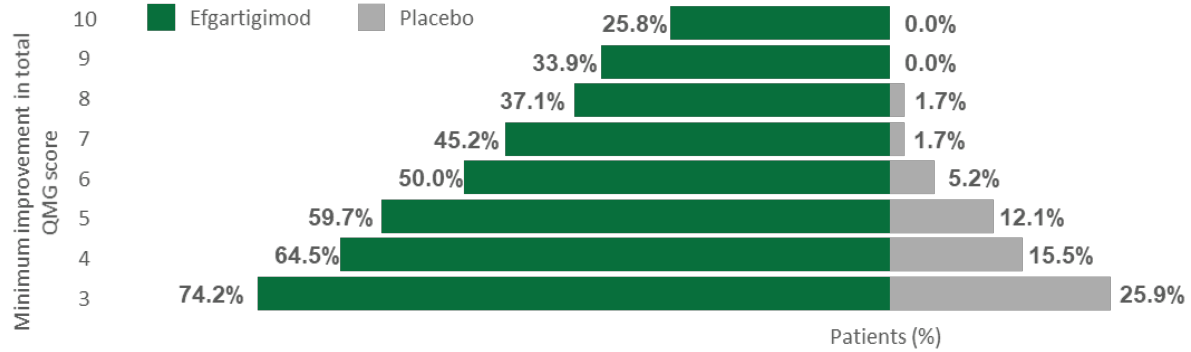
Treatment with efgartigimod demonstrated a substantial magnitude of effect on both the MG-ADL and QMG scales as demonstrated by the level of reduction (improvement) in scores among patients. One week after the last infusion of cycle 1, a greater proportion of AChR-Ab+ patients treated with efgartigimod achieved a higher level of improvement in both MG-ADL and QMG scores than patients treated with placebo (Figure 26).[28]

Figure 29. Proportion of AChR-Ab+ patients with point improvements of 2–9 in MG-ADL (A) and 3–10 in QMG (B) score at week 4 of cycle 1

(A) MG-ADL



(B) QMG



Source: Howard et al, 2021[28]

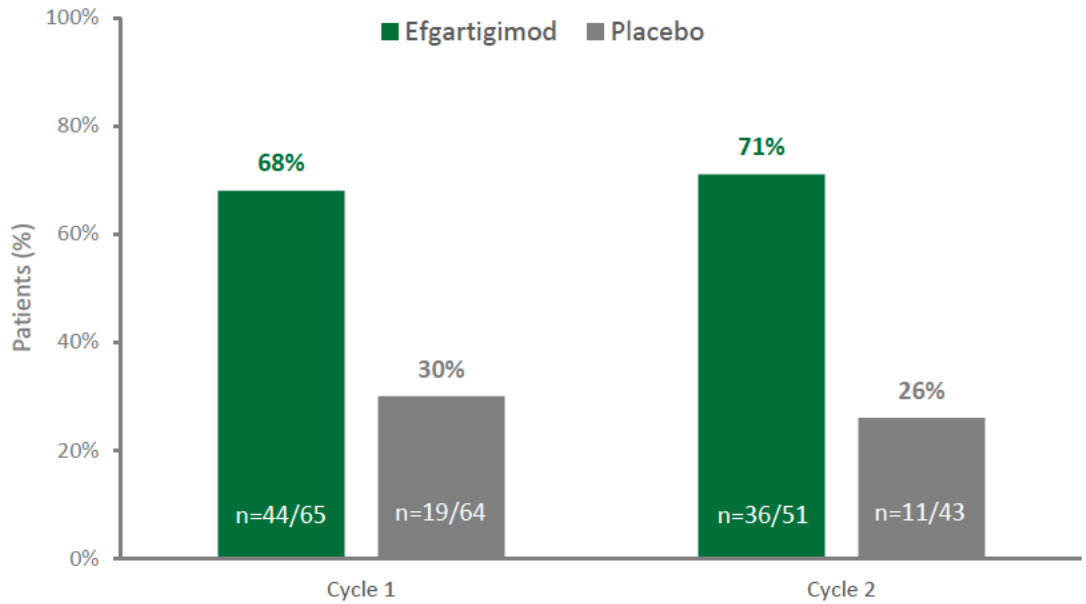
11.12.4. MG-ADL: Responders in cycle 2

MG-ADL responder rates in cycle 2 were similar to those in cycle 1 in patients who needed retreatment. In AChR-Ab+ patients who received a second treatment cycle, 71% (36/51) of patients in the efgartigimod group were MG-ADL responders compared with 26% (11/43) of patients in the placebo group (Figure 27).

Of the 44 AChR-Ab+ patients in the efgartigimod group who were MG-ADL responders in cycle 1, 32 (73%) qualified for retreatment, and 29 (90%) of these were MG-ADL responders again in cycle 2. Among the 21 AChR-Ab+ patients in the efgartigimod group who were not MG-ADL responders in cycle 1, 19 were retreated and 7 (37%) were MG-ADL responders in cycle 2, demonstrating that patients who have limited benefit in the first cycle may still respond with a second cycle.[28] Across cycles 1 and 2, 78.5% (51/65) of efgartigimod-treated patients were MG-ADL responders, demonstrating the effect of efgartigimod is repeatable across multiple treatment cycles.

Six (86%) of seven patients in the efgartigimod group who received a third cycle were MG-ADL responders (data not shown).

Figure 30. Proportion of MG-ADL responders during Cycle 1 and Cycle 2 in the AChR-Ab+ population



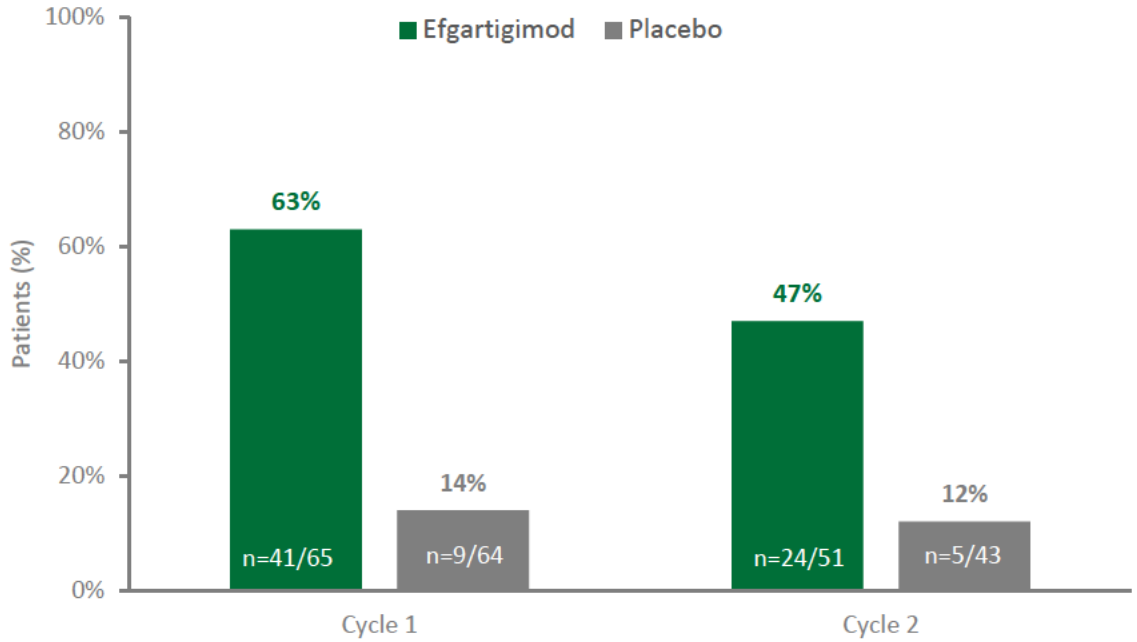
Source: Howard et al, 2021 [28]; argenx, 2020[127]

11.12.5. QMG: Responders in cycle 2

QMG responder rates in cycle 2 were similar to those in cycle 1 in patients who needed retreatment. In AChR-Ab+ patients who received a second treatment cycle, 47% (24/51) of patients in the efgartigimod group were QMG responders compared with 12% (5/43) of patients in the placebo group (Figure 28).

The lower proportion of QMG responders in cycle 2 is affected by patients continuing to have a CMI in QMG score at the time of retreatment. Patients were considered eligible for retreatment on the basis of their MG-ADL score only. Therefore, several patients who continued to have CMI improvement did not achieve a further 3-point reduction on the QMG scale after retreatment, as their score was already improved compared with baseline.

Figure 31. Proportion of QMG responders during cycle 1 and cycle 2 in the AChR-Ab+ population



Source: Howard et al, 2021[28]; argenx, 2020[127]

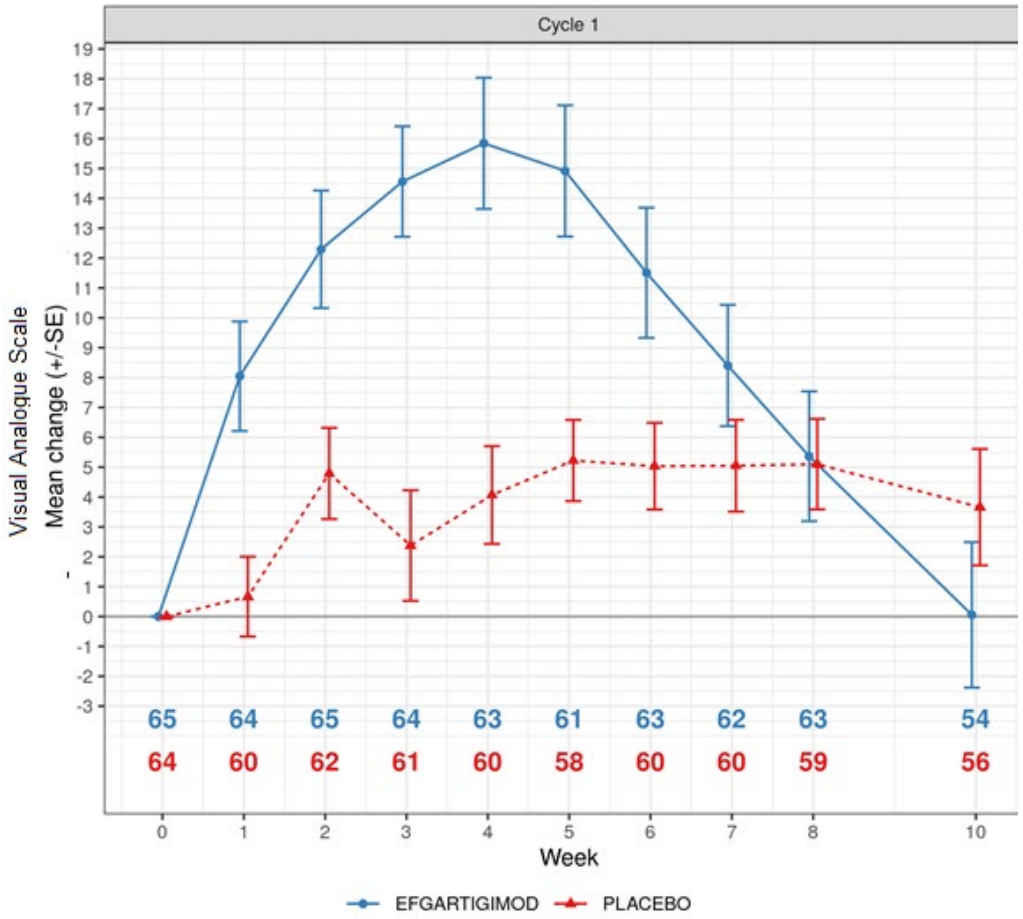
11.12.6. MG-ADL: Minimal symptom expression

Minimal symptom expression is defined as an MG-ADL total score of 0 or 1. In the AChR-Ab+ population, 40% (26/65) of patients in the efgartigimod group attained an MG-ADL score of 0 or 1 at any point in cycle 1 compared with 11% (7/63) in the placebo group ($p<0.0001$).[127]

11.12.7. EQ-5D-5L VAS

Results of the mean change from baseline on the VAS of the EQ-5D-5L during C1 in the AChR-Ab+ population are presented in Figure 29.[127] Positive changes indicate higher HRQoL as reported by the patient. The maximum mean (SE) change in the EQ-5D-5L VAS at week 4 in the AChR-Ab+ population was 15.8 (2.20) in the efgartigimod group compared to 4.1 (1.64) in the placebo group.

Figure 32. EQ-5D-5L VAS: Mean change from baseline in the AChR-Ab+ population



SE, standard error
Source: argenx, 2020[127]

11.13. ADAPT: supplemental AUC efficacy analyses (AChR-Ab+ population)

After an initial treatment cycle, patients enrolled in ADAPT were re-treated with efgartigimod according to clinical response as measured by the MG-ADL. Patients therefore received different numbers of treatment cycles and had different inter-treatment cycle lengths (i.e., time periods in which no efgartigimod treatment was received). To confirm the efficacy of efgartigimod compared with placebo over the complete study period rather than pre-defined cycles, a post-hoc efficacy analysis was conducted using an area under the curve (AUC) analysis for the change in total MG-ADL, QMG and MG-QoL15R scores from baseline to Week 18.

For all three scales, the mean differences in the AUC from baseline to Week 18 were statistically significant in favour of efgartigimod:

- **MG-ADL:** Least squares (LS) mean (SE) AUC change from baseline to Week 26 was -55.6 (10.9) for patients receiving efgartigimod compared with -20.2 (11.2) for the placebo group, resulting in a statistically significant LS mean difference of -35.4 (SE: 10.0; 95% CI: -55.1, -15.7; p<0.001).
- **QMG :** LS mean (SE) AUC change from baseline to Week 26 was -81.0 (16.3) for efgartigimod compared with -5.8 (17.0) for placebo, resulting in a statistically significant LS mean difference of -75.2 (SE : 14.7 ; 95% CI : -104.3, -46.1; p<0.001.
- **MG-QoL15R** : LS mean (SE) AUC change from baseline to Week 26 -121.8 (19.6) for efgartigimod compared with -36.8 (20.0) for placebo, resulting in a statistically significant LS mean difference of -84.9 (SE : 17.8; 95% CI -120.1, -49.8; p<0.001).

These analyses demonstrate the overall average improvement of patients receiving efgartigimod compared with placebo during a follow up period of 18 weeks and confirm the response to efgartigimod was deep and prolonged. Based on these scales, patients who received efgartigimod experienced crucial symptom control and improved HRQoL across the entire duration of the trial.

11.14. ADAPT +: Clinical efficacy results

ADAPT+ is an ongoing, open-label, single-arm, multicentre, 3-year extension of ADAPT designed to evaluate the long-term safety, tolerability, and efficacy of efgartigimod for the treatment of gMG. The purpose of the study is to evaluate the long-term safety and tolerability of efgartigimod administered in participants with gMG. This extension study was designed to collect additional safety data to supplement that from the randomized placebo-controlled study ADAPT, and to offer efgartigimod treatment for participants who were randomized to receive placebo in ADAPT.

Therefore, the patients in the Placebo group are patients that were in the Placebo-arm in the ADAPT study, but they are crossing over in ADAPT+ and receiving active treatment with efgartigimod.

Table 56. ADAPT+: Summary of primary and secondary endpoints (AChR-Ab+ population only)

ADAPT+				
Trial name:	ADAPT+ (A Long-Term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Trial of ARGX-113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness)			
NCT number:	NCT03770403			
Outcome (AChR-Ab+ population)	**Study arm**	**N**	**Result – Mean (SE)**	**Reference**
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 1)	Efgartigimod	59	-5.08 (0.49)	[128]
	Placebo	49	-4.1 (0.40)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 1	Efgartigimod	61	9.9 (0.44)	
	Placebo	50	9.1 (0.36)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 2)	Efgartigimod	52	–6.2 (0.54)	
	Placebo	45	–4.3 (0.43)	
	Efgartigimod	53	10.3 (0.48)	

ADAPT+				
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 2	Placebo	48	9.2 (0.38)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 3)	Efgartigimod	48	−6.1 (0.51)	
	Placebo	41	−4.3 (0.49)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 3	Efgartigimod	49	10.7 (0.51)	
	Placebo	41	9.3 (0.45)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 4)	Efgartigimod	43	−6.8 (0.59)	
	Placebo	37	−4.9 (0.56)	
	Efgartigimod	44	10.6 (0.55)	

ADAPT+				
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 4	Placebo	37	9.8 (0.55)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 5)	Efgartigimod	41	−6.6 (0.56)	
	Placebo	33	−4.7 (0.51)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 5	Efgartigimod	41	10.5 (0.58)	
	Placebo	33	9.6 (0.55)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 6)	Efgartigimod	40	−6.2 (0.60)	
	Placebo	31	−5.0 (0.61)	
	Efgartigimod	40	10.5 (0.56)	

ADAPT+				
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 6	Placebo	31	9.8 (0.59)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 7)	Efgartigimod	36	−6.8 (0.64)	
	Placebo	23	−5.7 (0.70)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 7	Efgartigimod	35	10.8 (0.55)	
	Placebo	23	9.7 (0.78)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 8)	Efgartigimod	35	−7.1 (0.68)	
	Placebo	23	−5.3 (0.7)	
	Efgartigimod	31	10.06 (0.56)	

ADAPT+				
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 8	Placebo	22	10.1 (0.7)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 9)	Efgartigimod	26	−8.0 (0.63)	
	Placebo	19	−6.1 (0.72)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 9	Efgartigimod	27	11.1 (0.54)	
	Placebo	19	10.9 (0.78)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 10)	Efgartigimod	21	−8.2 (0.86)	
	Placebo	15	−6.5 (0.96)	
	Efgartigimod	23	11.3 (0.71)	

ADAPT+				
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 10	Placebo	15	10.9 (0.99)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 11)	Efgartigimod	13	−5.6 (0.92)	
	Placebo	10	−5.7 (1.69)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 11	Efgartigimod	14	8.4 (0.74)	
	Placebo	11	10.8 (1.39)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 12)	Efgartigimod	11	−6.6 (0.87)	
	Placebo	8	−6.8 (1.31)	
	Efgartigimod	11	9.2 (0.78)	

ADAPT+				
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 12	Placebo	9	11.0 (1.30)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 3 (cycle 13)	Efgartigimod	9	−6.4 (0.96)	
	Placebo	6	−5.7 (1.98)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 13	Efgartigimod	9	8.8 (0.57)	
	Placebo	6	11.2 (1.85)	
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at week 14	Efgartigimod	8	−6.4 (1.27)	
	Placebo	5	−3.4 (1.81)	
	Efgartigimod	8	9.4 (0.84)	

ADAPT+				
MG-ADL total score in the total efgartigimod AChR-Ab+ population observed at actual cycle 14	Placebo	5	10.6 (2.16)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at week 3 (cycle 1)	Efgartigimod	54	-5.1 (0.64)	
	Placebo	46	-4.2 (0.52)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at actual cycle 1	Efgartigimod	61	14.9 (0.83)	
	Placebo	50	15.7 (0.64)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at week 3 (cycle 2)	Efgartigimod	48	−5.7 (0.65)	
	Placebo	42	−4.7 (0.50)	
	Efgartigimod	52	15.9 (0.91)	

ADAPT+				
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at actual cycle 2	Placebo	47	16.4 (0.71)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at week 3 (cycle 3)	Efgartigimod	36	−5.5 (0.82)	
	Placebo	37	−3.6 (0.63)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at actual cycle 3	Efgartigimod	47	15.4 (0.99)	
	Placebo	40	15.7 (0.76)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at week 3 (cycle 4)	Efgartigimod	29	−5.2 (0.90)	
	Placebo	28	−3.5 (0.77)	
	Efgartigimod	37	14.2 (1.02)	

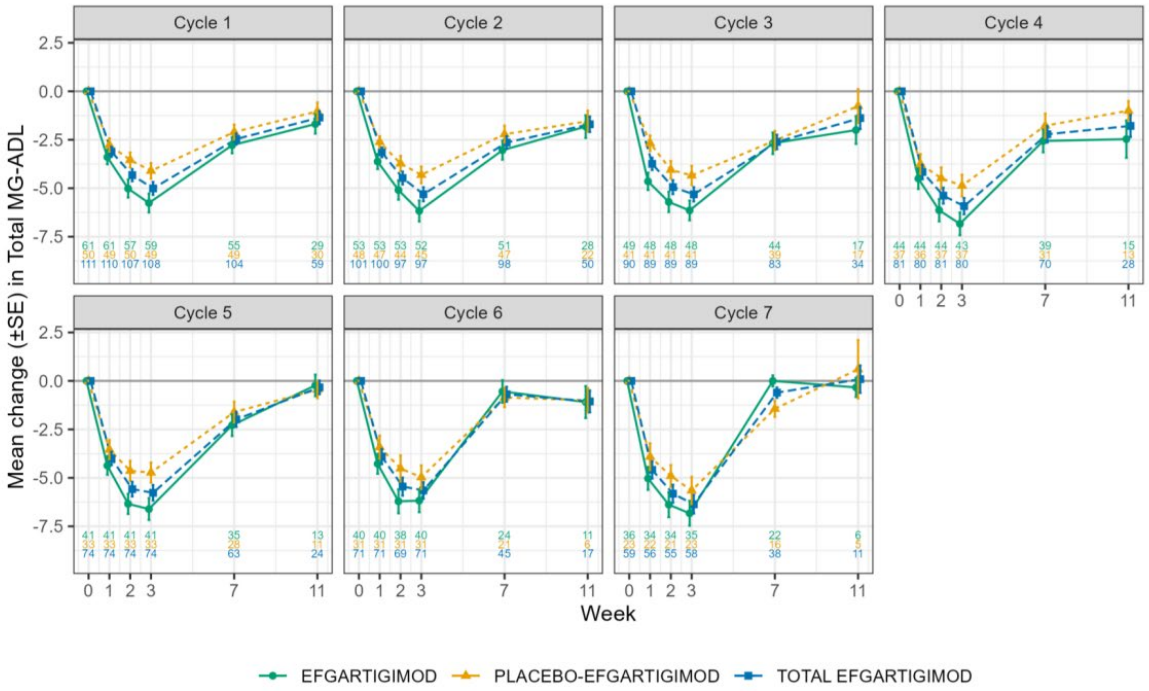
ADAPT+				
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at actual cycle 4	Placebo	33	15.6 (0.95)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at week 3 (cycle 5)	Efgartigimod	23	−5.7 (0.82)	
	Placebo	22	−3.0 (0.67)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at actual cycle 5	Efgartigimod	29	15.8 (1.28)	
	Placebo	27	15.9 (0.98)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at week 3 (cycle 6)	Efgartigimod	15	−4.3 (1.19)	
	Placebo	19	−4.5 (1.03)	
	Efgartigimod	24	14.9 (1.38)	

ADAPT+				
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at actual cycle 6	Placebo	25	16.8 (1.03)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at week 3 (cycle 7)	Efgartigimod	12	−5.7 (0.86)	
	Placebo	11	−5.1 (1.16)	
QMG Total Score—mean change from cycle baseline in the AChR-Ab+ population at actual cycle 7	Efgartigimod	15	16.5 (1.30)	
	Placebo	17	18.0 (1.33)	
Participants with MG-ADL total score, reduction criterion of ≥2 points from cycle baseline in the AChR-Ab+ population score at cycle 1, %	Efgartigimod	55/61	90.2%	
	Placebo	46/50	92%	
	Efgartigimod	52/61	85.2%	

ADAPT+				
Participants with MG-ADL total score, reduction criterion of ≥3 points from cycle baseline in the AChR-Ab+ population score at cycle 1, %	Placebo	39/50	78 %	

Below in Figure 31 the mean changes from cycle baseline in the MG-ADL total score are presented over time during cycle 1 to cycle 7 for the AChR-Ab+ population.

Figure 33. MG-ADL Total Score—Mean Change From Cycle Baseline by Cycle in the AChR-Ab Seropositive Population (Safety Analysis Set)



AChR-Ab=anti-acetylcholine receptor antibody; MG-ADL=Myasthenia Gravis Activities of Daily Living Notes: Efgartigimod refers to the cohort of participants who received efgartigimod in the antecedent study ADAPT and are receiving it in this study. Placebo-efgartigimod refers to the cohort of participants who received placebo in ADAPT and are receiving efgartigimod in this study. For clarity, only data from the first 7 cycles are shown.

The percentage of participants with a ≥2-point and ≥3-point reduction in the MG-ADL total score from cycle baseline for cycle 1 to cycle 14 is provided for the AChR-Ab seropositive population in Table 56.

Table 57. MG-ADL Total Score—Percentage of Participants With Reduction Criterion of ≥2 or ≥3 Points From Cycle Baseline in the AChR-Ab Seropositive Population (Safety Analysis Set)

		n/N (%) Reaching total MG-ADL change criterion at any time point during the cycle		
Cycle	MG-ADL total score change criterion	EFG-EFG (N=61)	PBO-EFG (N=50)	Total EFG (N=111)
1	MG-ADL reduction ≥ 2	55/61 (90.2)	46/50 (92.0)	101/111 (91.0)
	MG-ADL reduction ≥ 3	52/61 (85.2)	39/50 (78.0)	91/111 (82.0)
2	MG-ADL reduction≥ 2	50/53 (94.3)	43/47 (91.5)	93/100 (93.0)
	MG-ADL reduction ≥ 3	47/53 (88.7)	39/47 (83.0)	86/100 (86.0)
3	MG-ADL reduction≥ 2	46/48 (95.8)	36/41 (87.8)	82/89 (92.1)
	MG-ADL reduction ≥ 3	44/48 (91.7)	32/41 (78.0)	76/89 (85.4)

4	MG-ADL reduction ≥ 2	43/44 (97.7)	35/37 (94.6)	78/81 (96.3)
	MG-ADL reduction ≥ 3	39/44 (88.6)	30/37 (81.1)	69/81 (85.2)
5	MG-ADL reduction ≥ 2	40/41 (97.6)	31/33 (93.9)	71/74 (95.9)
	MG-ADL reduction ≥ 3	38/41 (92.7)	29/33 (87.9)	67/74 (90.5)
6	MG-ADL reduction ≥ 2	37/40 (92.5)	29/31 (93.5)	66/71 (93.0)
	MG-ADL reduction ≥ 3	36/40 (90.0)	26/31 (83.9)	62/71 (87.3)
7	MG-ADL reduction ≥ 2	33/36 (91.7)	22/23 (95.7)	55/59 (93.2)
	MG-ADL reduction ≥ 3	33/36 (91.7)	21/23 (91.3)	54/59 (91.5)
8	MG-ADL reduction ≥ 2	32/33 (97.0)	21/22 (95.5)	53/55 (96.4)
	MG-ADL reduction ≥ 3	31/33 (93.9)	21/22 (95.5)	52/55 (94.5)

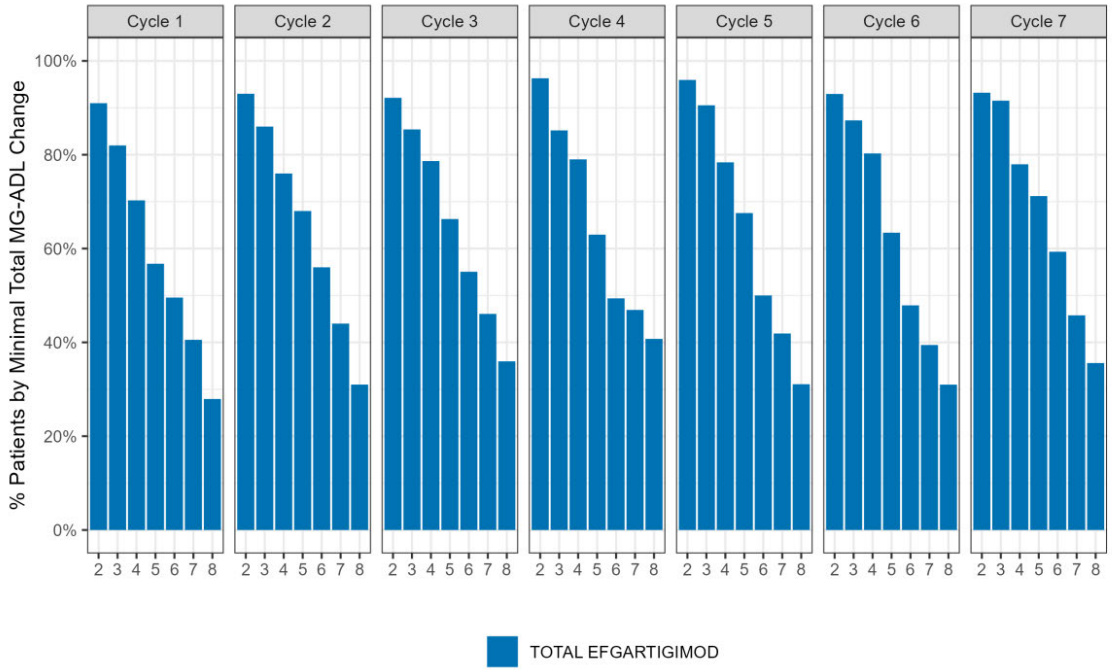
9	MG-ADL reduction ≥ 2	27/27 (100)	18/19 (94.7)	45/46 (97.8)
	MG-ADL reduction ≥ 3	26/27 (96.3)	18/19 (94.7)	44/46 (95.7)
10	MG-ADL reduction ≥ 2	23/23 (100)	15/15 (100)	38/38 (100)
	MG-ADL reduction ≥3	21/23 (91.3)	14/15 (93.3)	35/38 (92.1)
11	MG-ADL reduction ≥ 2	12/14 (85.7)	8/11 (72.7)	20/25 (80.0)
	MG-ADL reduction ≥3	12/14 (85.7)	8/11 (72.7)	20/25 (80.0)
12	MG-ADL reduction ≥ 2	11/11 (100)	9/9 (100)	20/20 (100)
	MG-ADL reduction ≥3	10/11 (90.9)	8/9 (88.9)	18/20 (90.0)
13	MG-ADL reduction ≥ 2	8/9 (88.9)	5/6 (83.3)	13/15 (86.7)
	MG-ADL reduction ≥3	8/9 (88.9)	4/6 (66.7)	12/15 (80.0)

14	MG-ADL reduction ≥ 2	7/8 (87.5)	4/5 (80.0)	1 1/13 (84.6)
	MG-ADL reduction ≥3	7/8 (87.5)	3/5 (60.0)	10/13 (76.9)

AChR-Ab=anti-acetylcholine receptor antibody; EFG=efgartigimod; MG-ADL=Myasthenia Gravis Activities of Daily Living; N=number of participants in the analysis set; n=number of participants for whom the observation occurred; PBO=placebo Notes: The efgartigimod-efgartigimod cohort comprises participants who received efgartigimod in ADAPT and continue to receive efgartigimod in this study. The placebo-efgartigimod cohort comprises participants who received placebo in ADAPT and began receiving efgartigimod in this study. Data are only shown for the first 14 cycles because of the low number of participants who received more treatment cycles.

The proportions of participants with increasing thresholds of reduction in the MG-ADL total score during cycle 1 to cycle 7 are shown in Figure 32 for the AChR-Ab seropositive population. More than 90% of participants in the AChR-Ab seropositive population had a minimum improvement from cycle baseline in MG-ADL total score of ≥2 points in the majority of cycles (11 out of 14) and including the first 10 cycles.

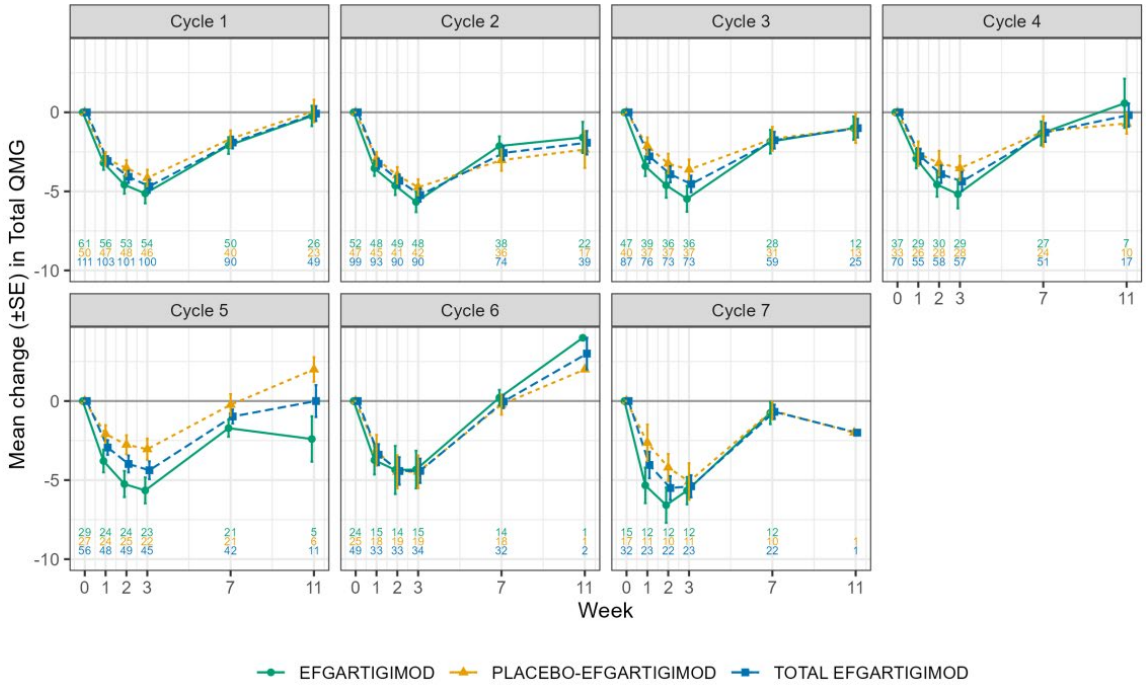
Figure 34. MG-ADL Total Score—Percentage of Participants With Minimum Point Improvement by Cycle in the AChR-Ab Seropositive Population (Safety Analysis Set)



AChR-Ab=anti-acetylcholine receptor antibody; MG-ADL=Myasthenia Gravis Activities of Daily Living Note: For clarity, only data from the first 7 cycles are shown.

The mean change from cycle baseline in the QMG total score is presented for cycle 1 to cycle 7 in Figure 33 for the AChR-Ab seropositive.

Figure 35. QMG Total Score—Mean Change From Cycle Baseline by Cycle in the AChR-Ab Seropositive Population (Safety Analysis Set)



AChR-Ab=anti-acetylcholine receptor antibody; QMG=Quantitative Myasthenia Gravis Note: Efgartigimod refers to the cohort of participants who received efgartigimod in the antecedent study ADAPT and are receiving it in this study. Placebo-efgartigimod refers to the cohort of participants who received placebo in ADAPT and are receiving efgartigimod in this study.

Appendix E: Safety data for intervention and comparator(s)

11.15. Treatment-emergent serious AEs – ADAPT study

Four (5%) patients treated with efgartigimod had a treatment-emergent serious AE (SAE): thrombocytosis, rectal adenocarcinoma, MG worsening, and depression.[28] Only the SAE of thrombocytosis was considered by the investigator to be treatment-related and led to treatment discontinuation. The SAEs of rectal adenocarcinoma and MG worsening also led to treatment discontinuation. In the placebo group, seven (8%) patients had a treatment-emergent SAE: myocardial ischaemia, atrial fibrillation, and spinal ligament ossification, all of which led to treatment discontinuation; upper respiratory infection, spinal compression fracture, myasthenia gravis worsening, and myasthenia gravis crisis were also reported. No deaths occurred during the study.

11.16. Discontinuations – ADAPT study

Fifteen (9%) patients discontinued treatment during the study: 5 (6%) patients in the efgartigimod group and 10 (12%) patients in the placebo group.[127] The primary reason for discontinuation from treatment was the occurrence of a TEAE, which was reported in 5 (3.0%) patients overall: 3 (3.6%) patients in the efgartigimod group and 2 (2.4%) patients in the placebo group. Withdrawal by subject was reported for 3 (1.8%) patients overall, all of which were in the placebo group. Administration of rescue therapy resulted in the discontinuation of treatment in 3 (1.8%) patients overall: 1 (1.2%) patient in the efgartigimod group and 2 (2.4%) patients in the placebo group. Additional discontinuations were due to prohibited medication (n=1, placebo); protocol deviation (n=1, efgartigimod); and sponsor decision (n=2, placebo).

11.17. Infections and infestations (AEs of special interest) – ADAPT+ study

Infections and infestations (as reported in Table 15) were considered AEs of special interest (AESIs) in ADAPT+. The majority of AESIs were mild to moderate in severity; grade ≥3 AESIs included: COVID-19 pneumonia, urinary tract infection, septic shock, COVID-19, dysentery, pneumonia Escherichia, pharyngitis streptococcal, influenza, pneumonia, pseudomonal sepsis, and bacterial infection. The incidence rate of AESIs did not increase with subsequent efgartigimod cycles and no opportunistic infections were reported.

11.18. Discontinuations – ADAPT+ study

Overall, 91 (62.8%) participants discontinued treatment during ADAPT+ and, 35 (24.1%) patients have discontinued treatment with efgartigimod.[128] The primary reasons for discontinuation from treatment in the overall population were other (56 [38.6%] patients), withdrawal by patient (11 [7.6%] patients), treatment failure and AE (8 [5.5%] patients), death (4 [2.8%] patients), receiving prohibited medication (2 [1.4%]), and rescue therapy and sponsor decision (in 1 [0.7%] patient each).

Appendix F: Comparative analysis of efficacy and safety

Not applicable

Appendix G: Extrapolation

The follow-up in clinical trials have limited duration. In order to estimate long term the per-cycle probability of discontinuing the efgartigimod treatment due to unplanned reasons, statistical survival models were adjusted to ADAPT and ADAPT+ data studies. The description of extrapolation methods used and a graph of Kaplan-Meier plots with the fitted extrapolation curves have been reported directly in Section 8.3.2. All parametric survival curves was estimated using SAS V9.4, The SAS Institute, Cary NC.

Appendix H: Literature search for HRQoL data

See Appendix A for details of the Non-Clinical SLR, which was designed to capture utilities specific to gMG from the literature.

Appendix I: Mapping of HRQoL data

Not applicable

Appendix J: Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to assess the robustness of the model to parameter uncertainty. In the PSA, 1,000 simulations were performed in which model parameters were varied simultaneously by sampling at random from hypothetical distributions. The distributions used for each variable in the PSA are reported in Table 53.

Table 58.Parameter limits used in the univariate sensitivity analyses and distributions and standard error (SE) used in the probabilistic sensitivity analysis

Parameter name	Base case	Lower value	Upper value	Distribution (SE)
Discount rate outcomes, 0-35 years in model	0.035	0.000	0.060	-
Discount rate outcomes, 36-70 years in model	0.025	0.000	0.050	-
Discount rate outcomes, >70 years in model	0.015	0.000	0.040	-
Discount rate costs, 0-35 years in model	0.035	0.000	0.060	-
Discount rate costs, 36-70 years in model	0.025	0.000	0.050	-
Discount rate costs, >70 years in model	0.015	0.000	0.040	-
Initial age (years)	46.933	44.28	49.58	-
Proportion of females	0.667	0.536	0.797	-
Weight, kg	80.568	76.23	84.91	-

Parameter name	Base case	Lower value	Upper value	Distribution (SE)
% of patients in MG-ADL <5 health state	0.000	0.000	0.000	Dirichlet (0.00)
% of patients in MG-ADL 5-7 health state	0.264	0.212	0.315	Dirichlet (0.03)
% of patients in MG-ADL 8-9 health state	0.419	0.337	0.501	Dirichlet (0.04)
% of patients in MG-ADL ≥10 health state	0.318	0.256	0.380	Dirichlet (0.03)
Efgartigimod non-responders	0.185	0.148	0.221	Beta (0.02)
Prob of crises from MG-ADL <5	0.000	0.000	0.000	Beta (0.00)
Prob of crises from MG-ADL 5-7	0.0009	0.0007	0.0010	Beta (0.0001)
Prob of crises from MG-ADL 8-9	0.0009	0.0007	0.0010	Beta (0.0001)
Prob of crises from MG-ADL ≥10	0.009	0.0007	0.0010	Beta (0.0001)
Transition probs - From Crises to MG-ADL <5	0.000	0.000	0.000	Beta (0.00)
Transition probs - From Crises to MG-ADL 5-7	0.000	0.000	0.000	Beta (0.00)
Transition probs - From Crises to MG-ADL 8-9	0.000	0.000	0.000	Beta (0.00)
Transition probs - From Crises to MG-ADL ≥10	1.000	0.804	1.000	Beta (0.10)
Probs of exacerbations - Conventional therapy	0.003	0.002	0.003	Beta (0.0003)
Probs of exacerbations - Efgartigimod	0.001	0.001	0.002	Beta (0.0001)
Mortality HR vs general population in health state MG-ADL <5	1.000	1.000	1.196	Lognormal (0.10)
Mortality HR vs general population in health state MG-ADL 5-7	1.000	1.000	1.196	Lognormal (0.10)
Mortality HR vs general population in health state MG-ADL 8-9	1.000	1.000	1.196	Lognormal (0.10)
Mortality HR vs general population in health state MG-ADL ≥10	1.000	1.000	1.196	Lognormal (0.10)
Prob of death during Crises	0.123	0.099	0.147	Beta (0.01)
Extra mortality associated with CS use - CS high-dose	2.033	1.635	2.432	Lognormal (0.20)
Extra mortality associated with CS use - CS low-dose	1.010	0.812	1.208	Lognormal (0.10)

Parameter name	Base case	Lower value	Upper value	Distribution (SE)
AE incidence - Conventional therapy - Infection	0.002	0.002	0.003	Normal (0.00)
AE incidence - Conventional therapy - Asthenia (fatigue)	0.002	0.002	0.003	Normal (0.00)
AE incidence - Conventional therapy - Cardiovascular disorders (incl. thrombosis)	0.002	0.002	0.003	Normal (0.00)
AE incidence - Conventional therapy - Eyelid disorders	0.002	0.002	0.003	Normal (0.00)
AE incidence - Conventional therapy - Myalgia	0.000	0.000	0.000	Normal (0.00)
AE incidence - Conventional therapy - Headache or procedural pain	0.002	0.002	0.003	Normal (0.00)
AE incidence - Conventional therapy - Gastrointestinal	0.000	0.000	0.000	Normal (0.00)
AE incidence - Conventional therapy - Other	0.007	0.005	0.008	Normal (0.00)
AE incidence - Efgartigimod - Infection	0.004	0.004	0.005	Normal (0.00)
AE incidence - Efgartigimod - Asthenia (fatigue)	0.000	0.000	0.000	Normal (0.00)
AE incidence - Efgartigimod - Cardiovascular disorders (incl. thrombosis)	0.000	0.000	0.000	Normal (0.00)
AE incidence - Efgartigimod - Eyelid disorders	0.000	0.000	0.000	Normal (0.00)
AE incidence - Efgartigimod - Myalgia	0.002	0.002	0.003	Normal (0.00)
AE incidence - Efgartigimod - Headache or procedural pain	0.002	0.002	0.003	Normal (0.00)
AE incidence - Efgartigimod - Gastrointestinal	0.002	0.002	0.003	Normal (0.00)
AE incidence - Efgartigimod - Other	0.009	0.007	0.011	Normal (0.00)
General pop. utility - All, age 18–29	0.871	0.700	1.000	Beta (0.09)
General pop. utility - All, age 30–39	0.848	0.682	1.000	Beta (0.08)
General pop. utility - All, age 40–49	0.834	0.671	0.997	Beta (0.08)
General pop. utility - All, age 50–59	0.818	0.658	0.978	Beta (0.08)
General pop. utility - All, age 60–69	0.813	0.654	0.972	Beta (0.08)
General pop. utility - All, age 70+	0.721	0.580	0.862	Beta (0.07)

Parameter name	Base case	Lower value	Upper value	Distribution (SE)
Utility - MG-ADL <5, Conventional therapy	0.831	0.785	0.876	Beta (0.02)
Utility - MG-ADL <5, efgartigimod	0.914	0.881	0.946	Beta (0.02)
Utility - MG-ADL 5-7, Conventional therapy	0.786	0.740	0.833	Beta (0.02)
Utility - MG-ADL 5-7, efgartigimod	0.869	0.836	0.903	Beta (0.02)
Utility - MG-ADL 8-9, Conventional therapy	0.727	0.680	0.774	Beta (0.02)
Utility - MG-ADL 8-9, efgartigimod	0.810	0.776	0.844	Beta (0.02)
Utility - MG-ADL ≥10, Conventional therapy	0.656	0.606	0.705	Beta (0.03)
Utility - MG-ADL ≥10, efgartigimod	0.739	0.702	0.775	Beta (0.02)
Utility - Crises	0.414	0.382	0.446	Beta (0.02)
Disutility per exacerbation event	-0.160	-0.191	-0.129	Normal (0.02)
Exacerbation duration (days)	20.725	16.663	24.787	Normal (2.07)
Utility decrement - High-dose CS	-0.175	-0.209	-0.141	Normal (0.02)
Utility decrement - Low-dose CS	-0.070	-0.084	-0.056	Normal (0.01)
Immunoglobulin in MG-ADL 8-9 – Conventional therapy cohort (%)	0.500	0.402	0.598	Beta (0.05)
Immunoglobulin in MG-ADL≥ 10 - Conventional therapy cohort (%)	1.000	0.804	1.000	Beta (0.10)
Conventional therapy treatments - Cohort on CS, %	0.752	0.605	0.899	Beta (0.08)
Conventional therapy treatments - Cohort on AChEi, %	0.884	0.711	1.000	Beta (0.09)
Conventional therapy treatments - Cohort on NSIST, %	0.597	0.480	0.714	Beta (0.06)
CS use in conventional therapy - % on corticosteroid high-dose	0.907	0.729	1.000	Beta (0.09)
CS use in conventional therapy - Average dose/day, high-dose	18.023	14.490	21.555	Gamma (1.80)
CS use in conventional therapy - Average dose/day, low-dose	9.000	7.236	10.764	Gamma (0.31)
Efgartigimod % change in CS use vs baseline - MG-ADL <5	-1.000	-1.000	-0.804	Beta (0.10)
Efgartigimod % change in CS use vs baseline - MG-ADL 5-7	0.000	0.000	0.000	Beta (0.00)

Parameter name	Base case	Lower value	Upper value	Distribution (SE)
Efgartigimod % change in CS use vs baseline - MG-ADL 8-9	0.000	0.000	0.000	Beta (0.00)
Efgartigimod % change in CS use vs baseline - MG-ADL ≥10	0.000	0.000	0.000	Beta (0.00)
Efgartigimod % on CS high-dose - MG-ADL <5	0.000	0.000	0.000	Beta (0.00)
Efgartigimod % on CS high-dose - MG-ADL 5-7	0.907	0.729	1.000	Beta (0.09)
Efgartigimod % on CS high-dose - MG-ADL 8-9	0.907	0.729	1.000	Beta (0.09)
Efgartigimod % on CS high-dose - MG-ADL ≥10	0.907	0.729	1.000	Beta (0.09)
Administration costs - Hospital administration, IVIG	28064.440	22563.810	33565.070	Gamma (2,806.44)
Administration costs - Hospital administration, efgartigimod IV	908.034	730.060	1,086.009	Gamma (90.80)
Cost of MG related hospitalizations - Cost of crises/cycle (Kr)	139,891.000	112,472.364	167,309.636	Gamma (12,727,60)
Cost of MG related hospitalizations - Cost of exacerbation/event (Kr)	34,896.000	28,056.384	41,735.616	Gamma (3,319,00)
Disease monitoring (HC visits, examinations) - MG-ADL <5	380.720	306.099	455.341	Gamma (37.44)
Disease monitoring (HC visits, examinations) - MG-ADL 5-7	473.626	380.795	566.457	Gamma (46.80)
Disease monitoring (HC visits, examinations) - MG-ADL 8-9	803.286	645.842	960.730	Gamma (76.66)
Disease monitoring (HC visits, examinations) - MG-ADL ≥10	879.019	706.731	1051.307	Gamma (84.70)
CS related chronic conditions cost - High-dose CS use	2175.929	1749.447	2602.411	Gamma (215.44)
CS related chronic conditions cost - Low-dose CS use	579.450	465.877	693.022	Gamma (57.37)
AE costs - Infection	1,234.00	992.14	1475.86	Gamma (218.00)
AE costs - Asthenia (fatigue)	3,618.00	2908.87	4327.13	Gamma (361.80)
AE costs - Cardiovascular disorders (incl. thrombosis)	35,525.00	28562.10	42487.90	Gamma (3,344.70)
AE costs - Eyelid disorders	1,362.00	1095.05	1628.95	Gamma (131.50)
AE costs - Myalgia	1,510.00	1214.04	1805.96	Gamma (164.50)

Parameter name	Base case	Lower value	Upper value	Distribution (SE)
AE costs - Headache or procedural pain	2,321.00	1866.08	2775.92	Gamma (361.80)
AE costs - Gastrointestinal	1,529.00	1229.32	1828.68	Gamma (235.80)
AE costs - Other	2,240.00	1800.96	2679.04	Gamma (317.60)
Average km per visit (return journey)	40.000	32.160	47.840	Gamma (4.00)
Cost per km	3.510	2.822	4.198	Gamma (0.35)
Value of 1 hour of time (DKK)	181.000	18.100	145.524	Gamma (18.10)
Hours per day to be valued	7.400	0.740	5.950	Gamma (0.74)
Patients use of time, Hours per IV administration - Ig	7.692	0.769	6.185	Gamma (0.77)
Patients use of time, Hours per IV administration - efgartigimod	2.500	0.250	0.025	Gamma (0.25)
Patients use of time, Hours per adverse event	1.000	0.100	0.804	Gamma (0.10)
Patients use of time, Days per exacerbation	20.725	2.073	16.663	Gamma (2.07)
Patients use of time, Days per crisis	28.000	2.800	22.512	Gamma (2.80)
Caregivers use of time during exacerbation and crisis, Hours per day in hospital	1.000	0.100	0.804	Gamma (0.010)

Appendix K: Transition probabilities

11.19. Efgartigimod

As described previously, separate transition probabilities are estimated for the on- and off-treatment periods, based on ADAPT and ADAPT+ efgartigimod data. The cohort enters the simulation and receives a first treatment cycle (ie, 4 weekly infusions). Following the first treatment cycle, the cohort located in the MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health states remains off-treatment for 1 model cycles (ie, 4 weeks) and transitions between health states based on probabilities estimated in the off-treatment period of the first cycle in ADAPT.[28] The cohort located in the MG-ADL <5 health state at the end of the first model cycle remains in this health state for a minimum of 4 weeks or until it worsens to MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10. In ADAPT and ADAPT+, patients did not receive a

subsequent cycle of treatment with efgartigimod as long as they remained in the MG-ADL <5 health state. The probabilities of transitioning out of the MG-ADL <5 health state were estimated by following the cohort with MG-ADL <5 at week 4 of the first cycle in ADAPT.[28] Such schema is repeated over the time horizon of the analysis. MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states are therefore separated into on- and off-treatment sub-states, and tunnel states are used to trace the off-treatment cohort from time of entry into a given health state.

To summarize, the following data were used to model the transition of the efgartigimod cohort between MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states over the time horizon of the analysis:

- On-treatment cycle:
    - Model cycle 1: MG-ADL change from baseline to week 4 of the first treatment cycle in ADAPT[28]
    - From model cycle 2: Average MG-ADL change from baseline to week 4 of each treatment cycle, based on ADAPT and ADAPT+ reconstructed data (from cycle 2 to cycle 13; beyond cycle 13 too few observations were available)
- Off-treatment cycles in MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health states: MG-ADL change from week 4 to week 8 of the first treatment cycle in ADAPT in placebo arm.
- Off-treatment cycles in MG-ADL <5 health state: MG-ADL change from week 4 to week 8, from week 8 to week 12, from week 12 to week 16 and from week 16 to week 20 in the first treatment cycle of ADAPT, placebo arm; data are sparse beyond 20 weeks, so transitions at week 20 are recycled.

11.20. Non-responder stopping rule

Overall, 18% of the efgartigimod treatment arm is classified as non-responsive and has treatment permanently discontinued. Post permanent discontinuation, the cohort has the costs and effects of the conventional therapy arm applied. The percentage (18%) is derived by dividing the number of patients in ADAPT who do not respond to two consecutive treatment cycles (n=12) by the total number of patients in the efgartigimod arm (n=65). To avoid complex simulation of transition probabilities, the non-responder cohort is separated from the responder cohort at the beginning of the simulation, but the cost of two cycles of efgartigimod treatment is still applied.

11.21. On-treatment transition probabilities

As described above, the transition probabilities for the first model cycle were calculated based on the number of patients that were in each health state at baseline of the first treatment cycle in ADAPT and the shifts to other health states that occurred by week 4 of the same cycle. In line with the population at baseline in ADAPT, at the beginning of the simulation, the entire cohort is distributed between MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states. The transition matrix defining the cycle probabilities applied in the first model cycle is shown in Table 54.

Table 59. On-treatment health-state transition probabilities, efgartigimod model cycle 1

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL 5–7	0.90	0.10	0.00	0.00	1.00

MG-ADL 8–9	0.76	0.19	0.05	0.00	1.00
MG-ADL ≥10	0.45	0.30	0.15	0.10	1.00

The on-treatment transition probabilities applied in the model after cycle 1 were estimated by averaging the observed health-state transitions between baseline and week 4 of each treatment cycle, combining ADAPT and ADAPT+ data to permit consideration of cycles 2 to 8. Table 55 shows the resulting on-treatment cycle transition probabilities applied after model cycle 1.

Table 60. On-treatment health-state transition probabilities, efgartigimod beyond model cycle 1

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL 5–7	0.97	0.03	0.00	0.00	1.00
MG-ADL 8–9	0.90	0.07	0.03	0.00	1.00
MG-ADL ≥10	0.65	0.20	0.09	0.06	1.00

11.22. Off-treatment transition probabilities in the MG-ADL <5 health state

The proportion of the cohort in the MG-ADL <5 health state at the end of each on-treatment model cycle is considered to remain off-treatment for a minimum of 4 weeks or until worsening to MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health states. Tunnel states were created in the model to simulate cycle transition probabilities that varied by time of entry into a given state, as observed in data from ADAPT. After one model cycle (i.e., 4 weeks) in the MG-ADL <5 health state, the cohort is at risk of worsening to the MG-ADL 5–7, MG-ADL 8–9, or MG-ADL ≥10 health state, which would lead to starting a new treatment cycle. Observations in the placebo arm of the ADAPT trial were used to inform transition probabilities since patients in MG-ADL <5 remain on conventional therapy only (i.e., off efgartigimod treatment) until they worsen to MG-ADL of 5 or higher. The patients in this group are tracked for a total of 16 weeks (from week 4 to week 20 of the first treatment cycle in ADAPT). Beyond week 20 the number of observations was too low to be informative. After the last tunnel state, the probabilities of the previous time interval (from week 16 to week 20) are recycled.

As explained previously, the visits in the ADAPT+ study are taken at different time points and, for the period after the last efgartigimod infusion, at a reduced frequency than in ADAPT.[28] Although it is possible to pool the observations of the two trials from week 0 to week 4 and from week 4 to week 8, it is overly complex to use the same approach to pool the observations of the two trials after the eighth week of each treatment cycle. Moreover, this would be associated with a high level of uncertainty. For this reason, the transition matrices for the cohort in the MG-ADL <5 health state are based only on the data from the first treatment cycle in ADAPT,[28] and no pooling of the two trials was implemented. The second treatment cycle of ADAPT is not used since many patients underwent this cycle after they entered ADAPT+. Using the first treatment cycle of ADAPT allows inclusion of the largest number of patients with the lowest level of uncertainty.

Table 56 shows the transition matrix used to inform the probabilities to shift from the MG-ADL <5 health state to any of the non–MG-ADL <5 health states during each tunnel state.

Table 61. Off-treatment probabilities from the MG-ADL <5 health state to any other non–MG-ADL <5 health state from time of entry into state, efgartigimod arm

Probability from entry in MG ADL <5 at:	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
Model cycle 1 (w4 to w8)	0.56	0.38	0.00	0.06	1.00
Model cycle 2 (w8 to w12)	0.88	0.13	0.00	0.00	1.00
Model cycle 3 (w12 to w16)	0.83	0.17	0.00	0.00	1.00
Model cycle 4+ (w16 to w20, applied thereafter)	0.40	0.40	0.20	0.00	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale; w: week. Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00.

11.23. Off-treatment probabilities in MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states

The proportion of the cohort in MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states at the end of each on-treatment cycle is assumed to remain off-treatment for 4 weeks (as previously explained) before a new treatment cycle is started. The transition probabilities during the off-treatment model cycle were informed by patient-level changes in MG-ADL from week 4 to week 8 in the first treatment cycle in the efgartigimod arm in ADAPT. Table 57 presents the resulting transition probabilities applied to define transitions from MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 off-treatment substate.

Table 62. Off-treatment probabilities from MG-ADL 5–7, MG-ADL 8–9, and MG-ADL ≥10 health states in the off-treatment model cycle, efgartigimod model arm, based on observations from ADAPT placebo arm

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL 5–7	0.27	0.36	0.27	0.09	0.27
MG-ADL 8–9	0.00	0.00	0.25	0.75	0.00
MG-ADL ≥10	0.00	0.00	0.00	1.00	0.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00

11.24. Conventional therapy

To model the transition probabilities in the conventional therapy arm, the placebo arm of ADAPT was used.

The number of patients in ADAPT who shifted to a different health state during each 4-week period starting from baseline up to the sixteenth week is used to calculate the transition matrices of the first four model cycles. After the fifth model cycle, the cohort is assumed to remain in the same health state unless a crisis or death occurs. The transition matrices are obtained by averaging those of the first four

cycles. The cohort in the conventional therapy arm is assumed to be treated constantly over the entire time horizon.

Tables 58 - 62 show the transition matrices used to define the probabilities from MG-ADL <5, MG-ADL 5–7, MG-ADL 8–9 and MG-ADL ≥10 in the conventional therapy arm at the first, second, third, fourth, and fifth+ cycles of the model, respectively. At the fifth cycle, the model assumes that the cohort remains in the last observed health state.

Table 63. Transition matrix used for the conventional therapy arm during the first model cycle

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL 5–7	0.47	0.35	0.18	0.00	1.00
MG-ADL 8–9	0.19	0.26	0.48	0.07	1.00
MG-ADL ≥10	0.19	0.19	0.19	0.44	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00

Table 64. Transition matrix used for the conventional therapy arm during the second model cycle

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL <5	0.56	0.38	0.00	0.06	1.00
MG-ADL 5–7	0.20	0.60	0.13	0.07	1.00
MG-ADL 8–9	0.00	0.32	0.47	0.21	1.00
MG-ADL ≥10	0.00	0.00	0.33	0.67	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00

Table 65. Transition matrix used for the conventional therapy arm during the third model cycle

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL <5	0.90	0.10	0.00	0.00	1.00
MG-ADL 5–7	0.06	0.78	0.00	0.17	1.00
MG-ADL 8–9	0.14	0.29	0.29	0.29	1.00
MG-ADL ≥10	0.00	0.17	0.00	0.83	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00

Table 66. Transition matrix used for the conventional therapy arm during the fourth model cycle

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL <5	0.75	0.17	0.00	0.08	1.00
MG-ADL 5–7	0.19	0.62	0.19	0.00	1.00
MG-ADL 8–9	0.00	0.67	0.33	0.00	1.00
MG-ADL ≥10	0.00	0.22	0.17	0.61	1.00

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Individual values are rounded for ease of presentation; therefore, rows may not precisely total 1.00

Table 67. Transition matrix used for the conventional therapy arm during and after the fifth model cycle (the cohort is assumed to return towards baseline health-state distribution)

From/To	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Total
MG-ADL <5	0.00	0.26	0.42	0.32	1.00
MG-ADL 5–7	0.00	0.26	0.42	0.32	1.00
MG-ADL 8–9	0.00	0.26	0.42	0.32	1.00
MG-ADL ≥10	0.00	0.26	0.42	0.32	1.00

Identity matrix is included to model recycling of the cohort in the same health-state.

Appendix L: Costs inputs

11.25. Drug acquisition and administration

Efgartigimod is dosed at 10 mg per kg of body weight per administration, and for the dose calculation the model considers a 10% dose banding. The model base case estimates the number of vials based on the average weight of the AChR-Ab+ patients in ADAPT, yielding an average of 2 vials per administration.

The model assumes that 50% and 100% of the conventional therapy cohort in the MG-ADL 8-9 and MG-ADL ≥10 health states, respectively, receives IVIg therapy.[160] This assumption is in line with the definition of refractory patients provided in the REGAIN study, which investigated the effect of eculizumab in AChR-Ab+ gMG patients. In the REGAIN trial, one of the criteria used to define refractory is the need for ongoing IVIg therapy. This is also consistent with what is reported in other papers,[161] [162] and it has been validated by a Danish clinical expert who treats patients with gMG.

Health effects for patients receiving SoC in the model are based on the placebo arm from ADAPT until trial data are available to define health-state transitions, and do not explicitly consider the effect of IVIg. To extrapolate beyond the availability of data from ADAPT, the model assumes that the cohort would be distributed as observed at baseline in ADAPT and maintained stable at a population level for the entire duration of the simulation. This represents a conservative assumption for the analysis, meaning that the

condition will not worsen for the entire patient's lifetime. This means that the baseline distribution in ADAPT is representative of the distribution expected to be observed at the population-level in patients treated with SoC (which includes the use of IVIg for some patients in clinical practice), i.e., there may be some patients improving and some patients worsening because of changes in treatment dosing/schedule, but the population level distribution is expected to remain constant. Following the same rationale, although patients receiving IVIg were excluded from ADAPT, the cost-effectiveness analysis assumes that the inclusion of these treatments for a proportion of the cohort in each health-state does not influence the population-level distribution between health-states of the cohort on SoC. This assumption is further supported by the lack of evidence on efficacy of IVig in gMG.

Immunoglobulin vial size and price is based on the price of Privigen, as reported in Medicinpriser.dk.[163] Immunoglobulin therapy is administered as intravenous infusion (IVIg) in Denmark, dosed at 1 g/kg, yielding an average of 5 vials per administration; this usage was validated with a Danish clinical expert.

Table 68. Drug price (efgartigimod, IVIg, SCIg)

	mg per vial	vials per pack	Pack price (DKK)	Price per mg (DKK)	Price per vial (DKK)
Efgartigimod	400	1	[redacted]	[redacted]	[redacted]
IVIg (2.5 mg/25 mL)	25	1	2,0671,530.00	0.8361	1,530.00
IVIg (200 mg/200 ml)	20000	1	16,41812,240.00	0.8261	12,240.00

As efgartigimod is administered as four weekly administrations during any treatment cycle, four administrations are considered per treatment cycle of the analysis. A relative dose intensity of 0.96 is considered for efgartigimod based on the observation of 3.82 administrations out of 4 planned during a treatment cycle. IVIg is administered once every four weeks and therefore one administration per model cycle is considered.

Table 69. Drug cost per cycle (efgartigimod, IVIg)

	Admin per cycle	Drug cost per vial (DKK)	Drug cost per administration (DKK)	Drug cost per cycle (DKK)
Efgartigimod	4.00*0.96	[redacted]	[redacted]	[redacted]
IVIg (2.5 mg/25 mL)	1	1,530.00	1,530.00	1,530.00
IVIg (200 mg/50 ml)	0	3,060.00	0	0
IVIg (2.5 mg/100 mL)	1	6,120.00	6,120.00	6,120.00
IVIg (2.5 mg/200 mL)	1	12,240.00	12,240.00	12,240.00

IVIg (2.5 mg/400 mL)	1	24,480.00	24,480.00	24,480.00

The 10% dose banding was included for both efgartigimod and the SoC arm. The rationale behind it was that the average weight of patients is 80.6 kg. The recommended dose is 10 mg/kg and 1 vial have 400 mg. It means that 1 vial could treat a patient with 40 kg and 2 vials could treat a patient with 80 kg. The 10% of dose banding on efgartigimod was implemented to reflect the expectation that patients with weight up to 10% greater than the weight to be treated with 2 vials (up to 88 kg) could still use 2 vials to avoid wasting a large proportion of a third vial. This was also seen in real world evidence from the United States, where 50% of patients weighing between 80 and 90 kg were receiving 2 vials instead of 3 (argenx, data on file). To ensure the consistency between both treatment arms, the current model also includes this 10% dose banding for SoC, in addition to efgartigimod.

In terms of IVIg cost per administration, assuming a recommended dose of 1000 mg/Kg, an average weight of 80.568 Kg and the 10% dose banding it can be assumed that only 72,511.33 mg of IVIg would be administered. The model includes all the available packages of Privigen and we are considering the most efficient use of IVIg, i.e. using 1 vial of 400 ml, 1 vial of 200 ml, 1 vial of 100 ml and 2 vials of 25 ml (or 1 vial of 50 ml). Please, note that the price per mg is the same across all the packages considered, so the focus was on avoiding drug wastage. In other words, the model assumes 2 vials of 25 ml instead of 1 vial of 50 ml, but as the price per mg is the same and the wastage as well, it does not impact the results (Table 64).

The model includes the option to consider the impact of loss of market exclusivity for efgartigimod. This is done by considering a price discount of 24% after 10 years from the start of the simulation. This option is not considered in the model base case but is explored in a scenario analysis.

Conventional therapy includes CS, AChEis, and NSISTs. The proportion of the cohort treated with each therapy was informed based on patient distribution in ADAPT. The cohort treated with corticosteroids was further divided into high- (18.02 mg/day) and low-dose (3.11 mg/day). The high-dose threshold was defined as 5 mg/day, based on Danish clinical expert opinion.

Table 70. Allocation of the cohort between the conventional therapies

Cohort	Percentage
CS, %	75
CS – high dose, % out of total cohort on CS	91
CS – low dose, % out of total cohort on CS	9
AChEi, %	88
NSIST, %	60

The information on the vial size and prices was as reported in Medicinpriser.dk.[163]

Table 71. Conventional therapy price (DKK)

	mg per unit	Units per pack	Pack price	Price per mg	Price per unit	mg per week	Price per week
Azathioprine	25.00	50.00	68.00	0.05	1.36	1409.94	76.70
Methotrexate	2.50	100.00	35.00	0.14	0.35	7.50	1.05
Ciclosporin	25.00	50.00	391.00	0.31	7.82	1691.93	529.24
Tacrolimus	1.00	90.00	1957.00	21.74	21.74	21.00	456.63
Mycophenolate	500.00	100.00	481.00	0.01	4.81	7000.00	67.34
Cyclophosphamide	50.00	100.00	922.50	0.18	9.23	1127.95	208.11
Prednisolone, high dose	5.00	100.00	36.30	0.07	0.36	126.16	9.16
Prednisolone, low dose						21.77	1.58
Pyridostigmine	60.00	150.00	135.50	0.02	0.90	5040.00	75.88

Conventional therapy was assumed to be administered continuously over the entire time horizon unless the cohort transitioned to the crisis health state within which they would receive rescue therapy.

Table 72. Conventional therapy cost per cycle

Therapy	Cost per cycle (DKK)
Corticosteroid	8.90
AChEi	303.52
NSIST	804.82
Conventional therapy mix	761.55

The administration costs were informed based on the Medicinrådet: Værdisætning af. 2021 and DRG 2022 (Table 63 and Table 64).[164, 165] In the base case, efgartigimod is administered intravenously in a hospital setting only. The model therefore considers the hospital nurse cost (Medicinrådet: Værdisætning af. 2021, hourly rate of 441, inflated 454.02) multiplied by the mean time of efgartigimod infusion as reported in the ADAPT study (ie, 2 hours).

IVIg is administered in a hospital setting. In addition to administration time, it requires monitoring of patients for adverse events. Moreover, the administration of IVIg usually occurs over multiple days to

minimize the risk of side effects. Based on clinical validation with two local neurologists, the model considers the DRG code 01MP08 (139,891 DKK) for the estimation of administration costs of IVIg. It should be noted that the referred DRG code includes the costs for the medication and the resource use, that's why we are subtracting the per cycle Privigen cost. In other words, to the 139,891 DKK we subtracted the 45,900 DKK of Privigen to avoid the double count of costs, resulting in a cost per administration of 93,991 DKK.

Conventional therapy does not have administration costs given that all of the treatments are administered orally.

Table 73. Cost per administration

Administration modality	Per administration cost (DKK)
Hospital administration, IVIg	93,991.00
Hospital administration, efgartigimod	908.03

Table 74. Cost of administration per cycle

Treatment	Per-cycle cost (DKK)
IVIg	
Efgartigimod	3,632.14

11.26. Reduction in corticosteroid use

Due to the large burden of chronic CS use on mortality, QoL, and costs, an important potential benefit of efgartigimod treatment is the potential reduction in CS use. An SLR was conducted to obtain evidence of the impact of CS use on HRQoL, costs, and mortality.

Initial discussions with clinicians indicate that patients on efgartigimod will receive much lower doses of CS, and ideally there will be no corticosteroid use in MG-ADL <5 patients. This is also supported by treatment guidelines which advise to reduce/remove CS treatment as soon as the disease is under control. Given the CS side-effect profile, MG-specific treatment guidelines recommend a gradual tapering once treatment goals are reached and to continue with the lowest CS effective dose as maintenance therapy.[41]

The ADAPT trial cannot be used as source of evidence to model changes in CS use since the treatment schedule could not be modified by protocol; however, based on existing supporting evidence, the model considers the following three options to model changes in CS use:

- Based on existing gMG treatment guidelines that recommend reducing CS dose as soon as possible, the cohort in the MG-ADL <5 health state in both treatment arms of the model is assumed to have 0% CS use. This option is considered in the base case.
- Based on existing guidelines and support from clinicians, 100% of MG-ADL <5 and MG-ADL 5–7 cohorts in the efgartigimod and conventional therapy arms are assumed to receive low-dose CS (<10–5 mg/day). This option is explored in a scenario analysis.

11.27. Patient-monitoring costs by health state

Monitoring healthcare resource use by health state was obtained from the MyRealWorld MG study. The study data allowed the estimation of annual frequency of monitoring visits by health state (Table 66). The annual frequency was divided by 12 to transform it into the model cycle frequency. Emergency and in-hospital visits were not considered since they are likely to occur for treatment exacerbation and crises rather than being part of routine patient monitoring. Costs were inflated to 2020/2021 amounts to calculate the monitoring cost per cycle.

Table 75. Annual average frequency of monitoring visits by health state

HCRU	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10
GP	1.3	1.71	2.77	2.95
Hospital outpatient	0.67	0.64	1.76	1.56
Nurse visit	0.03	0.18	0.95	1.51
Physiotherapist	0.28	0.25	1.64	1.43
Specialist	3.11	4.02	4.61	5.69

Table 76. Healthcare resource unit cost

HCRU	Unit cost (DKK) - original	Unit cost (DKK) – inflated to 2022	Source
General practitioner visit	954.62	964.15	Kommunernes og Regionernes Løndatakontor
Specialist visit, hospital	1,024.00	1,054.23	Medicinrådet: Værdisætning af
Nurse, hospital	441.00	454.02	Medicinrådet: Værdisætning af
Physiotherapist	674.88	681.62	Medicinrådet: Værdisætning af enhedsomkostninger – Medicinrådet (version 1.6; Feb 2022)
Specialist visit, neurology out-patient	765.49	773.13	Medicinrådet: Værdisætning af

Table 77. Patient monitoring cost per cycle

Health state	HRCU cost per cycle (DKK)
MG-ADL <5	384.60
MG-ADL 5–7	478.64

MG-ADL 8–9	809.03
MG-ADL ≥10	886.11

11.28. Cost of complications associated with chronic CS use

The association between CS chronic use and costs has been reported in the literature, including the extra expenditure required to treat complications and CS-related AEs. In addition, studies have reported the impact of high and low CS doses on total annual cost—increases in HCRU, costs, and complications were more pronounced with higher doses of CS.[145, 167]

The SLR covering the humanistic and economic burden of chronic CS use, previously described in this dossier, was used as a source of evidence to define the additional costs associated with the consequence of chronic systemic CS use. No Danish studies were identified. Therefore, the geographical scope was broadened to Nordic countries. Among all studies included in the SLR, two studies conducted in Sweden[154, 168] were used to populate the extra costs associated with the consequences of systemic CS in the model. In the model, the extra cost related to chronic CS use is applied to patients receiving high- or low-dose CS as maintenance therapy. The average cost was estimated by CS dose and the extra cost per cycle among CS users was implemented in the model (Table 73).

Table 78. Chronic CS use, extra cost per cycle

Corticosteroid dose	Cost per cycle (DKK)
High-dose CS use	2,175.93
Low-dose CS use	579.45

11.29. Rescue treatment costs

Rescue treatment costs included the cost of gMG exacerbations requiring hospitalization and gMG crises. Both inputs were based on the DRG (2022).[165]

Table 79. Cost of MG-related hospitalizations

Event	Cost (DKK)	Reference
gMG exacerbation (per event)	34,896.00	01MA06
gMG crisis (per cycle)	139,891.00	01MP08

11.30. Treatment-emergent adverse events cost

The unit (one-off) cost of each treatment-emergent grade 3 AE is applied per event to the proportion of the cohort having each respective AE at each cycle of the analysis. The cost of the AEs was informed based on the DRG (2022).[165]

Table 80. Cost of adverse events

AE	Cost (DKK)	Reference
Infection	1,234.00	04MA98
Asthenia (fatigue)	2,321.00	01MA98
Cardiovascular disorders (incl. thrombosis)	35,525.00	05MA04
Eyelid disorders	1,362.00	02PR01
Myalgia	1,510.00	08MA98
Headache or procedural pain	2,321.00	01MA98
Gastrointestinal	1,529.00	06MA98
Other	2,240.00	16MA98

11.31. Transportation costs

The transportation cost has been calculated by multiplying the average kilometres (km) travelled by the unit cost per km. It is assumed that patients travel a total of 40 km to go to the follow-up visit. The unit cost per km is equal to DKK 3.51.[164] The resulting total transportation cost per visit to the hospital is DKK 140.40.[164]

Appendix M: Sensitivity analysis

11.32. One-way sensitivity analysis

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way sensitivity analyses was performed in which key model parameters were varied one at a time around their base-case values. High and low values were approximated by calculating the base-case value ± 1.96×SE. When the SE was not reported, 10% of the base-case value was used as a proxy for SE. Each parameter was varied to assess the impact on incremental LYs, QALYs and costs. High and low values used in the one-way sensitivity analyses are presented in Table 76 .

Table 81. Parameter limits used in the univariate sensitivity analyses

Parameter name	Base case	Lower value	Upper value
Discount rate outcomes, 0-35 years in model	0.035	0.000	0.060
Discount rate outcomes, 36-70 years in model	0.025	0.000	0.050
Discount rate outcomes, >70 years in model	0.015	0.000	0.040
Discount rate costs, 0-35 years in model	0.035	0.000	0.060
Discount rate costs, 36-70 years in model	0.025	0.000	0.050

Parameter name	Base case	Lower value	Upper value
Discount rate costs, >70 years in model	0.015	0.000	0.040
Initial age (years)	46.933	37.734	56.131
Proportion of females	0.667	0.536	0.797
Weight, kg	80.568	76.225	84.911
% of patients in MG-ADL <5 health state	0.000	0.000	0.000
% of patients in MG-ADL 5-7 health state	0.264	0.212	0.315
% of patients in MG-ADL 8-9 health state	0.419	0.337	0.501
% of patients in MG-ADL ≥10 health state	0.318	0.256	0.380
Efgartigimod non-responders	0.185	0.148	0.221
Prob of crises from MG-ADL <5	0.000	0.000	0.000
Prob of crises from MG-ADL 5-7	0.001	0.001	0.001
Prob of crises from MG-ADL 8-9	0.001	0.001	0.001
Prob of crises from MG-ADL ≥10	0.001	0.001	0.001
Transition probs - From Crises to MG-ADL <5	0.000	0.000	0.000
Transition probs - From Crises to MG-ADL 5-7	0.000	0.000	0.000
Transition probs - From Crises to MG-ADL 8-9	0.000	0.000	0.000
Transition probs - From Crises to MG-ADL ≥10	1.000	0.804	1.000
Probs of exacerbations - Conventional therapy	0.003	0.002	0.003
Probs of exacerbations - Efgartigimod	0.001	0.001	0.002
Mortality HR vs general population in health state MG-ADL <5	1.000	1.000	1.196
Mortality HR vs general population in health state MG-ADL 5-7	1.000	1.000	1.196
Mortality HR vs general population in health state MG-ADL 8-9	1.000	1.000	1.196
Mortality HR vs general population in health state MG-ADL ≥10	1.000	1.000	1.196
Prob of death during Crises	0.123	0.099	0.147
Extra mortality associated with CS use - CS high-dose	2.033	1.635	2.432
Extra mortality associated with CS use - CS low-dose	1.010	0.812	1.208
AE incidence - Conventional therapy - Infection	0.002	0.002	0.003
AE incidence - Conventional therapy - Asthenia (fatigue)	0.002	0.002	0.003
AE incidence - Conventional therapy - Cardiovascular disorders (incl. thrombosis)	0.002	0.002	0.003
AE incidence - Conventional therapy - Eyelid disorders	0.002	0.002	0.003
AE incidence - Conventional therapy - Myalgia	0.000	0.000	0.000
AE incidence - Conventional therapy - Headache or procedural pain	0.002	0.002	0.003

Parameter name	Base case	Lower value	Upper value
AE incidence - Conventional therapy - Gastrointestinal	0.000	0.000	0.000
AE incidence - Conventional therapy - Other	0.007	0.005	0.008
AE incidence - Efgartigimod - Infection	0.004	0.004	0.005
AE incidence - Efgartigimod - Asthenia (fatigue)	0.000	0.000	0.000
AE incidence - Efgartigimod - Cardiovascular disorders (incl. thrombosis)	0.000	0.000	0.000
AE incidence - Efgartigimod - Eyelid disorders	0.000	0.000	0.000
AE incidence - Efgartigimod - Myalgia	0.002	0.002	0.003
AE incidence - Efgartigimod - Headache or procedural pain	0.002	0.002	0.003
AE incidence - Efgartigimod - Gastrointestinal	0.002	0.002	0.003
AE incidence - Efgartigimod - Other	0.009	0.007	0.011
General pop. utility - All, age 18–29	0.871	0.700	1.000
General pop. utility - All, age 30–39	0.848	0.682	1.000
General pop. utility - All, age 40–49	0.834	0.671	0.997
General pop. utility - All, age 50–59	0.818	0.658	0.978
General pop. utility - All, age 60–69	0.813	0.654	0.972
General pop. utility - All, age 70+	0.721	0.580	0.862
Utility - MG-ADL <5, Conventional therapy	0.831	0.785	0.876
Utility - MG-ADL <5, efgartigimod	0.914	0.881	0.946
Utility - MG-ADL 5-7, Conventional therapy	0.786	0.740	0.833
Utility - MG-ADL 5-7, efgartigimod	0.869	0.836	0.903
Utility - MG-ADL 8-9, Conventional therapy	0.727	0.680	0.774
Utility - MG-ADL 8-9, efgartigimod	0.810	0.776	0.844
Utility - MG-ADL ≥10, Conventional therapy	0.656	0.606	0.705
Utility - MG-ADL ≥10, efgartigimod	0.739	0.702	0.775
Utility - Crises	0.414	-0.168	0.995
Disutility per exacerbation event	-0.160	-0.191	-0.129
Exacerbation duration (days)	20.725	16.663	24.787
Utility decrement - High-dose CS	-0.175	-0.209	-0.141
Utility decrement - Low-dose CS	-0.070	-0.084	-0.056
Impact of MG on the QoL of caregivers - MG-ADL <5, Conventional therapy	-0.020	-0.024	-0.016
Impact of MG on the QoL of caregivers - MG-ADL <5, efgartigimod	0.000	0.000	0.000

Parameter name	Base case	Lower value	Upper value
Impact of MG on the QoL of caregivers - MG-ADL 5-7, Conventional therapy	-0.070	-0.084	-0.056
Impact of MG on the QoL of caregivers - MG-ADL 5-7, efgartigimod	0.000	0.000	0.000
Impact of MG on the QoL of caregivers - MG-ADL 8-9, Conventional therapy	-0.130	-0.155	-0.105
Impact of MG on the QoL of caregivers - MG-ADL 8-9, efgartigimod	-0.042	-0.050	-0.034
Impact of MG on the QoL of caregivers - MG-ADL ≥10, Conventional therapy	-0.190	-0.227	-0.153
Impact of MG on the QoL of caregivers - MG-ADL ≥10, efgartigimod	-0.100	-0.120	-0.081
Impact of MG on the QoL of caregivers - Crises	-0.278	-0.332	-0.223
Efgartigimod - Loss of exclusivity from year	10.000	8.040	11.960
Efgartigimod - Price discount due to loss of exclusivity	[redacted]	[redacted]	[redacted]
Immunoglobulin in MG-ADL 8-9 – Conventional therapy cohort (%)	0.500	0.402	0.598
Immunoglobulin in MG-ADL≥ 10 - Conventional therapy cohort (%)	1.000	0.804	1.000
Conventional therapy treatments - Cohort on CS, %	0.752	0.605	0.899
Conventional therapy treatments - Cohort on AChEi, %	0.884	0.711	1.000
Conventional therapy treatments - Cohort on NSIST, %	0.597	0.480	0.714
CS use in conventional therapy - % on corticosteroid high-dose	0.907	0.729	1.000
CS use in conventional therapy - Average dose/day, high-dose	18.023	14.490	21.555
CS use in conventional therapy - Average dose/day, low-dose	9.000	7.236	10.764
Efgartigimod % change in CS use vs baseline - MG-ADL <5	-1.000	-1.000	-0.804
Efgartigimod % change in CS use vs baseline - MG-ADL 5-7	0.000	0.000	0.000
Efgartigimod % change in CS use vs baseline - MG-ADL 8-9	0.000	0.000	0.000
Efgartigimod % change in CS use vs baseline - MG-ADL ≥10	0.000	0.000	0.000
Efgartigimod % on CS high-dose - MG-ADL <5	0.000	0.000	0.000
Efgartigimod % on CS high-dose - MG-ADL 5-7	0.907	0.729	1.000
Efgartigimod % on CS high-dose - MG-ADL 8-9	0.907	0.729	1.000
Efgartigimod % on CS high-dose - MG-ADL ≥10	0.907	0.729	1.000
Administration costs - Hospital administration, IVIG	28064.440	22563.810	33565.070
Administration costs - Hospital administration, efgartigimod IV	908.034	90.803	730.060

Parameter name	Base case	Lower value	Upper value
Cost of MG related hospitalizations - Cost of crises/cycle (Kr)	127276.000	102329.904	152222.096
Cost of MG related hospitalizations - Cost of exacerbation/event (Kr)	33190.000	26684.760	39695.240
Disease monitoring (HC visits, examinations) - MG-ADL <5	374.448	301.056	447.840
Disease monitoring (HC visits, examinations) - MG-ADL 5-7	468.027	376.293	559.760
Disease monitoring (HC visits, examinations) - MG-ADL 8-9	766.553	616.308	916.797
Disease monitoring (HC visits, examinations) - MG-ADL ≥10	846.989	680.979	1012.999
CS related chronic conditions cost - High-dose CS use	2154.423	1732.156	2576.690
CS related chronic conditions cost - Low-dose CS use	573.723	461.273	686.172
AE costs - Infection	2180.000	1752.720	2607.280
AE costs - Asthenia (fatigue)	3618.000	2908.872	4327.128
AE costs - Cardiovascular disorders (incl. thrombosis)	33447.000	26891.388	40002.612
AE costs - Eyelid disorders	1315.000	1057.260	1572.740
AE costs - Myalgia	1645.000	1322.580	1967.420
AE costs - Headache or procedural pain	3618.000	2908.872	4327.128
AE costs - Gastrointestinal	2358.000	1895.832	2820.168
AE costs - Other	3176.000	2553.504	3798.496
Average km per visit (return journey)	40.000	32.160	47.840
Cost per km	3.510	2.822	4.198
Value of 1 hour of time (DKK)	181.000	18.100	145.524
Hours per day to be valued	7.400	0.740	5.950
Patients use of time, Hours per IV administration - Ig	7.692	0.769	6.185
Patients use of time, Hours per IV administration - efgartigimod	2.500	0.250	0.025
Patients use of time, Hours per adverse event	1.000	0.100	0.804
Patients use of time, Days per exacerbation	20.725	2.073	16.663
Patients use of time, Days per crisis	28.000	2.800	22.512
Caregivers use of time during exacerbation and crisis, Hours per day in hospital	1.000	0.100	0.804

11.32.1. Scenario analyses

11.32.1.1. Conventional therapy transitions: only 1 cycle then freeze

A scenario analysis was performed to mitigate the impact of the placebo effect observed in ADAPT (ie, patients in conventional therapy arm improved, probably due to the placebo effect). Transitions were applied only in the first 4 weeks rather than over 26 weeks (base case).

11.32.1.2. CS high-dose threshold

A scenario analysis was performed that changed the CS high-dose threshold from 5 mg/day (base case) to 10 mg/day.

11.32.1.3. Low-dose CS in MG-ADL <5 cohort

To address uncertainty regarding CS tapering in controlled patients (ie, despite guideline recommendations to taper treatment it is unknown whether all patients completely stop CS), a scenario analysis was performed that assumed the MG-ADL <5 cohort would remain on CS, but switch to low dose (ie, 0% of the cohort on high-dose).

11.32.1.4. Utilities from mixed model regression using MyRealWorld MG data

To provide real-world context, a scenario analysis was performed using observed utilities derived from the MyRealWorld MG study.

11.32.1.5. Vial sharing

In order to explore potential cost-saving measures, a scenario analysis was performed that included vial sharing.

11.32.1.6. Loss of exclusivity discount

A scenario analysis was performed that included a loss of exclusivity discount of [redacted]

Appendix N: Systematic literature review: Clinical and economic impact of chronic use of corticosteroids

11.33. Clinical SLR

11.33.1. Objectives

The primary objective of this project was to systematically identify available evidence from the literature to assess the impact of chronic CS use on mortality in adult patients (including adults with MG) in comparison with non-users. Additionally, this SLR provided inputs for the Efgartigimod cost effectiveness model (CEM).

The SLR addressed the research questions by summarizing published evidence on:

- The impact on mortality of chronic CS use, assumed in this study as CS use of minimum 3 months as maintenance therapy to treat chronic diseases.

- The impact of the CS dose (high vs low dose) on mortality, if this is described in the studies identified.

11.33.2. Methods

Procedures for this SLR followed the Cochrane guidelines for conduction systematic reviews of interventions and the guidance for identification and selection of relevant studies for single technology assessment by the National Institute for Health and Care Excellence (NICE).

This task involved identifying and retrieving all potentially relevant literature describing CS impact on mortality in chronic CS users vs non-users in adults diagnosed with chronic diseases. As mentioned, mortality outcomes due to CS use compared to non-use within the same baseline condition was considered.

11.33.3. Literature search

The literature search was conducted in both electronic and non-electronic databases listed below.

11.33.3.1. Electronic databases

Studies indexed from January 2012 in MEDLINE (via OvidSP), EMBASE (via OvidSP), the Cochrane Central Register of Controlled Trials (CENTRAL, via OvidSP) and DARE (databases of abstracts of reviews of effect), were retrieved using search strategies containing free text and controlled vocabulary terms developed for each database. Searches for conference abstracts were conducted in Embase via OvidSP.

11.33.3.2. Non-Electronic databases and grey literature

To ensure all relevant publications and studies were identified, the following additional sources were searched.

- Google scholar
- Opengrey
- Clinical trial.gov
- World Health Organization clinical trial registry
- Bibliographies of relevant identified studies
- Conference proceeding (from 2019) not index in Embase

11.33.4. Study selection and eligibility criteria

To be eligible for inclusion in this SLR, studies yielded from the above search must have avoided any exclusion criteria and satisfy all inclusion criteria listed in Table N1.

The study selection followed a two-stage process. In the first phase, the title and abstract of the retrieved articles were screened after removal of duplicates identified between the databases. Studies were excluded if they clearly met any of the exclusion criteria and included if they met the inclusion criteria or required further assessment of the full-text. In phase two, the full text of all articles retained in phase one were screened for inclusion into the SLR. Each stage of the study selection was conducted by two independent reviewers and their disagreements resolved through discussion or by a third reviewer if a consensus was not reached between them. In reviewing the studies, the eligibility criteria below were

applied. After the screenings were completed, a list of included and excluded studies during full-text screening, organized by reasons for exclusion, was created and presented to Argenx. After approval by Argenx, all studies accepted at full-text screening were thereafter eligible for extraction. A PRISMA flow chart, which presents the number of papers included in the different phases of the SLR (identification, screening, and eligibility) was structured at the end of this phase.

Table N82: SLR Eligibility criteria

PICOS framework	Inclusion criteria	Exclusion criteria
Patient population	• Adult patients (>18 years) with chronic CS use (at least 3 months as maintenance therapy) to treat chronic diseases.	• Non-human studies • Patients <18 years. • Non chronic treatment (less than 3 months) • Oncology population
Intervention	• Systemic corticosteroids (oral or intravenous administration).	• Non-systemic CS (topic, inhaled, perineural or neuro-axial)
Comparator	• Non-CS users among the same baseline disease • Placebo • Best supportive care	• Comparison between CS medications • Comparison CS users with a baseline condition vs healthy patients or other disease.
Outcomes	• Mortality or death	• Lack of relevant data on outcomes of interest and other AEs data
Study design	• Randomized control trials • Quasi experiment • Before and after study Observational cohort studies • Cross sectional studies	• SLRs and meta-analysis • Narrative reviews • Clinical guidelines • Commentary • Letters to the editor • No abstract or full-text to inform decision • News • Animal or in vitro studies • Pharmacokinetic or pharmacodynamic studies
Other criteria: Date of study publication, language of study publication	• Full texts and abstract from 2012 in English language	• Other languages • Full-texts and abstracts published pre-2012

AEs, adverse event; CS, corticosteroid; HRQoL, health related quality of life data.

11.33.5. Results

Figure N1 shows the disposition of publications identified for the analysis. The number of potentially relevant publications identified and screened for retrieval was 1300 (1259 publications identified by database search and 41 publications by manual search), of which 14 were included in the data extraction. Of the 14 studies evaluated for quality, a total of 3 studied were excluded from the analysis because of poor quality, thus 11 publications were included in the analysis. Seven of the studies were conducted in Europe; United states 2; South Korea 2; and Canada 1.

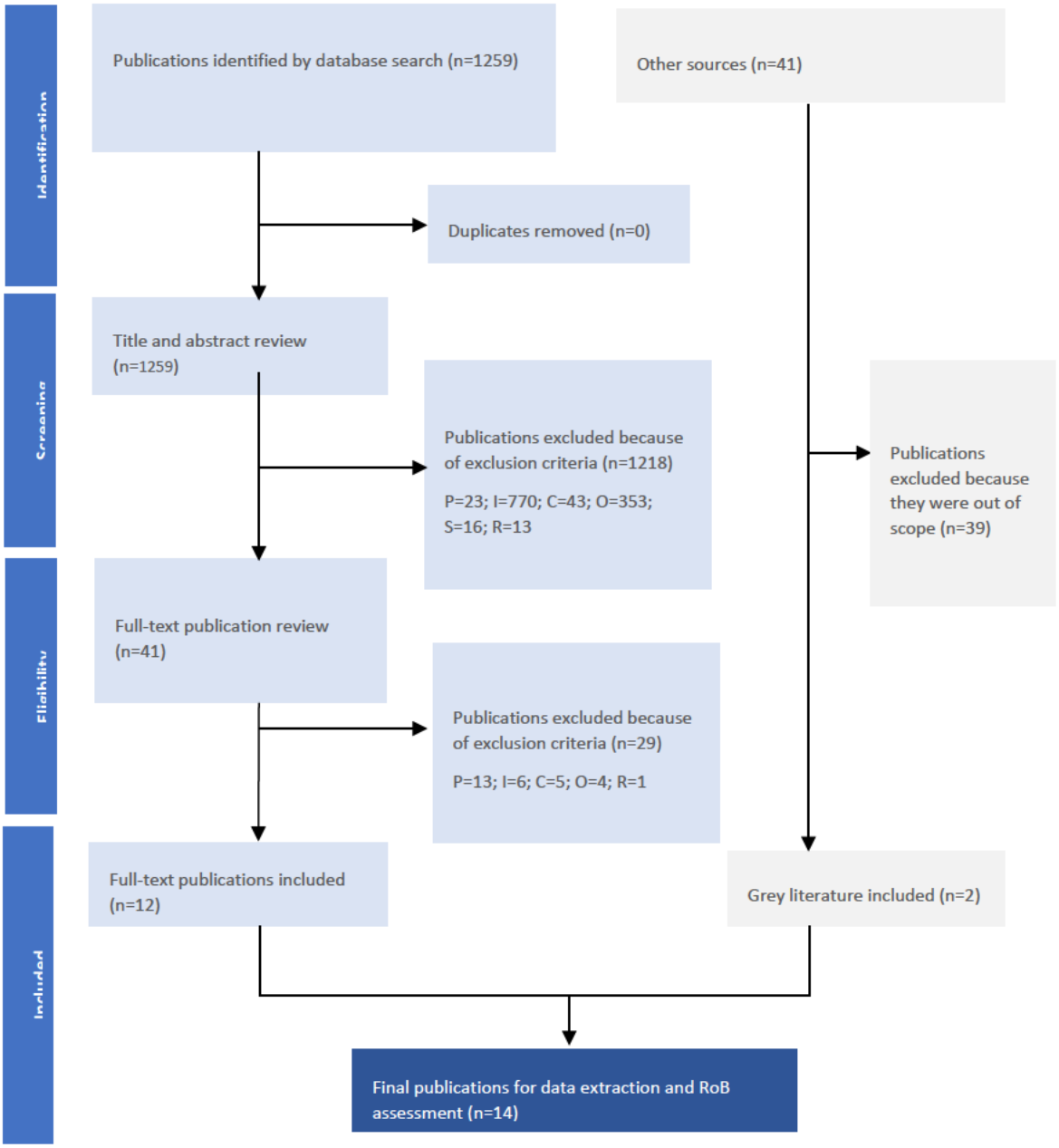


Figure N1. PRISMA chart for clinical SLR studies

All the studies were conducted in patients with chronic conditions, including asthma, giant cell arteritis, polymyalgia rheumatica, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, vasculitis, and other chronic conditions. The use of CS among the selected studies were extrapolated to prednisolone dose, and the comparison in terms of mortality between CS users vs. non-CS users, independent of the baseline condition, was estimated.

11.33.6. Search strategy

Search Number	Search Algorithm	Results
1	exp corticosteroid/ or exp glucocorticosteroid/ or exp glucocorticoids/ or exp prednisolone/ or exp prednisone/ or exp steroid/	2641517
2	(corticosteroid or glucocorticosteroid or glucocorticoids or prednisolone or prednisone or steroid).ti,ab.	648950
3	1 or 2	2822859
4	((systemic* or oral or chronic or maintenance or users or non-users or non users or dependent or dose or ever users or never users) adj3 (corticosteroid or glucocorticoids or glucocorticosteroid or prednisone or prednisolone or steroid)).ti,ab.	96262
5	3 and 4	96262
6	('anabolic' or 'inhale$' or 'topical' or 'topic' or 'acute' or 'non chronic' or 'dental' or 'pediatric' or 'paediatric' or 'children' or 'infant' or neonat$ or 'childhood' or 'juvenile' or 'boy' or 'girl' or 'pregnan$' or 'intra articular' or 'intra-articular' or 'epidural' or 'perineural' or 'oral health').mp.	13007748
7	5 not 6	53155
8	('mortality' or 'death' or 'survival').ti,ab.	5596718
9	exp mortality/	1660860
10	exp death/	928036
11	or/8-10	6392893
12	7 and 11	7595
13	exp case control study/ or exp cohort studies/ or exp cross sectional/ or exp longitudinal study/ or exp retrospective study/ or exp prospective study/ or exp observational study/ or exp Randomized Controlled Trial/ or exp randomi$/ or exp follow up studies/	7632839
14	12 and 13	3359
15	exp Narrative/ or exp Introductory Journal Article/ or exp News/ or exp Newspaper Article/ or exp Editorial/ or exp Comment/ or exp letter/ or exp case report$/ or exp case series/ or exp anecdote/ or exp commentary/ or exp case study/ or exp short survey/ or exp survey/ or exp review/ or exp meta analysis/ or exp meta-analy$/ or exp note/ or exp systematic/ or exp target literature review/ or exp evidence/ or exp protocol/ or exp guidelines/ or exp update/ or exp consensus/ or exp expert opinion/ or exp overall/ or exp erratum/	17003443
16	14 not 15	2856
17	(exp nonhuman/ or exp animal/) not exp human/	11738833
18	(In Vitro Techniques or in vitro study or rodent or mice or rat or mouse or animal).mp.	11140717
19	or/17-18	15317525
20	16 not 19	2779
21	(tumor or cancer or oncology or oncological or oncolog$ or malignancy or malignan$ or irradiation or metastatic or metastas$ or lymphoma or leukemia or chemotherap$ or radiotherap$).mp.	10215531
22	20 not 21	1834

23	limit 22 to english language	1790
24	limit 23 to yr="2012 -Current" [Limit not valid in DARE; records were retained]	1259

EBM Reviews - Cochrane Central Register of Controlled Trials <January 2022>. EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>. Embase <1974 to 2022 March 16>. Ovid MEDLINE(R) <1946 to March Week 2 2022>.

11.34. Non-Clinical SLR

11.34.1. Objectives

The primary objective of this search was to systematically identify available evidence from the literature to assess the impact of chronic CS use on QoL and costs in adult patients (including adults with MG) in comparison with non-CS users within the same baseline disease. Additionally, this SLR provided inputs for the Efgartigimod cost effectiveness model (CEM).

The SLR addressed the research questions by summarizing published evidence on:

- The impact on costs related to chronic CS use.
- The impact on QoL of chronic CS use.
- The impact of CS dose (high vs low dose) on costs and QoL related to treatment (if it is described among the selected publications).

11.34.2. Methods

Procedures for this review followed the Cochrane guidelines for conduction systematic reviews of interventions and the guidance for identification and selection of relevant studies for single technology assessment by NICE.

This task involved identifying and retrieving all potentially relevant literature describing chronic CS treatment related to costs and the impact on QoL of CS users vs non-users.

11.34.3. Literature search

The literature search was conducted in both electronic and non-electronic databases listed below.

11.34.3.1. Electronic databases

Studies indexed from January 2012 in the NHS Economic Evaluation database (via OvidSP), MEDLINE (via OvidSP), EMBASE (via OvidSP), the Cochrane Central Register of Controlled Trials (CENTRAL, via OvidSP) and DARE (databases of abstracts of reviews of effect), were retrieved using search strategies containing free text and controlled vocabulary terms developed for each database. Searches for conference abstracts were conducted in Embase via OvidSP.

11.34.3.2. Non-Electronic databases

To ensure all relevant published and studies were identified, the following additional sources were searched.

- Google scholar
- Opengrey
- Bibliographies of relevant identified studies

- Value in health or ISPOR (search for years do not index in Embase i.ie from 2019)
- HTA agencies websites in Europe

11.34.4. Study selection and eligibility criteria

To be eligible for inclusion in this SLR, studies yielded from the above search must have avoided any exclusion criteria and satisfy all inclusion criteria listed Table N2.

The study selection followed a two-stage process. In the first phase, the title and abstract of the retrieved articles were screened after removal of duplicates identified between the databases. Studies were excluded if they clearly met any of the exclusion criteria and included if they met the inclusion criteria or required further assessment of the full-text. In phase two, the full text of all articles retained in phase one were screened for inclusion into the SLR. Each stage of the study selection was conducted by two independent reviewers and their disagreements resolved through discussion or by a third reviewer if a consensus was not reached between them. In reviewing the studies, the eligibility criteria below were applied. After the screenings were completed, a list of included and excluded studies during full-text screening, organized by reasons for exclusion, were created and presented to Argenx. After approval by Argenx, all studies accepted at full-text screening were thereafter eligible for extraction. A PRISMA flow chart, which presents the number of papers included in the different phases of the SLR (identification, screening, and eligibility) was structured at the end of this phase.

Table N2: SLR Eligibility criteria

PICOS framework	Inclusion criteria	Exclusion criteria
Patient population	• Adult patients (>18 years) with chronic CS use (at least 3 months as maintenance therapy) to treat chronic diseases.	• Non-human studies • Studies not reporting outcomes of CS use • Paediatric population (age below 18 years) • Oncology population
Intervention	• Systemic corticosteroids (oral or intravenous administration).	• Non - systemic corticosteroids (topic, inhaled, perineural or neuro-axial administration).
Comparator	• Non-CS treatment • Placebo • Best supportive care *Comparison within the same underlying disease.	• Comparison between CS medications • Comparison CS users with a baseline condition vs healthy patients or other baseline disease.
Outcomes	• Costs related to chronic CS use • Quality of life reported in terms of utility or utility decrement estimated using EQ-5D-3L or EQ-5D-5L.	• Lack of relevant data on outcomes of interest • QoL reported using another form/questionnaire than EQ-5D.
Study design	• Budget impact analysis • Resource use studies • Cost/economic burden of illness studies • Cost-benefit analysis • Cost-effectiveness analysis • Cost-minimization analysis • Cost-utility analysis • Cost analysis studies	• SLRs • Narrative reviews • Clinical guidelines • Commentary • Letters to the editor • No abstract or full text to inform decision • News • Animal or in vitro studies

	• Vignette studies • Other studies that report resource use and utilities (observational cohort studies, cross sectional studies, randomized control trials)	Pharmacokinetic or pharmacodynamic studies
Other criteria: Date of study publication Language of study publication	• Full texts and abstracts from 2012 in English language	• Other languages • Full-text and abstract published pre-2012

AEs, adverse event; CS, corticosteroid; HRQoL, health related quality of life data.

11.34.5. Results

Figure N2 shows the disposition of publications identified for the analysis. The number of potentially relevant publications identified and screened for retrieval was 1656 (1607 publications identified by database search and 49 publications by manual search), of which 20 were included in the data extraction. Of the 20 studies evaluated for quality, a total of 3 studied were excluded from the analysis because of poor quality, thus 17 publications were included in the analysis. All the publications included in the analysis were observational studies, and 6 of them were available as conference abstracts. Six of the studies were conducted in Europe and eleven in the United States.

All the studies were conducted in patients with chronic conditions, including asthma, systemic erythematosus lupus, rheumatoid arthritis, ulcerative colitis, Crohn's disease, and other rheumatologic conditions. The use of CS among the selected studies were extrapolated to prednisolone dose, and the comparison in terms of costs and QoL between CS users vs. non-CS users, independent of the baseline condition, was estimated.

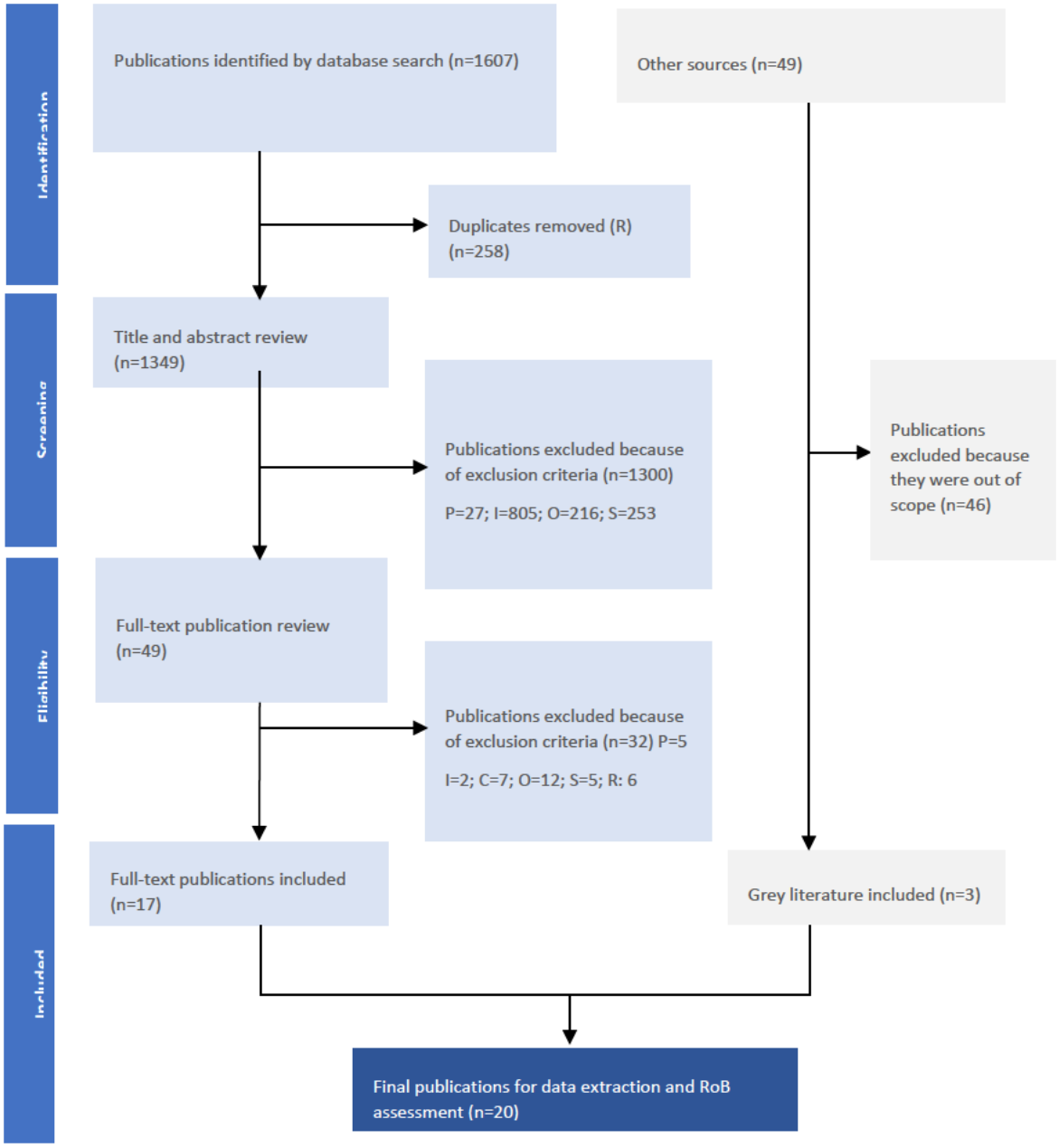


Figure N2. PRISMA chart for non-clinical SLR studies

11.34.6. Search strategy

Search Number	Search Algorithm	Results
1	(steroid$ or glucosteroid$ or glucocorticosteroid$ or corticosteroid$).mp.	1238838
2	(economic$ or cost$ or resource$).mp.	3639082
3	('quality of life' or hrqol or eq5d or eq?5d or utilit$ or burden).mp.	2286367
4	2 and 3	419606
5	1 and 4	10753

6	('anabolic' or 'inhale$' or 'topical' or 'topic' or 'acute' or 'non chronic' or 'dental' or 'pediatric' or 'peadiatric' or 'children' or 'infant' or 'childhood' or 'juvenile' or 'pregnan$' or 'intra articular' or 'intra articular' or 'epidural' or 'oral health').mp.	12572747
7	(cancer or oncolog$ or malignancy or irradiation or metastatic or metastas$ or lymphoma or leukemia or chemotherap$).mp.	8002709
8	(In Vitro Techniques or in vitro study or rodent or mice or rat or mouse or animal or non human).mp.	11150973
9	or/6-8	27991414
10	5 not 9	3858
11	(letter or editorial or historical or case report$ or case study or anecdote or commentary or comment or note or systematic or meta-analy$ or metanaly$ or metaanaly$ or meta analy$ or overview or protocol or guidelin$ or consensus).ti,ab,pt.	11471041
12	10 not 11	2804
13	limit 12 to english language	2608
14	limit 13 to yr="2012 -Current" [Limit not valid in DARE; records were retained]	1607
15	***remove duplicates from 14***	***1349***

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2022>. EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>. EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>. Embase <1974 to 2022 March 14>. Ovid MEDLINE(R) <1946 to March Week 1 2022>

Appendix O: Efgartigimod budget impact analysis: technical report

The full technical report of the budget impact analysis is included in the submission package.

11.35. Clinical data used in the budget impact analysis

The treatment effect is modelled as change in MG-ADL score. The distribution of the patient cohort into different health states and transitions between health states was obtained from the CEM. Reduced MG-ADL score is also modelled with a lower probability of MG crises. Thus, changes in MG-ADL score also impact the probability of transitioning to the crisis health state. The analysis also considers the effect of treatment on the incidence of MG exacerbations, as per the CEM.

11.36. Treatment-emergent adverse event rates

The BIM considers the economic impact for the management of grade ≥3 treatment-emergent AEs only. Incidence rates used in the model are mainly extracted from the published literature and the Excel model.

11.37. Economic data used in the budget impact analysis

Cost inputs were derived from the CEM. The costs considered in this analysis are described in Table 77.

Table 83. Cost categories considered in the BIM

Cost type	Detail
Drug acquisition costs	Includes calculations to determine acquisition costs of pharmacological treatment.
Drug administration costs	Includes costs required to administer therapy (eg, if administration occurs in inpatient or ambulatory setting).
Costs of crisis / exacerbations management	Includes costs associated with the management of gMG crisis and exacerbation. The frequency of events depends on received treatment.
Costs for disease monitoring	Includes costs associated with follow-up visits.
Costs of treatment related AEs	Includes costs for the management of serious (ie, grade ≥3) treatment related AEs which occur with ≥2% frequency. For simplicity, grade 1-2 AEs are not considered in this analysis.
Costs of corticosteroids related AEs	Includes costs associated with the management of AEs related to the use of corticosteroids. Effective treatments can spare CS use and reduce the burden of related complications.
Costs for transportation	Includes costs required to reach the treatment center.

11.37.1. Drug acquisition costs

For each treatment considered in the analysis, costs are calculated using the ex-factory price according to treatment posology. Costs related to treatment with efgartigimod are provided in Table 78.

Table 84. Efgartigimod treatment costs.

Treatment costs	Efgartigimod
Efgartigimod – pack price (DKK)	[redacted]
mg per unit	[redacted]
Number of units per pack	[redacted]
Drug cost per unit (DKK)	[redacted]
Drug cost per mg (DKK)	[redacted]
Unit per administration (N)	[redacted]
Number of administrations per cycle (N)	[redacted]

Cost per cycle (DKK)	[redacted]
Dose intensity (%)	[redacted]
Cost per cycle, adjusted by dose intensity (DKK)	[redacted]

*Based on a weight of 80 kg and 10% vial banding

The conventional therapy includes CS, AChEis, and NSISTs. The proportion of the cohort treated with each therapy was informed based on patient distribution in ADAPT (75%, 88%, and 60% treated with CS, AChEis and NSISTs, respectively). The population treated with corticosteroids was further divided into high- (18.02 mg/day; 91% of patients) and low-dose (3.11 mg/day) cohorts. The high-dose threshold was defined as 5 mg/day, based on Danish clinical expert opinion.

Immunoglobulin vial size and price is based on the price of Privigen, as reported in Medicinpriser.dk (DKK 12,240; 1 vial 20,000 mg).[163] Immunoglobulin therapy is administered as IV infusion (IVIg), dosed at 1 g/kg, yielding an average of 5 vials per administration; this usage was validated with a Danish clinical expert.

Pharmacological cost per cycle of all the treatment options considered in the model are reported in Table 79, in line with the CEM.

Table 85. Treatment costs

Treatment	Cost per cycle* (DKK)
Efgartigimod	[redacted]
IVIg	61,200.00
Corticosteroids	9.42
AChEis	682.57
NSISTs	804.61
Conventional therapy mix	1,090.56

*4 weeks. Further details on calculation methods are available in the BIM Technical report and Excel model.

11.37.2. Drug administration costs

Costs for treatment administration have been included in the analysis (Table 80). It is assumed that:

- IVIg will be administered in inpatient setting with an associated cost of DKK 139,891 (see CEM report for further details).
- Efgartigimod will be administered in inpatient setting with an associated cost of DKK 908.03 (see CEM report for further details).
- Administration of oral drugs (conventional therapy) will be performed by the patients at home without any additional costs.

Table 86. Administration costs (DKK)

Treatment	No. administration per cycle	Unit cost	Average cost per cycle

Efgartigimod	[redacted]	[redacted]	[redacted]
IVIg	1.00	139,891.00	139,891.00

11.37.3. Cost of crises/exacerbations management

The cost for the treatment of crises and disease exacerbations was based on DRG 01MP08 (Treatment with high dose IG for disease in the nervous system) and DRG 01MA06 (Degenerative disease in the nervous system), respectively.[165] The total cost for the management of one crisis and exacerbation event is equal to DKK 139,891 and DKK 34,896, respectively.

11.37.4. Cost of disease management

The cost for routine care has been calculated using a micro-costing approach. The total routine care cost per cycle, for each health state, is shown in Table 81. Please refer to CEM for further details.

Table 87. Disease management costs

Health state	Average cost per cycle
MG-ADL <5	380.72
MG-ADL 5-7	473.63
MG-ADL 8-9	803.29
MG-ADL ≥10	879.02

11.37.5. Costs of treatment-related AEs

Costs for the management of grade 3+ treatment-emergent AEs were included. The cost was calculated by multiplying the frequency of events by the unit treatment cost. It is assumed that all grade 3+ AEs require an inpatient treatment. The unit costs are based on national tariffs[165]; further details are available in the BIM Technical report and Excel model.

11.37.5.1. Costs of CS-related AEs

The costs of management of CS treatment-related AEs were included. The association between CS chronic use and costs has been reported in the literature, including the extra expenditure required to treat complications and CS-related AEs. In addition, studies have reported the impact of high and low CS doses on total annual cost—increases in HCRU, costs, and complications were more pronounced with higher doses of CS.[145, 167] As per the CEM, it was assumed that cost of CS-related AE management was dependent on the dose of CS (Table 82).

Table 88. Costs of CS-related adverse event management

CS use	Management cost (DKK)	Source
High-dose CS	2,175.93	Bexelius et al, 2013 Janson et al, 2018[154, 168]
Low-dose CS	579.45	

Further details on calculation methods are available in the CEM, and Excel models.

11.37.6. Transportation costs

As per the CEM, the transportation cost was calculated by multiplying the average kilometres (km) travelled by the unit cost per km. It is assumed that patients travel a total of 40 km to go to the follow-up visit. The unit cost per km is equal to DKK 3.51.[164] The resulting total transportation cost per visit to the hospital is DKK 140.40.[164]

11.38. Scenarios analysis results

Table 83 provides a detailed overview of the budget impact by cost type, in both the Current and Future scenarios, plus the number of crises and exacerbations.

Table 89. Results of the budget impact analysis: costs by type (DKK)

Scenario without efgartigimod (Current)						
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Cumulative**
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS related chronic complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Crises	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transportation costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario with efgartigimod (Future)						
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Cumulative**
Efgartigimod acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Administration cost	[redacted]					
Disease monitoring	[redacted]					
Exacerbations	[redacted]					
CS related chronic complications	[redacted]					
Crises	[redacted]					
AEs	[redacted]					
Transportation costs	[redacted]					
Total costs	[redacted]					
Difference: with vs without efgartigimod (Future - Current)						
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Cumulative**
Drug cost	[redacted]					
Administration cost	[redacted]					
Disease monitoring	[redacted]					
Exacerbations	[redacted]					
CS related chronic complications	[redacted]					
Crises	[redacted]					
AEs	[redacted]					
Transportation costs	[redacted]					
Total costs	[redacted]					

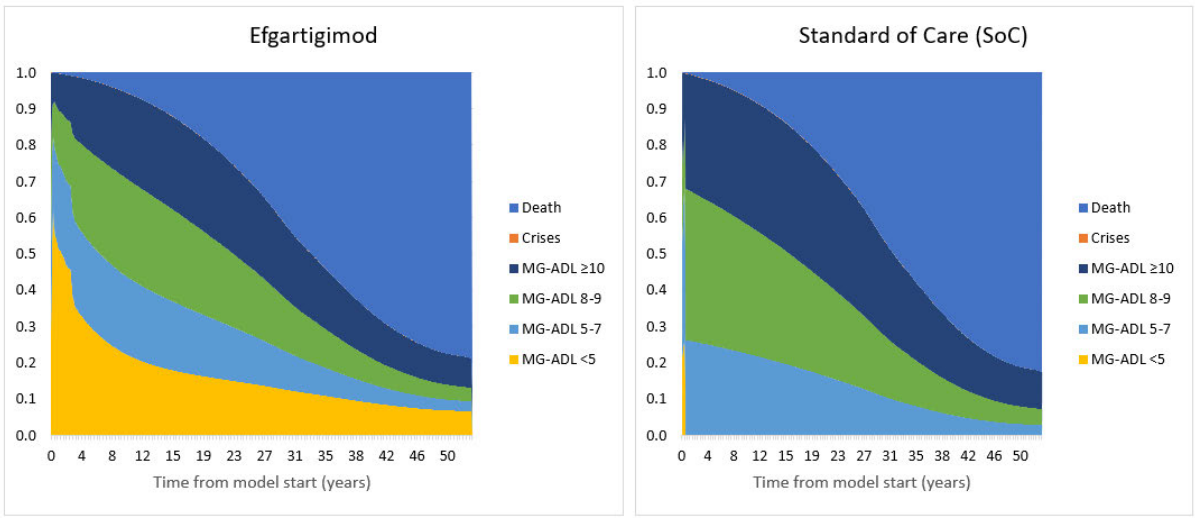
The introduction of efgartigimod will reduce the clinical burden of gMG. The analysis of the budget impact difference (between Future and Current Scenario) at Year 5 shows that the increase of pharmacological expenditure [redacted] is partially offset by the reduction of administration, gMG crisis/exacerbation, AEs, and CS-related AE management costs (Figure 30)

[redacted]

Appendix P: Health state distribution over time

Health-state distributions over time are shown in Figure 31. The model predicts that more than 50% of patients in the efgartigimod arm rapidly achieve the MG-ADL <5 health state. In contrast, most patients in the SoC arm are predicted to remain in health states with more active disease for the majority of the time horizon.

Figure 37 Distribution of the patient cohort over the time horizon of the analysis, by treatment arm



MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Table 84 and Table 85 summarise the distribution of the overall patient cohort across all health states over time for the efgartigimod and SoC arms, respectively.

Table 90. Distribution of the patient cohort across all health states over time, efgartigimod arm

Time from model start	Proportion of cohort, %					
	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Crises	Death
Week 4	28.5%	23.8%	27.6%	20.1%	0.0%	0.0%
Week 26	56.9%	22.3%	12.8%	7.8%	0.0%	0.1%
Year 5	29.9%	23.0%	25.3%	19.7%	0.1%	2.1%
Year 10	21.7%	21.4%	27.0%	23.9%	0.1%	6.0%
Year 15	18.1%	19.2%	25.5%	25.6%	0.1%	11.6%
Year 20	15.9%	16.5%	22.5%	25.4%	0.1%	19.6%
Year 25	14.2%	13.6%	18.6%	23.6%	0.0%	29.9%
Year 30	12.3%	10.3%	14.1%	20.0%	0.0%	43.2%
Year 35	10.6%	7.5%	10.4%	16.3%	0.0%	55.1%
Year 40	9.0%	5.3%	7.3%	12.8%	0.0%	65.5%
Year 45	7.6%	3.8%	5.2%	10.0%	0.0%	73.3%
Year 50	6.8%	3.0%	4.1%	8.6%	0.0%	77.6%

MG-ADL, Myasthenia Gravis Activities of Daily Living scale

Table 91. Distribution of the patient cohort across all health states over time, SoC arm

Time from model start	Proportion of cohort, %					
	MG-ADL <5	MG-ADL 5–7	MG-ADL 8–9	MG-ADL ≥10	Crises	Death
Week 4	13.0%	26.2%	36.3%	24.4%	0.0%	0.0%
Week 26	27.0%	43.9%	15.9%	12.9%	0.1%	0.2%
Year 5	0.0%	24.5%	39.0%	33.7%	0.1%	2.7%
Year 10	0.0%	22.3%	35.4%	35.1%	0.1%	7.1%
Year 15	0.0%	19.8%	31.5%	35.3%	0.1%	13.3%
Year 20	0.0%	17.0%	27.0%	34.1%	0.1%	21.8%
Year 25	0.0%	13.9%	22.1%	31.1%	0.1%	32.8%
Year 30	0.0%	10.5%	16.7%	26.0%	0.0%	46.7%
Year 35	0.0%	7.7%	12.3%	21.1%	0.0%	58.8%

Year 40	0.0%	5.5%	8.7%	16.4%	0.0%	69.4%
Year 45	0.0%	3.9%	6.2%	12.8%	0.0%	77.1%
Year 50	0.0%	3.0%	4.8%	10.9%	0.0%	81.3%

MG-ADL, Myasthenia Gravis Activities of Daily Living scale