12 December 2023
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Zilbrysq (zilucoplan)
Treatment of myasthenia gravis
EU/3/22/2650

Sponsor: UCB Pharma

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Zilucoplan
Other name(s)	-
International Non-Proprietary Name	Zilucoplan
Tradename	Zilbrysq
Orphan condition	Treatment of myasthenia gravis
Sponsor's details:	UCB Pharma Researchdreef 60 1070 Anderlecht Brussels-Capital Region Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	UCB Pharma
COMP opinion	16 June 2022
EC decision	18 July 2022
EC registration number	EU/3/22/2650
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Kristina Dunder / Alexander Moreau
Applicant	UCB Pharma
Application submission	31 August 2022
Procedure start	29 September 2022
Procedure number	EMA/H/C/005450
Invented name	Zilbrysq
Proposed therapeutic indication	ZILBRYSQ is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. Further information on the product can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/ZILBRYSQ
CHMP opinion	14 September 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Penninga / Darius Matusevicius
Sponsor's report submission	29 November 2022
COMP discussion and adoption of list of questions	5-7 September 2023
Oral explanation	3 October 2023
Sponsor's removal request	4 October 2023

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2022 designation was based on the following grounds:

"The sponsor UCB Pharma submitted on 21 March 2022 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing zilucoplan (ZLP) for treatment of myasthenia gravis (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing zilucoplan was considered justified based on clinical data showing positive responses on myasthenia gravis specific outcome measures in patients affected by the condition;
- the condition is chronically debilitating due to muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing and life-threatening due to respiratory impairment;
- the condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ZLP will be of significant benefit to those affected by the condition. The sponsor has provided clinical data showing positive responses on myasthenia gravis specific outcome measures in a broader population including non-refractory generalized myasthenia gravis which is not covered by the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing ZLP as an orphan medicinal product for the orphan condition: treatment of myasthenia gravis".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Myasthenia gravis is an autoimmune disorder characterised by a combination of weakness and fatigability of skeletal muscles, including ocular, bulbar, limb, and respiratory muscles. Weakness is the result of an IgG antibody mediated, T-cell dependent immunological reaction against proteins in the postsynaptic membrane of the neuromuscular junction (NMJ) of skeletal muscles (nicotinic acetylcholine receptors [AChR] and/or receptor-associated proteins). Patients present with muscle weakness, which typically worsens with continued activity (fatigue) and improves on rest. Exacerbations and remissions may occur, particularly during the first few years after the onset of the disease (Drachman, 2001). Remissions are rarely complete or permanent.

Antibodies are present at (neuromuscular junctions) NMJ, the site of pathology (Engel et al, 1979). About 80% to 90% of patients have detectable antibodies against the nicotinic AChR on the postsynaptic muscle membrane at the NMJ. Another 3% to 7% of patients have antibodies directed against MuSK, another NMJ protein.

The approved therapeutic indication "ZILBRYSQ is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive" falls within the scope of the designated orphan condition "treatment of myasthenia gravis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The course of MG is often variable. Exacerbations and remissions may occur, particularly during the first few years of the disease. However, remissions are rarely complete or permanent. Myasthenia gravis might impair vision (diplopia and ptosis), facial muscles, chewing, speech, swallowing, walking, or talking. Difficulty in swallowing may occur because of weakness of the palate, tongue, or pharynx, which could lead to nasal regurgitation and aspiration of liquids or foods with the risk of a dangerous and difficult to treat infection of the upper and lower airways. Dysphagia and respiratory failure are factors known to be caused by MG, and several reports have highlighted the importance of dysphagia and aspiration precipitating a myasthenic crisis. Fifteen to 20% of myasthenic patients are affected by myasthenic crisis at least once in their lives. Myasthenic crisis is a life-threatening complication of MG where the majority of patients require endotracheal intubation and mechanical ventilation.

The diagnosis of MG in AChR-antibody-seropositive patients has been associated with increased estimated mortality rates (1.41 compared to healthy individuals) especially in patients with late-onset disease (>50 years old at onset) (Hansen et al, 2016).

The condition is therefore both life threatening and chronically debilitating.

Number of people affected or at risk

In the initial ODD (Orphan Drug Designation) for the treatment of myasthenia gravis in 2022, the COMP agreed on a prevalence estimate of approximately 2 per 10,000 persons. The estimate was supported by literature references from 2010 to 2020. At the time of maintenance, no new articles were identified in an updated literature search covering publications from Jan 2010 to Dec 2022.

The strategy for identifying prevalence data was to search for primary publications in Medline that reported on the prevalence ratio of MG in EU populations (or provided raw data that enabled

estimation of the same). Hand searching of full text articles and published reviews was used to check for additional references.

Due to the observed time-trend of prevalence of MG, studies published since 2010 to 2022 were included and a meta-analysis was conducted of reported prevalence for the period from 2010 until 2019 (Westerberg and Punga, 2020; Martinka et al, 2018; Zieda et al, 2018; Aragones et al, 2017; Santos et al, 2016; Fang et al, 2015).

The pooled prevalence of MG as derived from 6 estimates (based on data from different EU countries) was 2.61 (95% CI: 2.56, 2.68) per 10,000 inhabitants, and crude estimates were all below the designation threshold. Furthermore, all published literature references identified the estimated prevalence rate of MG from databases and other sources ranging from 0.8 to 2.0 per 10,000. Thus, an estimated prevalence of 2.61 per 10,000 inhabitants was assumed as the most conservative approach to estimate the current number of MG patients.

Using the total EU population in 2022, and the most conservative prevalence scenario, the estimated number of patients would fall between the range 114,388 to 119,750 patients in the EU for 2022.

In addition, the sponsor discussed time-trends of prevalence for MG prevalence rates which would be rising across Europe over time. These increases are attributed mainly to the following factors:

- Greater awareness of the disease

- Improvements in epidemiologic methodology

- Improvements in diagnostic testing, including increased recognition of milder cases

- Improvements in treatment of the disease leading to better survival

- Impact of an ageing population.

In summary, an MG prevalence of 2.61 per 10,000 was used as the most representative approach to calculate the current number of MG patients in the EU, and which was selected due to an apparent increasing trend of incidence and prevalence of MG is observed across Europe over time, which is most likely due to greater awareness of the disease, improved diagnostics and medical care, and potentially increased life expectancy.). Due to the very small number of publications, and the small patient samples, it cannot be determined if this increase is indeed indicative of a general trend towards higher prevalence. Therefore, the previously accepted prevalence estimates of approximately 2 in 10,000 persons in the European Union (EU) would be considered to be applicable.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The below table provides an overview of therapies currently used for myasthenia gravis (Table 1). The table also indicates which of these medicinal products are authorised for use in the condition in the EU.

Table 1. Therapies Currently Used for Myasthenia Gravis .

Therapy	Mechanism of Action (MoA) & Side Effects/Limitations	Approval Status (national and centrally)
AChE inhibitors; e.g. Pyridostigmine, Neostigmine, Distigmine, Ambenonium	MoA Acetylcholine breakdown inhibition, increasing its availability in the NMJ Limitations Short-acting and often need to be taken several times daily (Grob et al, 2008; Gilhus et al, 2019) Reduced efficacy in AChR-Ab seronegative population	Approved for the treatment of MG
Eculizumab	MoA Complement inhibitor, prevents C5 cleavage and inhibits IgG autoantibody-initiated complement activation Limitations Limited to treatment of refractory gMG (Gilhus, 2017) Limited to AChR-Ab seropositive [28] Increased risk of Neisseria meningitidis infection and the need for vaccination prior to commencing treatment (Soliris Product information, 2021).	Approved for the treatment of AChR-Ab positive patients with refractory gMG
Corticosteroids More commonly used: oral prednisone	MoA Nonspecific immunosuppression Limitations Widespread short- and long-term adverse effects (Schneider-Gold et al, 2019; Pascuzzi et al, 1984; Liu et al, 2013; Mehndiratta et al, 2014)	Approved for the treatment of MG in some member states only (e.g., in Germany)
NSISTs More commonly used: Azathioprine, cyclosporine, and mycophenolate Also used: tacrolimus, methotrexate, and cyclophosphamide	MoA Multiple nonspecific mechanisms of action, including suppression of B and T cells Limitations Delayed onset of action. Various side effects, including liver and bone marrow toxicities, malignancies, and increased risk of infection for the more commonly used NSIDs (Hart et al, 2007; Mantegazza et al, 2011; Skeie et al, 2010)	Azathioprine tablets approved since 2004 for treatment of MG in some member states. Oral suspension (Jayempi®) recently approved in the EU following an application under Art 10(3) of Directive 2001.83 based on Imurek approved in Germany
Intravenous immunoglobulins (IVIg) (e.g., Gamunex)	MoA Multiple mechanisms postulated including effects on autoantibodies, B and T cells Limitations IVIg use is limited in patients who are at risk of renal dysfunction and a history of hypertension or risk factors for thrombotic events (Privigen package insert, 2017) Burdensome administration Supply chain shortages are common Nausea, headache, fever, hypotension or hypertension, local skin reactions, IgA deficiency, allergic reactions (Privigen package insert, 2017)	Gamunex approved in MG for treatment of severe acute exacerbations in some member states only.
Rituximab	MoA B-cell depletion Limitations Nausea, infections, infusion-related problems	Off-label use. Not approved for the treatment of MG

	Progressive multifocal leukoencephalopathy Eliminates B lymphocytes causing broad immunosuppression	
Vyvgart (Efgartigimod)	Efgartigimod alfa binds to FcRn, resulting in a reduction in the levels of circulating IgG including pathogenic IgG autoantibodies.	Approved as an add-on to standard therapy for the treatment of adult AChR-Ab seropositive generalized Myasthenia Gravis (MG) patients
Ultomiris (Ravulizumab)	Ravulizumab is a recombinant humanized IgG2/4 monoclonal antibody. Ravulizumab binds to complement component 5 (C5) and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin C5a and the formation of the terminal complement complex via C5b.	Ultomiris is indicated as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody-positive.

AChE=acetylcholinesterase; AChR-Ab=acetylcholine receptor – antibody; C5=complement component 5; gMG=generalised myasthenia gravis; IgA=immunoglobulin A; IgG=immunoglobulin G; IVIg=intravenous immunoglobulin; MG=myasthenia gravis; NMJ=neuromuscular junction; NSIST=nonsteroidal immunosuppressive drug

The mainstays of the routine management of MG are defined in international consensus guidelines, most recently in the International Consensus Guidance for Management of Myasthenia Gravis (Narayanaswami et al, 2021). This guidance includes the following recommendations:

1. The AChE inhibitor pyridostigmine should be part of the initial treatment in most patients with MG.
2. Corticosteroids or NSIST therapy for patients who have not met treatment goals after an adequate trial of pyridostigmine. NSISTs may be used alone when corticosteroids cannot be used. NSISTs that can be used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus.
3. Patients with refractory MG may be treated with chronic IVIg and chronic plasmapheresis/plasma exchange (PLEX) as maintenance therapy, cyclophosphamide, Rituximab.

It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Patients must be monitored for potential adverse effects and complications from immunosuppression and changing treatment may be required.

Thymectomy is recommended to be considered early in disease in patients aged 18–50 years who have non-thymomatous gMG, AChR-Ab seropositive patients who have failed to respond to immunotherapy or who have intolerable side effects. It may also be considered in patients without AChR-Abs (Hehir and Silvestri, 2018).

Eculizumab is only authorised for the treatment of (AChR-Ab+) patients with refractory MG, and as ZILBRYSQ will target a broader patient population it is not considered a satisfactory method in this case.

Other treatment options such as the short-term immune therapies of plasmapheresis/ plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) are indicated and used in a subset of the MG population in which zilucoplan approval is not being sought (i.e., patients with refractory MG and/or severe acute exacerbations). AChR-Ab seropositive patients with refractory gMG represent only

approximately 10% of gMG patients and ZILBRYSQ offers treatment to approximately 80 to 85% of the myasthenia gravis population with gMG.

In conclusion, the following products are considered satisfactory methods, and will be considered for the significant benefit assessment, as the therapeutic indications completely overlaps with the one sought for Zilbrysq: **AChE inhibitors, NSISTs, corticosteroids, Vyvgart (efgartigimod), Ultomiris (ravulizumab)**.

Significant benefit

The sponsor claims that ZLP will be of significant benefit over relevant existing treatments for those affected by that condition, based on the following considerations:

Significant benefit over AChE inhibitors, NSISTs, corticosteroids

Efficacy was studied in one Phase II dose-finding study (MG0009) and two Phase III studies, one **blinded and controlled (MG0010) and one open label (MG0011)**. Characteristics of these studies are presented below.

- Efficacy at 12 weeks in the main study MG0010

Study MG0010, the single pivotal Phase 3 study, was a randomised double-blind placebo-controlled study comparing the efficacy of ZLP 0.3 mg/kg with placebo. Patients included were to be AChR-Ab seropositive, MGFA class II-IV, have at least an Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 6 and a Quantitative Myasthenia Gravis (QMG) score of at least 12 with a score of at least 2 in at least 4 items. More than 70% of participants had at least moderate weakness according to the MGFA classification, mean MG-ADL was 10.6 and mean QMG was 19.1.

For comparison, the baseline QMG ranged between 8.5 and 19.4 in the 27 MG studies analysed in the systematic literature report submitted by the Applicant. The highest QMG score (19.4) was reported in a study by Liu et al (2010) and in the PB group of Study MG0010. The cohort of patients selected from the MG-registry for the external reference of study MG0011 (requirement of baseline MG-ADL≥6), had a baseline QMG of 12.9 and baseline MG-ADL 7.4. The two cohorts from the MGTX study included in the modelling for the reference group, had an index mean QMG of 13.0 and mean MG-ADL of 8.0.

The effect of ZLP 0.3 mg/kg started early as measured with change from baseline (CBL) in MG-ADL. The effect of PB and of ZLP stabilised after approximately four weeks with a steady difference up to week 12 at primary endpoint assessment. A statistically significant difference to PB in CBL of – 2.09 ($p<0.001$) was found. All sensitivity analyses showed highly significant treatment difference between PB and ZLP of slightly more than 2 points, which has been found clinically relevant (Muppidi et al, Muscle Nerve 44: 727–731, 2011).

- Supportive data from Study MG0011, efficacy at week 12

Study MG0011 was an open label Phase III study which included participants who had completed either of studies MG0009 or MG0010. As there is no PB control and participants knew that they received ZLP 0.3 mg/kg, efficacy data cannot be directly compared to the other results but contribute with some information of interest. With conservative imputation participants who received ZLP in study MG0011 but had received PB in parent study MG0010, decreased their LS mean MG-ADL score with 2.87 points after 12 weeks of ZLP treatment. In study MG0010 (ZLP treated participants) the CBL not corrected for the PB effect was -4.68. Corresponding data for QMG were MG0011 –3.77 and MG0010 -6.48, MCG MG0011 –5.56 and MG0010 -8.85, MG-QOL15r MG0011 -4.54 and MG0010 -6.21. These 12-week data support the findings of study MG0010.

- Overall

ZILBRYSQ demonstrated superior efficacy as add-on to SOC therapy versus SOC therapy plus placebo, in adult AChR-Ab seropositive patients with gMG in a randomised, controlled clinical trial (pivotal study RAISE). The observed Baseline disease characteristics demonstrated that a broadly selected gMG population with a range of disease severity and disease duration, and with prior and concurrent exposure to SOC therapies, was successfully enrolled. All SOC therapy medications for gMG were kept at the same dose throughout the 12-week study, including AChE inhibitors, corticosteroids and immunosuppressant therapy drugs.

The primary endpoint was the change from Baseline (CFB) to Week 12 in MG-ADL total score. The MG-ADL is an 8-item patient reported outcome measure assessing impact of gMG on daily function of 8 signs and symptoms. The total score is the sum of the 8 individual scores and ranges from 0 to 24, with higher scores indicating more severe impact of gMG on these signs and symptoms. A 2-point change in MG-ADL score is considered clinically meaningful (Muppidi et al, 2011; Wolfe et al, 1999).

The change from baseline (CFB) to Week 12 (MG0010) and Week E12 (MG0011) in MG-ADL and QMG by concomitant use at Baseline of steroid and immunosuppressive therapy is presented in the table below. Based on MG-ADL and QMG results, ZLP is effective in patients with or without steroids or immunosuppressive therapy at Baseline.

It is, however, considered that significant benefit over non-steroidal immunosuppressive agents is not yet demonstrated for the different available options since the sponsor is claiming benefit only over the overall therapeutic drug-class. The sponsor should justify why it is possible to extrapolate the significant benefit over each separate medicinal product based on the data submitted.

Table 2.

Studies	**MG0010 Week 12**				**MG0011 Week E12**			
Subgroup	**Placebo N=88**		**ZLP 0.3mg/kg N=86**		**Placebo/ ZLP 0.3mg/kg N=90**		**ZLP 0.3/0.3mg/kg N=93**	
Category	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
CFB in MG-ADL								
Overall CFB	85	-2.85 (3.60)	84	-4.70 (3.93)	86	-3.16 (3.69)	89	-1.48 (3.19)
Steroid therapy taken at Baseline								
Yes	50	-2.80 (3.84)	59	-4.58 (3.59)	50	-3.02 (3.48)	57	-1.16 (3.21)
No	35	-2.91 (3.28)	25	-5.00 (4.69)	36	-3.36 (4.01)	32	-2.06 (3.12)
Immunosuppressive therapy (non-steroidal) at Baseline[a]								
Yes	15	-1.07 (2.25)	12	-3.83 (4.09)	45	-3.18 (4.05)	42	-1.62 (3.18)
No	70	-3.23 (3.73)	72	-4.85 (3.91)	41	-3.15 (3.31)	47	-1.36 (3.23)
CFB in QMG								
Overall CFB	84	-3.38 (4.21)	83	-6.31 (4.92)	84	-4.02 (4.83)	87	-1.90 (3.67)
Steroid therapy taken at Baseline								
Yes	50	-3.00 (4.26)	59	-6.14 (4.94)	49	-4.27 (5.05)	56	-1.46 (3.36)
No	34	-3.94 (4.13)	24	-6.75 (4.95)	35	-3.69 (4.54)	31	-2.68 (4.13)
Immunosuppressive therapy (non-steroidal) at Baseline[a]								

Yes	15	-2.27 (5.01)	12	-4.33 (4.21)	43	-5.19 (5.32)	41	-2.00 (4.02)
No	69	-3.62 (4.01)	71	-6.65 (4.98)	41	-2.80 (3.96)	46	-1.80 (3.38)

CFB=change from Baseline; MG-ADL=myasthenia gravis-activities of daily living; OLE=open-label extension; QMG=quantitative myasthenia gravis; SD=standard deviation; ZLP=zilucoplan
Note: The MG-ADL Total Score ranged from 0 to 24 with a higher score indicating more severe symptoms of gMG.
Note: The CFB was defined as post baseline value – baseline value. A decrease from Baseline indicated improvement.
Note: MG0010: Baseline was the last available value prior to the first injection of IMP in the Treatment Period, or if missing, the Screening value.
Note: MG0011: CFB was calculated using the OLE Baseline.
[a] In MG0010 immunosuppressive therapy (non-steroidal) at Baseline did not include Group B (aziatropine and mycophnolate), i.e., 65 participants in total.
Note: Clinical cutoff date of 08 Sep 2022 for MG0011.
Data source: MG0010 CSR Table 14.2.1.4, MG0010 CSR Table 14.2.2.4, MG0011 Interim CSR Table 14.2.1.7, MG0011 Interim CSR Table 14.2.2.7

Significant benefit over Ultomiris (ravulizumab) based on better efficacy.

Ravulizumab is a humanised monoclonal antibody complement protein C5 inhibitor that has been re-engineered from eculizumab to extend its half-life (Vu et al, 2022).

There is no direct comparison between ravulizumab and zilucoplan. The sponsor claims significant benefit based on a better efficacy of ZLP. This is based on an indirect comparison of results obtained in the pivotal studies (the CHAMPION study and the RAISE study for ravulizumab and ZLP, respectively).

For this purpose, 1) a Bayesian network meta-analysis for the primary and key secondary endpoints, and 2) a Matching-adjusted indirect comparison at Week 60 was presented .

- Bayesian network meta-analysis

A Bayesian network meta-analysis was conducted to understand the comparative efficacy of ZLP to other available treatment options in gMG. This would indicate that ZLP was numerically favourable compared to ravulizumab in the CFB for MG-ADL (i.e., primary endpoint in both studies), QMG and MG-QoL15r (Family 1 secondary endpoints in MG0010, also assessed in CHAMPION MG). This analysis included the identified relevant Phase 3 studies and used data from the end of the double-blind treatment period for each comparator, in a fixed-effects model. Results are provided in Table 3.

Whilst the results were not statistically significant, the sponsor claims that the network meta-analysis showed that there was likely a stronger magnitude of benefit for ZLP versus ravulizumab for all continuous efficacy endpoints (MG-ADL, QMG and MG-QoL15r) even though the 95% credible intervals included 0.

Table 3. Mean differences between the change from Baseline zilucoplan to ravulizumab using a fixed-effects Bayesian network meta-analysis

Endpoint	Zilucoplan to ravulizumab mean difference (95% CrI)
MG-ADL	-0.38 (-2.00, 1.23)
QMG	-0.94 (-2.94, 1.04)
MG-QoL15r	-1.00 (-3.88, 1.82)

CrI=credible interval, MG-ADL=myasthenia gravis-activities of daily living; MG-QoL15r=myasthenia gravis quality of life 15-item scale revised, QMG=quantitative myasthenia gravis score for disease severity

However, substantial differences are observed in the placebo arms (-1.4 and -2.30, respectively).

For QMG, a reduction in the Placebo arm from Baseline is observed that is clinically relevant which may be driven by the SoC treatment. In addition, the description of the Bayesian NMA is too limited and lacks detail for any proper assessment to be done. No information or justification on elements such as the model, covariates, choice of priors, heterogeneity, inconsistency, choice of fixed and/or random effects are provided.

- Matching-adjusted indirect comparison at Week 60

To adjust for cross-study differences, participants from the ZLP Phase 3 study (RAISE) were reweighted to match the Baseline characteristics of the ravulizumab Phase 3 study (CHAMPION) participants. Weights were determined using a logistic regression adjusted for age at Baseline, Baseline MG-ADL score (randomised control period [RCP] Baseline), Gender, Ethnicity (White versus non-white) and MGFA Class (Class II versus Class III/IV). The effective sample size (ESS) was 50 for ZLP. Using this matching-adjusted indirect comparison analysis, the mean difference (95% CI) in MG-ADL of ZLP versus ravulizumab was -1.92 (-3.26, -0.57) and was statistically significant (p=0.006) and close to the threshold of clinical meaningfulness of 2 points difference. Similarly, the mean difference CFB in QMG score of ZLP was -3.22 (-4.94, -1.50) and was clinically meaningful (threshold of 3 points) and statistically significant (p-value <0.001). This was based on an effective sample size of 50 for the RAISE study (Table 4).

For this analysis, an initial side by side comparison is missing. In addition, there are differences between the unadjusted and adjusted results, most notably for MGFA, and to a maybe smaller extent for sex. The ESS reduction is to 61% and it is to be noted that the description of the MAIC, just like the Bayesian NMA, is too limited for a more detailed assessment. In addition, differences in the results and in the magnitude of the treatment effect between the Bayesian NMA and the MAIC were observed.

Table 4. MAIC of zilucoplan versus ravulizumab

Study	Treatment (N/ESS)	MG-ADL mean (95%CI)	QMG mean (95%CI)
CHAMPION	Ravulizumab/ravulizumab (N=78)	-4.00 (-4.86, -3.14)	-4.10 (-5.37, -2.83)
RAISE	Zilucoplan/zilucoplan (unadjusted) (N=82)	-6.40 (-7.30, -5.51)	-7.70 (-8.87, -6.52)
	Zilucoplan/zilucoplan (adjusted) (ESS=50)	-5.92 (-6.78, -5.06)	-7.32 (-8.37, -6.27)
MAIC	MAIC/zilucoplan vs. ravulizumab[a]	-1.92 (-3.26, -0.57) p-value = 0.006	-3.22 (-4.94, -1.50) p-value <0.001

CI=confidence interval; ESS=effective sample size; MAIC=matching-adjusted indirect comparison; MG-ADL=myasthenia gravis-activities of daily living; QMG=quantitative myasthenia gravis; vs.=versus
[a] Study participants randomized to ravulizumab in the CHAMPION study (with 24 weeks double-blind and 36 weeks open-label) are compared to study participants randomized to ZLP in MG0010 (12 weeks double-blind) who continued in MG0011 (48 weeks open-label) after matching.
Data source: Data on file

Significant benefit over Efgartigimod alfa based on efficacy.

Efgartigimod alfa is a human IgG1 antibody Fc-fragment engineered for increased affinity to FcRn compared with endogenous IgG. It outcompetes endogenous IgG binding, thereby reducing IgG recycling and increasing IgG degradation (Howard et al, 2021a).

There is no direct comparison between efgartigimod alfa and ZLP. The sponsor claims significant benefit to be based on a better efficacy of ZLP. This is based on an indirect comparison of results obtained in the pivotal studies for each product.

For this purpose, a Bayesian network meta-analysis for the primary and key secondary endpoints was used.

- Bayesian indirect comparison

Due to the cyclic administration of efgartigimod alfa, the sponsor indicates that in order to compare symptom reduction and treatment maintenance, an indirect comparison approach was performed to compare the area under the curve (AUC) in CFB in MG-ADL (primary assessment scale in both studies) between ZLP and efgartigimod alfa from Baseline to Week 12. The AUCs for each treatment group (ZLP and matched placebo, efgartigimod alfa and matched placebo) were calculated using the absolute mean CFB at each timepoint up to Week 12 (all observed CFB values were negative). Therefore, a higher AUC would indicate an improved treatment effect, according to the sponsor.

Observed mean CFB and SEs were extracted using and rounded to 1 decimal place for efgartigimod alfa and matched placebo using an appropriate software (Digitizelt). Since Cycle 1 of efgartigimod alfa lasted 10 weeks, it was assumed in this analysis that the observed CFB and SE at Week 12 for efgartigimod alfa was the same as Week 10, which is a conservative assumption, considering the cyclic nature of efgartigimod alfa and the trend of worsening symptoms towards the end of each treatment cycle. Observed mean CFB and SE were estimated for ZLP and matched placebo using the MG0010 mITT population.

To estimate the variance of the AUC, the correlation matrix of CFB at different time points was needed. It was estimated using individual level data from MG0010 (both treatment groups combined). Efgartigimod alfa was assumed to have the same correlation matrix as the MG0010 study for both treatment groups (efgartigimod alfa and matched placebo), since only aggregated data was available in the literature for efgartigimod alfa.

A fixed-effects Bayesian indirect comparison approach using non informative priors was then used to compare ZLP to efgartigimod alfa.

Results are presented in Table 5. This indirect comparison showed a slight numerical benefit in the AUC based on the CFB in MG-ADL of ZLP versus efgartigimod alfa although this was not statistically significant.

As part of this comparison, differences are observed in the placebo arms between both studies. In addition, the interpretability and relevance of the AUC values is not clear or how that translates into the treatment effect and disease progression.

Table 5. Bayesian fixed effects meta-anaysis based on area under the curve to compare zilucoplan to efgartigimod alfa

Endpoint	RAISE Study		ADAPT Study		Fixed Effects, Bayesian Indirect Comparison
	Zilucoplan AUC (SE)	Placebo AUC (SE)	Efgartigimod Alfa AUC (SE)	Placebo AUC (SE)	Zilucoplan vs. Efgartigimod Alfa AUC (95% CI)
MG-ADL	48.63 (4.18)	28.48 (3.65)	34.60 (4.27)	16.35 (3.45)	1.92 (-13.69, 17.33)

AUC=area under the curve, CI=confidence interval; MG-ADL= myasthenia gravis-activities of daily living; QMG=quantitative myasthenia gravis; SE=standard error; vs.=versus
Data source: Data on file

Significant benefit over Ultomiris (ravulizumab) and Vyvgart (efgartigimod alfa) based on a major contribution to patient care:

The sponsor claims that ZLP treatment is more convenient and less burdensome for patients than Ultomiris (ravulizumab) and Vyvgart (efgartigimod alfa).

Ravulizumab is administered as an IV infusion weight-based dose (ravulizumab vial for IV administration) in adult patients with gMG by a healthcare professional at 2400 to 3000 mg induction on Day 1, then 3000 to 3600 mg every 8 weeks on Day 15.

Efgartigimod alfa recommended dosage is 10 mg/kg administered as an IV infusion over 1 hour once weekly for 4 weeks. In patients weighing ≥120kg, the recommended dose of efgartigimod alfa is 1200mg (3 vials) per infusion.

The IV route of administration is claimed to be burdensome for patients and requires repeated venepuncture or even the placement of a port-a-cath device in a population that frequently suffers from poor venous access associated with longstanding steroid therapy. While infusion reactions such as allergic or hypersensitivity reactions may lead to headache, increased blood pressure, fever, chills, dyspnoea and many other symptoms, IV access complications specifically refer to AEs that occur as a direct result of this invasive procedure. Besides potential problems to obtain IV access repeatedly for chronic therapy, most common complications of IV access regardless of its purpose or location are phlebitis, thrombophlebitis, infiltration, hematoma, extravasation and cellulitis (Chaudhary et al, 2020; Dychter et al, 2012). Nevertheless, such complications in the IV administration in general do not necessarily reflect the situation for the patient population in the proposed orphan condition.

In contrast, ZLP is administered by SC injection once a day which takes seconds. The daily injection volume for the clinical recommended dose of ZLP will be less than 1 mL, due to the high solubility and bioavailability of ZLP. It is therefore claimed that ZLP brings the convenience of SC administration allowing self-administration at home and consequently reducing the treatment burden, costs and time/economic losses associated with IV administration by healthcare professional. Also, no complications of IV infusion such as loss of IV access, access site or port infections, and venous thrombophlebitis would be associated with SC therapies.

The clinical need for daily SC injections compared to currently available IV infusions with a less frequent dosing with ravulizumab has been investigated in a preference study involving 200 gMG participants (US N=150, UK N=25, Germany N=25). This preference study was conducted in

accordance with best practice guidelines (Bridges et al, 2014) and used a discrete choice experiment method to explore patient preferences for the following treatment attributes: administration setting, mode of administration and time, administration frequency, time until a meaningful improvement, annual risk of mild-to-moderate injection site reactions, annual risk of severe injection site reactions.

Participants were asked to assume treatment effectiveness to be constant across the choice tasks. The mean age of the participants was 45.8 years (SD=13.4) and there were 167 (83.5%) females. Comparing the treatment profile for a daily SC injection with attribute levels that resemble ZLP and IV injections with attribute levels that resemble ravulizumab and efgartigimod alfa.

Regarding ravulizumab, the predicted uptake probability demonstrates a 65.2% probability of an average patient in this sample selecting the ZLP-like profile to 34.8% probability of selecting the ravulizumab-like profile. In general, participants preferred at home administration by the patient themselves, less frequent administrations, a short rapid injection and with a fast onset of action when considering these individual treatment attributes.

Regarding efgartigimod alfa, the predicted uptake probability demonstrates a 65.4% probability of an average patient in this sample selecting the ZLP-like profile to 34.6% probability of selecting the efgartigimod-like profile.

Patient-experience with self-administration was further assessed using the Self-Injection Assessment Questionnaire (SIAQ; domain scores 0–10; higher scores indicate more positive experience). SIAQ was completed by 63 US participants, directly after ZLP self-injection and measured, amongst others, patient satisfaction with self-injection. Participants reported a high rate of satisfaction with self-injection (median: 8.2; range: 3.9 to 10.0) and reported that the self-injection device was easy to use (median 8.4; range: 1.2 to 10) (Figure 3-18). Moreover, 84.2% of the respondents reported that they would probably (30.2%) or definitely (54.0%) choose to continue self-injecting their medication after the study.

However, it is not clear how the probability calculation has been performed, what elements have been included as part of the questionnaire, the weight of the different elements, and what the relevance is for the assumption of a major contribution of patient care of a daily administration. In addition, the claims presented for the IV route of administration in general may not be applicable for this patient population affected by the proposed orphan condition.

Overall, the COMP is not convinced that significant benefit has been successfully established in the context of authorised treatments and invites the sponsor to provide additional information.

4. COMP list of issues

Significant benefit of Zilucoplan over the authorised medicinal products is not considered established, based on the data presented. The sponsor should therefore further justify the claim of significant benefit of Zilucoplan over non-steroidal immunosuppressive therapy, Ultomiris and Vyvgart for the target patient population.

In particular the sponsor is invited to:

- Elaborate on the significant benefit claim over non-steroidal immunosuppressive agents for each product and not for the overall therapeutic drug-class. The sponsor is invited to present data supporting significant benefit for each of the following non-steroidal immunosuppressive agents: (1) azathioprine, (2) methotrexate, (3) ciclosporine, and (4) mycophenolate mofetil.

- Explain the details of the indirect comparison intended to support the claims of significant benefit over Ultomiris (the Bayesian Network Meta-Analysis and the Matching-adjusted indirect comparisons). In particular, the methodology used, the differences in the placebo arms across studies, and the interpretability of the results obtained.
- Explain the details of the indirect comparison intended to support the claims of significant benefit over Vyvgart (the Bayesian indirect comparison approach and the interpretability of the AUC values and its relevance). In particular, the methodology used, the differences in the placebo arms across studies, and the interpretability of the results obtained.
- Further discuss the predicted uptake probability for the major contribution to patient care claim for both Ultomiris and Vyvgart.

Comments on sponsor's response to the COMP list of issues

The sponsor further justified the claim for significant benefit of zilucoplan over non-steroidal immunosuppressive agents, Ultomiris and Vyvgart. The sponsor emphasised that zilucoplan is offering a significant benefit over these products by providing a clinically relevant advantage based on efficacy, and a major contribution to patient care.

Clinically relevant advantage for patients over non-steroidal immunosuppressive agents: (1) azathioprine, (2) methotrexate, (3) ciclosporine, and (4) mycophenolate mofetil

In response to the first question, the sponsor has provided a breakdown of the change from baseline (CFB) to Week 12 (MG0010) and Week E12 (MG0011) in Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scores by immunosuppressive therapy (azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil) (Table 6). This new analysis represents *post hoc* descriptive statistics in addition to the pre-planned analyses.

The CFB to Week 12 (MG0010) in MG-ADL and QMG scores by immunosuppressive therapy, showed generally numerically higher responses for ZLP vs placebo, and these responses further improved at Week E12 (MG0011). As such, this *post hoc* analysis would support the significant benefit of ZLP for azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil.

It is also indicated that given the large number of subgroups analysed, it can also be expected that, given the small number of individuals in certain subgroups, there might be some inconsistencies.

The COMP considered this question to be resolved.

Table 6.

Studies	**MG0010 Week 12**				**MG0011 Week E12**			
Subgroup	**Placebo N=88**		**ZLP 0.3mg/kg N=86**		**Placebo/ ZLP 0.3mg/kg N=90**		**ZLP 0.3/0.3mg/kg N=93**	
Category	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
CFB in MG-ADL								
Overall CFB	85	-2.85 (3.60)	84	-4.70 (3.93)	86	-3.16 (3.69)	89	-1.48 (3.19)
Azathioprine taken at Baseline								

Yes	16	-2.56 (2.92)	13	-5.46 (2.93)	14	-2.86 (4.62)	14	-1.07 (3.15)
No	69	-2.91 (3.76)	71	-4.56 (4.08)	72	-3.22 (3.52)	75	-1.56 (3.21)
Methotrexate taken at Baseline								
Yes	1	0	3	-3.33 (3.51)	1	-10.00	2	-3.00
No	84	-2.88 (3.61)	81	-4.75 (3.95)	85	-3.08 (3.64)	87	-1.45 (3.22)
Cyclosporine taken at Baseline								
Yes	7	-0.71 (2.81)	6	-2.17 (3.97)	6	-4.17 (5.95)	6	-3.00 (5.59)
No	78	-3.04 (3.62)	78	-4.90 (3.88)	80	-3.09 (3.52)	83	-1.37 (2.97)
Mycophenolate mofetil taken at Baseline								
Yes	17	-4.41 (4.03)	16	-4.13 (4.88)	19	-2.21 (2.90)	17	-1.47 (2.50)
No	68	-2.46 (3.41)	68	-4.84 (3.70)	67	-3.43 (3.87)	72	-1.49 (3.35)
CFB in QMG								
Overall CFB	84	-3.38 (4.21)	83	-6.31 (4.92)	84	-4.02 (4.83)	87	-1.90 (3.67)
Azathioprine taken at Baseline								
Yes	16	-2.44 (2.48)	13	-7.92 (4.73)	14	-5.21 (4.71)	14	-1.43 (5.08)
No	68	-3.60 (4.50)	70	-6.01 (4.93)	70	-3.79 (4.85)	73	-1.99 (3.38)
Methotrexate taken at Baseline								
Yes	1	-6.00	3	-3.67 (2.89)	1	-6.00	2	-4.50
No	83	-3.35 (4.22)	80	-6.41 (4.96)	83	-4.00 (4.85)	85	-1.84 (3.69)
Cyclosporine taken at Baseline								
Yes	7	-0.86 (4.53)	6	-2.50 (3.45)	6	-6.50 (10.21)	6	-2.33 (3.14)
No	77	-3.61 (4.13)	77	-6.61 (4.91)	78	-3.83 (4.22)	81	-1.86 (3.72)
Mycophenolate mofetil taken at Baseline								
Yes	17	-4.41 (3.34)	16	-6.00 (6.12)	17	-3.65 (3.60)	16	-2.06 (3.75)
No	67	-3.12 (4.38)	67	-6.39 (4.64)	67	-4.12 (5.11)	71	-1.86 (3.68)

CFB=change from Baseline; MG-ADL=myasthenia gravis-activities of daily living; OLE=open-label extension; QMG=quantitative myasthenia gravis; SD=standard deviation; ZLP=zilucoplan
Note: The MG-ADL Total Score ranged from 0 to 24 with a higher score indicating more severe symptoms of gMG. The QMG Total Score ranges from 0 to 39 with a higher score indicating more severe symptoms of gMG. A decrease from Baseline indicates improvement
Note: The CFB was defined as post baseline value – baseline value. A decrease from Baseline indicated improvement.
Note: MG0010: Baseline was the last available value prior to the first injection of IMP in the Treatment Period, or if missing, the Screening value.
Note: MG0011: CFB was calculated using the OLE Baseline.
Note: Clinical cutoff date of 08 Sep 2022 for MG0011.
Data source: Data on file

Clinically relevant advantage for patients over Ultomiris

As part of the responses, the sponsor provided details on the Bayesian Network Meta-Analysis (NMA) and the Matching-adjusted indirect comparisons (MAIC).) are provided.

The Bayesian NMA was used to estimate the relative treatment effect of ZLP to other gMG therapies anchored on placebo. In the response by the sponsor, only the comparison of ZLP vs ravulizumab anchored on placebo using the double-blind placebo-controlled studies (RAISE and CHAMPION-MG) is presented using methods outlined by the Professional Society for Health Economics and Outcomes Research (IPSOR) task force Good Research Practices (Jensen et al, 2011).

To compare the long-term effect of ZLP and ravulizumab, the open-label extension (OLE) studies of ZLP (RAISE-XT) and ravulizumab (CHAMPION-MG OLE) were also used for up to 60 weeks of active treatment. These studies have no comparator arm, therefore NMA methods using a common comparator are not possible. Such single-arm studies can be 'naïvely' compared side by side. However, this naïve comparison is subject to bias since some baseline characteristics of each study participant may affect the treatment response. Therefore, the sponsor has used a MAIC to adjust the baseline characteristics that may be predictors of treatment effect.

As outlined below, the sponsor is first providing details on the NMA including a description of the model; choice of the priors; assessment of model assumptions (inconsistency, heterogeneity, and similarity) with results on the fixed and random effects model. Differences in the baseline characteristics of the placebo arm as well as interpretability of results are discussed. Subsequently, the sponsor is providing more details on the MAIC explaining the benefits compared to a naïve side by side comparison.

- Bayesian Network Meta-Analysis (NMA) methodology to compare ZLP to ravulizumab at the end of the double-blind placebo-controlled studies.

A Bayesian NMA was conducted to understand the comparative efficacy of ZLP to other available treatment options in gMG. This NMA was performed in a Bayesian framework which involves a model with parameters, data and a likelihood distribution, and prior distributions. The NMA included all the randomised controlled studies deemed to be sufficiently similar for the population of interest after a systematic literature review (SLR). The approach and the methodology used were chosen to ensure that no randomised, double-blind placebo-controlled studies in patients with MG would be missed. A total of 73 unique studies qualified for inclusion in the clinical SLR. Of those, 60 studies were assessed and excluded from the NMA due to interventions not of interest, resulting in the inclusion of 13 unique studies in the analysis. Of these 13 studies, 5 studies provided CFB in MG-ADL scores. These 5 studies also provided CFB in QMG and MG-QoL15r.

Even though this NMA included 5 studies assessing 7 treatments, given the star shape of the network of evidence, it is statistically acceptable to focus on the comparison of ZLP to ravulizumab anchored on

placebo and only the studies involved in this comparison. Other studies in the network have a very limited impact on the relative efficacy of ZLP versus ravulizumab. As part of the methodology, items such as Inconsistency and Heterogeneity, Similarity, Primary and Sensitivity models are discussed.

It is then concluded that zilucoplan was more effective at improving all efficacy scores compared to ravulizumab (MG-ADL, QMG and MG-QoL15r), although the 95% credible intervals included 0. The results of the random-effects model showed estimates with larger credible intervals, which is expected since this model considers both the sampling error and other sources of variation in the effect size. In addition, sensitivity analyses using not only Phase 3 studies but also Phase 2 studies confirmed these results for both MG-ADL and QMG.

As part of the initial assessment, a potential bias was identified. This is the higher placebo response observed in RAISE compared to other gMG studies. The sponsor acknowledged that a discrepancy in the placebo response may affect a naïve comparison of competing interventions. However, it is indicated that the advantage of the NMA over a naïve comparison is that the difference in the placebo response is considered and therefore does not *per se* bias pairwise treatment effect comparisons from NMA (Nikolapoulou et al, 2022). To conclude, this NMA shows that ZLP has a **numerical benefit** in all available efficacy scores over ravulizumab at the end of the randomised placebo-controlled studies.

- Matched Indirect Comparison (MAIC) methodology to compare ZLP to ravulizumab at Week 60 in the Open-label extension (OLE) studies

Matching-adjusted indirect comparison methods are used in absence of head-to-head clinical studies. The level of evidence of MAIC is lower than in a head-to-head study, however in the absence of a head-to-head study and in absence of a connected network of evidence allowing for a standard NMA, this method is accepted by the statistical community as being the best methodology (Phillippo et al, 2018); allowing to avoid some bias inherent to naïve comparisons between studies.

For the comparison of ZLP with ravulizumab at Week 60, a standard NMA is not feasible due to the lack of a control arm. The MAIC method aims to provide a framework allowing to compare two interventions by adjusting for cross-study differences, when individual patient-level data (IPD) are available for at least one intervention (Signorovitch et al, 2012). In this analysis, IPD from RAISE-XT were used to match aggregated baseline characteristics of the CHAMPION-MG OLE.

The MAIC analyses were conducted in accordance with the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 18 (NICE DSU TSD18) for a robust population adjusted indirect treatment comparison (ITC) (Phillippo et al, 2018). The strategy followed the clinical study selection for matching, the identification of outcome measures, and the Matching study population and propensity score weighted analysis.

The baseline characteristics post-matching for ZLP are reported in the table below with the baseline characteristics of ravulizumab for the 5 variables included in the matching.

Table 7. Baseline characteristics of zilucoplan and ravulizumab study participants after matching.

Baseline Characteristics	**Ravulizumab (N=78)**	**Zilucoplan (adjusted) (ESS=50)**
MGFA n (%)	36 (46.2)	23 (46.2)
Age Mean (SD)	58.2 (13.6)	58.2 (13.6)

Baseline MG-ADL Mean (SD)	9.2 (2.6)	9.2 (2.6)
Male n (%)	38 (48.7)	24 (48.7)
Ethnicity n (%)	61 (78.2)	39 (78.2)
MGFA n (%)	36 (46.2)	23 (46.2)

ESS=effective sample size; MG-ADL=myasthenia gravis-activities of daily living; MGFA=Myasthenia Gravis Foundation of America; SD=standard deviation
Data source: Data on file

Outcomes from RAISE were recalculated applying the weights from the propensity score analysis, and the relative effect of ZLP vs. ravulizumab was estimated at Week 60. The difference of the weighted outcome of ZLP with the outcome of ravulizumab and the variance of the relative effect is estimated as the sum of the variance of the weighted ZLP outcomes and the variance of the ravulizumab outcome.

The mean difference CFB in MG-ADL for ZLP versus ravulizumab was -1.92 (-3.26, -0.57) and was statistically significant (p=0.006) in favour of ZLP. The mean difference CFB in QMG score of ZLP was -3.22 (-4.94, -1.50) and was also statistically significant (p=<0.001) in favour of ZLP.

In addition, the sponsor performed a side-by-side naïve comparison using the same mixed model for repeated measures (MMRM). The difference between ZLP and ravulizumab was above the clinically relevant threshold of 2 points for MG-ADL and above the clinically relevant threshold of 3 points for QMG (Muppidi et al, 2011; Katzberg et al, 2014). This analysis remains a naïve comparison and results are subject to bias due to the potential imbalance of prognostic factors or disease modifiers between the two interventions.

During the oral explanation, further questions were asked in this domain given the difficulty to interpret the results. The committee could not conclude that significant benefit had been successfully demonstrated vs. Ultomiris.

The COMP did not consider this question to be resolved.

Clinically relevant advantage for patients over Vyvgart

As part of this response, the sponsor provided details first on the interpretation of the area under the curve (AUC) and its relevance, and then on the Bayesian NMA performed on the AUC calculated for both studies in order to support the significant benefit of ZLP over efgartigimod alfa.

In brief, due to the cyclic nature of the efgartigimod alfa treatment regimen, the NMA on the CFB in efficacy scores to Week 12 (±2 weeks) was not deemed as a fair comparison by the sponsor between efgartigimod alfa and ZLP, as this would have favoured ZLP. Therefore, the sponsor has performed a NMA on AUC that adjusts for the fact that the effect of efgartigimod alfa on MG-ADL is highly variable over time with a maximum around Week 4 followed by a decreased effect up to Week 10.

Area under the curve is a measure of the aggregated effect over a period of time, which can be understood as the cumulative disability improvement over time. It allows for a comparison between the cyclic effect of efgartigimod alfa vs. the sustained effect of ZLP. Results of the NMA on the AUC, where the comparison between ZLP and efgartigimod alfa is anchored on placebo, showed a difference of 1.92, favouring ZLP. This corresponds to an increase of 10% in effect size with ZLP. Since the effect with ZLP is maintained up to 60 weeks of active treatment and given that study participants with

efgartigimod alfa have an average of 5 cycles, this 10% improvement in effect size is claimed to be likely to increase over long-term treatment.

The AUCs for each treatment group were calculated using the absolute mean CFB at each timepoint up to Week 12 (all observed CFB values were negative). Therefore, a higher AUC indicates an improved treatment effect. A Bayesian NMA (fixed effects models with non-informative prior) was then performed to compare ZLP to efgartigimod alfa anchored on placebo.

The AUC at week 12 is 48.63 and 34.60 for ZLP and efgartigimod alfa respectively. However, with the unusually high placebo effect in the ZLP study (AUC 28.48, which is almost equalling the drug effect on AUC in the efgartigimod alfa study) and the unusually low placebo effect in the efgartigimod alfa study (AUC 16.35) the resulting placebo-corrected difference (95% CrI) (from the NMA) in AUC over 12 Weeks between the two treatments is 1.92 (-13.69, 17.33). A difference of AUC of 1.92 shows the benefit of ZLP over efgartigimod alfa, which is the aggregated effect over 12 weeks of treatment and not a difference at Week 12 only that can be compared to the clinically meaningful threshold of 2 (Muppidi et al, 2011). The sponsor acknowledged that a difference in absolute AUC might be difficult to interpret in terms of effect size and proposes to rather interpret a ratio.

The adjusted mean difference of ZLP vs. placebo of 20.15 compared to the adjusted difference of 18.25 of efgartigimod alfa vs. placebo corresponds to a ratio of 1.10 in favour of ZLP. This new analysis represents *post hoc* calculation in addition to the originally submitted. The results from this NMA show an improvement of 10% in effect size for the first 12 weeks of treatment.

In the ADAPT+ (ADAPT OLE), on average, efgartigimod alfa-treated participants received 5 cycles of treatment, showing the same curve for the 5 cycles over approximately 60 weeks of treatment on average. In RAISE-XT, the effect of ZLP is maintained up to 60 weeks, if not further improved. The AUC of ZLP over the first 12 weeks (AUC0-12Weeks) is less than AUC12-24Weeks, which is less than AUC24-36Weeks showing an overall increase of AUC for each 12-week period up to 60 weeks. Given that the AUC (as a proxy for disability improvement) for each cycle (i.e., 10-week period) for efgartigimod alfa remains similar (Figure 4), and that AUC for each 12-week period increase over time, the 10% increase in effect size of ZLP compared to efgartigimod alfa over the first cycle (i.e., 12 weeks) is claimed that would probably increase with long-term treatment use.

<u>major contribution to patient care for patients over Ultomiris and Vyvgart</u>

The patient preference study was conducted by the sponsor in Germany, UK and US in 2021/22 with the objective to better understand treatment preferences of gMG patients with respect to administration setting, mode of administration, frequency of administration, time until meaningful improvement, risk of mild to moderate injection site reactions and risk of severe injection site reactions.

A discrete choice experiment (DCE) was conducted via an online survey. The survey design was developed in collaboration with patient advisors and medical experts. The survey was pre-tested across the 3 countries using semi-structured individual interviews with a convenience sample of 20 patients.

The data from the 3 countries were pooled and a random-parameters logit (RPL) regression model was used to analyse and estimate the preference weights and conditional attribute importance. The conditional relative importance of an attribute is a measure of the overall importance of that attribute relative to the other attributes in the study.

Predicted uptake probabilities were calculated for treatment profiles with treatment characteristics similar to ZLP and other clinically relevant gMG treatments currently available (ravulizimab and efgartigimod alfa). The predicted uptake probabilities were calculated by weighting the treatment

characteristics associated with each treatment profile using the preference weights generated. The preference share for each treatment profile represents the predicted probability that an average respondent in the sample would choose each of the treatment profiles, conditional on the attributes and levels used in the study, if these were the only treatment alternatives offered.

The final sample included 200 adult patients who have experienced uncontrolled gMG. More than half of respondents were diagnosed with gMG 5 or more years ago (57%).

Nearly all respondents (99.0%) reported that they currently experience gMG symptoms. The mean score for the MG-ADL was 8.0 (with respondent scores ranging from 0-19). Ninety eight percent of respondents were receiving treatment for their gMG at the time of the survey.

The DCE results showed greater preference weights (i.e., greater preferences) for treatments with lower risks of mild to moderate and severe injection site reactions, less frequently administered, shorter time to meaningful response, delivered as a subcutaneous (SC) injection, and self-administered at home.

For the predicted uptake probabilities comparing the treatment profile for a daily SC injection with attribute levels that resemble ZLP and an intravenous (IV) injection every 8 weeks with attribute levels that resemble ravulizumab, the results demonstrate a 65.2% probability of an average patient in this sample selecting the ZLP-like profile to 34.8% probability of selecting the ravulizumab-like profile.

Comparing the treatment profile for a daily SC injection with attribute levels that resemble ZLP and a cyclical IV therapy administered in a medical facility by a doctor or nurse, the predicted uptake probability demonstrates a 65.4% probability of an average patient in this sample selecting the ZLP-like profile to 34.6% probability of selecting the efgartigimod alfa-like profile.

Overall, the results showed that when given the option respondents preferred a daily self-administered SC injection over profiles that resembled ravulizumab or efgartigimod alfa.

As part of the major contribution to patient care discussion, the rationale put forward by the sponsor was understood, however, multiple concerns were raised during the discussion on whether the proposed product posology (daily) and route of administration could constitute a major contribution to patient care over authorised IV treatments that are administered with a lower frequency. As part of this discussion, comments were shared from the patient representative in the sense that the treatment modality would depend on individual patients and preferences. A subcutaneous route of administration could allow a better planning and flexibility, but it remains the uncertainty on whether this SC treatment modality could also interfere with the day-to-day activities. In addition, comments were made in that an IV administration by a healthcare professional would give the reassurance that the right storage and handling is performed. It is recognised that for some patients this administration might be preferred but other patients could prefer the less frequent IV administration. Therefore, a clear preference for the SC administration could not be concluded upon and the criterion of a major contribution to patient care was not supported.

The COMP did not consider this question to be resolved.

Overall, the committee was not of the opinion that a significant advantage versus Ultomiris and Vyvgart could be stablished.

After the oral explanation, the sponsor requested the withdrawal from the union register.